

Fig. 26.21 Context-sensitive effect-site decrement times for alfentanil, fentanyl, sufentanil, and remifentanil showing the time required for decreases of a given percentage (labeled for each curve) from the maintained effect-site concentration after termination of the infusion.

recovery is hastened by a steep concentration-versus-response relationship, in which emergence from anesthesia occurs after a relatively small fractional decrease in concentration. Most intravenous hypnotics have a moderately steep concentration-versus-response relationship.

Pharmacodynamic drug interactions also play a role in recovery from anesthesia. Interaction relationships predict that the same anesthetic state can be achieved by different ratios of two drugs. One way of selecting the best ratio might be the combination that offers the most rapid recovery. For example, when an opioid is combined with a hypnotic, the rate of recovery from anesthesia depends on the opioid and hypnotic concentrations, the rate of decrease in both drug concentrations, and the relative synergy between them for loss of response to noxious stimulation (i.e., the state maintained during anesthesia) versus the relative synergy for loss of consciousness. Although the time course of decreases in opioid and hypnotic concentrations can be approximately described by their respective context-sensitive decrement times for both drugs (Fig. 26.22; see Fig. 26.15), the influence of relative synergy for different endpoints must be captured by separate models of the interaction of the drugs for adequate anesthesia and emergence from anesthesia.

Vuyk and coworkers⁵⁴ modeled the predicted time to awakening from adequate anesthesia when propofol is combined with fentanyl, sufentanil, alfentanil, or remifentanil. Their calculations took into account the interaction between propofol and these opioids to provide adequate

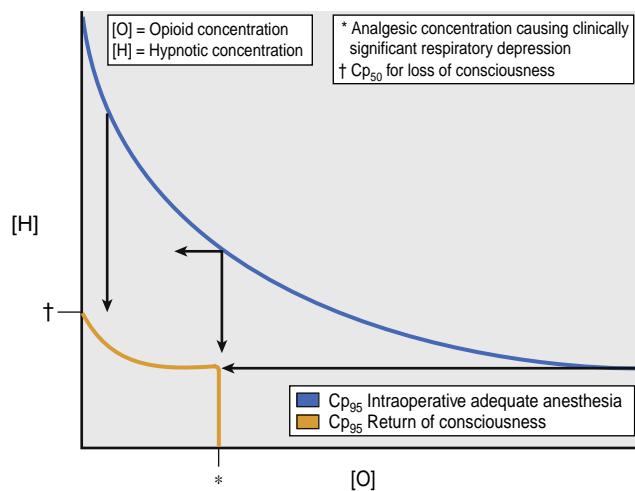


Fig. 26.22 Interaction between hypnotics and opioids for the prevention of movement after a noxious stimulus and for awakening and adequate spontaneous ventilation at the end of a surgical procedure. The time to recover at the end of a procedure is dependent on the concentration of both drugs used during surgery and the time for both to decrease below that required for consciousness and adequate spontaneous ventilation (i.e., their context-sensitive decrement times).

anesthesia and the interaction between propofol and opioids on consciousness levels on emergence from anesthesia (Figs. 26.23 and 26.24). Recovery times vary with the choice of opioid and the relative balance of opioid and

propofol during maintenance of anesthesia. For example, the upper left of **Fig. 26.23** simulates the emergence from a propofol-fentanyl anesthetic of 15-minute duration. The simulations assume a steady concentration of fentanyl and propofol throughout the anesthesia, similar to the underlying assumption of context-sensitive decrement times. The lowest curve on the response surface is the interaction curve between fentanyl and propofol; it ranges from no fentanyl and 12 $\mu\text{g}/\text{mL}$ of propofol on the left to 5.33 ng/mL of fentanyl and 1.8 $\mu\text{g}/\text{mL}$ of propofol on the right. In theory, any point along this curve would ensure maintenance of equivalent depth of anesthesia. When the infusion is turned off after 15 minutes of anesthesia, the concentrations of both drugs decrease. The decreasing concentrations of propofol

and fentanyl when the infusion is turned off can be found by the upward lines drawn from different points on the interaction curve, with the distance away from the lower plane representing time. Taken together, these upward lines represent a *recovery surface*. The blue line drawn on the recovery surface shows the points at which the fentanyl-propofol interaction model predicts emergence.

After 15 minutes of maintaining 1.8 $\mu\text{g}/\text{mL}$ of propofol and 5.33 ng/mL of fentanyl (right margin of the interaction curve), approximately 12 to 17 minutes is needed for the concentrations of both drugs to decrease sufficiently to permit emergence (see **Fig. 26.23**). However, if one maintains concentrations of 3.5 $\mu\text{g}/\text{mL}$ of propofol and 1.5 ng/mL of fentanyl (toward the middle of the interaction curve),

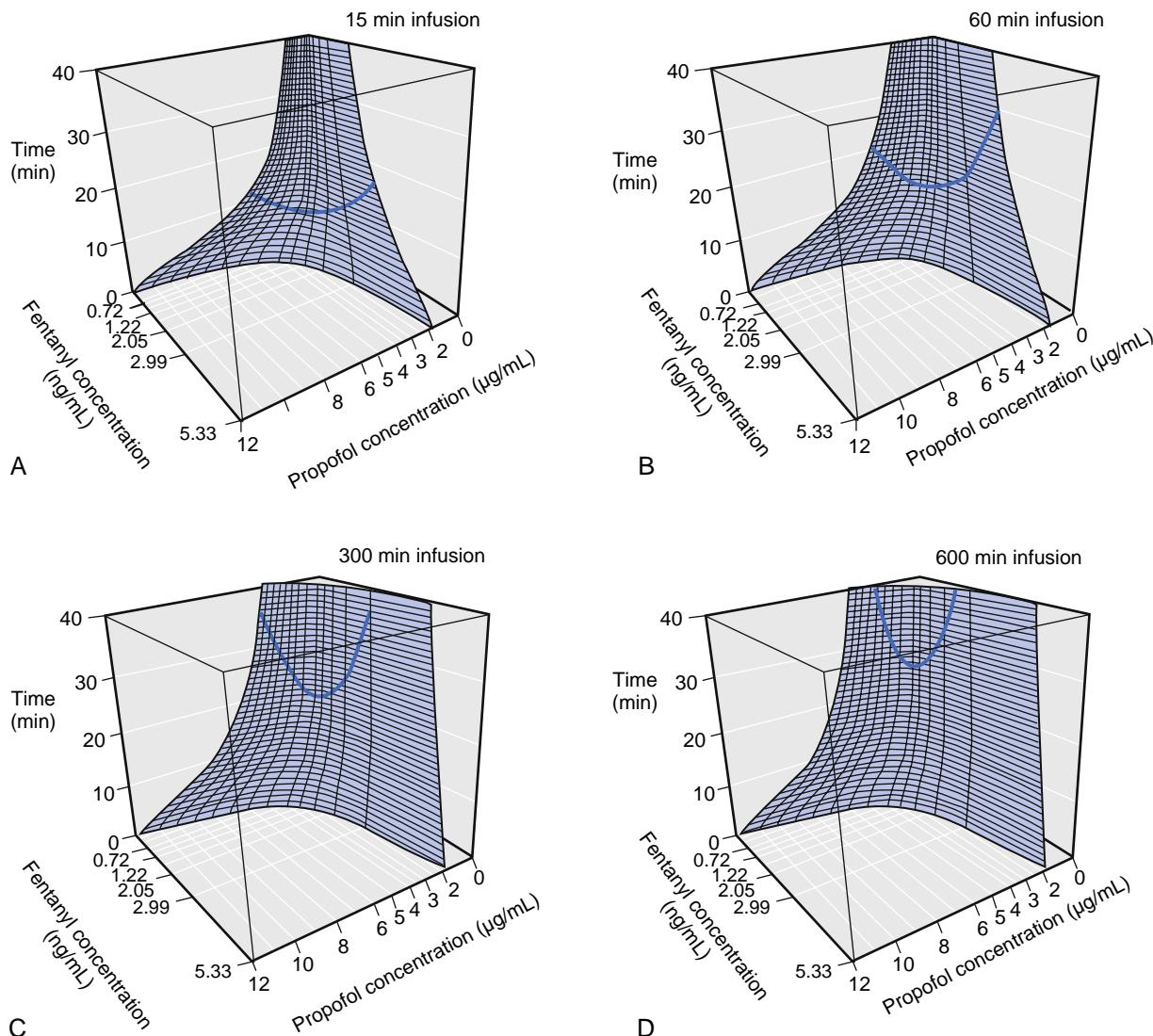


Fig. 26.23 Simulation of the interaction of propofol and fentanyl in preventing a somatic response at skin incision and time to recovery. On the x axis is the fentanyl concentration, and on the y axis is the propofol concentration. The blue curve in the lower plane shows the propofol-fentanyl interaction required to provide adequate anesthesia. When the infusion is turned off, the concentrations of each drug decrease, as shown on the z axis. The blue curve drawn on the recovery surface shows the time to emergence from anesthesia for combinations of fentanyl and propofol after an anesthetic of 15 minutes' (A), 60 minutes' (B), 300 minutes' (C), and 600 minutes' (D) duration. The optimal combination for the most rapid recovery is a propofol concentration of 3.0 to 3.5 $\mu\text{g}/\text{mL}$, combined with 1.5 ng/mL fentanyl. As the concentration of propofol or fentanyl increases, the time for recovery increases. In addition, the longer the duration of drug infusion, the longer recovery takes, especially if the optimal combination is not used. (Modified from Vuyk J, Mertens MJ, Olofson E, et al. Propofol anesthesia and rational opioid selection. Determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*. 1997;87:1549–1562.)

then emergence can be expected only 8 minutes after the infusions are turned off. Examination of the curves for 60, 300, and 600 minutes of propofol-fentanyl anesthesia suggests that the fentanyl target concentration that provides the most rapid emergence is approximately 1.0 to 1.5 ng/mL, which requires a propofol concentration of approximately 3.0 to 3.5 μ g/mL to maintain adequate anesthesia. In similar simulations, Vuyk and colleagues demonstrated that maintaining alfentanil and sufentanil concentrations in excess of the analgesic range (i.e., approximately 80 ng/mL for alfentanil and 0.15 ng/mL for sufentanil) is of little clinical benefit and can be expected to delay recovery from anesthesia. A second conclusion from these simulations is that if the patient demonstrates inadequate anesthesia, increasing the hypnotic concentration rather than increasing the opioid concentration beyond the analgesic range is preferable, so as to prevent prolongation of recovery.

The situation is different for remifentanil because of its unusual pharmacokinetic properties (see Fig. 26.24). When a remifentanil infusion is terminated, the extraordinarily fast clearance of remifentanil results in a very rapid offset of opioid drug effect. The lower plane again shows equivalent anesthetic states during maintenance with remifentanil and propofol (see Fig. 26.24). High doses of remifentanil permit a modest reduction in the dose of propofol needed for adequate anesthesia.¹¹⁴ However, the recovery surfaces show that high doses of remifentanil, with a modest reduction in the propofol dose, permit considerably faster emergence

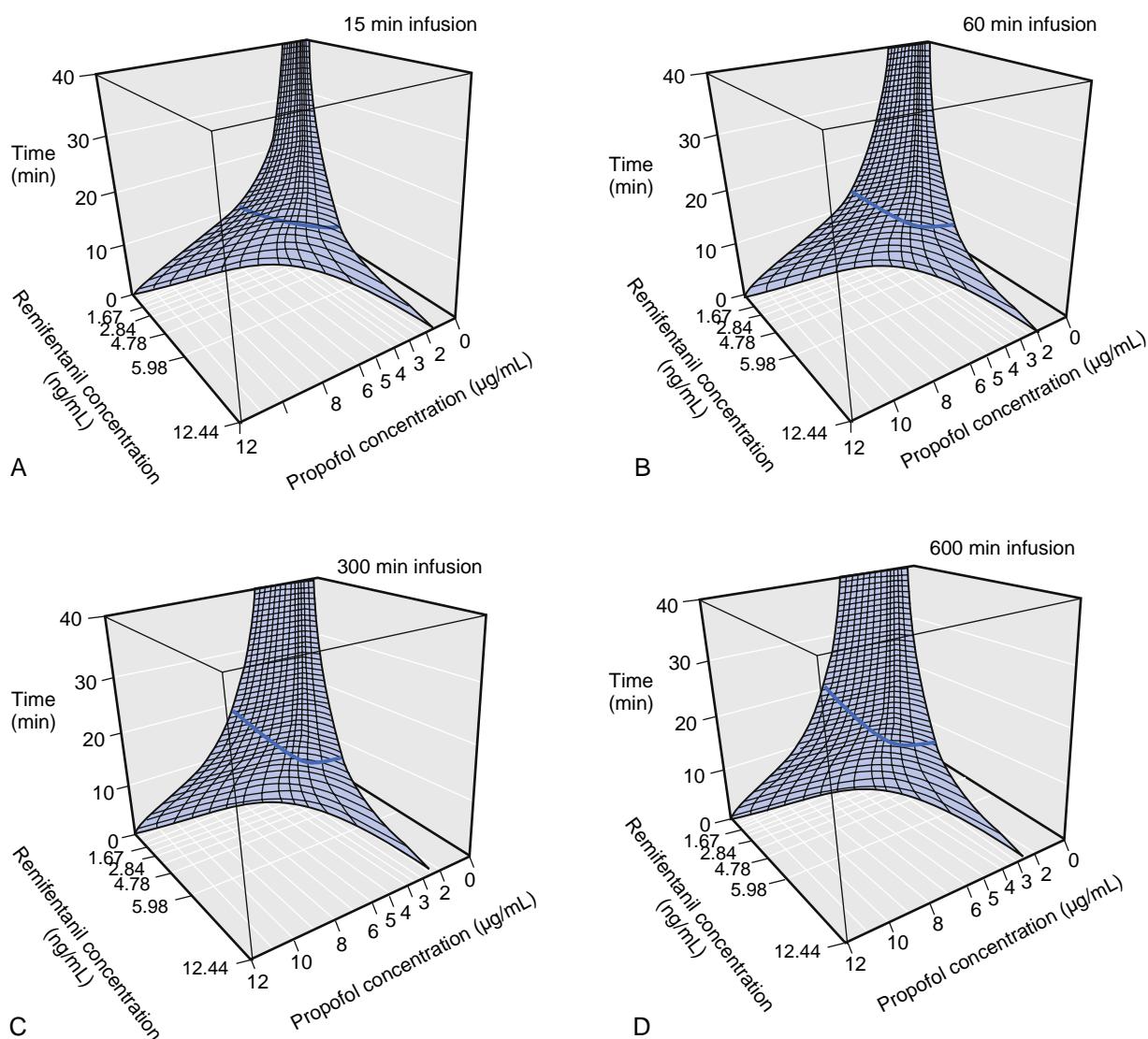


Fig. 26.24 Simulation of the interaction of propofol and remifentanil in preventing a somatic response at skin incision and time to recovery. The remifentanil concentration is on the x axis, and the propofol concentration is on the y axis. The blue curve in the lower plane shows the propofol-remifentanil interaction required to provide adequate anesthesia. When the infusion is turned off, the concentrations of each drug decrease, as shown on the z axis. The blue line drawn on the recovery surface shows the time to emergence from anesthesia for combinations of remifentanil and propofol after an anesthetic of 15 minutes' (A), 60 minutes' (B), 300 minutes' (C), and 600 minutes' (D) duration. With remifentanil, the optimal combination is a propofol concentration of 2.5 μ g/mL and with remifentanil, 5 to 7 ng/mL. In addition, increasing the duration of the infusion has minimal impact on recovery time if the optimal dose of remifentanil is not used. However, if the propofol dose is increased, then recovery is prolonged. (Modified from Vuyk J, Mertens MJ, Olofsson E, et al. Propofol anesthesia and rational opioid selection. Determination of optimal EC₅₀-EC₉₅ propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*. 1997;87:1549-1562.)



Fig. 26.25 On-line advisory displays including characteristics of drug behavior and interaction. The SmartPilot (Dräger, Lübeck, Germany) (upper display) is a two-dimensional display that shows the effect-site concentrations of combined drugs (opioids and intravenous or inhalation hypnotics), based on pharmacokinetic models and the resulting anesthetic effect and on pharmacodynamic models. Grey shaded areas indicate different levels of anesthesia. The orange point indicates the current combination of effect-site concentrations; the white line shows the retrospective concentrations; and a 10- and 15-minute prediction is marked by a black point and arrow—already calculated during presetting of delivery. Event markers may be set to show specific states of the patient related to the level of anesthesia. The time-based real-time curves, trends, and prediction of effect-site concentrations of individual drugs, resulting anesthetic effect (noxious stimulus response index [NSRI]), correlated bispectral index (BIS), vital signs, and event markers are shown as reference for interpretation. The Medvis display (Medvis, Salt Lake City, Utah) (lower display) shows a real-time visualization of anesthesia using pharmacokinetic and pharmacodynamic models to predict drug effect-site concentrations and drug effects in the past, current time, and 10 minutes into the future. Drug doses as boluses and infusions are administered via a separate data interface or user interface. Drugs are categorized according to sedation (top plot), analgesia (middle plot), and muscle relaxation (bottom plot). Effects are depicted as a population-based probability of unconsciousness (top plot), no response to tracheal intubation (middle plot), and no twitch response to a train of four stimulus (bottom plot). In addition, a second pharmacodynamic endpoint, POST-OP ANALG, represents a guideline therapeutic window for postoperative pain. Synergistic interactions of sedative-hypnotics and analgesics are shown by the white curves in the plot. For example, the top plot shows that with only propofol, the probability of unconsciousness is between 50% and 95% (yellow curve), but because propofol interacts with the opioids, the probability of unconsciousness is greater than 95% (white curve). Similarly, propofol potentiates the effect of the opioids in the middle plot.

from anesthesia. For example, it takes approximately 12 minutes to awaken from 600 minutes of anesthesia maintained with 3 $\mu\text{g}/\text{mL}$ of propofol and 2.5 ng/mL of remifentanil (see Fig. 26.24D). On the other hand, if the remifentanil concentration is increased to 5 ng/mL , then the propofol concentration can be reduced to between 2 and 2.5 $\mu\text{g}/\text{mL}$, and emergence can be anticipated within 6 minutes of discontinuation of the infusions. One might be concerned that such a technique places patients at increased risk for awareness because a propofol concentration of 2 $\mu\text{g}/\text{mL}$ is below the C_{50} value for wakefulness.¹¹⁵ Therefore combining such a technique with intraoperative EEG monitoring to assess anesthetic adequacy is reasonable.^{21,115}

DISPLAYING PHARMACOLOGIC INFORMATION

Integrating all sources of pharmacologic information including drug interaction together with measurements of patient response to a specific drug dose might offer a powerful advisory tool to depict the complete dose-response relationship of multiple drugs, thereby optimizing drug administration and improving patient care.^{116,117} For example, Fig. 26.25 shows a drug interaction advisory display.

Intravenous Infusion Devices and Technologies

MANUAL INTRAVENOUS INFUSION

When an infusion of an intravenous anesthetic is administered, the infusion regimen can be controlled by a variety of mechanisms varying from the simple Cair clamp or Dial-a-Flo (Abbott Laboratories) to complex computer-controlled infusion pumps. Simplicity of mechanical design, however, is not necessarily correlated with ease of use, which has prompted ongoing advances in infusion device technology over the past decades.

Infusion devices can be classified as either controllers or positive displacement pumps. Explicit in their title, controllers contain mechanisms that control the rate of flow produced by gravity, whereas positive displacement pumps contain active pumping mechanisms.

The most commonly used pumps for administration of intravenous anesthetics are positive displacement syringe pumps that use a variety of mechanisms. These pumps have acceptable accuracy and have several features that make them particularly suitable for anesthetic delivery. An important advance has been the introduction of a calculator feature within the pump so that the clinician can input the weight of the patient, the drug concentration, and the infusion rate in dose/unit weight/unit time and the pump will then calculate the infusion in volume/unit time. These pumps also permit simple application of a staged infusion scheme by allowing an initial dose and a maintenance infusion rate to be programmed into the pump. Numerous syringe pumps also include automated recognition of syringe size. Further enhancements are drug libraries by class of drug, suggested dosing schemes, and maximal dosing alerts. These modest advances in pump technology and design enable intravenous anesthetics to be conveniently and safely delivered.

In addition to the pumps, the complete intravenous delivery systems' hardware must perform perfectly,⁵ which means that the correct amount of drug should be delivered to the venous circulation in each unit of time. When the drug administration set has too large a *dead space*, the actual delivery rate can be altered, depending on the flow rate of coadministered fluid.¹¹⁸ The use of an antireflux valve is certainly advisable to prevent flow of the medication backward into the intravenous fluid bag rather than into the patient. Other factors include excessive compliance within the administration system (in the syringe plunger or in the administration lines) and the use of syringes with suboptimal lubrication, causing the plunger to advance in small jumps when infusion rates are slow; that is, with

TABLE 26.5 Manual Infusion Schemes

Drug	ANESTHESIA		SEDATION OR ANALGESIA	
	Loading Dose ($\mu\text{g}/\text{kg}$)	Maintenance Infusion ($\mu\text{g}/\text{kg}/\text{min}$)	Loading Dose ($\mu\text{g}/\text{kg}$)	Maintenance Infusion ($\mu\text{g}/\text{kg}/\text{min}$)
Alfentanil	50-150	0.5-3	10-25	0.25-1
Fentanyl	5-15	0.03-0.1	1-3	0.01-0.03
Sufentanil	0.5-5	0.01-0.05	0.1-0.5	0.005-0.01
Remifentanil	0.5-1.0	0.1-0.4	*	0.025-0.1
Ketamine	1500-2500	25-75	500-1000	10-20
Propofol	1000-2000	50-150	250-1000	10-50
Midazolam	50-150	0.25-1.5	25-100	0.25-1
Methohexitol	1500-2500	50-150	250-1000	10-50
Dexmedetomidine			0.5-1 over 10 min	0.2-0.7

*For analgesia or during sedation, an initial loading dose of remifentanil should not be given because its very rapid onset may result in apnea or muscle rigidity. After the loading dose, an initially high infusion rate to account for redistribution should be used and then titrated to the lowest infusion rate that will maintain adequate anesthesia or sedation. When using opiates as part of a nitrous-narcotic technique or for cardiac anesthesia, the dosing scheme listed under anesthesia is used. When the opiate is combined as part of balanced anesthesia, dosing listed for analgesia is needed.

small patients, low target concentrations, drug solutions of high concentration, or large-volume syringes.⁵

Manual intravenous drug delivery consists of a combination of a bolus dosage and a continuous infusion, as explained earlier when discussing the pharmacokinetic considerations. Table 26.5 offers recommendations for delivering intravenous anesthetics via conventional infusion pumps based on integrated pharmacokinetic-pharmacodynamic models. Ultimately, the adequate rate of drug administration is based on observation and examination. Individual patients vary significantly in their response to a given drug dose or concentration; therefore titrating to an adequate drug level for each individual patient is essential. Drug concentrations required to provide adequate anesthesia also vary according to the type of surgery (e.g., superficial surgery vs. intraabdominal surgery). Drug concentration requirements are often smaller during the end phase of surgery; therefore titration often involves judicious reduction of the infusion rate toward the end of surgery to facilitate rapid recovery.

If the infusion rate is insufficient to maintain adequate anesthesia, then both an additional loading (bolus) dose and an increase in infusion are required to increase the plasma (biophase) drug concentration rapidly. Various interventions also require larger drug concentrations, usually for brief periods (e.g., laryngoscopy, endotracheal intubation, skin incision). Consequently, the infusion scheme should be tailored to provide peak concentrations during these brief periods of intense stimulation. An adequate drug level for endotracheal intubation is often achieved with the initial loading dose; however, for procedures such as skin incision, an additional bolus dose may be necessary.

Infusion schemes (see Table 26.5) do not approach the convenience and precision of use associated with the delivery of an inhaled anesthetic via a calibrated vaporizer, particularly when the user is still required to calculate volume infusion rates (mL/hr) from the mass-based infusion rates given in the infusion schemes. The use of “calculator” pumps helps to simplify the task of the anesthesiologist. At start-up the user is required to input the weight of the patient and the drug concentration. Thereafter, the pumps are able to accept as input mass-based rates, from which they calculate and implement volume infusion rates. The level of convenience and precision of vaporizers can however be achieved by using TCI devices, such as the commercially available TCI pumps.

COMPUTER-CONTROLLED DRUG DELIVERY

As discussed in the introduction of this chapter, optimal patient-individual dosing may be achieved by the application of pharmacokinetic and pharmacodynamic principles. Using the dose-response relationship, drug titration should be performed as close as possible to the drug effect. Titrating to a specific effect or, if not possible, a specific effect-site concentration offers advantages. Because the effect-site or plasma concentrations are not continuously measurable online for most intravenous anesthetics (in contrast to inhaled anesthetics), a drug model using a computer that continuously updates the anesthetic administration rate to maintain an estimated drug effect or drug concentration is required (Fig. 26.26).

If a specific plasma or effect-site concentration is titrated, then this technique is called TCI. TCI is a *closed-loop control* system. The history of the development of TCI systems has recently been summarized.¹¹⁹ In these systems the clinician serves as the *human controller* in the loop and, as a consequence, the control actions are intermittent and irregular in time.¹²⁰ Control theory is increasingly being applied in the development of computer-controlled drug delivery systems, among others in anesthetic closed-loop control applications. The aim of computer-controlled closed-loop systems is to formalize this process of observation and intervention to provide fine-tuned and more accurate control. Such systems use a near continuous signal of drug effect, calculate the error between the observed value and the set point value (selected by the user), and use this error figure in an algorithm to make frequent and regular adjustments to drug administration rates. Some computer-controlled drug delivery systems try to predict the future drug effect to make appropriate adjustments well in advance.¹²⁰

TARGET-CONTROLLED INFUSION

Devices

The development of microprocessor-controlled syringe pumps and a better understanding of the dose-response relationship have enabled the development of TCI systems. A TCI is a computer- or microprocessor-controlled system that aims to achieve a user-defined estimated drug concentration in a body compartment or tissue. A clinician using a TCI system to administer an anesthetic drug is thus able to set and adjust a desired drug concentration, usually referred to as the *target concentration*, based on clinical observation of the patient or measurement of drug effect. Multicompartment pharmacokinetic-pharmacodynamic models are used by TCI systems to calculate the infusion rates required to achieve the target concentration (see Fig. 26.4). A computer or microprocessor is required to perform the complex calculations and to control the infusion pump. Typically, plasma or effect-site concentrations are targeted.³

TCI systems in use today still apply the theoretical approach described by Kruger-Thiemen¹²¹ to achieve and maintain a steady-state blood concentration of a drug whose pharmacokinetic can be described by a multicompartment model. This approach was first clinically implemented by Schwilden.⁷ The infusion schemes used, better known as bolus-elimination-transfer (BET) schemes (see Fig. 26.4), were initially designed for two-compartment models. Briefly, the infusion starts with an initial bolus of drug required to achieve the initial target concentration. Second, an infusion is administered to replace drug lost by elimination. Since the elimination rate constant is fixed, the amount of drug eliminated in each unit of time is proportional to the plasma concentration; accordingly, at steady-state plasma concentrations, drug removal by elimination can be compensated for by a constant rate infusion. Third, a second infusion is administered to replace drug distributed or transferred to peripheral tissues. The amount redistributed exponentially declines over time as the gradient between the central compartment and the peripheral compartment decreases. Replacing distributed drug requires an infusion at an exponentially declining rate to replace drug *lost* from the central compartment by distribution until steady state.⁴

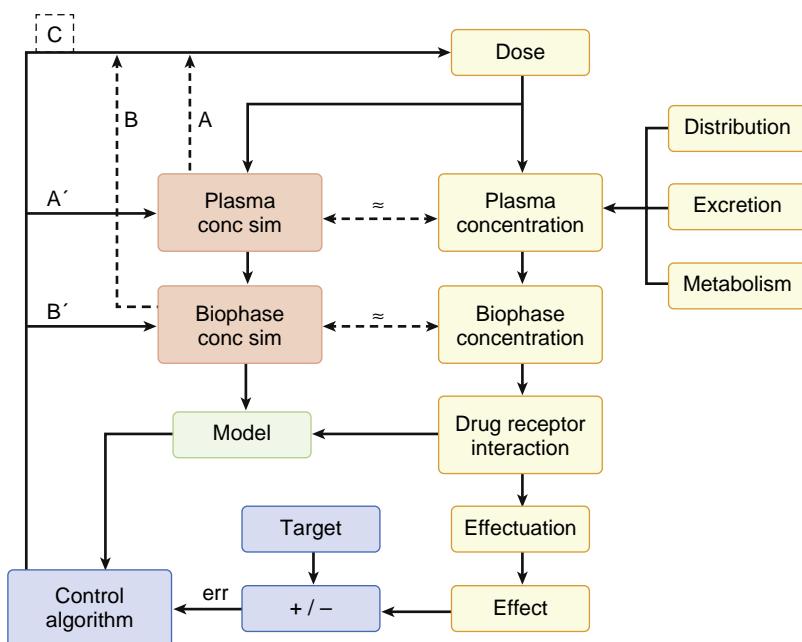


Fig. 26.26 Schematic representation of the pharmacokinetic and pharmacodynamic processes determining the relationship between administered doses and resulting effect intensity of a drug (yellow). Pharmacokinetic factors such as distribution, metabolism, and/or excretion determine the relationship between drug dose and drug concentration in the biophase. In the biophase, the drug interacts with the receptor, and the pharmacologic effect is accomplished via effectuation processes. Target-controlled infusion (TCI) will use a model to estimate the plasma or biophase drug concentration (red), and will calculate the dose needed to approach a target concentration in plasma (A) or biophase/effect-site (B). Computer-controlled, closed-loop feedback measures the error between the effect and the target effect to control the dose administration (blue). Better closed-loop performance can result if, rather than using the dose as a direct actuator, the simulated variable of a TCI system is used as actuated variable (A/A; B/B). The TCI system then compensates for part of the complexity of the dose–interaction relationship. Advanced control algorithms may take into account a continuously updated model of the interaction (light green). (Modified from Struys M, de Smet T. Principles of drug actions: target-controlled infusions and closed-loop administration. In: Evers AS, Maze M, Kharasch ED, eds. *Anesthetic Pharmacology: Basic Principles and Clinical Practice*. Cambridge: Cambridge University Press; 2011:103–122. Used with permission.)

BET schemes have some disadvantages such as the requirement of a no-drug status before infusion, which disables a change in the target concentration. In addition, more recent research concluded that the pharmacokinetics of most anesthetics is better described using a three-in instead of a two-compartment model. Lastly, as previously discussed in this chapter, the plasma is not the site of drug effect. Consequently, effect compartment–controlled TCI algorithms were developed.²⁹ During the 1990s, various computer-based TCI prototypes were developed by researchers at Stanford (STANPUMP, California), Stellenbosch (STELPUMP, South Africa), Duke (computer-assisted continuous infusion [CACI], North Carolina), and Ghent (RUGLOOP, Belgium) universities. Groups in Erlangen, Germany, and Leiden, The Netherlands, produced software able to simulate pharmacokinetic trajectories (IVA-SIM and TIVA Trainer, respectively). Finally, the Diprifusor (AstraZeneca, London) became the first commercially available TCI pump. It was based on a prototype from the Kenny group¹²² and was able to control a set plasma target concentration using specific prefilled syringes from AstraZeneca. Although the technology never became available in the United States,⁸ this TCI pump was the first breakthrough in an attempt to optimize drug administration in daily clinical practice in many countries. More recently, various companies have commercialized more flexible *open TCI* pumps capable of administering multiple drugs in both plasma and effect compartment–control mode (Fig. 26.27).^{8,119}

Effect compartment–control requires a rate constant that accurately describes the rate of equilibration between plasma (Fig. 26.28A) and effect-site concentrations (Fig. 26.28B). The benefits of effect compartment–controlled TCI were demonstrated for propofol by Wakeling and associates¹²³ and Struys and associates.⁴⁷ This mode is commonly used throughout Europe.

A detailed description of the history of the development of TCI and of the development and availability of TCI devices was published in 2016.^{8,124}

Evaluation of Target-Controlled Infusion Delivery

Acceptance of target-controlled drug delivery of intravenous anesthetics requires evaluation of accuracy (defined as the difference between predicted and measured concentrations) and outcomes among patients in whom automated drug delivery has been used. The inaccuracies associated with pharmacokinetic model–driven devices are attributed to possible problems with the software and hardware, and more importantly to pharmacokinetic variability (Fig. 26.29).

Inaccuracy in the software results from incorrect mathematical implementation of the pharmacokinetic model. Computer simulations can be used to test the infusion rates as calculated by a software program, and thus software errors are fairly simple to identify and correct.¹²⁵ Inaccurate drug delivery from the infusion pump (i.e., failure to correctly infuse the amount intended by the system) infrequently



Fig. 26.27 Target-controlled infusion (TCI) pumps. (A) Fresenius Base Primea. (B) Fresenius Injectomat TIVA. (C) CareFusion Alaris PK. (D) Arcomed μ SP 6000. (E) Arcomed μ VP 7000. (F) Binet PION TCI pump. (G) B. Braun Infusomat Space and Perfusor Space. (H) Veryark Concert-CL. (I) MedCaptain HP TCI. ([A and B] Courtesy Fresenius Kabi AG, Homburg, Germany; [C] Courtesy BD, Franklin Lakes, NJ; [D and E] Courtesy Arcomed, Zurich, Switzerland; [F] Courtesy Binet, Seoul, Korea; [G] Courtesy B. Braun Medical Inc., Bethlehem PA; [H] Courtesy PRHOINSA, Madrid, Spain; [I] Courtesy Medcaptain, Shenzhen, P.R. China.)

occurs with present syringe-pump technology and contributes little to the overall inaccuracy of these devices.¹²⁶ The aforementioned safety review identified only two company reports of problems with TCI devices that were attributable to software programming errors, neither of which caused actual patient harm.¹²⁷

The major cause of inaccuracy is biologic variability, of which there are two sources: (1) the pharmacokinetic model is always wrong,¹⁰⁶ and (2) the pharmacokinetics of the individual patient are not as programmed into the model. The pharmacokinetic model is always wrong because individuals are far more complex than implied by simple compartment models,¹⁰⁶ and no model can precisely predict the concentrations, even if the pharmacokinetic parameters in the individual were known with absolute precision. However, even if the pharmacokinetic

model truly reflected the underlying biologic variables, the parameters of the model would be average parameters for the population and not the exact parameters of the patient. Even if the parameters were modified to reflect the influence of demographic factors such as age, gender, hypovolemia, and coadministration of other drugs, they would still deviate from the true pharmacokinetic parameters in the individual. Thus biologic variability fundamentally precludes the possibility of precisely achieving the desired target concentration when automated drug delivery devices are used. Realizing that biologic variability always exists, no matter how drugs are given, and that this same biologic variability affects all methods of drug delivery is important. Nonetheless, the variability with TCI devices will always be less than the variability observed after a single bolus injection.¹²⁸ The performance of computer-controlled drug administration



Fig. 26.27 cont'd

must be interpreted in terms of the therapeutic expectations of the clinician. Possible goals include accurately producing a desired concentration in plasma, precisely titrating the plasma drug concentration, achieving the desired drug effect, and producing the desired time course of drug effect. Over the past decade, investigators have addressed each of these goals and have refined the performance of automated drug delivery devices accordingly.

The ability of an automated drug delivery system to rapidly achieve and then maintain a selected target concentration is a logical measure of the performance of such a device. The difference between the measured and target concentrations can be expressed in several ways. Classic graphic representations are X-Y plots depicting predicted versus measured blood (plasma) drug concentrations (Fig. 26.30) or the relationship of the measured and predicted drug

concentration versus time of administration (Fig. 26.31). Numerically, the primary concern is how far the measured concentration is from the predicted one; this relationship is now most frequently described in terms of performance errors, which is the difference between measured and target concentrations as a percentage of the desired target—for example, $[(\text{measured} - \text{target}) \div \text{target}] \times 100\%$.¹²⁹ The median value of the performance error for a patient or population is referred to as the median performance error (MDPE) and represents the average overshoot or undershoot of the system. The median absolute performance error (MDAPE) is the median of the absolute values of all performance errors. The MDAPE is commonly used as a measure of the inaccuracy of an automated drug delivery device. An MDAPE of zero is perfect performance, and an MDAPE of 20% means that one half the plasma concentrations will

be within 20% of the target and one half will be outside that range. A further assessment of accuracy is whether the system maintains a stable target concentration, which is best measured by the wobble of the system. Varvel and colleagues¹²⁹ asked a group of clinicians to evaluate the performance of automated drug delivery devices and demonstrated that the MDAPE best predicted the adequacy of performance of the automated delivery device, as judged by experienced clinicians.

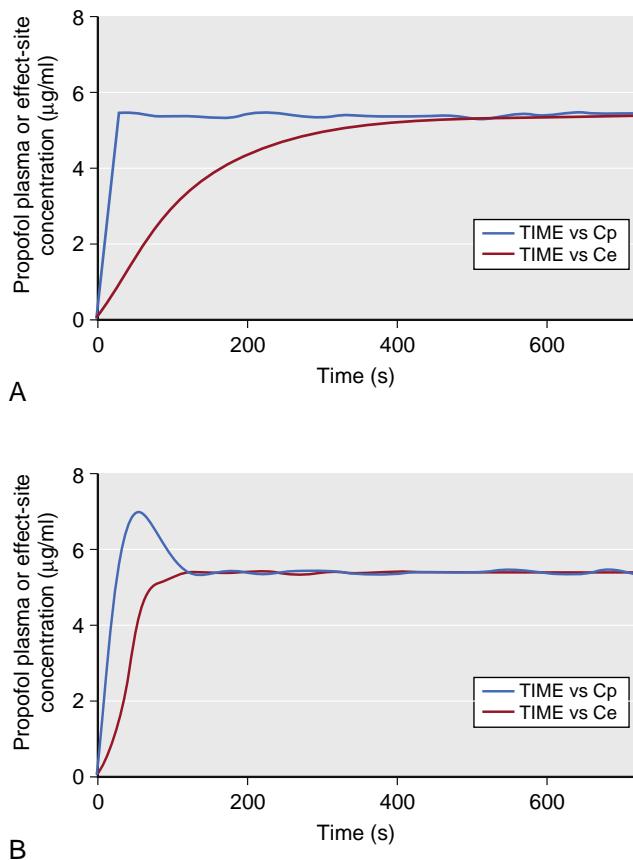


Fig. 26.28 Simulation of propofol plasma (A) versus effect compartment-controlled (B) target-controlled infusion.

As observed earlier, expecting all performance errors to be zero is not reasonable. However, it would be desirable if positive and negative errors offset each other so that the MDPE of an automated drug delivery device were 0%. The MDPE does not indicate the range of performance errors (because positive and negative performance errors offset each other), but it does indicate whether the plasma concentrations achieved with the device tend to overshoot (+MDPE) or undershoot (-MDPE) the desired target.

Many groups have evaluated the accuracy of many different pharmacokinetic sets for virtually all the intravenous hypnotics and analgesics. Most studies have involved healthy volunteers or lower-risk patients undergoing procedural sedation or anesthesia, and in these settings the authors have studied adult models for propofol,^{13,31,130-137} midazolam,¹³⁸ ketamine,¹³⁹ dexmedetomidine,^{140,141} fentanyl,¹⁴²⁻¹⁴⁴ alfentanil,^{67,145-147} sufentanil,^{138,148,149} and remifentanil.^{150,151} Pediatric models for propofol have also been evaluated.¹⁵²⁻¹⁵⁵

Few studies have been performed in the intensive care unit (ICU) setting. The performance of the Marsh model for propofol sedation in different adult populations has however been studied.^{156,157}

Based on many of these studies, the expected predictive performance of such pharmacokinetic models, at best, tends to be around 20% to 30% MDAPE.

Model Selection for Target-Controlled Infusion: Adult Propofol Models

For most intravenous drugs, various multicompartment pharmacokinetic-pharmacodynamic models have been published. The pharmacokinetics of propofol have been the most frequently tested (see Fig. 26.6) of all anesthetic drugs. Coetzee and coworkers compared the accuracy of some of the models published before 1995 and found that propofol TCI using the model published by Marsh and coworkers resulted in acceptable performance (MDPE -7%; MDAPE 18%).¹³⁰

The Marsh model was incorporated in the first commercially available TCI system (Diprifusor). Clinical studies using this plasma-controlled TCI system showed that the technique and model were clinically useful in various clinical situations.¹⁵⁸⁻¹⁶² The major drawback of the Marsh model is the lack of effect compartment information and

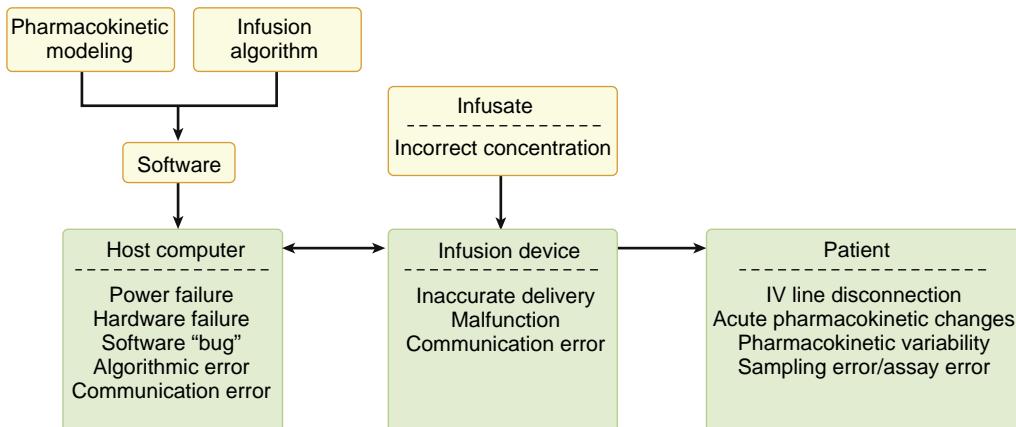


Fig. 26.29 Major sources of potential error in pharmacokinetic model-driven drug delivery. In a commercial device, the computer functions are incorporated into the infusion device. IV, Intravenous.

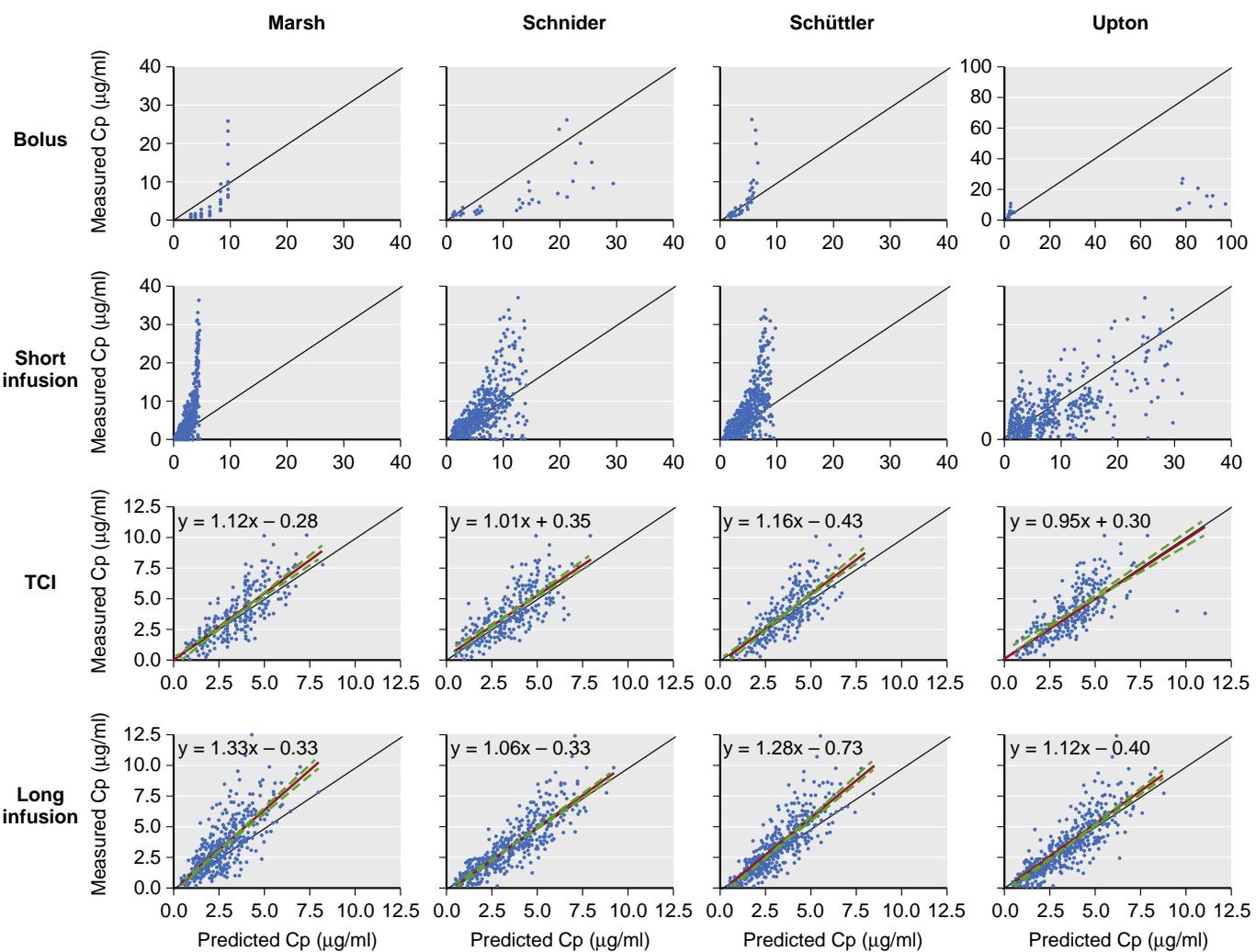


Fig. 26.30 Predicted versus measured propofol plasma concentration for the four pharmacokinetic models. Each point represents a single sample. Thin black line represents the line of identity. For target-controlled infusion (TCI) and long infusion conditions, the bold red line shows the regression line and the bold dashed green line indicates the 95% confidence interval for the regression line. The formula represents the equation from the linear regression. (From Masui K, Upton RN, Doufas AG, et al. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol. A comparison using bolus, continuous, and target-controlled infusion data. *Anesth Analg*. 2010;111:368–379. Used with permission.)

the fact that weight is the only covariate. Later, Schnider and coworkers^{163,164} evaluated age, height, weight, and lean body mass as covariates in a new combined pharmacokinetic-pharmacodynamic three-compartment model. The large variability of the study population (age 18–81 years, weight 44–123 kg) provides a wide applicability of the model. Several validation studies rated this model accurate under various conditions. For example, Masui and colleagues¹³ compared the measured propofol plasma concentrations with the predictions of four published models and revealed bias in all three compartment models during the bolus and short infusion regimens (see Figs. 26.30 and 26.31). During long infusions, a worse measured/predicted propofol plasma concentration at higher concentration was observed for the Marsh¹⁵² and Schüttler¹⁶⁵ models than for the two other models. Less biased measured/predicted propofol plasma concentration was found for all models during TCI. In the bolus group, after 1 minute, a clear overprediction was observed for all three-compartment models for the entire 5-minute period; however, this initial error resolved after 4 minutes in the Schnider model. During the bolus and

short infusion conditions, the Marsh model demonstrated worse MDPE and MDAPE when compared with the other models. During short infusion, MDAPE for the Schnider and Schüttler models was better. All models showed similar MDPE and MDAPE during TCI simulations. During long infusion, the Marsh and the Schüttler models underestimated the higher plasma concentrations. Interestingly, the physiologically based recirculatory model developed by Upton and coworkers¹⁴ did not reveal a better description of the pharmacokinetic time course. The Schüttler model has a major practical drawback; it defined the infusion characteristics, being bolus or infusion, as a significant covariate, thereby discouraging TCI applicability.

An additional drawback of the Schnider model is the use of lean body mass as calculated using the equation developed by James.¹² The quadratic behavior of the lean body mass function makes it invalid (negative values!) when used in patients who are very obese. Therefore as changing population demographics such as obesity might influence the pharmacokinetics of propofol, models should ideally be applicable to a broad range of population demographics

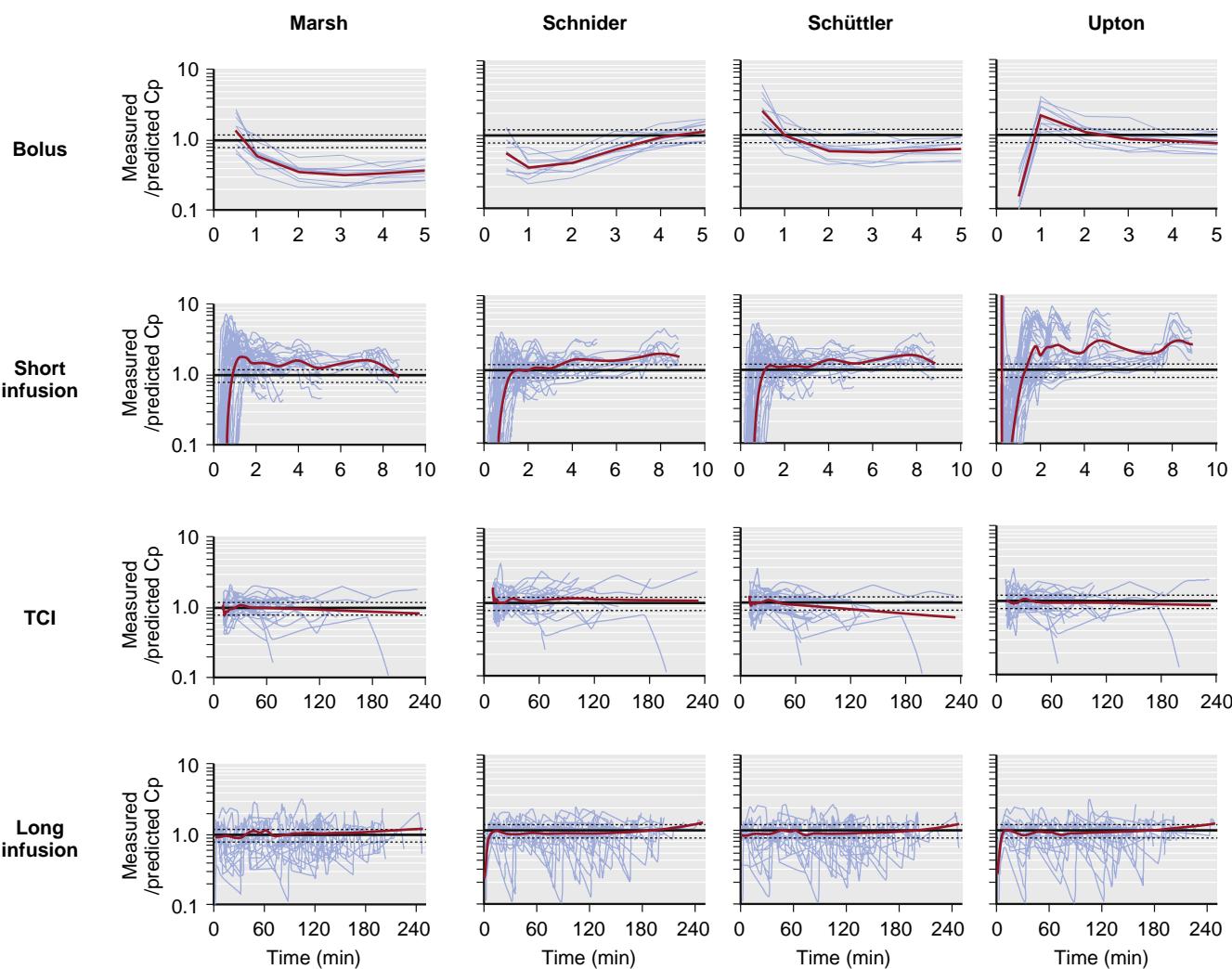


Fig. 26.31 Time course of the measured/predicted concentration relationship versus time of drug administration. The dotted lines indicate an acceptable range of measured/predicted plasma drug concentration (C_p). The red line indicates the Friedman Super Smoother curve for the population data. (From Masui K, Upton RN, Doufas AG, et al. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: a comparison using bolus, continuous, and target-controlled infusion data. *Anesth Analg*. 2010;111:368–379. Used with permission.)

before being used in clinical practice. One potential solution to the problem of scaling for size in obese patients is the application of allometric scaling. When using allometric scaling, growth and development can be studied using classic covariates (e.g., weight, age, sex). Size is the primary covariate and can be referenced to a 70-kg person with allometric scaling using a coefficient of 0.75 for clearance and 1 (one) for volume. Anderson and Holford¹⁶⁶ promote this approach because the use of these coefficients is supported by fractal geometric concepts and observations from biologically diverse areas.¹⁶⁷

Cortinez and coworkers¹⁶⁸ derived a population pharmacokinetic model using obese and nonobese data to describe the pharmacokinetics of propofol over a wide range of body weights. A model using allometric scaling of total body weight as the size descriptor of volumes and clearances was better able to characterize propofol pharmacokinetics in obese patients than a model using size descriptors. The same model was later used to control TCI propofol administration in a new cohort of obese patients, and the predictive performance of this model was then compared with that of four

other models (Marsh, Schnider, Eleveld, and van Kralingen).¹³³ While all models tended to underestimate measured concentrations in this study (i.e., measured concentrations were higher than those estimated), the Eleveld model provided the most accurate predictions. When, instead of using the total body weight with the Marsh and Schnider models, an adjusted body weight was used (adjusted weight = ideal weight + 40% × [total – ideal weight]), the predictive performance of these two models were then associated with the lowest MDPE and MDAPE of all models.¹³³

Most recently, Cortinez and colleagues used the data from 47 patients enrolled in three previous studies to develop and prospectively evaluate a new pharmacokinetic-pharmacodynamic model for obese patients.¹⁶⁹ Interestingly, during the development phase, allometric scaling did not improve the fit of their new model, and thus their newest model uses linear scaling of compartmental volumes and clearances, with total body weight. When, in the second phase of their study, this newer model was tested prospectively in obese patients, the pharmacokinetic and pharmacodynamic components performed adequately; with regard to the

pharmacokinetic component, the predictive performance of the Eleveld model was better than that of their older and newer models, and that of the Schnider model.

Attention has also been focused recently on the performance of propofol models in underweight patients. Lee and colleagues studied the predictive performance of the Marsh and Schnider model in underweight adults and showed that although predictive performance of both models was within limits considered clinically acceptable, the former tended to overestimate plasma concentrations, whereas the Schnider model tended to underestimate plasma concentrations.¹³⁵

Interestingly, when the performance of the older Cortinez model, which uses allometric scaling of total body weight, was studied in volunteers of normal weight, the predictive performance was acceptable and similar to that of the Schnider model.¹⁷⁰ As mentioned earlier, the newer Cortinez model scales volumes and clearances linearly with total weight.¹⁶⁹ It may not extrapolate that well to patients of normal weight, and for this reason the authors do not recommend using it in patients of normal weight.

Different pharmacokinetic-pharmacodynamic models for propofol are associated with different k_{e0} values, which were sometimes derived in very different ways.¹² When effect-site targeting is used, not only is the accuracy of the pharmacokinetic model important for accurate drug administration, the validity of the k_{e0} is also important. First, the value of the k_{e0} will determine the degree of plasma concentration overshoot when the target concentration is increased, and second, it will determine the estimated values of the effect-site concentrations during periods when the plasma and effect-site are not in equilibrium. If one assumes that there is no hysteresis in the relationship between effect-site drug concentration and clinical effect, then it might be rational to evaluate the overall accuracy of propofol pharmacokinetic-pharmacodynamic models by experiments in which propofol is administered by effect-site TCI, by recording a measure of the clinical effect observed over a period of time and then comparing the time course of the estimated effect-site concentrations and clinical effect.

Barakat and colleagues compared the Marsh and Schnider models by observing BIS and MOAA/S scores after starting an effect-site targeted propofol TCI infusion at a fixed target concentration of 2 $\mu\text{g}/\text{mL}$.¹⁷¹ Subsequently they compared the shapes of the curves of the time course of the estimated effect-site concentration and of measures of clinical effect (BIS and MOAA/S). They found that the shape of the effect-site concentration curve estimated by the Marsh model (with k_{e0} 0.26 min^{-1}) was more similar to the curves for clinical effect than the curve of the effect-site concentration estimated by the Schnider model.¹⁷¹

A more objective application of the preceding rationale is to observe clinical effect over a time period when a TCI system estimates that the effect-site concentration is stable. With this approach, one can reason that if the effect-site (target) concentration is kept constant, and there are no other changes (i.e., no other drugs are administered, and no new stimuli), then the most appropriate model will be the one for which a measure of clinical effect is most stable over time.

Using this approach to compare the Schnider and Marsh models, Coppens and coworkers¹⁷² administered propofol by manual infusion until loss of consciousness. They then

continued propofol administration in effect-site targeting TCI mode, using as target concentration the estimated effect-site concentration at the moment of loss of consciousness. They found that among 20 patients assigned to effect-site TCI propofol with the Marsh model, BIS values rose and all patients regained consciousness within the subsequent 20 minutes. On the other hand, among the 40 patients assigned to effect-site TCI propofol with the Schnider model (20 with a fixed k_{e0} , and 20 in whom an individual-specific k_{e0} was calculated using the Schnider pharmacokinetic parameters and a fixed time-to-peak effect of 1.6 minutes), only one regained consciousness and there was a general trend for the BIS to decline during the subsequent 20 minutes.

Thomson and colleagues applied the same rationale to a study in which they sought to determine the most suitable k_{e0} for use with the Marsh model when used in effect-site targeting mode for sedation.¹⁷³ Six sequential groups received sedation with the Marsh model with the k_{e0} set to 1.2, 0.8, 0.7, 0.6, 0.5, and 0.2 min^{-1} , respectively. In each patient, the initial target concentration was 0.5 $\mu\text{g}/\text{mL}$. Once the effect-site and plasma concentrations were calculated to have equilibrated, the effect-site target concentration was increased in increments of 0.2 $\mu\text{g}/\text{mL}$, until a MOAA/S score of 3 was reached. Thereafter the effect-site target concentration was fixed, and two-choice visual reaction times were recorded. Interestingly, while a k_{e0} of 0.6 min^{-1} seemed best overall, it should be noted that there was considerable interindividual variability. In every group there were patients where the sedation level (just by reaction times) remained stable, whereas in all groups except the 1.2 min^{-1} group there were patients where reaction times decreased (suggesting lightening of sedation depth) and in every group except the 0.2 min^{-1} group there were patients where reaction times increased (suggesting increasing sedation depth).

As mentioned previously, there is no strong consensus on which model is best for propofol administration. Clinician choices concerning which model to use and the mode of use (plasma versus effect-site targeting and method of implementation of effect-site targeting) are largely pragmatically made, based on geographical and historical issues, availability of equipment, and the choices made by the supplier of the equipment.^{8,12} More fundamental research is required to better understand the mechanisms of anesthetic-induced loss of consciousness, to determine whether the aforementioned hysteresis occurs, and to subsequently fine-tune our understanding of the pharmacometric principles governing effect-site modeling.¹²⁰

At present a variety of different adult and pediatric models for propofol are used in studies, but also in clinical use, having been implemented in commercially available TCI systems. This generates a potential source of confusion and error. A group in Groningen, The Netherlands, thus combined the data from a large number of pharmacokinetic-pharmacodynamic studies of propofol, involving subjects with a wide range of characteristics (age, weight, and patients vs. volunteers), and used nonlinear mixed effects modeling to generate a single model that applies to all patients. Initially, a pharmacokinetic-only model was produced.¹⁷⁴ This model is able to provide pharmacokinetic parameters for a wide range of patients, from small children

to elderly patients, as well as for obese patients. Later a complete pharmacokinetic-pharmacodynamic model was produced, with the pharmacokinetic part involving the same structure as the previous model, but slightly updated parameters, and a sigmoidal Emax pharmacodynamic model.⁷⁶ Internal testing of the pharmacokinetic components of both models showed similar or better performance than that of specialist models designed for specific subpopulations (children, elderly, and obese).^{76,174}

Model Selection for Target-Controlled Infusion: Pediatric Propofol Models

Two pharmacokinetic models for propofol in children are available in clinical TCI systems. Kataria and colleagues described the time course of propofol plasma concentration in a population of children between ages of 3 and 11 years using a three-compartment model with weight as the sole significant covariate. Weight-adjusting the volumes and clearances significantly improved the accuracy of the pharmacokinetics. Adjusting the pharmacokinetics for inclusion of additional patient covariates or using a mixed-effects model did not further improve the ability of the pharmacokinetic parameters to describe the observations.¹⁷⁵ An alternative propofol TCI model called *Paedfusor*,¹⁵³ developed by the Glasgow research group, incorporated a preliminary model published by Schüttler and coworkers¹⁶⁵ and was recently found to be more accurate than the Kataria model. Coppens and associates³¹ were the first to publish a combined pharmacokinetic-pharmacodynamic model for propofol in children, revealing a k_{e0} of 0.79 min⁻¹ and a C_{e50} of 3.85 µg/mL as measured using the BIS (Table 26.6). A recent study compared the predictive performance of 11 different models for propofol in children during long-duration anesthesia,¹⁷⁶ and found that in this setting, the Short¹⁷⁷ pediatric model performed best.

As can be seen in Table 26.6, several different models for children are available, and this can lead to errors. This problem, and the potential solution of the Eleveld general purpose model,^{76,174} has been discussed previously.

Model Selection for Target-Controlled Infusion: Opioids

Table 26.7 shows the clinically used pharmacokinetic-pharmacodynamic models for remifentanil, fentanyl, sufentanil, and alfentanil. For sufentanil, the covariate model developed by Gepts and colleagues¹⁷⁸ is accurate with MDPE between -2.3% and 22.3% and MDAPE between 18.5% and 29%, even in patients who are obese.^{138,148,149} Multiple pharmacokinetic models were developed for alfentanil. A combined analysis of these early study results using a true population analysis was used to develop a new alfentanil model.¹⁷⁹ A comparison showed a better performance for the Maitre alfentanil model (MDPE, 35%; MDAPE, 36%) than the Scott model (MDPE, 12%; MDAPE, 28%).¹⁸⁰ Other studies found contradictory results.¹⁸¹

A compartment fentanyl model without covariates specifically aiming for TCI was developed¹⁴³ and tested in both lean and obese patients.¹⁴⁴ A simulated plasma concentration required a specific correction in patients who were obese.¹⁴⁴ Various three-compartment combined pharmacokinetic-pharmacodynamic models for remifentanil were developed from studies with both volunteers and patients;

however, only the model published by Minto and colleagues is applied in TCI.^{61,182} Evaluation of this model showed an acceptable performance, with an MDPE of -15% and an MDAPE of 20%.¹⁵⁰ Because combined pharmacokinetic-pharmacodynamic models are lacking for some of the opioids, the times to peak effect after a bolus administration of alfentanil (1.4 minutes), fentanyl (3.6 minutes), and sufentanil (5.6 minutes) can be applied to calculate the effect-site concentration using the *tpeak* algorithm.³²

Preliminary remifentanil models in children have been developed. For example, Rigby-Jones and colleagues¹⁸³ applied allometric scaling during a study of remifentanil pharmacokinetics in children and reported a single fixed allometric function scaled to a body mass of 10.5 kg that performed well across a broad range of patient weights. More recently, Eleveld and colleagues, using data from a variety of pharmacokinetic-pharmacodynamic studies of remifentanil, involving patients with a wide range of age, height, and weight characteristics, developed a model in which clearances are also allometrically scaled.¹⁸⁴ This model performed well on internal testing and is thought to be suitable for use in all patients, but now requires external prospective validation.

In addition to propofol and the opioids, compartment models have been published describing the time course of the plasma concentration and clinical effect of benzodiazepines, neuromuscular blocking agents, ketamine, and dexmedetomidine, although these drugs have not yet been included in the commercially available TCI pumps.

Rational Target Concentration Selection

No single regimen, concentration, or drug combination applies to all patients. While some sources of interindividual pharmacokinetic and pharmacodynamic variability are known, much of this variability remains unexplained.

Most of the previously mentioned pharmacokinetic-pharmacodynamic models have been derived from population pharmacologic studies. Interpatient variability limits the accuracy of the estimated drug concentration for the individual but can be counteracted if the model is built while exploring a wide variety of possible covariates using parametric modeling, optionally nonlinear mixed-effects modeling. Consequently, caution is needed when applying these models to patients who are obese, older, very young, diabetic, alcoholic, or unwell if similar participants were not part of the study population. The current commercial implementations of TCI, therefore, do not function well when used for patients with characteristics beyond the range of the model's development study population. As illustrated by Absalom and coworkers, the use of specific TCI algorithms outside the original studied population might result in dangerous drug infusion profiles.¹²

These investigators compared two currently used methods for calculating the effect-site concentration for propofol in patients who were obese, one using a fixed k_{e0} and the other using a fixed t_{peak} (see also "Direct-Effect Models" earlier in this chapter).

As the models in clinical use were not developed from data from obese patients, they should not be expected to perform accurately in obese patients. Tachibana and colleagues studied the influence of obesity on the predictive performance of the Marsh model, which scales compartment

TABLE 26.6 Commonly Applied Pharmacokinetic-Pharmacodynamic Models for Target-Controlled Infusion Systems for Hypnotics

Drug/Model	V_1	V_2	V_3	$K_{10} (\text{min}^{-1})$	$K_{12} (\text{min}^{-1})$	$K_{13} (\text{min}^{-1})$	$K_{21} (\text{min}^{-1})$	$K_{31} (\text{min}^{-1})$	$k_{e0} (\text{min}^{-1})$	$TPPE (\text{min})$
Propofol/ Marsh ⁴⁹	0.228 L/kg	0.363 L/kg	2.893 L/kg	0.119	0.112	0.042	0.055	0.0033	0.26*	NA
Propofol/ Schnider ^{228,229}	4.27 L	18.9 – 0.391 (age 53) L	238 L	0.443 + 0.0107 × (weight – 77) – 0.0159 × (LBM – 59) + 0.0062 × (height – 177)	0.302 – 0.0056 (age 53)	0.196	(1.29 – 0.024 × [age – 53]) ÷ (18.9 – 0.391 × [age – 53])	0.0035	0.456	1.69
Propofol/Paedfusor ²³⁰	0.458 L/kg	1.34 L/kg	8.20 L/kg	70 × weight ^{-0.3} ÷ 458.3	0.12	0.034	0.041	0.0019	NA	NA
Propofol/Kataria ²²⁹	0.52 L/kg	1.0 L/kg	8.2 L/kg	0.066	0.113	0.051	0.059	0.0032	NA	NA
Ketamine/Domino ²³²	0.063 L/kg	0.207 L/kg	1.51 L/kg	0.4381	0.5921	0.59	0.2470	0.0146	NA	NA

LBM, Lean body mass; TPPE, time to peak effect.

* k_{e0} derived independently from the PK model by Schüttler and colleagues.²³¹

TABLE 26.7 Commonly Applied Pharmacokinetic-Pharmacodynamic Models for Target-Controlled Infusion Systems for Analgesics

Drug	Remifentanil	Sufentanil	Fentanyl	Alfentanil
Model	Minto ^{54,173}	Gepts ¹⁷⁰	Shafer ¹⁴⁷	Maitre ¹⁷¹
V_1	$(5.1 - 0.0201[\text{age} - 40]) + 0.072 \times (\text{LBM} - 55) \text{ L}$	14.3 L	6.09 L	$\sigma = 0.111 \text{ L/kg}$ $\sigma = 1.15 \times 0.111 \text{ L/kg}$
V_2	$(9.82 - 0.0811[\text{age} - 40]) + 0.108(\text{LBM} - 55) \text{ L}$	63.4 L	28.1 L	12.0 L
V_3	5.42 L	251.9 L	228 L	10.5 L
$k_{10} (\text{min}^{-1})$	$(2.6 - 0.0162[\text{age} - 40]) + 0.0191(\text{LBM} - 55) \div V_1$	0.0645	0.083	$<40 \text{ year} = 0.356/V_1$ $>40 \text{ year} = 0.356 - (0.00269[\text{age} - 40]) \div V_1$
$k_{12} (\text{min}^{-1})$	$(2.05 - 0.0301[\text{age} - 40]) \div V_1$	0.1086	0.4713	0.104
$k_{13} (\text{min}^{-1})$	$(0.076 - 0.00113[\text{age} - 40]) \div V_1$	0.0229	0.22496	0.017
$k_{21} (\text{min}^{-1})$	$k_{12} \times V_1 \div V_2$	0.0245	0.1021	0.067
$k_{31} (\text{min}^{-1})$	$k_{13} \times V_1 \div V_2$	0.0013	0.00601	$<40 \text{ year} = 0.0126$ $>40 \text{ year} = 0.0126 - 0.000113(\text{age} - 40)$
$k_{e0} (\text{min}^{-1})$	$0.595 - 0.007(\text{age} - 40)$	NA	0.147*	0.77*

LBM, Lean body mass.

* k_{e0} is derived independently from the PK model by Scott and colleagues.³⁹

volumes linearly with body weight.¹³⁴ In their study, they used a single target plasma propofol concentration (4 $\mu\text{g}/\text{mL}$) and found that whereas in nonobese patients the bias was reasonably low, in obese patients measured concentrations were consistently higher than those predicted, to the extent that they found that when they applied a correction factor involving the BMI to the predicted concentration, the bias was reduced.

Growing evidence suggests that gender, ethnic, and racial differences may be important sources of population pharmacokinetic-pharmacodynamic variability and should be considered when designing dosage regimens.¹⁸⁵

The influence of different factors is often very complex. In one study involving the influence of age and gender on propofol clearance, clearance tended to be higher in females (and it declined with age), whereas age did not appear to have an influence in males.¹⁸⁶ Another study showed that different phases of the menstrual cycle were associated with significant differences in EC_{50} of propofol (predicted concentrations).¹⁸⁷ Xu and coworkers⁵⁵ confirmed that race can significantly influence propofol pharmacokinetics and pharmacodynamics. They evaluated the C_{50} for propofol-remifentanil TCI and the BIS at loss of consciousness and the response to noxious stimulus in patients of Chinese ethnicity and revealed that the predicted blood and effect-site concentrations at loss of consciousness were lower than those in previous publications involving Caucasian populations.

An additional caveat is required with the use of different formulations of a drug. For propofol, Calvo and colleagues¹⁸⁸ found that pharmacokinetics and pharmacodynamics were not equal for all formulations, which contributed to an increase in variability of the observed effect. Because of the aforementioned factors, no single regimen, concentration, or drug combination applies to all patients. Some guidance can be found in the ECs at which 50% and 95% of patients have accurate clinical effect (see Table 26.3). As with all drug administration in anesthesia, clinical judgment is always required, and the target concentration should be titrated according to the clinical response of the patient.

One of the major sources of variability in the clinical effect of propofol is interaction with concurrently administered drugs (see prior discussion). The interacting drugs may cause changes in the pharmacokinetics and/or pharmacodynamics of propofol. In this regard, the (mutual) interactions between hypnotics and opioids are currently best understood, but in fact, a wide array of drugs may interact with the hypnotics, including drugs that have been chronically administered during the preoperative phase.¹⁰⁷

Finally, in individual cases, other obvious sources of reduced single-drug model accuracy are errors such as drug spills, excessive blood loss causing shock, or pharmacokinetic drug interaction.¹⁸⁹⁻¹⁹¹ The number of factors that can influence drug pharmacokinetics and pharmacodynamics is so large that it would not be practicable to develop models taking all the factors into account, and even less so to have different models to take into account factors such as race. Thus regardless of the accuracy and complexity of available models, it will probably always be necessary for clinicians to titrate anesthetic drug administration to clinical effect.

Benefits of Target-Controlled Infusion

The ability of TCI to rapidly achieve and maintain a steady concentration facilitates attainment of a desired drug effect, irrespective of the absolute achieved drug concentration in the target compartment. The application of TCI in most cases even reduces the variability of intersubject drug-response relationships.¹²⁸ As a result, clinical outcomes when comparing TCI versus manual infusion were found to be improved in various early studies, although contradictions exist in the literature.

In the 1980s, Ausems and coworkers¹⁹² compared pharmacokinetic model-driven administration with intermittent bolus administration of alfentanil. Automated drug delivery produced fewer episodes of muscular rigidity, hypotension, and bradycardia on induction. Automated drug delivery during maintenance resulted in a significantly less frequent incidence of hemodynamic response, which resulted in a larger percentage of anesthesia time within

15% of the desired arterial blood pressure and heart rate. Recovery after TCI was associated with significantly less use of naloxone for adequate ventilation. Pharmacokinetic model–driven infusion of fentanyl during cardiac surgery resulted in better hemodynamic control with fewer additional drug interventions and significantly fewer episodes of either hypotension or hypertension than with bolus dose administration.¹⁹³

Theil and colleagues¹⁹⁴ compared double-blind manual administration of fentanyl–midazolam with pharmacokinetic model–driven infusion of these two drugs in a small group of patients undergoing cardiac surgery. Both systems were simultaneously titrated (one containing placebo), with the aim of maintaining hemodynamics within 20% of baseline values. Both systems were equally effective in providing hemodynamic control as dictated by the protocol. The most significant difference between the two modes of delivery was the greater variability in drug plasma concentrations in the manual group, which suggested that pharmacokinetic model–driven infusion maintained patients within a more narrow therapeutic range.

TCI remifentanil provides improved hemodynamic control both intraoperatively and postoperatively with less remifentanil and similar propofol infusion rates.¹⁹⁵ Age dramatically influences the pharmacokinetics of remifentanil; consequently, a TCI model that includes age will result in a beneficial drug titration compared with a standard $\mu\text{g}/\text{kg}/\text{min}$ infusion. For deep sedation in spontaneously breathing patients, Moerman and associates¹⁹⁶ found that the combination of remifentanil and propofol offered better conditions for colonoscopy than propofol alone; and that TCI remifentanil administration was associated with reduced propofol dosing and a less frequent incidence of apnea and respiratory depression, compared with manually controlled administration. Others have confirmed this finding.¹⁹²

Using the first commercially available TCI system (Diprufusor), early studies administering propofol by plasma-targeted TCI showed some benefits.^{159,197,198} These revealed a significant preference of clinicians for the TCI system, although this was their first use of the device.

Passot and coworkers¹⁹⁹ compared TCI and manual propofol infusion in high-risk older patients undergoing hip fracture surgery and concluded that TCI improved the time course of propofol-induced hemodynamic effects in these patients. Chen and colleagues found that similar induction and total doses of propofol were used when anesthesia was induced and maintained with either a manual or a TCI system, and the propofol administration was titrated to achieve a specific BIS value.²⁰⁰

Wang and colleagues compared the clinical conditions associated with TCI and manual propofol infusion during asleep–awake–asleep epilepsy surgery. TCI was associated with significantly improved awakening times and higher BIS values after the first asleep phase.²⁰¹ Chiang and associates found similar results when they compared TCI with manually controlled propofol infusions for combined upper and lower endoscopy.²⁰² Patients in the TCI group had better hemodynamic and respiratory stability and recovered more quickly from sedation than patients assigned to the manually controlled infusion group.

The Irwin group recently compared TCI and manual propofol administration in children.²⁰³ Although they found

that in children assigned to TCI propofol administration, higher total propofol doses were given, the amount of time the BIS was in an optimal range was greater and recovery times were similar. The authors concluded that TCI might facilitate easier titration of propofol to clinical effect.

TCI can theoretically facilitate rational drug administration for patients in the ICU, where drugs are commonly administered for prolonged periods. In this situation, by taking account of drug redistribution and eventually equilibration between compartments and thus reducing infusion rates, TCI systems have the potential to assist with maintenance of more stable sedation levels. McMurray and coworkers¹⁵⁶ studied TCI propofol in 122 adult ICU patients. Bias and median absolute performance error were within acceptable ranges at 4.3% and 19.6%, respectively. Acceptable sedation levels occurred for 84% of the sedation period. They proposed propofol plasma targets between 0.2 and 2.0 $\mu\text{g}/\text{mL}$ for ICU sedation.

Overall, there is little high-quality evidence of improved outcome with the use of TCI as opposed to manual drug administration. Nonetheless, the popularity of TCI use has grown significantly since the introduction of the first commercially available devices. The systems are registered for use in at least 93 countries of the world, and we recently estimated that in Europe alone, more than 2 million patients per year received one or more drugs administered with a TCI system.⁸

Plasma Versus Effect-Site Targeting

Using experimental systems, Glass¹²³ and Struys⁴⁷ and their colleagues conducted similar studies in which they targeted either plasma or effect-site concentration of propofol and then observed the time and plasma versus effect-site concentration at loss of consciousness. In both studies, regardless of whether the effect-site or plasma concentration was targeted, loss of consciousness occurred when the appropriate effect-site concentration for loss of consciousness was achieved, thus validating the concept. Two other important observations were made during these studies. First, hemodynamic stability was not different for plasma or the effect-site targeting, although higher plasma concentrations were achieved in the effect-site group. This finding implies, at least for propofol, that the time course for its hemodynamic effects is similar or longer²⁰⁴ to that for its anesthetic effects. Second, k_{e0} is dependent on the pharmacokinetic set from which it is derived.³² A k_{e0} value cannot be taken from one pharmacokinetic set and used with another pharmacokinetic set.³¹ Just as various demographics may alter the pharmacokinetics, they may also alter k_{e0} . Therefore using the k_{e0} best adapted for the clinical milieu is desirable. An ideal test of whether targeting plasma or the effect site is better is to compare their use in a closed-loop system in which a measure of effect (e.g., the BIS) is used as the target of control. In a small study of 10 patients per group, Absalom and Kenny showed that maintenance of the targeted BIS (as measured by MDPE, MDAPE, and wobble) was somewhat improved and induction times were significantly shorter when the pharmacokinetic model was for the effect site rather than for the plasma.²⁰⁵ Effect compartment–controlled TCI systems are currently commercially available in many countries (not the United States).⁸ They may offer better control of the dose-response relationship.^{47,206,207}

Safety of Target-Controlled Infusion

In noncomparative studies, pharmacokinetic model–driven infusion has been used to administer most of the potent opioids, as well as the hypnotics. Different anesthetic techniques have also been tested with pharmacokinetic model–driven infusion devices, including nitrous oxide–opioid anesthesia, supplementation of volatile anesthetics, total intravenous anesthesia, sedation for monitored anesthesia care, and ICU sedation. In all these studies, outcome as measured by hemodynamics and recovery has been within the expectations of normal clinical care. Etomidate, methohexitol, midazolam, propofol, thiopental, dexmedetomidine, alfentanil, fentanyl, remifentanil, and sufentanil have all been used with TCI. When these drugs were used with target-controlled drug delivery systems for total intravenous anesthesia or to supplement nitrous oxide or volatile anesthetics, hemodynamics were well maintained during induction and intubation, as well as during maintenance. Recovery milestones were reached at times comparable with those achieved with similar drug combinations used in manual infusion schemes. None of these studies have reported adverse outcomes resulting from target-controlled drug delivery.

A recent review shows that the safety and reliability of commercially available TCI systems has been exemplary, suggesting that the systems perform as intended and programmed.¹²⁷ Despite use of TCI systems in millions of patients around the world, a search of the medical literature, regulatory reports, and company safety statements revealed only a handful of possible problems specific to TCI device use, many of which were the result of user error and none of which resulted in product recalls or patient harm.

PATIENT-CONTROLLED ANALGESIA AND SEDATION

A particular method of intravenous drug administration is patient-controlled analgesia, mostly used for the postoperative administration of analgesics or for patient-controlled sedation (PCS) during therapeutic procedures. Although PCA can be considered as a method of computer-controlled or even closed-loop drug administration, most of these pumps currently do not include pharmacokinetic or pharmacodynamic algorithms. In some cases, the PCA or PCS pump is set to deliver a low, constant or *background* flow of medication. Additional doses of medication can be self-administered by the patient pressing a button as needed. Most commonly, no background infusion is provided, and the patient controls when he or she receives an analgesic bolus. To avoid overdosing, these pumps have built-in safety mechanisms such as lock-out times and limitations of the total amount of drug delivered per time unit. PCA is a common technique for delivery of postoperative pain medication such as morphine, piritramide, fentanyl, tramadol, and other drugs.²⁰⁸⁻²¹² In a systematic review, Walder and colleagues showed that the literature presented some evidence that in the postoperative pain setting, PCA with opioids, compared with conventional opioid treatment, improved analgesia and decreased the risk of pulmonary complications; in general, patients preferred the technique.²¹³ Strict hospital guidelines may help avoid side effects such as oversedation and respiratory depression.²¹⁴ When epidural

analgesia is contraindicated during labor, remifentanil PCA has been suggested as an alternative. Pilot trials suggested that this alternative is safe under strict observation.²¹⁵⁻²²⁰ However, a more recently published randomized-controlled trial showed that, in comparison with epidural analgesia, not only was remifentanil PCA associated with lower satisfaction scores, it was also associated with lower maternal oxygen saturation values.²²¹

Although popular, PCA systems are imperfect, as they administer boluses that result in a time course of clinical effect that is unlikely to accurately match the time course of the painful stimulus the patient is suffering. The same applies to PCS systems, except that here the bolus will provide a time course of sedation or anxiolysis that does not match the experience of the patient. TCI technology has thus also been applied to PCA and PCS. With these patient-maintained analgesia and patient-maintained sedation systems, the system administers a TCI of analgesic or sedative, usually starting at a fixed low-target concentration, and after an initial period the patient is able to influence the target concentration. In some initial studies the target concentration was increased or decreased by a researcher using an algorithm,^{70,74,180,211,222,223} but in others the patient was able to activate target concentration increases by pressing the button of a handset, once a lockout period had passed.²²⁴

Van den Nieuwenhuyzen and colleagues demonstrated the advantages of PCA-TCI with alfentanil over routine morphine PCA for postoperative analgesia.^{74,180,222,223} Analgesia support using effect-site targeted TCI of remifentanil or fentanyl during extracorporeal shock-wave lithotripsy was tested by Cortinez and colleagues.⁷⁰ They found a remifentanil and fentanyl EC₅₀ of 2.8 ng/mL and 2.9 ng/mL. At EC₅₀, the probability of having a respiratory rate less than 10 was 4% for remifentanil and 56% for fentanyl. Hypoxemia, vomiting, and sedation were more frequent in the fentanyl group, making this drug less suitable for this clinical application than remifentanil. Lipszyc and associates²¹¹ used remifentanil effect-site PCA-TCI with a slow and progressive adapted algorithm for treatment of acute pain after uterine artery embolization and showed that it provided better care than PCA morphine in the first 4 hours of administration.

Schraag and colleagues studied the efficacy and safety of a remifentanil patient-maintained analgesic system for early analgesia after orthopedic surgery.²²⁴ If the patient operated an activating handset then the target concentration was increased by 0.2 ng/mL; otherwise the system gradually reduced the target. The system was found to provide satisfactory analgesia, with little sedation and few respiratory adverse effects.

Jeleazcov and colleagues have developed and studied a TCI-PCA system for hydromorphone.²²⁵ With this system the patient is also able to request higher target concentrations by means of a button push. The authors found that patients using this system after cardiac surgery had satisfactory pain control with only moderate adverse effects.

The initial developments of PCS systems enabled the patient to request bolus drug administration (propofol or midazolam), or occasionally an increase in drug infusion rate.²²⁶⁻²³⁰ Studies on the quality and outcomes after PCS have shown that it reduces discomfort and fear by inducing

sedation and amnesia during uncomfortable therapeutic procedures such as colonoscopy. Additionally, PCS facilitates the procedure by increasing the patient's tolerance. Although propofol offers no analgesic effect, several studies of patient control of propofol administration (bolus or short infusions) during procedures showed that it provided reasonably safe, light sedation, and that patients expressed a preference for being in control.^{227,229,230} A recent study compared physician-controlled TCI propofol with PCS with boluses of propofol during endoscopic retrograde cholangiopancreatography. It showed that with PCS lower doses of propofol were used and recovery was more rapid.²³¹

As bolus or even manual infusion regimens might produce fluctuating levels of sedation, Kenny and colleagues in Glasgow combined PCS with TCI of propofol to overcome this problem. Using a patient-maintained sedation system, the patient can set a specific propofol target concentration using an activating handset button. With the system, the patient was required to press twice within one second to request a target increase. If no validated presses occurred, the system initially kept the target propofol concentration unchanged, but if after 6 minutes no further presses occurred, then the target concentration was reduced by the incremental amount. A starting concentration and a lock-out time is set by the clinician (commonly with the default being approximately the equilibration time between plasma and effect-site concentrations). In various applications requiring sedation, their experimental system was shown to be feasible²³²⁻²³⁵; however, even when using an effect-site controlled TCI system, some volunteers rendered themselves unconscious.²³⁶ Whereas the system developed by Kenny and colleagues incorporated the Marsh model, Stonell and colleagues developed and tested a system enabling propofol effect-site targeted patient-maintained sedation with the Schnider model. They compared patient-maintained sedation with anesthetist-administered sedation and found that patient-maintained sedation was associated with fewer adverse events, higher sedation scores, and BIS values, but at the cost of slower induction times, while patient and operator satisfaction was similar.²³⁷

It is possible that safety can be improved further, particularly if a test or measure of responsiveness to a stimulus is added and if the control algorithm is incorporated to allow the facility to stop the infusion should the response become inadequate.²³⁸⁻²⁴¹

Doufas and colleagues tested an automatic response test to optimize propofol administration for conscious sedation.^{242,243} Although volunteers were required to push a delivery button in response to auditory and tactile stimuli, a TCI-like algorithm guided the propofol administration. The study showed that failure to respond to automated responsiveness monitoring precedes potentially serious adverse effects of sedation such as loss of responsiveness, and that the monitor was not susceptible to false-positive responses.²⁴⁴

An enlarged commercial version of this device, SEDASYS (Ethicon Endo-Surgery, Cincinnati, Ohio), was tested in two studies. It incorporated the automated responsiveness monitoring and built-in capnography and pulse oximetry. If the patient's responses to stimuli were inadequate, then the subsequent increases in infusion rates were limited. If apnea or hemoglobin oxygen desaturation were detected,

then the infusion was stopped and additional oxygen given. After a successful feasibility study,²⁴⁵ the system was then used in a large randomized study of sedation during upper gastrointestinal endoscopy and colonoscopy and was found to be associated with a reduced incidence of adverse events compared with standard care (5.8% vs. 8.7%, respectively).²⁴⁶ Although the device was approved by the FDA in 2013 for the provision of moderate sedation during routine endoscopic procedures in ASA 1 and 2 patients, poor sales figures prompted a commercial decision by the vendor to cease marketing the device.^{247,248}

Closed-Loop Controlled Intravenous Drug Delivery

The next step in computer-controlled drug delivery is to feed a continuous measure of drug effect directly back to the automated drug delivery device, thus providing a continuous closed-loop system. This system avoids the requirement of a clinician to titrate the target concentration manually, based on intermittent observations of the desired therapeutic effect. With manual control, attempts to achieve tight titration of hypnosis require high clinical expertise and a labor-intensive process and may divert the clinician's attention from critical actions resulting in a suboptimal therapy or even threatening the patient's safety. Applying closed-loop drug administration techniques could optimize this process of dose titration.⁴ The application of closed-loop systems for drug administration is complex and requires a perfect balance for all the basic components of such a system: (1) a control variable representative for the targeted therapeutic effect; (2) a clinically relevant set-point or target value for this variable; (3) a control actuator which is, in this case, the infusion pump driving the drug; (4) a system, in this case a patient; and (5) an accurate, stable control algorithm.²⁴⁹

Control algorithms are all based on measuring the error between the target and the observed effect. Various control strategies are described in the literature to steer this closed-loop administration. Proportional-integral differential (PID) controllers are frequently used in engineering applications. This controller will adjust the infusion rates in a manner that is proportional to the magnitude of the error, the integral of the error over time, and the derivative of the error over time. The fine-tuning of a PID controller might be difficult in this particular setting because of the complexity of the system to control and the interindividual pharmacologic variability, and because directly counteracting the administration of excessive drug is not possible. A more appropriate approach could be to use a PID control system connected to a TCI system to decrease the order of complexity between dose and response (see Fig. 26.26).²⁵⁰ An alternative control strategy is called *model-based adaptive control*. This controller has an internal model of the system, typically set up as an integrated pharmacokinetic-pharmacodynamic model that relates dose to concentration (pharmacokinetics) and concentration to drug effect (pharmacodynamics). The model is updated to explain the difference between the measured and predicted drug effect.

A reliable physiologic signal, which is a measure of the clinical drug effect, is the most important component of closed-loop technology. Vital signs such as arterial blood pressure or muscle activity have been used to guide intravenous closed-loop drug administration. For example, Kenny

and coworkers²⁵¹ successfully evaluated closed-loop control of arterial blood pressure using a mixture of trimethaphan camsylate and sodium nitroprusside during controlled hypotensive anesthesia for local resection of intraocular melanoma. In the 1980s and the 1990s, various researchers investigated the accuracy of closed-loop controlled administration of atracurium^{252,253} and vecuronium.²⁵⁴ However, since the introduction of the novel reversal drug, sugammadex, interest in closed-loop administration of vecuronium or rocuronium has significantly declined.

The commercialization of various EEG-based *depth of anesthesia* monitors, such as the BIS, spectral entropy, and auditory-evoked potential, has renewed the interest of various research groups in closed-loop administration of intravenous hypnotics. Using an early version of the BIS as the control variable, Sakai and colleagues²⁵⁵ concluded that their closed-loop system provided intraoperative hemodynamic stability and a prompt recovery from sedative-hypnotic effects of propofol. A similar propofol closed-loop system using the BIS and PID control of a plasma-controlled TCI system showed acceptable control during major orthopedic surgery²⁵⁶ and during sedation.²⁵⁷ Although these investigators improved the performance of their control system by switching toward effect-site targeted TCI, they also concluded that the PID controller might still face some stability problems. Similarly, Liu and colleagues used a closed-loop titration of TCI based on a proportional-differential algorithm guided by the BIS, allowing induction and maintenance of general anesthesia and compared this with manual propofol TCI. They found that closed-loop control resulted in less propofol consumption and longer induction times but with better hemodynamic stability, less excessive anesthetic levels (BIS <40), similar hemodynamic stability, and faster recovery.^{250,258}

Liu and colleagues have developed a more advanced version of their initial system, now using full PID control, for closed-loop coadministration of both propofol and remifentanil, using the BIS as the controlled variable. A rule-based algorithm decides when to change the propofol or remifentanil targets. In a multicenter study, this system showed a better overall performance versus manual administration.²⁵⁹ A similar approach was used with an alternative EEG-derived index, spectral entropy.²⁶⁰ The same group has since used their system in various groups of patients in a variety of clinical settings, such as during sedation, pediatric surgery, and liver transplantation—and in a variety of applications in which it is used to provide an objective evaluation of the influence of pharmacological (e.g., use of dexmedetomidine) and nonpharmacological interventions (e.g., hypnosis) on anesthetic drug requirements for general anesthesia.²⁶¹⁻²⁶⁹

Puri and colleagues in India developed a system that incorporates an adaptive PID algorithm to control propofol administration guided by the BIS. It has been extensively tested in a variety of circumstances, for general anesthesia and postoperative sedation, in adults and children, at high altitude, and in patients with pheochromocytoma and heart failure, and found to perform satisfactorily.²⁷⁰⁻²⁷⁶ In a randomized controlled trial involving more than 200 patients, the system was shown to provide significantly more accurate control (defined as BIS within target range) than manually controlled anesthesia.²⁷⁷

A Canadian group lead by Dumont and Ansermino have also developed a PID-based closed-loop controller. For their system, they developed their own monitor (NeuroSENSE, NeuroWave Systems, Cleveland Heights, OH), which calculates the wavelet-based anesthetic value for central nervous system monitoring (WAV_{CNS}) and the burst suppression ratio.^{278,279} The WAV_{CNS}, which has a range of 0 to 100, has also been used for monitoring sedation in the ICU.²⁸⁰ A study comparing the performance of WAV_{CNS} with BIS and response entropy found that WAV_{CNS} performed well, and was particularly good at capturing rapidly occurring changes.²⁸¹ The system includes a PID algorithm, and initially was only used to control a propofol infusion.²⁸² It contains an infusion safety system to manage the infusion rate when the feedback variable (WAV_{CNS}) is unavailable or when the drug infusion exceeds predefined limits. Later, they developed and tested a so-called multi-input single-output system, in which the output remained the WAV_{CNS}, but the controller was able to control both a propofol and a remifentanil infusion.²⁸² The authors have shown that their system provides robust, stable, and safe control of anesthetic depth, even under challenging conditions such as significant bleeding,²⁸³ and that the addition of automatic control of remifentanil administration improved the quality of control.²⁸²

Another group in Canada have gradually taken their closed-loop system (McSleepy) to the next level. Their initial version of McSleepy used a PID algorithm and the BIS to automatically control a propofol infusion and was shown to be able to provide more accurate and stable control of the BIS than an anesthesiologist manually controlling the propofol infusion rate.²⁸⁴ They then developed McSleepy further to enable closed-loop control of three drugs: propofol and remifentanil infusions, and rocuronium boluses.²⁸⁵ For propofol, a proportional integral algorithm is used with the BIS the control variable, whereas for remifentanil a rule-based proportional algorithm is used to control the Analgescore (a nociception score based on heart rate and blood pressure),²⁸⁶ and finally, rocuronium boluses are administered on the basis of simple rule set, to keep the train of four count less than 25%. This system has been shown to provide accurate control of all variables. The system has been adapted (the Analgescore was adapted and the name changed to NociMap) and used for general anesthesia for cardiac surgery,²⁸⁷ and more recently also adapted to provide propofol sedation²⁸⁸ and used during transcatheter aortic valve implantation.²⁸⁹

Model-based adaptive control of BIS-guided propofol administration was previously used by Struys and colleagues for sedation during spinal anesthesia and for general anesthesia.^{290,291} The control algorithm is based on a patient-specific pharmacodynamic profile estimated during induction. Compared with manually titrated propofol administration, patients in the closed-loop group reached the target BIS at a somewhat slower rate, but this resulted in less BIS overshoot and better hemodynamics after induction. During the maintenance phase, improved control of the BIS and systolic blood pressure was found in the closed-loop group and recovery was faster. Using simulations, these authors compared their model-based control system with a previously published PID controller

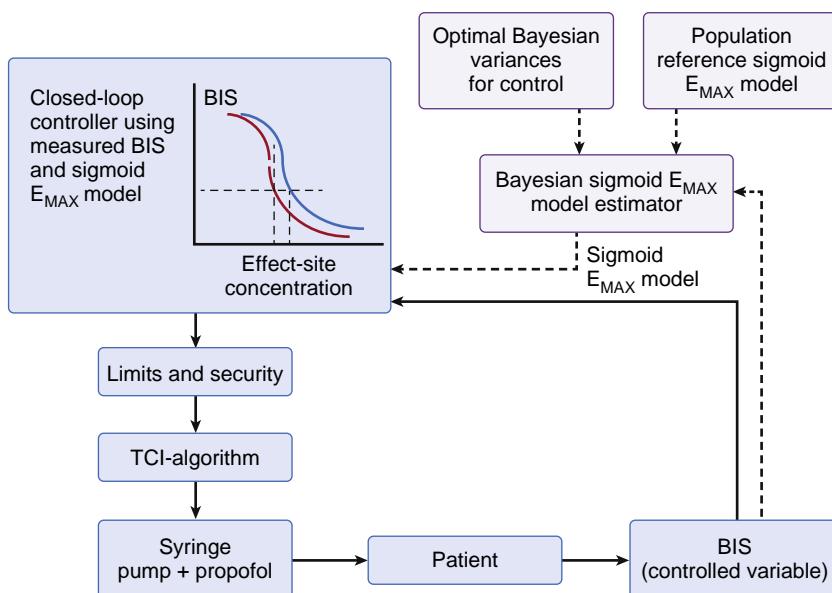


Fig. 26.32 Flow chart of the closed-loop system. The *solid lines* represent the closed-loop control system. Each time the required effect-site concentration is calculated by the controller this value is sent to an additional algorithm, taking the safety limits into account. The result of these calculations is the required effect-site concentration sent to the target-controlled infusion (TCI) algorithm, which steers a pump injecting propofol to the patient. The measured bispectral index (BIS) is used as the input of the closed-loop controller. The *dotted lines* represent the Bayesian sigmoid E_{MAX} model estimator. The estimator receives a priori information from the population sigmoid E_{MAX} model, the optimal Bayesian variances for control, and the patient-measured BIS values. (From De Smet T, Struys MM, Greenwald S, et al. Estimation of optimal modeling weights for a Bayesian-based closed-loop system for propofol administration using the bispectral index as a controlled variable: a simulation study. *Anesth Analg*. 2007;105:1629–1638. Used with permission.)

and found that the model-based controller outperformed, even under extreme control conditions such as low and high BIS levels and abrupt changes in the BIS levels.²⁹² De Smet and Struys later developed the adaptive part of the controller using Bayesian optimization (Fig. 26.32)²⁹³ and compared the feasibility and accuracy of this system with manually controlled BIS-guided, effect compartment–controlled propofol TCI during ambulatory gynecologic procedures. They found that the closed-loop control system accurately titrated propofol administration resulting in BIS values close to the set point. The closed-loop control system was able to induce anesthesia in the patients within clinically accepted time limits and with less overshoot than the manual control group. Automated control resulted in beneficial recovery times. This closed-loop control group showed related acceptable clinical performance specified by similar hemodynamic respiratory stability, comparable movement rates, and quality scores as the manual control group.²⁹⁴

Alternative closed-loop systems have been developed for isoflurane administration using a controller with a cascade structure, originally described by Gentilini and associates.^{295,296} More recently, Moore and Doufas designed a closed-loop system using an intelligent system technique called *reinforcement learning*, known as a mathematically robust method of achieving optimal control in systems challenged with noise, nonlinearity, time delay, and uncertainty.^{297,298}

So far, closed-loop systems have only been used under strict experimental conditions. The challenge is now to prove their safety and utility when applied in clinical practice.^{299,300} Liu and associates have shown improved stability of control of depth of anesthesia with their system

in a large multicenter study.²⁵⁹ More recently two meta-analyses have evaluated the available data concerning the performance of closed-loop systems for intravenous anesthesia and other applications.^{301,302} Both found improved accuracy of control with closed-loop technology.

Liu and associates have also been able to show that the use of their system produces several secondary benefits, such as a reduction in the workload of the anesthesiologist.³⁰³ Ultimately, clinicians will have to determine whether adaptive, intelligent computer systems with dual, interacting, closed-loop systems will facilitate better control and improve patient outcomes.¹²⁰

Although closed-loop technology and automation are almost ubiquitous in our daily lives, closed-loop anesthesia is still only used within research settings. Recent editorials have discussed the relevance of closed-loop technology to anesthesia, and the likely time course over which applications will become a routine part of our daily work.^{304–306} The theoretical benefits, however, are compelling, and so it is not surprising that the FDA recently held a workshop on the regulatory considerations for physiological closed-loop controlled medical for automation in critical care and anesthetic environments, and is currently formulating recommendations and regulatory proposals.³⁰⁷

Future Perspectives

For all existing drugs there is broad pharmacokinetic and pharmacodynamic variability. In anesthesia practice, inaccurate dosing can have serious consequences. Whereas overdosing might be associated with hemodynamic compromise and prolonged recovery, underdosing

is particularly undesirable since it can result in unintended awareness during general anesthesia, with severe psychological consequences.³⁰⁸ A recent study involving all hospitals in the United Kingdom and Ireland showed that accidental awareness during general anesthesia was more common with intravenous anesthesia compared with inhalational anesthesia.³⁰⁹ Thus for intravenous drug delivery, there remains a strong need for methods to ensure accurate and individualized estimation and titration of dosing. Currently there exist several emerging techniques and technologies that might help realize this goal.

Hypnotic drugs used in anesthesia are known to have strong interaction reactions with other commonly used drugs. While pharmacokinetic interactions are common, pharmacodynamic interactions are much larger in magnitude, and thus clinically highly relevant. In the case of the hypnotics and opioid analgesics, the interactions are strongly synergistic, and so when these drugs are coadministered, dose adjustments are usually necessary to avoid adverse effects. These interactions are very complex, with the magnitude of the interaction effect dependent on the plasma and effect-site concentrations of all of the interacting drugs. Interactions between two drugs are best depicted on three-dimensional response surface plots.^{80,96,99} As mentioned earlier, advisory displays have been developed to provide the anesthesiologist with real-time information on the likely magnitude of the clinical effect of drug combinations (see Fig. 26.25). Although seldom used in clinical practice, it is likely that these and similar systems will be more widely employed in the future, to help guide anesthesiologists to optimize anesthetic dosing.

A development that could potentially improve safety and accuracy is the broader implementation and clinical use of the new “universal” pharmacokinetic-pharmacodynamic models that have been developed for propofol⁷⁶ and remifentanil.¹⁸⁴ The models currently used to implement TCI were developed from studies of patients or volunteers with a rather narrow range of age, weight, and height characteristics; and so naturally these models are only applicable in patients of similar characteristics. On the other hand, the universal models were developed from a combined analysis of the data from a significant number of studies involving a large number of patients with different characteristics. The origin of the underlying data, along with the use of allometric scaling, should broaden the applicability of these models. Once these models have been prospectively validated, it is hoped that availability of a single, accurate model for propofol and remifentanil will enhance patient safety and encourage infusion system manufacturers to incorporate these models into their TCI pumps. This might also help reduce the likelihood of drug errors (e.g., those resulting from choice of an inappropriate model, or a lack of understanding of the model chosen), and this too might help improve the popularity and broaden the applications of TCI systems.

TCI systems contain population pharmacokinetic models, designed to provide the best estimate of the parameters of drug kinetics in a population, but not necessarily for an individual. Inevitably, there will be some degree of error when a pharmacokinetic-pharmacodynamic model is used to guide or determine drug infusion rates to a single patient. One possible solution to the inevitable problem of any mismatch between

the pharmacokinetic behavior of a drug and the pharmacokinetic model used to guide administration is to perform real-time measurements of achieved concentrations, and to individualize the model. Recently, a system has become available that provides accurate point-of-care measurement of plasma propofol concentrations within 5 minutes.³¹⁰ Plasma propofol concentrations measured by this apparatus were thus used in a system that used Bayesian methodology to update the pharmacokinetic-pharmacodynamic model being used for TCI administration of propofol.¹³⁶ Although the results were somewhat disappointing—after adaptation bias improved, but precision did not—this was an initial effort using this system, and future research developments might show better results.

At present, no real-time plasma concentration measurements of intravenous drugs are routinely available for clinical use. Such measurements may improve drug delivery or might optimize TCI administration for the individual patient.³¹¹ Several promising techniques have been described. Takita and colleagues found a strong and linear correlation between exhaled propofol concentrations measured by proton transfer mass spectrometry and estimated and measured arterial propofol concentrations.³¹² Miekisch and coworkers³¹³ used headspace solid-phase microextraction coupled with gas chromatography mass spectrometry to measure alveolar (exhaled), arterial, central venous, and peripheral blood propofol concentrations, and found a good correlation between exhaled and arterial concentrations. Perl and colleagues³¹⁴ used an ion mobility spectrometer coupled to a multicapillary column for preseparation (multicapillary column-ion mobility spectrometer [MCC-IMS]). Hornuss and colleagues used ion molecule reaction mass spectrometry,^{315,316} and Grossherr and colleagues used gas chromatography mass spectrometry.³¹⁷ The latter group also described the difference between blood/gas partition coefficient and pulmonary extraction ratio for propofol between species, which will be important when studying this technique in an animal setting.³¹⁸

Varadajan,³¹⁹ Ziaian and colleagues,³²⁰ and Kreuer and colleagues³²¹ have applied compartmental modeling to describe the kinetics of exhaled propofol. Colin et al. were able to show that standard compartmental models can easily be extended with an additional lung compartment (with a rate constant to model time delay) and a scaling factor (to convert units) to enable predictions of plasma propofol concentration, as well as online Bayesian model adaptation.³²² With this model it was also possible to estimate BIS values from exhaled propofol measurements.

Recently a system using MCC-IMS (Edmon, B. Braun, Germany) has become commercially available and is able to provide measurements every minute. Studies with a prototype system used a reference gas generator to confirm accuracy and precision over the clinical range of exhaled propofol measurements.³²³

Even with an online method for measurement of drug concentrations and/or of perfecting pharmacokinetic models, the clinician still faces the challenge of the broad variability in pharmacodynamic response to any given drug concentration. Automatic closed-loop control systems, which have been discussed extensively in this chapter, might provide a solution to this problem. A well-designed system with a robust measure of clinical effect should help

to optimize drug administration and titration on an individual level by accurately titrating drug administration to clinical effect.

Finally, the use of nonlinear mixed effects modeling (NON-MEM) techniques is currently considered to be the state-of-the-art for pharmacokinetic-pharmacodynamic analysis and for development of new models. Such development involves use of infusion rate, measured plasma concentration, and measures of clinical effect to generate mathematical models that are consistent with our knowledge of pharmacology.

This process produces the parameters for a structural model comprising two or more compartments, redistribution clearance, and metabolic clearance parameters that describe exponential processes. Artificial intelligence approaches using neural networks are providing powerful and effective solutions to modern problems, eliminating the need to start with models based on current knowledge.³²⁴ This “deep learning” approach was recently applied to data from 231 patients to learn how to predict the BIS values associated with differing plasma and effect-site concentrations of propofol and remifentanil.³²⁵ Remarkably the system was able to learn to predict BIS values more accurately than traditional pharmacokinetic-pharmacodynamic model-based approaches. Given the widespread ease of access of almost all anesthesiologists to web-based technology, it is reasonable to imagine a situation where the data from millions of patients around the world are fed into machine-learning systems that can learn to predict responses to different combinations of drugs, and, inversely, learn to accurately predict the doses required for given responses, without the need for complex models.

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KEY POINTS

- Two different populations of nicotinic acetylcholine receptors exist at the mammalian neuromuscular junction. In the adult, the nicotinic acetylcholine receptor at the postsynaptic (muscular) membrane is composed of $\alpha_2\beta\delta\epsilon$ subunits, while the fetal (immature) receptor is composed of $\alpha_2\beta\gamma\delta$. The presynaptic (neuronal) nicotinic receptor is a pentameric complex composed of $\alpha_3\beta_2$ subunits. Each of the two α subunits of the postsynaptic receptors has a ligand (acetylcholine) binding site.
- Nondepolarizing muscle relaxants produce neuromuscular blockade by competing with acetylcholine for the postsynaptic α subunits. In contrast, succinylcholine acts directly with the recognition sites and produces prolonged depolarization that results in decreased sensitivity of the postsynaptic nicotinic acetylcholine receptor and inactivation of sodium channels so that propagation of the action potential across the muscle membrane is inhibited.
- Different patterns of stimulation examine neuromuscular blockade at different areas of the motor end plate. Depression of the response to single twitch stimulation is likely caused by blockade of postsynaptic nicotinic acetylcholine receptors, whereas fade in the response to tetanic and train-of-four stimuli results from blockade of presynaptic nicotinic receptors.
- Succinylcholine is the only available depolarizing neuromuscular blocking drug for clinical use. It is characterized by rapid onset of effect and ultrashort duration of action because of its rapid hydrolysis by butyrylcholinesterase.
- Available nondepolarizing neuromuscular blocking drugs can be classified according to chemical class (aminosteroid, benzylisoquinolinium, or other compounds) or by duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses.
- The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blocking drugs. With the exception of atracurium, molar potency is highly predictive of a drug's rate of onset of effect. Rocuronium has a molar potency that is approximately 13% that of vecuronium and 9% that of cisatracurium. Its onset of effect is more rapid than either of these muscle relaxants.
- Neuromuscular blockade develops faster, lasts a shorter time, and recovers faster in the more centrally located neuromuscular units (e.g., laryngeal adductors, diaphragm, and masseter muscle) than in the more peripherally located adductor pollicis muscle.
- Many long-acting neuromuscular blocking drugs undergo minimal or no metabolism, and they are primarily eliminated, largely unchanged, by renal excretion. Neuromuscular blocking drugs of intermediate duration of action have faster distribution and more rapid clearances than the long-acting drugs because of multiple pathways of degradation, metabolism, and elimination. Mivacurium, a short-acting neuromuscular blocking drug, is cleared rapidly and almost exclusively by metabolism by butyrylcholinesterase.
- After the administration of nondepolarizing neuromuscular blocking drugs, it is essential to ensure adequate return of normal neuromuscular function using objective (quantitative) means of monitoring. Residual neuromuscular paralysis decreases upper esophageal tone, coordination of the esophageal musculature during swallowing, and hypoxic ventilatory drive. Residual paralysis can increase healthcare costs and the patient hospital length of stay, morbidity, and mortality.

History and Clinical Use

In 1942, Griffith and Johnson described *d*-tubocurarine (*d*Tc) as a safe drug to provide skeletal muscle relaxation during surgery.¹ One year later, Cullen described the use of

this drug in 131 patients who had received general anesthesia for surgery.² In 1954, Beecher and Todd reported a six-fold increase in mortality in patients receiving *d*Tc compared with patients who had not received a muscle relaxant.³ The increased mortality resulted from a general

lack of understanding of the clinical pharmacology and effects of neuromuscular blocking drugs (NMBDs). The effect of residual neuromuscular blockade postoperatively was not appreciated, guidelines for monitoring muscle strength had not been established, and the importance of pharmacologically antagonizing residual blockade was not understood.

Succinylcholine, introduced by Thesleff⁴ and Foldes and associates⁵ in 1952, rapidly gained widespread use and changed anesthetic practice drastically because the drug's rapid onset of effect and ultrashort duration of action allowed for both rapid endotracheal intubation and rapid recovery of neuromuscular strength.

In 1967, Baird and Reid reported on the clinical administration of the first synthetic aminosteroid, pancuronium.⁶ The development of the intermediate-acting NMBDs was based on the compounds' metabolism and resulted in the introduction of vecuronium,⁷ an aminosteroid, and atracurium,⁸ a benzylisoquinolinium, into clinical practice in the 1980s. Vecuronium was the first muscle relaxant to have an intermediate duration of action and minimal cardiovascular actions. Mivacurium, the first short-acting nondepolarizing NMBD, was introduced into clinical practice in the 1990s,⁹ as was rocuronium,¹⁰ an intermediate-acting NMBD with a very rapid onset of neuromuscular blockade. Other NMBDs have been introduced into clinical practice since the use of dTc was first advocated. These include pipercuronium, doxacurium, cisatracurium, and rapacuronium. Although not all remain in clinical use today, each represented an advance or improvement in at least one aspect over its predecessors. Still other NMBDs, such as CW 002¹¹ and CW 1759-50^{11a,11b} are undergoing investigation.

NMBDs should be administered only to anesthetized individuals to provide relaxation of skeletal muscles. Because this class of drugs lacks analgesic or amnestic properties, NMBDs should not be administered to prevent patient movement. Awareness during surgery¹² and in the intensive care unit (ICU)¹³ has been described in multiple publications. As stated by Cullen and Larson, "muscle relaxants given inappropriately may provide the surgeon with optimal [operating] conditions in...a patient¹⁴ [who] is paralyzed but not anesthetized—a state that [is] wholly unacceptable for the patient."¹⁵ Additionally, "muscle relaxants used to cover up deficiencies in total anesthetic management...represent an...inappropriate use of the valuable adjuncts to anesthesia."¹⁵ Administration of NMBDs intraoperatively to maintain neuromuscular block requires that the time course of block be monitored and the depth of anesthesia be assessed continuously.

NMBDs have been integrated into most anesthetic techniques for major surgery and have become key components in the continuous improvement of safe anesthetic practice and the development of advanced surgical techniques. As earlier stated by Foldes and colleagues,⁵ "...[the] first use of...muscle relaxants...not only revolutionized the practice of anesthesia but also started the modern era of surgery and made possible the explosive development of cardiothoracic, neurologic, and organ transplant surgery." Certainly, NMBDs are now used routinely to facilitate endotracheal intubation and mechanical ventilation, and are commonly used to maintain neuromuscular blockade through any number of different surgical procedures. This chapter reviews the pharmacology and clinical use of NMBDs and anticholinesterases in anesthesia and intensive care settings.

Principles of Action of Neuromuscular Blocking Drugs at the Neuromuscular Junction

A brief description of the physiology of neuromuscular blockade is presented in this chapter. A more comprehensive overview is provided in [Chapter 12](#).

POSTJUNCTIONAL EFFECTS

Nicotinic acetylcholine receptors (nAChRs) belong to a large pentameric family of ligand-gated ion channel receptors that include the 5-hydroxytryptamine₃ (5-HT₃), glycine, and γ -aminobutyric acid (GABA) receptors. They are synthesized in muscle cells and anchored to the end plate membrane by a special protein called rapsyn. Development of innervation in the first weeks of life leads to the replacement of the γ subunit by ϵ subunit. In adult mammalian skeletal muscle, the nAChR is a pentameric complex of two α subunits in association with single β , δ , and ϵ subunits ([Fig. 27.1](#)). Stoichiometrically, the receptor is represented as $\alpha 2\beta\delta$, while organizationally it is $\alpha\epsilon\alpha\delta\beta$.

The subunits are organized to form a transmembrane pore, or channel, as well as extracellular binding pockets for acetylcholine and other agonists or antagonists.¹⁶ The receptors are clustered on the crests of the junctional folds; the receptor density in this area is 10,000 to 30,000/ μm^2 . Each of the two α subunits has an acetylcholine-binding site. These sites are located in pockets within the receptor protein, approximately 3.0 nm above the surface membrane at the interfaces of the α_H - ϵ and α_L - δ subunits.¹⁷ α_H and α_L indicate the high- and low-affinity binding sites for dTc; the difference in affinity probably results from the contribution of the different neighboring subunits.¹⁸ For instance, the binding affinity of dTc for the α_H - ϵ site is approximately 100 to 500 times higher than that for the α_L - δ site.¹⁸ The fetal nAChR contains a γ subunit instead of an adult ϵ subunit. Once activated by acetylcholine, the mature nAChR has a shorter opening time and a higher conductance to sodium (Na⁺), potassium (K⁺), and calcium (Ca²⁺) than the fetal nAChR, which has a smaller, single-channel conductance and a much longer open channel time.¹⁶

Functionally, the ion channel of the acetylcholine receptor is closed in the resting state. Simultaneous binding of two acetylcholine molecules to the α subunits is required to initiate conformational changes that open the channel. If one molecule of a nondepolarizer NMBD (i.e., a competitive antagonist) is bound to a subunit at the AChR, two agonist molecules of acetylcholine cannot bind simultaneously, and neuromuscular transmission is inhibited.¹⁹

Succinylcholine, a depolarizing NMBD, produces prolonged depolarization of the end plate region, which is similar to, but more persistent than, the depolarization induced by acetylcholine. This mechanism results in (1) desensitization of the nAChR, (2) inactivation of voltage-gated Na⁺ channels at the neuromuscular junction, and (3) increases in K⁺ permeability in the surrounding membrane.¹⁹ The end results are failure of action potential generation and neuromuscular blockade.

The fetal nAChR is a low-conductance channel, in contrast to the high-conductance channel of the adult nAChR and upregulation of nAChRs found in states of functional

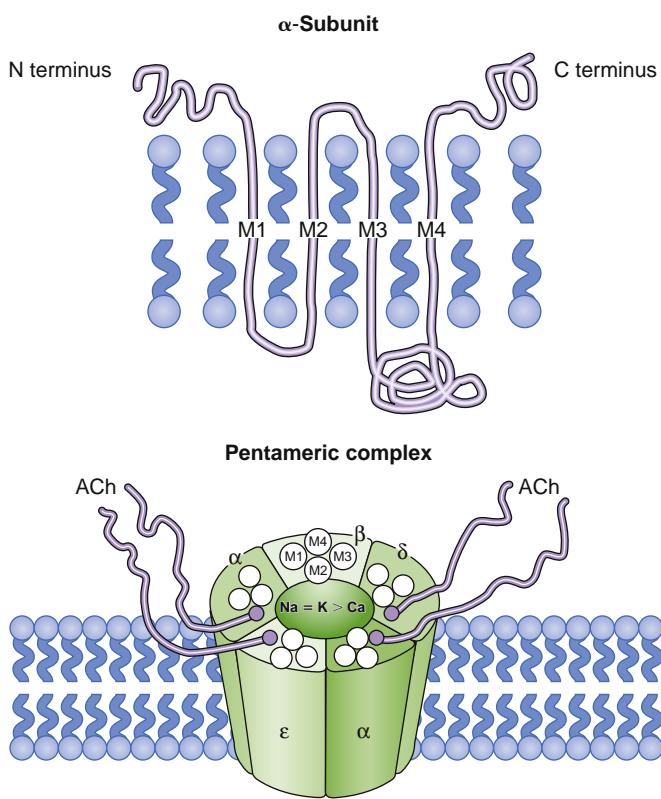


Fig. 27.1 Subunit composition of the nicotinic acetylcholine receptor (nAChR) in the end plate surface of adult mammalian muscle. The adult AChR is an intrinsic membrane protein with five distinct subunits ($\alpha_2\beta\delta\epsilon$). Each subunit contains four helical domains, labeled M₁ to M₄. The M₂ domain forms the channel pore. The upper panel shows a single α subunit with its N and C termini on the extracellular surface of the membrane lipid bilayer. Between the N and C termini, the α subunit forms four helices (M₁, M₂, M₃, and M₄), which span the membrane bilayer. The lower panel shows the pentameric structure of the nAChR of adult mammalian muscle. The N termini of two subunits cooperate to form two distinct binding pockets for acetylcholine. These pockets occur at the ϵ - α and the δ - α subunit interface. The M₂ membrane-spanning domain of each subunit lines the ion channel. The doubly liganded ion channel has equal permeability to sodium (Na⁺) and potassium (K⁺); calcium (Ca²⁺) contributes approximately 2.5% to the total permeability. (From Naguib M, Flood P, McArdle JJ, et al. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. *Anesthesiology*. 2002;96:202–231, with permission from Anesthesiology.)

or surgical denervation is characterized by the spreading of predominantly fetal-type nAChRs. These receptors are resistant to nondepolarizing NMBDs and are more sensitive to succinylcholine.^{20–22}

PREJUNCTIONAL EFFECTS

Prejunctional receptors are involved in the modulation of acetylcholine release in the neuromuscular junction. The existence of both nicotinic and muscarinic receptors on the motor nerve endings has been described. Prejunctional nicotinic receptors are activated by acetylcholine and function in a positive-feedback control system, which could mediate mobilization of the reserve store into the readily releasable store in case of high-frequency stimulation; this mobilization serves to maintain availability of acetylcholine when demand for it is high (e.g., during tetanic stimulation).²³ These presynaptic receptors are $\alpha_3\beta_2$ neuronal subtype receptors. Although most nondepolarizing NMBDs have a distinct affinity for the

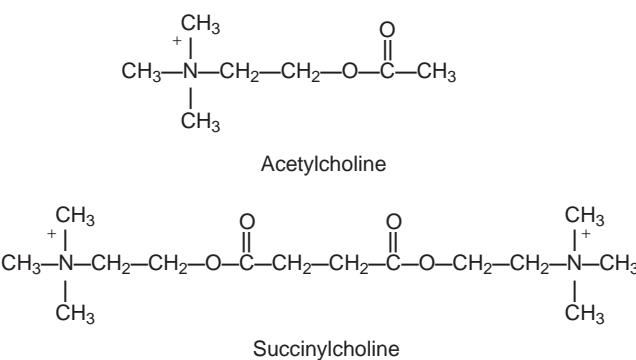


Fig. 27.2 Structural relationship of succinylcholine, a depolarizing neuromuscular blocking drug, and acetylcholine. Succinylcholine consists of two acetylcholine molecules linked through the acetate methyl groups. Like acetylcholine, succinylcholine stimulates nicotinic receptors at the neuromuscular junction.

$\alpha_3\beta_2$ cholinergic receptor, succinylcholine lacks this affinity. The action of nondepolarizing versus depolarizing NMBDs at this neuronal cholinergic receptor explains the typical fade phenomenon after any nondepolarizing drugs, and the lack of such effect in the clinical dose range for succinylcholine. The G-protein-coupled muscarinic receptors also are involved in the feedback modulation of acetylcholine release.²⁴ The prejunctional M₁ and M₂ receptors are involved in facilitation and inhibition of acetylcholine release, respectively, by modulating Ca²⁺ influx.²⁴ The prejunctional nicotinic receptors are involved with mobilization of acetylcholine but not directly with its release process.²⁵ Hence, blockade of the prejunctional nicotinic receptors by nondepolarizing NMBDs prevents acetylcholine from being made available fast enough to support tetanic or train-of-four (TOF) stimulation. In contrast, the prejunctional muscarinic receptors are involved with up-modulation or down-modulation of the release mechanism.

Pharmacology of Succinylcholine

STRUCTURE-ACTIVITY RELATIONSHIPS

All NMBDs contain quaternary ammonium compounds and as such are structurally closely related to acetylcholine. Positive charges at the quaternary ammonium sites of NMBDs mimic the quaternary nitrogen atom of acetylcholine and are the structural reason for the attraction of these drugs to muscle- and neuronal-type nAChRs at the neuromuscular junction. These receptors are also located at other sites throughout the body where acetylcholine is the transmitter. These sites include the neuronal-type nicotinic receptors in autonomic ganglia and as many as five different muscarinic receptors on both the parasympathetic and sympathetic sides of the autonomic nervous system. In addition, populations of neuronal nicotinic and muscarinic receptors are located prejunctionally at the neuromuscular junction.¹⁹

The depolarizing NMBD, succinylcholine, is composed of two molecules of acetylcholine linked through the acetate methyl groups (Fig. 27.2). As described by Bovet,²⁶ succinylcholine is a small, flexible molecule, and like the natural ligand acetylcholine, succinylcholine stimulates cholinergic receptors at the neuromuscular junction and muscarinic autonomic sites, thus opening the ionic channel in the acetylcholine receptor.

PHARMACOKINETICS AND PHARMACODYNAMICS

Succinylcholine is the only available NMBD with a rapid onset of effect and an ultrashort duration of action. The ED₉₅ (the dose causing on average 95% suppression of neuromuscular response) of succinylcholine is 0.51 to 0.63 mg/kg.²⁷ Using cumulative dose-response techniques, Kopman and coworkers estimated that its potency is far greater,²⁸ and it has an ED₉₅ of less than 0.3 mg/kg.

Administration of 1 mg/kg of succinylcholine results in complete suppression of response to neuromuscular stimulation in approximately 60 seconds.²⁹ In patients with genetically normal butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase), recovery to 90% muscle strength following administration of 1 mg/kg succinylcholine requires 9 to 13 minutes.³⁰

The ultrashort duration of action of succinylcholine results from its rapid hydrolysis by butyrylcholinesterase to succinylmonocholine and choline. Butyrylcholinesterase has a large enzymatic capacity to hydrolyze succinylcholine, and only 10% of the intravenously administered drug reaches the neuromuscular junction.³¹ The initial metabolite, succinylmonocholine, is a much weaker NMBD than succinylcholine and is metabolized much more slowly to succinic acid and choline. The elimination half-life of succinylcholine is estimated to be 47 seconds.³²

Because little or no butyrylcholinesterase is present at the neuromuscular junction, the neuromuscular blockade induced by succinylcholine is terminated by its diffusion away from the neuromuscular junction into the circulation. Butyrylcholinesterase therefore influences the onset and duration of action of succinylcholine by controlling the rate at which the drug is hydrolyzed before it reaches, and after it leaves, the neuromuscular junction.

BUTYRYLCHOLINESTERASE ACTIVITY

Butyrylcholinesterase is synthesized by the liver and found in the plasma. The neuromuscular blockade induced by succinylcholine is prolonged when the concentration or activity of the enzyme is decreased. The activity of the enzyme refers to the number of substrate molecules (μmol) hydrolyzed per unit of time, and it is often expressed in International Units. Because the normal range of butyrylcholinesterase activity is quite large,³⁰ significant decreases in activity result in only modest increases in the time required to return to 100% of baseline muscle strength (Fig. 27.3).

Factors that lower butyrylcholinesterase activity include liver disease,³³ advanced age,³⁴ malnutrition, pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, echothiophate, cytotoxic drugs, neoplastic disease, anticholinesterase drugs,³⁵ tetrahydroaminacrine,³⁶ hexafluorinenium,³⁷ and metoclopramide.³⁸ Bambuterol, a prodrug of terbutaline, produces marked inhibition of butyrylcholinesterase activity and causes prolongation of succinylcholine-induced blockade.³⁹ The β -blocker esmolol inhibits butyrylcholinesterase but causes only a minor prolongation of succinylcholine-induced blockade.⁴⁰

Decreased butyrylcholinesterase enzyme activity is not a major concern in clinical practice because even large decreases in butyrylcholinesterase activity result in only modest increases in the duration of action of succinylcholine.

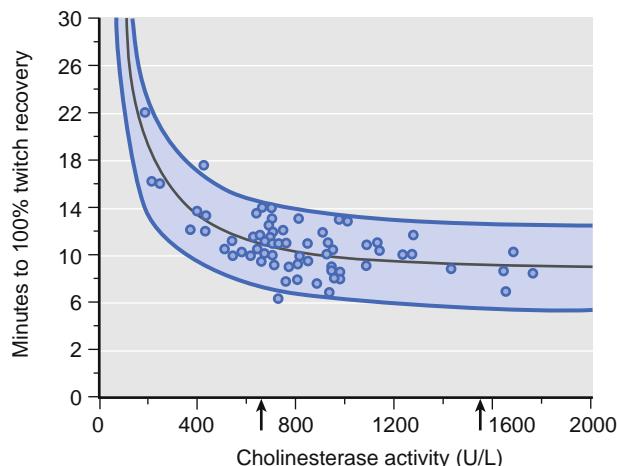


Fig. 27.3 Correlation between duration of succinylcholine neuromuscular blockade and butyrylcholinesterase activity. The normal range of activity lies between the arrows. (From Viby-Mogensen J. Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genetically normal enzyme. *Anesthesiology*. 1980;53:517–520.)

Even when butyrylcholinesterase activity is reduced to 20% of normal by severe liver disease, the duration of apnea after the administration of succinylcholine increases from a normal duration of 3 minutes to only 9 minutes. When glaucoma treatment with echothiophate decreased butyrylcholinesterase activity from 49% of control to no activity, the increase in the duration of neuromuscular blockade varied from 2 to 14 minutes. In no patient did the total duration of neuromuscular blockade exceed 23 minutes.⁴¹

DIBUCAIN NUMBER AND ATYPICAL BUTYRYLCHOLINESTERASE ACTIVITY

Succinylcholine-induced neuromuscular blockade can be significantly prolonged if a patient has an abnormal genetic variant of butyrylcholinesterase. Kalow and Genest discovered a variant that responded to dibucaine differently than it did to normal butyrylcholinesterase.⁴² Dibucaine inhibits normal butyrylcholinesterase to a far greater extent than the abnormal enzyme. This observation led to the establishment of the dibucaine number. Under standardized test conditions, dibucaine inhibits the normal enzyme by approximately 80% and the abnormal enzyme by approximately 20% (Table 27.1). Many other genetic variants of butyrylcholinesterase have since been identified, although the dibucaine-resistant variants are the most important. A review by Jensen and Viby-Mogensen provides more detailed information on this topic.⁴³

Although the dibucaine number indicates the genetic makeup of an individual with respect to butyrylcholinesterase, it does not measure the concentration of the enzyme in the plasma substrate. This is determined by measuring butyrylcholinesterase activity in plasma, and it may be influenced by comorbidities, medications, and genotype.

The molecular biology of butyrylcholinesterase is well understood. The amino acid sequence of the enzyme is known, and the coding errors responsible for most genetic variations have been identified.⁴³ Most variants result from a single amino acid substitution error or sequencing error at or near the active site of the enzyme. For example, in the

TABLE 27.1 Relationship Between Dibucaine Number and Duration of Succinylcholine or Mivacurium Neuromuscular Blockade

Type of Butyrylcholinesterase	Genotype	Incidence	Dibucaine Number*	Response to Succinylcholine or Mivacurium
Homozygous typical	$E_1^uE_1^u$	Normal	70-80	Normal
Heterozygous atypical	$E_1^uE_1^a$	1/480	50-60	Lengthened by 50%-100%
Homozygous atypical	$E_1^aE_1^a$	1/3200	20-30	Prolonged to 4-8 h

*The dibucaine number indicates the percentage of enzyme inhibited.

case of the “atypical” dibucaine-resistant (A) gene, a mutation occurs at nucleotide 209, where guanine is substituted for adenine. The resultant change in this codon causes substitution of glycine for aspartic acid at position 70 in the enzyme. In the case of the fluoride-resistant (F) gene, two amino acid substitutions are possible, namely, methionine for threonine at position 243, and valine for glycine at position 390. Table 27.1 summarizes many of the known genetic variants of butyrylcholinesterase: the amino acid substitution at position 70 is written as Asp \ominus Gly. New variants of butyrylcholinesterase genotypes continue to be discovered.⁴⁴

SIDE EFFECTS

Cardiovascular Effects

Succinylcholine-induced cardiac dysrhythmias are many and varied. The drug stimulates cholinergic autonomic receptors on both sympathetic and parasympathetic ganglia⁴⁵ and muscarinic receptors in the sinus node of the heart. At low doses, both negative inotropic and chronotropic responses may occur. These responses can be attenuated by prior administration of atropine. With large doses of succinylcholine, these effects may become positive,⁴⁶ causing tachycardia. The clinical manifestation of generalized autonomic stimulation is the development of sinus bradycardia, junctional rhythms, and ventricular dysrhythmias. Clinical studies have described these dysrhythmias under various conditions in the presence of the intense autonomic stimulus of tracheal intubation. It is not entirely clear whether the cardiac irregularities are caused by the action of succinylcholine alone or by the added presence of extraneous autonomic stimulation. An in vitro study using ganglionic acetylcholine receptors subtype $\alpha_3\beta_4$ expressed in *Xenopus laevis* oocytes suggested that succinylcholine at clinically relevant concentrations had no effect on the expressed receptors.⁴⁷ Only high doses of succinylcholine caused inhibition of ganglionic acetylcholine receptors.⁴⁷ Whether or not these findings are applicable to clinical practice is unclear because the methodology (*X. laevis* oocytes expression model) has no clinical equivalent.

Sinus Bradycardia. Stimulation of cardiac muscarinic receptors in the cardiac sinus node causes sinus bradycardia. This side effect is particularly problematic in individuals with predominantly vagal tone, such as in children who have not received atropine. Sinus bradycardia can occur in adults and appears more commonly after a second dose of the drug administered approximately 5 minutes after the initial dose.⁴⁸ The bradycardia may be prevented by administration of atropine, ganglion-blocking drugs, and nondepolarizing NMBDs.⁴⁹ The ability of these drugs to prevent bradycardia implies that direct

myocardial effects, increased muscarinic stimulation, and ganglionic stimulation may all be involved in the bradycardic response. The greater incidence of bradycardia after a second dose of succinylcholine suggests that the hydrolysis products of succinylcholine (succinylmonocholine and choline) may sensitize the heart to a subsequent dose.

Nodal (Junctional) Rhythms. Nodal rhythms occur commonly following administration of succinylcholine. The mechanism responsible for this likely involves relatively greater stimulation of muscarinic receptors in the sinus node, thus suppressing the sinus mechanism and allowing the emergence of the atrioventricular node as the pacemaker. The incidence of junctional rhythm is greater after a second dose of succinylcholine, and may be prevented by prior administration of dTc.⁴⁹

Ventricular Dysrhythmias. Under stable anesthetic conditions, succinylcholine decreases the threshold of the ventricle to catecholamine-induced dysrhythmias in monkeys and dogs. Circulating catecholamine concentrations increase fourfold, and K^+ concentrations increase by one third, following succinylcholine administration in dogs.⁵⁰ Similar increases in catecholamine levels occur following administration of succinylcholine to humans.⁵¹ Other autonomic stimuli, such as endotracheal intubation, hypoxia, hypercarbia, and surgery, may be additive to the effect of succinylcholine. The possible influence of drugs such as digitalis, tricyclic antidepressants, monoamine oxidase inhibitors, exogenous catecholamines, and anesthetic drugs such as halothane, which may lower the ventricular threshold for ectopic activity or increase the arrhythmogenic effect of the catecholamines, should also be considered. Ventricular escape beats may also occur as a result of severe sinus bradycardia and atrioventricular nodal slowing secondary to succinylcholine administration. The incidence of ventricular dysrhythmias is further increased by the release of K^+ from skeletal muscle as a consequence of the depolarizing action of the drug.

Hyperkalemia

The administration of succinylcholine to an otherwise healthy individual increases the plasma K^+ levels by approximately 0.5 mEq/dL. This slight increase in K^+ is well tolerated by most individuals and generally does not cause dysrhythmias. The increase in K^+ results from the depolarizing action of succinylcholine. With activation of the acetylcholine channels, movement of Na^+ into the cells is accompanied by movement of K^+ out of the cells.

Patients with renal failure are no more susceptible to an exaggerated response to succinylcholine than are those with normal renal function.⁵² Patients who have uremic

neuropathy may possibly be susceptible to succinylcholine-induced hyperkalemia, although the evidence supporting this view is scarce.^{52,53,53a}

However, severe hyperkalemia may follow the administration of succinylcholine to patients with severe metabolic acidosis and hypovolemia.⁵⁴ In experimental animals (rabbit), the combination of metabolic acidosis and hypovolemia results in a high resting K⁺ level and an exaggerated hyperkalemic response to succinylcholine.⁵⁵ In this situation, the K⁺ originates from the gastrointestinal tract, rather than from muscle.⁵⁶ In patients with metabolic acidosis and hypovolemia, correction of the acidosis by hyperventilation and sodium bicarbonate administration should be attempted before succinylcholine administration. Should severe hyperkalemia occur, it can be treated with immediate hyperventilation, infusion of 500-1,000 mg calcium chloride or calcium gluconate over 3 minutes intravenously, and 10 units of regular insulin in 50 mL of 50% glucose for adults or, for children, 0.15 units/kg of regular insulin in 1.0 mL/kg of 50% glucose intravenously.

Kohlschütter and associates found that four of nine patients with severe abdominal infections had an increase in serum K⁺ levels of as much as 3.1 mEq/L after succinylcholine administration.⁵⁷ The likelihood of a hyperkalemic response to succinylcholine increases in patients who have had intraabdominal infections for longer than 1 week.

Stevenson and Birch described a single, well-documented case of a marked hyperkalemic response to succinylcholine in a patient with a closed head injury without peripheral paralysis.⁵⁸

Hyperkalemia after administration of succinylcholine is also a risk in patients who have had physical trauma.⁵⁹ The risk of hyperkalemia occurs 1 week after the injury, at which time a progressive increase in serum K⁺ occurs during an infusion of succinylcholine. The risk of hyperkalemia can persist. Three weeks after injury, three of the patients studied in this series, who had especially severe injuries, became markedly hyperkalemic with an increase in serum K⁺ of more than 3.6 mEq/L. Birch and coworkers also found that the prior administration of 6 mg of dTc prevented the hyperkalemic response to succinylcholine.⁵⁹ In the absence of infection or persistent degeneration of tissue, a patient is likely susceptible to the hyperkalemic response for at least 60 days after massive trauma or until adequate healing of damaged muscle has occurred.

Additionally, patients with conditions that result in the proliferation of extrajunctional acetylcholine receptors, such as upper or lower motor denervation, immobilization, burn injuries, and neuromuscular disease, are likely to have an exaggerated hyperkalemic response following the administration of succinylcholine. The response of patients with neuromuscular disease to NMBDs is reviewed in detail later in this chapter. Some of these disease states include cerebrovascular accident with resultant hemiplegia or paraplegia, muscular dystrophies, and Guillain-Barré syndrome. The hyperkalemia following administration of succinylcholine may be severe enough that cardiac arrest ensues. For a review of succinylcholine-induced hyperkalemia in acquired pathologic states, see Martyn and Richtsfeld.²²

Increased Intraocular Pressure

Succinylcholine may cause an increase in intraocular pressure (IOP). The increased IOP develops within 1 minute of

injection, peaks at 2 to 4 minutes, and subsides by 6 minutes.⁶⁰ The mechanism by which succinylcholine increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils and/or transient dilatation of choroidal blood vessels. Sublingual administration of nifedipine may attenuate the increase in IOP caused by succinylcholine, a finding suggesting a circulatory mechanism.⁶¹ Despite this increase in IOP, the use of succinylcholine for eye operations is not contraindicated unless the anterior chamber is open. Although Meyers and colleagues were unable to confirm the efficacy of small (0.09 mg/kg) doses of dTc ("precurarization") in attenuating increases in IOP following succinylcholine,⁶² numerous other investigators have found that prior administration of a small dose of nondepolarizing NMBD (e.g., 3 mg of dTc or 1 mg of pancuronium) prevents a succinylcholine-induced increase in IOP.⁶³ Furthermore, Libonati and associates described the anesthetic management of 73 patients with penetrating eye injuries who received succinylcholine.⁶⁴ Among these 73 patients, no extrusion of vitreous occurred. Thus, despite the potential concerns, the use of succinylcholine in patients with penetrating eye injuries, after pretreatment with a nondepolarizing NMBD and with a carefully controlled rapid-sequence induction of anesthesia, can be considered. Succinylcholine is only one of many factors that may increase IOP.⁶² Other factors include endotracheal intubation and "bucking" on the endotracheal tube once it is positioned. Of prime importance in minimizing the chance of increasing IOP is ensuring that the patient is well anesthetized and is not straining or coughing. For instance, coughing, vomiting and maximal forced lid closure may induce increases in intraocular pressure that are 3-4 times greater (60-90 mm Hg) than those induced by succinylcholine administration.^{63a} Because a nondepolarizing NMBD with a rapid onset of effect, rocuronium, is available, it is possible to perform a rapid sequence induction of anesthesia and endotracheal intubation without administering succinylcholine. Finally, should a patient become too lightly anesthetized during intraocular surgery, succinylcholine should not be given to immobilize the patient. Rather, the surgeon should be asked to pause while anesthesia is deepened. If necessary, the depth of neuromuscular blockade can also be increased with nondepolarizing NMBDs.

Increased Intragastric Pressure

Unlike the rather consistent increase in IOP following administration of succinylcholine, increases in intragastric pressure (IGP) are much more variable. The increase in IGP from succinylcholine is presumed to result from fasciculations of the abdominal skeletal muscle. This is not surprising because more coordinated abdominal skeletal muscle activity (e.g., straight-leg raising) may increase the IGP to values as high as 120 cm H₂O (88 mm Hg). In addition to skeletal muscle fasciculations, the acetylcholine-like effect of succinylcholine may be partly responsible for the observed increases in IGP. Greenan observed consistent increases in IGP of 4 to 7 cm H₂O (3-5 mm Hg) with direct vagal stimulation.⁶⁵

Miller and Way found that 11 of 30 patients had essentially no increase in IGP after succinylcholine administration, yet 5 of the 30 had an increase in IGP of greater than 30 cm H₂O (22 mm Hg).⁶⁶ The increase in IGP from succinylcholine appeared to be related to the intensity of the fasciculations of

the abdominal skeletal muscles. Accordingly, when fasciculations were prevented by prior administration of a nondepolarizing NMBD, no increase in IGP was observed.

Whether the increases in IGP following succinylcholine administration are sufficient to cause incompetence of the gastroesophageal junction are debatable. Generally, an IGP greater than 28 cm H₂O (21 mm Hg) is required to overcome the competence of the gastroesophageal junction. However, when the normal oblique angle of entry of the esophagus into the stomach is altered, as may occur with pregnancy or an abdomen distended by ascites, bowel obstruction, or a hiatus hernia, the IGP required to cause incompetence of the gastroesophageal junction is frequently less than 15 cm H₂O (11 mm Hg).⁶⁶ In these circumstances, regurgitation of stomach contents following succinylcholine administration is a distinct possibility, and precautionary measures should be taken to prevent fasciculations. Endotracheal intubation may be facilitated with administration of either a nondepolarizing NMBD or a defasciculating dose of nondepolarizing relaxant before succinylcholine use. Although the increase in IGP from succinylcholine is well documented, the evidence of clinical harm is not clear.

Succinylcholine does not increase IGP appreciably in infants and children. This may be related to the minimal or absent fasciculations from succinylcholine in these young patients.⁶⁷

Increased Intracranial Pressure

Succinylcholine has the potential to increase intracranial pressure.⁶⁸ The mechanisms and clinical significance of this transient increase are unknown, but pretreatment with nondepolarizing NMBDs prevents intracranial pressure increases.⁶⁸

Myalgia

The incidence of muscle pain following administration of succinylcholine varies widely, from 0.2% to 89%.⁶⁹ Muscle pain occurs more frequently after minor surgery, especially in women and in ambulatory, rather than bedridden, patients.⁷⁰ Waters and Mapleson postulated that pain is secondary to damage produced in muscle by the unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.⁷⁰ This concept has been substantiated by finding myoglobinemia and increases in serum creatine kinase following succinylcholine administration.⁷¹ Prior administration of a small ("defasciculating") dose of a nondepolarizing NMBD clearly prevents fasciculations from succinylcholine.⁷¹ The efficacy of this approach in preventing muscle pain is not clear; however, most investigators report that pretreatment with a nondepolarizing NMBD has minimal effect.⁶⁹ Pretreatment with a prostaglandin inhibitor (e.g., lysine acetyl salicylate) has been shown effective in decreasing the incidence of muscle pain after succinylcholine.⁷² This finding suggests a possible role for prostaglandins and cyclooxygenases in succinylcholine-induced myalgias. Other investigators have found that myalgias following outpatient laparoscopic surgery (and atracurium administration) occur even in the absence of succinylcholine.⁷³ Other investigators reported a significant reduction in postoperative myalgia in elective oral surgery patients pretreated with rocuronium (20%) compared with vecuronium (42%) and placebo (70%).^{73a}

Masseter Muscle Rigidity

An increase in tone of the masseter muscle is a frequent response to succinylcholine in adults⁷⁴ as well as in children.⁷⁵ Several studies have reported that an increase in masseter muscle tone of up to 500 g lasting 1 to 2 minutes is a normal finding in adults.⁷⁶ Most cases of the so-called masseter muscle rigidity (MMR) may represent simply the extreme of a spectrum of muscle tension changes that occur in response to succinylcholine. Meakin and associates suggested that the high incidence of spasm in children may result from inadequate dosage of succinylcholine.⁷⁵ In all likelihood, this increase in tone is an exaggerated contractile response at the neuromuscular junction and cannot be used to establish a diagnosis of malignant hyperthermia. Although an increase in tone of the masseter muscle may be an early indicator of malignant hyperthermia, this finding is not consistently associated with that syndrome.⁷⁶ Currently, no indication exists to change to a "nontriggering" anesthetic technique in instances of isolated MMR.⁷⁷

Anaphylaxis

There is some controversy concerning the incidence of anaphylaxis following succinylcholine. The incidence of anaphylactic reactions may be close to 0.06%. Almost all cases of anaphylaxis have been reported in Europe or Australia. When the muscle relaxant cross-links with IgE, degranulation and release of histamine, neutrophil chemotactic factor, and platelet-activating factor occur. The release of these mediators can induce cardiovascular collapse, bronchospasm, and skin reaction.^{77a} Patients with a history of anaphylactic reaction to succinylcholine may exhibit a cross-reaction, at least in vitro, with other NMBDs. The cross-reactivity is related to the common structural features of these drugs, all of which contain quaternary ammonium ions.

CLINICAL USES

In spite of its many adverse effects, succinylcholine remains in clinical use. Its popularity is likely the result of its rapid onset of effect, the profound depth of neuromuscular blockade it produces, and its short duration of action. Succinylcholine is not used as regularly as in the past for routine endotracheal intubation, but it is still a muscle relaxant frequently used for rapid-sequence induction of anesthesia and tracheal intubation. Although 1.0 mg/kg of succinylcholine is recommended to facilitate endotracheal intubation at 60 seconds, as little as 0.5 to 0.6 mg/kg may result in adequate intubating conditions 60 seconds after administration.⁷⁸ Reduction in the succinylcholine dose from 1.0 to 0.6 mg/kg decreases the incidence of hemoglobin desaturation but does not shorten the time to spontaneous diaphragmatic movements.⁷⁹ Decreasing the dose of succinylcholine is appealing as long as it does not interfere with provision of adequate conditions for endotracheal intubation and subsequent adequate ventilation.⁷⁹

Typically, after administering succinylcholine for tracheal intubation, a nondepolarizing NMBD is given to maintain neuromuscular blockade. Prior administration of succinylcholine enhances the depth of blockade caused by a subsequent dose of nondepolarizing NMBD.^{80,81} However, the effect on duration of action is variable. Succinylcholine has no effect on the duration of pancuronium,⁸² but it

increases the duration of atracurium and rocuronium.^{80,83} The reasons for these differences are not clear.

With administration of large doses of succinylcholine, the nature of the block, as determined by a monitor of neuromuscular blockade, changes from that of a depolarizing drug (phase 1 block) to that of a nondepolarizing drug (phase 2 block). Clearly, both the dose and the duration of administration of succinylcholine contribute to this change. The relative contribution of each factor has not been established, however.

Posttetanic potentiation and fade in response to TOF and tetanic stimuli can be demonstrated after bolus administration of different doses of succinylcholine.⁸⁴ It seems that some characteristics of phase 2 blockade are evident from an initial dose (i.e., as small as 0.3 mg/kg) of succinylcholine.⁸⁴ Fade in response to TOF stimulation has been attributed to the pre-synaptic effects on NMBDs. The etiology of the appearance of fade phenomenon in the TOF response following excessive administration of succinylcholine has been suggested to be dependent on a concentration-dependent affinity for succinylcholine to the presynaptic $\alpha_3\beta_2$ neuronal subtype AChR in concentrations exceeding the normal clinical concentration range seen after routine doses.⁴⁷

INTERACTIONS WITH ANTICHOLINESTERASES

Neostigmine and pyridostigmine inhibit butyrylcholinesterase, as well as acetylcholinesterase. If succinylcholine is administered after antagonism of residual neuromuscular block, as it may be with postextubation laryngospasm, the effect of succinylcholine will be pronounced and significantly prolonged. The effect of succinylcholine (1 mg/kg) was prolonged from 11 to 35 minutes when it was given 5 minutes after administration of neostigmine (5 mg).³⁵ Ninety minutes after neostigmine administration, butyrylcholinesterase activity will have returned to less than 50% of its baseline value.

Nondepolarizing Neuromuscular Blocking Drugs

The use of NMBDs in anesthesia has its origin in the arrow poisons or curares of South American Indians. Several nondepolarizing NMBDs were purified from naturally occurring sources. For example, dTc can be isolated from the Amazonian vine *Chondodendron tomentosum*. Similarly, the intermediates for the production of metocurine and alcuronium,

which are semisynthetic, are obtained from *Chondodendron* and *Strychnos toxifera*. Malouetine, the first steroid NMBD, was originally isolated from *Malouetia bequaertiana*, which grows in the jungles of the Democratic Republic of Congo in central Africa. The NMBDs pancuronium, vecuronium, pipecuronium, rocuronium, rapacuronium, atracurium, doxacurium, mivacurium, cisatracurium, gantacurium, and gallamine are all synthetic compounds.

Available nondepolarizing NMBDs can be classified according to chemical class, based on structure (steroids, benzylisoquinoliniums, fumarates, and other compounds), or, alternatively, according to onset or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses (Table 27.2).

STRUCTURE-ACTIVITY RELATIONSHIPS

Nondepolarizing NMBDs were originally classified by Bovet as pachycurares,²⁶ or bulky molecules having the amine functions incorporated into rigid ring structures. Two extensively studied chemical series of synthetic nondepolarizing NMBDs are the aminosteroids, in which the internonium distance is maintained by an androstane skeleton, and the benzylisoquinolinium series, in which the distance is maintained by linear diester-containing chains or, in the case of curare, by benzyl ethers. For a detailed account on structure-activity relationships, see Lee.⁸⁵

Benzylisoquinolinium Compounds

dTc is an NMBD in which the amines are present in the form of two benzyl substituted tetrahydroisoquinoline structures (Fig. 27.4). Using nuclear magnetic resonance spectroscopy and methylation-demethylation studies, Everett and associates demonstrated that dTc contains three N-methyl groups.⁸⁶ One amine is quaternary (i.e., permanently charged with four nitrogen substituents), and the other is tertiary (i.e., pH-dependent charge with three nitrogen substituents). At physiologic pH, the tertiary nitrogen is protonated so that it is positively charged. The structure-activity relationships of the bis-benzylisoquinolines (see Fig. 27.4) have been described by Waser⁸⁷ and by Hill and associates,⁸⁸ and these relationships are as follows:

1. The nitrogen atoms are incorporated into isoquinoline ring systems. This bulky molecule favors a nondepolarizing rather than a depolarizing activity.

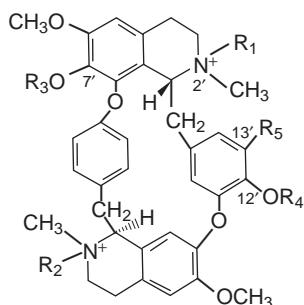
TABLE 27.2 Classification of Nondepolarizing Neuromuscular Blockers According to Duration of Action (Time to T1 = 25% of Control) after Twice the Dose Causing on Average 95% Suppression of Neuromuscular Response

CLINICAL DURATION				
	Long-acting (>50 min)	Intermediate-acting (20-50 min)	Short-acting (10-20 min)	Ultrashort-acting (<10 min)
Steroidal compounds	Pancuronium	Vecuronium Rocuronium		
Benzylisoquinolinium compounds	d-Tubocurarine	Atracurium Cisatracurium	Mivacurium	
Asymmetric mixed-onium fumarates		CW 002		Gantacurium

Most nondepolarizing neuromuscular blockers are bisquaternary ammonium compounds. d-Tubocurarine, vecuronium, and rocuronium are monoquaternary compounds.

T1, First twitch of train-of-four.

- The interonium distance (distance between charged amines) is approximately 1.4 nm.
- Both the ganglion-blocking and the histamine-releasing properties of dTc probably result from the presence of the tertiary amine function.
- When dTc is methylated at the tertiary amine and at the hydroxyl groups, the result is metocurine, a compound of greater potency (by a factor of two in humans) with much weaker ganglion-blocking and histamine-releasing properties than dTc (see Fig. 27.4). Metocurine contains three additional methyl groups, one of which quaternizes the tertiary nitrogen of dTc; the other two form methyl ethers at the phenolic hydroxyl groups.
- Bisquaternary compounds are more potent than their monoquaternary analogues. The bisquaternary derivative of dTc, chondocurine, is more than twice as potent as dTc (see Fig. 27.4).



Cyclic benzylisoquinoline

Cyclic benzylisoquinoline derivatives

Name	R ₁	R ₂	R ₃	R ₄	R ₅	1	1'
d-Tubocurarine	CH ₃	H	H	H	H	S	R
Metocurine	CH ₃	CH ₃	CH ₃	CH ₃	H	S	R
Chondocurine	CH ₃	CH ₃	H	H	H	S	R

R and S represent the stereochemical configuration about the designated carbon

Fig. 27.4 Chemical structures of *d*-tubocurarine, metocurine, and chondocurine.

- Substitution of the methyl groups on the quaternary nitrogen with bulkier groups causes a reduction in both potency and duration of action.

Atracurium is a bis-benzyltetrahydroisoquinolinium with isoquinolinium nitrogens connected by a diester-containing hydrocarbon chain (Fig. 27.5). The presence (in duplicate) of two-carbon separations between quaternary nitrogen and ester carbonyl renders it susceptible to the Hofmann elimination reaction.⁸⁹ The compound can also undergo ester hydrolysis. In a Hofmann elimination reaction, a quaternary ammonium group is converted into a tertiary amine through cleavage of a carbon-nitrogen bond. This is a pH- and temperature-dependent reaction in which higher pH and temperature favor elimination.

Atracurium has 4 chiral centers at each of the chiral carbons adjacent to the two amines. It is composed of 10 isomers.⁸⁹ These isomers have been separated into three geometric isomer groups that are designated *cis-cis*, *cis-trans*, and *trans-trans* according to their configuration about the tetrahydroisoquinoline ring system.⁸⁹ The ratio of the *cis-cis*, *cis-trans*, and *trans-trans* isomers is approximately 10:6:1, corresponding to 50% to 55% *cis-cis*, 35% to 38% *cis-trans*, and 6% to 7% *trans-trans* isomers.

Cisatracurium, the 1R *cis*–1'R *cis* isomer of atracurium, comprises approximately 15% of atracurium by weight but more than 50% in terms of neuromuscular blocking activity (see Fig. 27.5). R designates the absolute stereochemistry of the benzyl tetrahydroisoquinoline rings, and *cis* represents the relative geometry of the bulky dimethoxy and 2-alky-ester groups at C(1) and N(1), respectively.^{90,91} Like atracurium, cisatracurium undergoes Hofmann elimination. It is approximately four times as potent as atracurium, and in contrast to atracurium, it does not cause histamine release,^{90,92} thus indicating that histamine release may be stereospecific.^{90,93}

Mivacurium differs from atracurium by the presence of an additional methylated phenolic group (see Fig. 27.5). Compared with other isoquinolinium NMBDs, the interonium chain of mivacurium is longer (16 atoms).⁸⁸ Mivacurium consists of a mixture of three stereoisomers.⁹⁴ The two most active are the *trans-trans* and *cis-trans* isomers (57% and

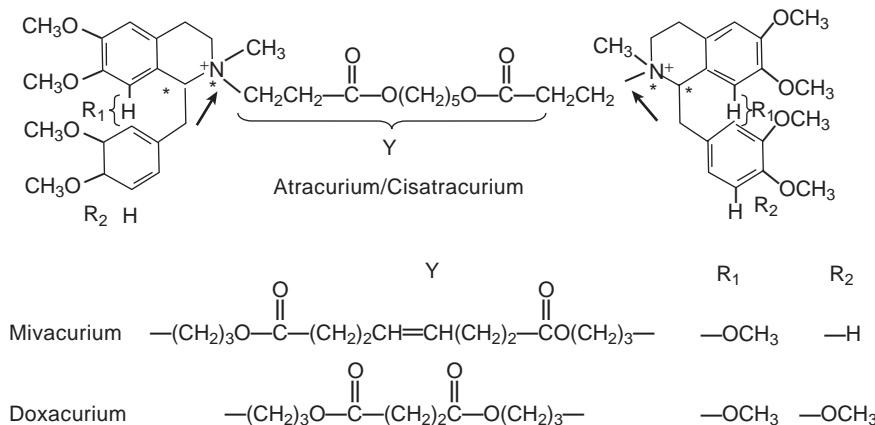


Fig. 27.5 Chemical structures of atracurium, cisatracurium, mivacurium, and doxacurium. The asterisk indicates the chiral centers; arrows show cleavage sites for Hofmann elimination.

37% weight/weight, respectively), which are equipotent; the *cis-cis* isomer (6% weight/weight) has only one tenth the neuromuscular blocking activity of the more potent isomers in cats and monkeys.⁹⁴ Mivacurium is metabolized by butyrylcholinesterase to a monoester and a dicarboxylic acid at 70% to 88% the rate at which succinylcholine is metabolized by the same enzyme.⁹

Steroidal Neuromuscular Blockers

For the steroid compounds to have neuromuscular blocking potential, it is likely that one of the compound's two nitrogen atoms be quaternized. The presence of an acetyl ester (acetylcholine-like moiety) facilitates their interaction with nAChRs at the postsynaptic muscle membrane.

Pancuronium is characterized by the presence of two acetyl ester groups on the A and D rings of the steroid molecule. Pancuronium is a potent NMBD with vagolytic properties. It is also an inhibitor of butyrylcholinesterase (Fig. 27.6).⁹⁵ Deacetylation at the 3 or 17 positions decreases its potency.⁹⁶

Vecuronium, in which the 2-piperidine substituent is not methylated, is the *N*-demethylated derivative of pancuronium (see Fig. 27.6).⁷ At physiologic pH, the tertiary amine is largely protonated, as it is in dTc. The minor molecular modification results in the following: (1) a slight increase in the potency when compared with pancuronium; (2) a marked reduction in its vagolytic properties; (3) molecular instability in solution; and (4) increased lipid solubility, which results in a greater biliary elimination of vecuronium than pancuronium.⁸⁸

Vecuronium is degraded by the hydrolysis of the acetyl esters at the C3 and the C17 positions. Hydrolysis at the C3

position is the primary degradation pathway because the acetate at the 3 position is more susceptible to hydrolysis in aqueous solutions than the acetate at the 17 position. This is because of the adjacent basic piperidine at the 2 position that facilitates hydrolysis of the 3-acetate. Therefore vecuronium cannot be prepared as a ready-to-use solution with a sufficient shelf life, even as a buffered solution. In contrast, the 2-piperidine of pancuronium is quaternized and no longer alkaline and therefore does not facilitate hydrolysis of the 3-acetate.

Rocuronium lacks the acetyl ester that is found in the A ring of the steroid nucleus of pancuronium and vecuronium (see Fig. 27.6). The introduction of cyclic substituents other than piperidine at the 2 and 16 positions results in a compound with a more rapid onset of effect than vecuronium or pancuronium.⁹⁷ The methyl group attached to the quaternary nitrogen of vecuronium and pancuronium is replaced by an allyl group in rocuronium. As a result of this change, rocuronium is approximately 6 and 10 times less potent than pancuronium and vecuronium, respectively.⁹⁷⁻⁹⁹ The replacement of the acetyl ester attached to the A ring by a hydroxy group means that rocuronium is stable in solution. At room temperature, rocuronium is stable for 60 days. In contrast, pancuronium is stable for 6 months. The reason for this difference in shelf life is related to the fact that rocuronium is terminally sterilized in manufacturing, and pancuronium is not. Terminal sterilization causes some degree of degradation.

Asymmetric Mixed-Onium Fumarates and Analogues

These compounds share some structural properties with mivacurium. Gantacurium and CW 002 represent a new

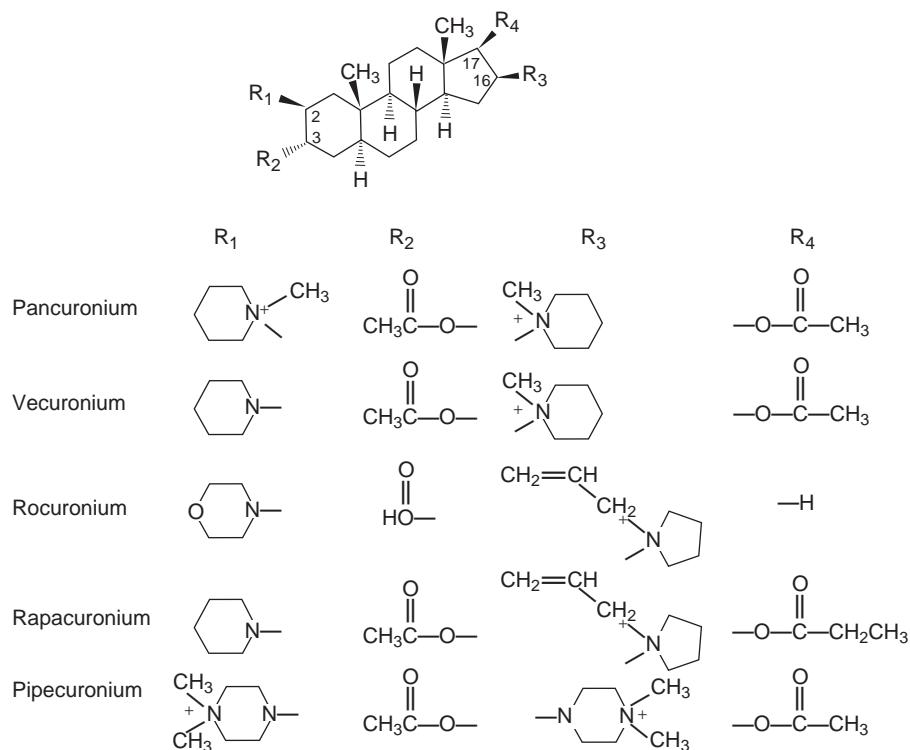


Fig. 27.6 Chemical structures of different steroidal neuromuscular blockers.

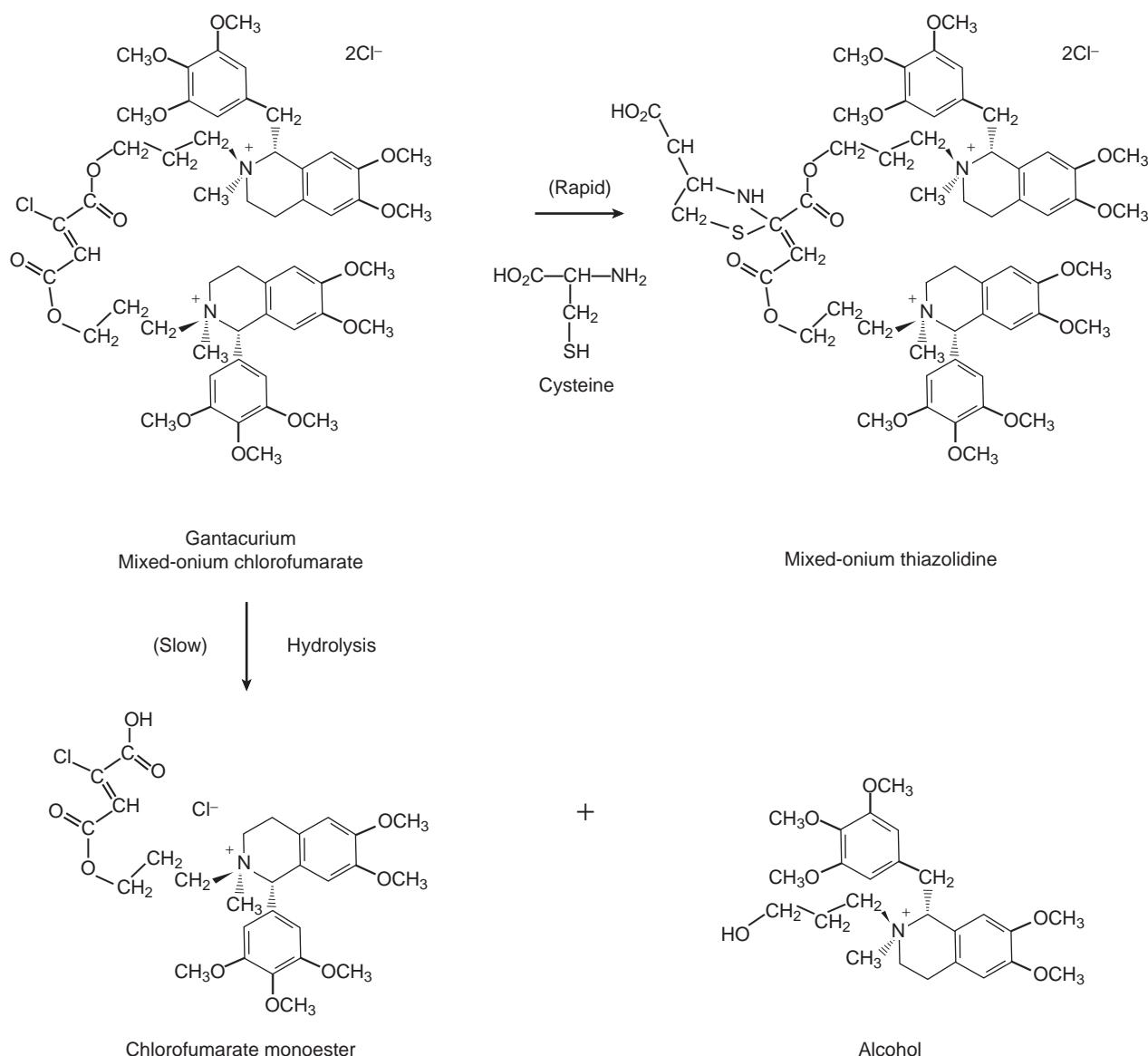


Fig. 27.7 Chemical structure of gantacurium (a mixed-onium chlorofumarate). In whole human blood, two pathways of deactivation occur, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product, with cysteine replacing chlorine; and (2) slower hydrolysis of the ester bond adjacent to the chlorine substitution to chlorofumarate monoester and alcohol. (From Boros EE, Samano V, Ray JA, et al. Neuromuscular blocking activity and therapeutic potential of mixed-tetrahydroisoquinolinium halofumarates and halosuccinates in rhesus monkeys. *J Med Chem*. 2003;46:2502–2515.)

class of bisquaternary nondepolarizing NMBDs (Fig. 27.7). Gantacurium, an asymmetric mixed-onium chlorofumarate, is unique among nondepolarizing compounds in terms of its rapid onset of effect, its short duration of action, and its unique means of inactivation.^{11,100} Because of the presence of three methyl groups between the quaternary nitrogen and oxygen atom at each end of the carbon chain, this compound does not undergo Hofmann elimination.¹⁰⁰

Gantacurium has an ultrashort duration of action in human volunteers and in different animal species. In human volunteers receiving a nitrous oxide–opioid anesthetic, the ED₉₅ of gantacurium is 0.19 mg/kg.¹⁰⁰ Onset of and recovery from block resemble those of succinylcholine. Following administration of approximately 2.5 times the ED₉₅ dose, onset of maximal block occurs in 1.5 minutes. Spontaneous recovery to a TOF of 0.9 or greater occurs 10 minutes after

administration of an ED₉₅ dose, and complete spontaneous recovery occurs in 14 to 15 minutes after administration of doses ranging from 2 to 3.5 times the ED₉₅. Recovery is accelerated by administration of edrophonium at the beginning of spontaneous recovery. Transient hypotension and tachycardia occur following administration of doses three times the ED₉₅ and greater, a finding suggesting that histamine release occurs with administration of these doses.¹⁰⁰

Gantacurium appears to undergo two pathways of inactivation. One is a slower ester hydrolysis, and the second one, which occurs much more quickly, occurs through the addition of cysteine, a nonessential amino acid, to create a new compound that can no longer bind to the nAChR of the neuromuscular junction.¹⁰¹ This unique means of inactivation likely accounts for the drug's ultrashort duration of effect. It also provides a novel means of shortening recovery

TABLE 27.3 Dose-Response Relationships of Nondepolarizing Neuromuscular Blocking Drugs in Human Subjects

	ED ₅₀ (mg/kg)	ED ₉₀ (mg/kg)	ED ₉₅ (mg/kg)	References
LONG-ACTING				
Pancuronium	0.036 (0.022-0.042)	0.056 (0.044-0.070)	0.067 (0.059-0.080)	98, 103
<i>d</i> -Tubocurarine	0.23 (0.16-0.26)	0.41 (0.27-0.45)	0.48 (0.34-0.56)	103
INTERMEDIATE-ACTING				
Rocuronium	0.147 (0.069-0.220)	0.268 (0.200-0.419)	0.305 (0.257-0.521)	98, 104-106
Vecuronium	0.027 (0.015-0.031)	0.042 (0.023-0.055)	0.043 (0.037-0.059)	103
Atracurium	0.12 (0.08-0.15)	0.18 (0.19-0.24)	0.21 (0.13-0.28)	103
Cisatracurium	0.026 (0.015-0.031)	—	0.04 (0.032-0.05)	107-109, 371
SHORT-ACTING				
Mivacurium	0.039 (0.027-0.052)	—	0.067 (0.045-0.081)	9, 110-112
ULTRASHORT-ACTING				
Gantacurium	0.09	—	0.19	100

Data are the medians and ranges of reported values. ED₅₀, ED₉₀, and ED₉₅ are the doses of each drug that produce, respectively, 50%, 90%, and 95% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle following ulnar nerve stimulation.

from gantacurium-induced neuromuscular block. Administration of L-cysteine (10 mg/kg) 1 minute after administration of gantacurium results in rapid return to complete neuromuscular function within 1 to 2 minutes.¹⁰²

An analogue of the asymmetric fumarate gantacurium, CW 002 has been synthesized to undergo slower L-cysteine adduction. Because of its slower metabolism, it has an intermediate duration of action. In animals, it causes a nondepolarizing block that can be antagonized by neostigmine. Administration of L-cysteine 1 minute after administration of CW 002 effectively speeds recovery of neuromuscular function, whereas neostigmine does not.²² Volunteer trials are required to determine whether onset, recovery, and ease of antagonism are improved over those using compounds that are currently available.

CW 011 (an asymmetrical maleate) is a nonhalogenated olefinic diester analogue of gantacurium¹⁰¹ that can undergo L-cysteine adduction in animal models. Because this adduction reaction is slower than that of gantacurium, its duration of neuromuscular block is longer (approximately 21 minutes). Exogenous L-cysteine (50 mg/kg) administration can induce full recovery of neuromuscular block (after five times ED₉₅ dose of CW 011) in 2 to 3 minutes.¹⁰¹

The clinical development of gantacurium was suspended in 2006, but since then, several other compounds similar to gantacurium have been tested. CW 1759-50 is a fast-onset, ultrashort-acting NMBA that is devoid of histaminoid side effects in animal testing.^{11a,11b} CW 1759-50 is ultrashort acting because it is inactivated by plasma L-cysteine. Spontaneous recovery (5%-95% interval) from either bolus or infusion was similar (5-6 minutes), and reversal by L-cysteine required about 2 minutes.

POTENCY OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Drug potency is commonly expressed by the dose-response relationship. The dose of an NMBD required to produce an effect (e.g., 50%, 90%, or 95% depression of baseline

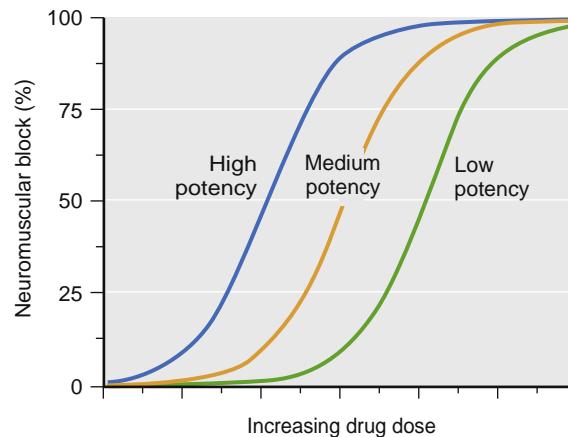


Fig. 27.8 Schematic representation of a semilogarithmic plot of a muscle-relaxant dose versus neuromuscular blockade. A drug of high potency is doxacurium, one of medium potency is atracurium, and one of low potency is gallamine. The graph illustrates that the relative potencies of the muscle relaxants span a range of approximately two orders of magnitude.

twitch height, commonly expressed as ED₅₀, ED₉₀, and ED₉₅, respectively) defines its potency.^{9,98,103-114} The NMBDs have different potencies, as illustrated in Table 27.3 and Fig. 27.8. For factors affecting the potency of NMBDs, see the section on drug interactions later in this chapter. The dose-response relationship for nondepolarizing NMBDs is sigmoidal (see Fig. 27.8) and has been derived in various ways. The simplest method is to perform linear regression over the approximately linear portion of a semilogarithmic plot between 25% and 75% neuromuscular blockade. Alternatively, the curve can be subjected to probit or logit transformation to linearize it over its whole length, or the data can be subjected to nonlinear regression using the sigmoid E_{max} model of this form:

$$\text{Effect } (e) = F \left(\frac{dose_e}{dose_{e50}}, \frac{dose_e}{dose_{e50}} + 1 \right)$$

More complex models relating the concentration of NMBDs at the neuromuscular junction to their pharmacologic effect have been developed, and are discussed later.^{115,116}

Factors that govern duration of action of NMBDs.

Onset

There is ample evidence that potent NMBDs have slower onset times than less potent drugs with similar physicochemical properties. These facts can be explained by the concept of the margin of safety. A critical number of receptors at the neuromuscular junction must be occupied before appearance of neuromuscular block, and at least 90% of the receptors must be occupied before block is complete at the adductor pollicis. When the drug reaches the synaptic cleft, most molecules will bind to receptors that are present with a high density. As the concentration of free drug decreases, more molecules are driven in and the process will continue until the concentrations of free drug within and outside the synaptic cleft are equal. When a potent drug is administered, fewer molecules are given than in a case of a less potent drug, and the onset will be slower compared to onset of lower potency NMBD.^{116a} Nondepolarizing NMBDs of low potency (e.g., rocuronium) have more molecules to diffuse from the central compartment into the effect compartment. Once in the effect compartment, all molecules act promptly. Weaker binding of the low-potency drugs to receptors prevents buffered diffusion, a process that occurs with more potent drugs. Buffered diffusion causes repetitive binding and unbinding to receptors, thus keeping potent drugs in the neighborhood of the effector sites and potentially lengthening the duration of effect. This phenomenon is probably what contributes to the slower onset time for cisatracurium than atracurium. However, for very short-acting drugs, the ideal ED₉₅ might be greater (0.5-1.0 mg/kg) because rapid metabolism in the plasma destroys some of the administered muscle relaxant before it reaches the neuromuscular junction. This phenomenon can explain the relatively slow onset time for mivacurium.

Plasma concentrations have only modest influence on onset time. Arterial plasma concentrations peak 25 to 35 seconds after administration, thus before onset of neuromuscular block. This paradox can be explained by assuming that the site of action, the neuromuscular junction, is represented by the effect compartment in which the concentration of the NMBD is directly related to the magnitude of neuromuscular blockade.^{116b} The rate constant for transfer into the effect compartment is similar for most intermediate duration action NMBDs and corresponds approximately to neuromuscular junction blood flow divided by neuromuscular junction/plasma partition coefficient. Whatever muscle relaxant, the limiting factor appears to be the time required for the drug to reach the neuromuscular junction, which in turn depends on cardiac output, the distance of the muscle (and neuromuscular junction) from the central circulation, and muscle blood flow. Therefore in most cases, the onset time will be dependent on blood flow to muscle. Under normal circumstances, muscle blood flow increases when cardiac output increases, with a direct relationship between speed of

onset and cardiac output. This may explain why infants and children have a faster onset of neuromuscular block, and elderly patients have a slower onset than younger individuals.

It is obvious that the intensity of maximum blockade is affected directly by the administered dose. However, when the dose increases in the subparalyzing range (that is, when maximum blockade is between 0% and 100%), time to reach maximum effect is dose-independent. This is because the time to peak concentration at the effect compartment is independent of the dose. When the administered dose, however, is sufficient to effect complete disappearance of neuromuscular response, time to maximum blockade becomes dose-dependent.

DURATION OF ACTION

Although it is commonly believed that the rate of decline of NMBD plasma concentrations during recovery from neuromuscular blockade determines the duration of action and the rate of recovery, further explanations are needed. It has been suggested that muscle blood flow is, to a certain extent, a limiting factor in the termination of action. For long-acting NMBDs, the dominant effect for the recovery from neuromuscular blockade is the rate of decrease of plasma concentration because there is pseudo-equilibrium between concentrations at the neuromuscular junction and plasma. Therefore changing blood flow will not affect the duration of action. For intermediate duration of action NMBD, after a single bolus dose, plasma concentrations decrease at a rate that differs slightly from the equilibrium half-life with muscle. It can induce a significant concentration gradient between neuromuscular junction and plasma during recovery, but provided that recovery rate is constant, the ratio of concentrations between the neuromuscular junction and plasma will remain relatively constant.

The most important factor is that the rate of decline of plasma concentration during recovery is not always related to the NMBD terminal half-life because after initial administration, plasma concentrations will decrease because of redistribution. It is only when redistribution will be complete that the decrease in plasma concentrations will be dependent on the terminal half-life and will decrease more slowly. For long-acting NMBD such as pancuronium, the recovery time will take place during the terminal half-life. In this situation the duration of action will be dependent on the rate of decrease of plasma concentrations. This is different for intermediate duration of action NMBDs. The terminal half-life of atracurium is around 20 minutes, whereas the elimination half-lives of both vecuronium and rocuronium are between 60 and 120 minutes. Although such differences can be observed, the duration of action and recovery from neuromuscular block of these three drugs are very similar. These apparent discrepancies can be explained by the fact that the distribution phase is the most important factor and extends for a much longer period than for long-acting NMBDs.^{116c} If their duration of action and recovery rates are almost identical, it is due to the decrease of plasma concentrations to levels compatible with recovery during the redistribution phase.

CLINICAL MANAGEMENT

The main goal of neuromuscular blockade during induction of anesthesia includes paralysis of the vocal cords and muscles of the jaw to facilitate endotracheal intubation. Relaxation of the respiratory muscles, particularly the diaphragm, allows controlled ventilation. Paralysis of the abdominal muscles and the diaphragm is often required intraoperatively, particularly during abdominal, robotic, or laparoscopic surgery. During recovery from neuromuscular block, restoration of complete neuromuscular strength is essential to ensure adequate spontaneous ventilation with normal regulation of breathing during hypoxia and the patency of the musculature of the upper airway with maintained airway protection. The choice of the initial dose of NMBD, timing of readministration of NMBD, timing of administration of anticholinesterase, and interpretation of monitoring require an understanding of the varying sensitivities of different muscle groups to NMBDs.

Although the practice of administering an NMBD to facilitate tracheal intubation may be routine, it has been suggested that the combination of propofol with a rapid-acting opioid may provide good to excellent intubating conditions in most patients. However, relatively large doses of opioids are required to obtain satisfactory intubating conditions. Mencke and coworkers demonstrated that adding atracurium to a propofol-fentanyl induction regimen significantly improved the quality of intubating conditions and decreased the frequency of vocal cord lesions following intubation from 42% to 8%.¹¹⁷ The rate of postoperative hoarseness was also significantly decreased to 16% from 44%.¹¹⁷ Combes and associates confirmed that the use of NMBD for tracheal intubation decreased the incidence of adverse postoperative upper airway symptoms, resulted in better intubating conditions, and also reduced the rate of adverse hemodynamic effects caused by deeper levels of anesthesia.¹¹⁸ Patients intubated without an NMBD had three to four times more Cormack scores of 3 to 4, and difficult intubation was more common (12% vs. 1%). In a cohort of more than 100,000 patients, Lundstrom and colleagues demonstrated that avoidance of NMBD was associated with more difficult tracheal intubation conditions compared with NMBD use, with an odds ratio of 1.5.^{118a} A recent Cochrane review supported the use of an NMBD (vs. avoidance of NMBD) in order to create the best intubating conditions.^{118b}

Several alternative approaches are available to enhance surgical relaxation when administration of additional NMBDs may be inappropriate. These options include increasing the depth of general anesthesia with a drug such as a volatile anesthetic or propofol, administering lidocaine, using regional anesthesia, positioning the patient properly on the operating table, and appropriately adjusting the depth of neuromuscular blockade. The choice of one or several of these options is determined by the estimated remaining duration of surgery, the anesthetic technique, and the surgical maneuver required. Importantly, the single best (and only) method to ensure appropriate dosing and timing of additional NMBD is assessment of the depth of neuromuscular block by objective (quantitative) means.^{118c}

It is important to keep these options in mind to avoid relying on only neuromuscular blockade to achieve a desired degree of surgical relaxation.

Varying Sensitivities of Different Muscle Groups

The sensitivity of the neuromuscular junctions to the effects of neuromuscular relaxants among various muscle groups varies greatly. Paton and Zaimis^{118d} demonstrated in 1951 that some of the muscles of respiration, such as the diaphragm, were more resistant to curare than others. The dose of nondepolarizing NMBDs needed to block the diaphragm is 1.5 to 2 times that of the adductor pollicis. Thus complete paralysis of the diaphragm is not expected with doses of NMBDs used to block neuromuscular transmission at the adductor pollicis.¹¹⁹ Similarly, the laryngeal adductor muscles are more resistant to nondepolarizing NMBDs than the more peripheral muscles such as the adductor pollicis,¹²⁰ at which all dosing recommendations for NMBDs and their antagonists have been made. The sparing effect of NMBDs on the laryngeal adductor muscles has been documented with vecuronium, rocuronium, cisatracurium, and mivacurium.¹²⁰⁻¹²² Plaud and colleagues studied the pharmacokinetic-pharmacodynamic relationship of NMBDs at the adductor pollicis and the laryngeal adductors.¹²³ These investigators found that the concentration in the effect compartment producing 50% of the maximum block was significantly greater at the laryngeal adductor muscles (1.5 µg/mL) than that at the adductor pollicis muscle (0.8 µg/mL). Convincing evidence indicates that the EC₅₀ for almost all drugs is 50% to 100% higher at the diaphragm or larynx than it is at the adductor pollicis. These differences may be caused by any of several factors. Waud and Waud found that following curare administration, neuromuscular transmission occurs when approximately 18% of the receptors are free at the diaphragm, whereas it does not occur at the peripheral muscles unless 29% of receptors are free.¹²⁴ The reason may be higher receptor density, greater release of acetylcholine, or less acetylcholinesterase activity. The lower density of acetylcholine receptors in slow muscle fibers, such as found in the peripheral muscles, explains, in part, the lower margin of safety for neuromuscular transmission when compared with that in the faster muscle fibers in the laryngeal adductors. Muscle sensitivity to succinylcholine is different from that of other NMBDs. Succinylcholine is the only muscle relaxant that, at equipotent doses, causes greater neuromuscular block at the vocal cords than at the adductor pollicis. Some data suggest that in contrast to nondepolarizing NMBDs, succinylcholine is more effective in blocking the muscles composed of primarily fast-contracting fibers.¹²⁵

In spite of the relative resistance to NMBDs, the onset of neuromuscular block is significantly faster at the diaphragm and the laryngeal adductors than at the adductor pollicis. Fisher and associates postulated that more rapid equilibration (shorter effect site equilibration half-life [$t_{1/2}k_{e0}$]) of the NMBD between plasma¹²⁶ and the effect compartment at these more centrally located muscles was the explanation for this observation. The accelerated rate of equilibrium probably represents little more than differences in regional blood flow. Therefore muscle blood flow (i.e., the rate of drug delivery to the tissue), rather than a drug's intrinsic potency, may be more important in determining the onset and offset time of nondepolarizing NMBDs. Greater blood flow per gram of muscle at the diaphragm or larynx results in delivery of a higher peak plasma concentration of drug in the brief period of time

TABLE 27.4 Guide to Nondepolarizing Relaxant Dosage (mg/kg) Under Different Anesthetic Techniques

DOSAGE FOR RELAXATION					
	ED ₉₅ Under N ₂ O/O ₂	Dose for Intubation	Supplemental Dose after Intubation	N ₂ O	Anesthetic Vapors*
LONG-ACTING					
Pancuronium	0.07	0.08-0.12	0.02	0.05	0.03
<i>d</i> -Tubocurarine	0.5	0.5-0.6	0.1	0.3	0.15
INTERMEDIATE-ACTING					
Vecuronium	0.05	0.1-0.2	0.02	0.05	0.03
Atracurium	0.23	0.5-0.6	0.1	0.3	0.15
Cisatracurium	0.05	0.15-0.2	0.02	0.05	0.04
Rocuronium	0.3	0.6-1.0	0.1	0.3	0.15
SHORT-ACTING					
Mivacurium	0.08	0.2-0.25	0.05	0.1	0.08
Continuous Infusion Dosage (µg/kg/min) Required to Maintain 90%-95% Twitch Inhibition Under N₂O/O₂ With Intravenous Agents					
Mivacurium	3-15				
Atracurium	4-12				
Cisatracurium	1-2				
Vecuronium	0.8-1.0				
Rocuronium	9-12				

*The potentiation of nondepolarizing relaxants by different anesthetic vapors has been reported to vary from 20% to 50%. More recent data suggest, however, that this variation may be much less, particularly in the case of the intermediate- and short-acting relaxants. Therefore for the sake of simplicity, this table assumes a potentiation of 40% in the case of all volatile anesthetics.

Suggested dosages provide good intubating conditions under light anesthesia. Satisfactory abdominal relaxation may be achieved at dosages listed after intubation without a relaxant or with succinylcholine. This table is intended as a general guide to dosage. Individual relaxant requirement should be confirmed with a neuromuscular monitor.

ED₉₅, Dose causing on average 95% suppression of neuromuscular response; N₂O, nitrous oxide; O₂, oxygen.

before rapid redistribution occurs. Plaud and colleagues confirmed this hypothesis by demonstrating a faster transfer rate constant (i.e., $t_{1/2}k_{e0}$) at the laryngeal adductors (2.7 minutes) than at the adductor pollicis (4.4 minutes).¹²³ Greater resistance to neuromuscular blockade accounts for the faster recovery of the respiratory muscles and the muscles of the abdominal wall than at the adductor pollicis muscle. Recovery occurs more rapidly because blood concentration of the NMBD must decrease more in the muscles of respiration than in the adductor pollicis for recovery of neuromuscular function to begin.

In contrast, the muscles of the upper airway are particularly sensitive to the effects of muscle relaxants. The masseter is 15% more sensitive to nondepolarizing NMBDs than is the adductor pollicis.¹²⁷ Significant weakness of the muscles of the upper airway may exist even when strength at the adductor pollicis has recovered almost to baseline values. A TOF ratio less than 0.9 at the adductor pollicis (with a calibrated neuromuscular monitor) is associated with impaired pharyngeal function, reduced resting tone in the upper esophageal sphincter muscle, and decreased coordination of the muscles involved in swallowing, all of which cause an increased incidence of misdirected swallows, or aspiration.¹²⁸ Because of the resistance of the diaphragm and laryngeal muscles to neuromuscular block, patients may be weak in pharyngeal muscle groups while being able to breathe as long as an endotracheal tube is in place. Once the trachea is extubated, however, patients may not be able to maintain a patent airway or protect

their airway.¹²⁹ This is likely the reason that patients with a TOF less than 0.9 in the postanesthesia care unit (PACU) are more likely to develop critical respiratory events than those whose TOF ratio is 0.9 or greater.^{129a} Some investigators^{129b} have demonstrated that among patients who received NMBD, those who did not receive reversal were more than twice as likely to develop pneumonia after surgery.

The increase in ventilation during hypoxia is mainly governed by afferent neuronal input from peripheral chemoreceptors of the carotid body. Acetylcholine is involved in the transmission of afferent neuronal activity from the carotid body to the central nervous system (CNS). Eriksson and associates have shown that partial neuromuscular block (TOF ratio of 0.7) reduces specifically the ventilatory responses to isocapnic hypoxia without altering the response to hypercapnia. The ventilatory response to hypoxia returns to control values after recovery of a TOF ratio to above 0.9.^{129c} The mechanism behind this interaction seems to be a spontaneous, reversible depression of carotid body chemoreceptor activity during hypoxia.^{129d}

DOSAGE

General Dosage Guidelines

Proper selection of the dose of nondepolarizing NMBD and quantitative monitoring are required to ensure that the desired effect is achieved without overdose of the relaxant (Tables 27.4 and 27.5).

TABLE 27.5 Pharmacodynamic Effects of Succinylcholine and Nondepolarizing Neuromuscular Blockers

Anesthesia		Intubating Dose (mg/kg)	Approximate ED ₉₅ Multiples	Maximum Block (%)	Time to Maximum Block (min)	Clinical Duration* (min)	References
Succinylcholine	Opioids or halothane	0.5	1.7	100	—	6.7	372
Succinylcholine	Desflurane	0.6	2	100	1.4	7.6	373
Succinylcholine	Opioids or halothane	1.0	2	100	—	11.3	372
Succinylcholine	Desflurane	1.0	3	100	1.2	9.3	373
Succinylcholine	Opioids	1.0	3	—	1.1	8	374
Succinylcholine	Opioids	1.0	3	—	1.1	9	375
Succinylcholine	Isoflurane	1.0	3	100	0.8	9	140
STEROIDAL COMPOUNDS							
Rocuronium	Opioids	0.6	2	100	1.7	36	142
Rocuronium	Isoflurane	0.6	2	100	1.5	37	140
Rocuronium	Isoflurane	0.9	3	100	1.3	53	140
Rocuronium	Isoflurane	1.2	4	100	0.9	73	140
Vecuronium	Isoflurane	0.1	2	100	2.4	41	140
Vecuronium	Opioids	0.1	2	100	2.4	44	376
Pancuronium	Opioids	0.08	1.3	100	2.9	86	148, 377
Pancuronium	Opioids	0.1	1.7	99	4	100	378
BENZYLISOQUINOLINIUM COMPOUNDS[†]							
Mivacurium	Opioids	0.15	2	100	3.3	16.8	9
Mivacurium	Opioids	0.15	2	100	3	14.5	142
Mivacurium	Halothane	0.15	2	100	2.8	18.6	379
Mivacurium	Opioids	0.2	2.6	100	2.5	19.7	9
Mivacurium	Opioids	0.25	3.3	100	2.3	20.3	9
Mivacurium	Opioids	0.25	3.3	—	2.1	21	375
Atracurium	Opioids	0.5	2	100	3.2	46	107
Cisatracurium	Opioids	0.1	2	99	7.7	46	323
Cisatracurium	Opioids	0.1	2	100	5.2	45	107
Cisatracurium	Opioids	0.2	4	100	2.7	68	107
Cisatracurium	Opioids	0.4	8	100	1.9	91	107
d-Tubocurarine	Opioids	0.6	1.2	97	5.7	81	378

*Time from injection of the intubating dose to recovery of twitch to 25% of control.

[†]For atracurium and mivacurium, slower injection (30 seconds) is recommended to minimize circulatory effects.

ED₉₅, Dose causing on average 95% suppression of neuromuscular response.

The intensity of maximum blockade is directly affected by dose. If a small dose of NMBD is administered, neuromuscular block may not occur because the amount administered is inadequate to overcome the margin of safety at the neuromuscular junction. When doses lower than those required to cause 100% neuromuscular blockade are administered, the time required to reach maximum effect is a function of the NMBD and blood flow to the muscles. It is independent of the dose administered. However, if the administered dose is high enough to cause 100% neuromuscular blockade, the time required for maximum block will depend on the dose of NMBD administered. Larger doses will, up to a certain point, produce

a faster onset of effect.¹³⁰ Increasing the dose of NMBD beyond that point will not further decrease the time to onset of maximal effect, and may significantly prolong the total duration of neuromuscular blockade, contributing to residual postoperative paralysis.

In addition to a general knowledge of the pharmacodynamics and pharmacokinetics of NMBDs and understanding of the guidelines for dosing, optimal practice requires that dosing be adjusted to account for variability in individual patients' responses to NMBDs. This adjustment cannot be made without using a quantitative (objective) monitor of neuromuscular blockade any time that an NMBD is administered to a patient. Overdosage must be avoided for several

TABLE 27.6 Suggested Definitions of the Depth of Neuromuscular Block Based on Subjective and Objective Criteria

Depth of Block	Posttetanic Count	Train-of-Four Count	Subjective Train-of-Four Ratio	Measured Train-of-Four Ratio
Intense (profound) block	0	0	0	0
Deep block	≥1	0	0	0
Moderate block	NA	1-3	0	0
Light (shallow) block	NA	4	Fade present	0.1-0.4
Minimal block (near recovery)	NA	4	No fade	>0.4 but <0.90
Full recovery (normal function)	NA	4	No fade	≥0.90-1.0

NA, Not applicable.

From Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring. Challenges and opportunities. *Anesthesiology*. 2017;126:173, see Table 1.

reasons: to limit the duration of drug effect so that it matches the anticipated length of surgery; to avoid unwanted cardiovascular side effects associated with large NMBD doses; and to minimize residual neuromuscular block postoperatively.

Initial and Maintenance Dosage

The initial dose of NMBD is determined by the reason for administration. Traditionally, doses used to facilitate tracheal intubation are twice the ED₉₅ (see Table 27.4). If, however, the trachea has been intubated without the use of an NMBD and the purpose in administering an NMBD is to produce surgical relaxation, a dose that is slightly less than the ED₉₅ (see Table 27.5) may be sufficient in most surgical settings. Administration of NMBDs solely for surgical relaxation does not prevent vocal cord injury and postoperative hoarseness caused by intubation without NMBD. Additionally, ensuring maximal neuromuscular block by using quantitative means (e.g., a TOF count of zero) rather than being guided by clinical judgment will result in less hemodynamic instability during laryngoscopy and better intubating conditions.^{130a} Administering a smaller initial dose may be sufficient in the presence of any of the potent inhalational anesthetics (see the later section on drug interactions), but the dosing should always be guided by quantitative monitoring.

To avoid prolonged residual paralysis, inadequate antagonism of residual blockade, or both, the main goal in dosing NMBDs should be to use the lowest possible dose that provides adequate relaxation for surgery. Moreover, clinical management of individual patients should be guided by monitoring of the neuromuscular block, ideally with an objective neuromuscular monitoring technique, to allow safe intraoperative administration of the NMBD and its antagonism by neostigmine or sugammadex (see also Chapter 43, Neuromuscular Monitoring).

In an adequately anesthetized and monitored patient, little reason exists to abolish the TOF responses to peripheral nerve stimulation completely. However, if deep levels of block are required to maintain paralysis of the diaphragm and the abdominal wall muscles, response of the adductor pollicis to stimulation of the ulnar nerve may disappear. In this case, monitoring the depth of neuromuscular block can be accomplished using the posttetanic count (PTC) at the adductor pollicis or TOF ratio at the corrugator supercilii.^{131,132} Supplemental (maintenance) doses of NMBDs should be approximately one tenth (in case of long-acting NMBDs) to one fourth (in the case of intermediate- and

short-acting NMBDs) the initial dose and should not be given until quantitative evidence of beginning recovery from the previous dose is present.

Relaxation can be maintained by continuous infusion of intermediate- and short-acting drugs. This approach is useful in maintaining a stable depth of neuromuscular blockade and allows adjustment of the depth of relaxation according to surgical needs. The depth of neuromuscular blockade maintained is moderate, if possible, to ensure complete spontaneous recovery of neuromuscular function at the end of a surgical procedure or prompt antagonism of residual effects. Suggested definitions of the depth of neuromuscular block are listed in Table 27.6.^{132a} Table 27.4 lists the approximate dose ranges that are typically required during infusions to maintain 90% to 95% blockade of the twitch (one twitch visible on TOF stimulation) during a nitrous oxide–oxygen anesthetic supplemented with intravenous anesthetics. Infusion dosage is usually decreased by 30% to 50% in the presence of potent volatile anesthetics.

NEUROMUSCULAR BLOCKING DRUGS AND TRACHEAL INTUBATION

Rapid onset of neuromuscular blockade is one of the requirements for securing an airway promptly. It is affected by several factors, including muscle blood flow, rate of delivery of the drug to the neuromuscular junction, receptor affinity, plasma clearance of the NMBD, and the mechanism of neuromuscular blockade (depolarizing vs. nondepolarizing)^{96,116a,133} (see Table 27.5 and Fig. 27.9). Onset time decreases as ED₅₀ increases. When a potent NMBD is administered, fewer molecules are administered than in the case of an equipotent dose of a less potent drug. Because of this lower concentration gradient, more time is required for sufficient molecules of a potent drug to be delivered to the neuromuscular junction. Thus onset time is longer. This concept was verified by Kopman and colleagues, who demonstrated that, when giving equipotent doses of gallamine, dTc, and pancuronium, onset time was slower with the more potent pancuronium and faster with the less potent gallamine. Except for atracurium,¹³⁵ the molar potency (the ED₅₀ or ED₉₅ expressed as μ M/kg) is highly predictive of a drug's initial rate of onset of effect (at the adductor pollicis muscle).¹³³ A drug's measured molar potency is the end result of many contributing factors: the drug's intrinsic potency (the CE₅₀, which is the biophase

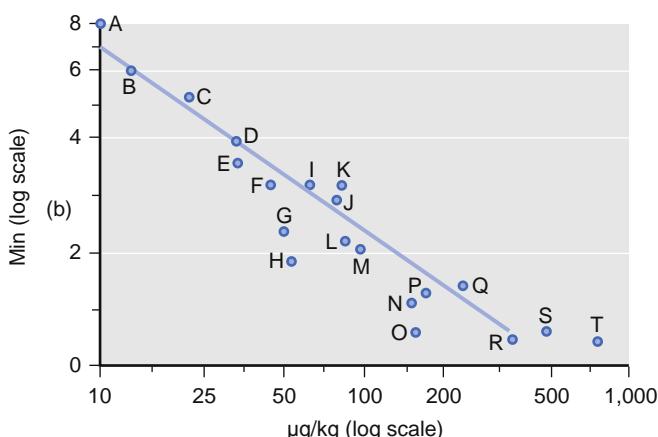


Fig. 27.9 Linear regression of onset of neuromuscular blockade (ordinate) versus potency of a series of steroid relaxants studied in the cat model by Bowman and associates.⁹⁶ The data show that onset may be increased in compounds of low potency and encouraged the eventual development of rocuronium and rapacuronium (ORG 9487). A, Pipercuronium; B, ORG 8788; C, pancuronium; D, vecuronium; E-M and O-T, ORG 9274, 9360, 9273, 8715, 6502, 9216, 7931, 8730, 7617, 9275, 6368, 8764, 9382, and 7684 (respectively); N, RGH-4201. Data from Reference 96.

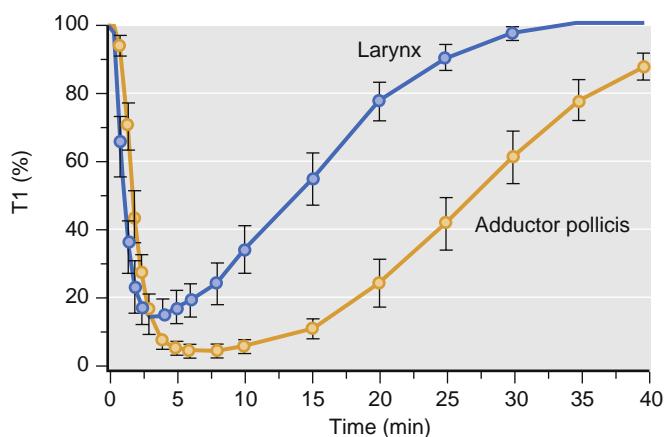


Fig. 27.11 Evolution of neuromuscular blockade in the larynx and thumb (adductor pollicis) after a 0.07 mg/kg dose of vecuronium. Onset and recovery from blockade occur more rapidly in the larynx. T1, First twitch of train-of-four. (From Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. *Anesthesiology*. 1991;74:833-837.)

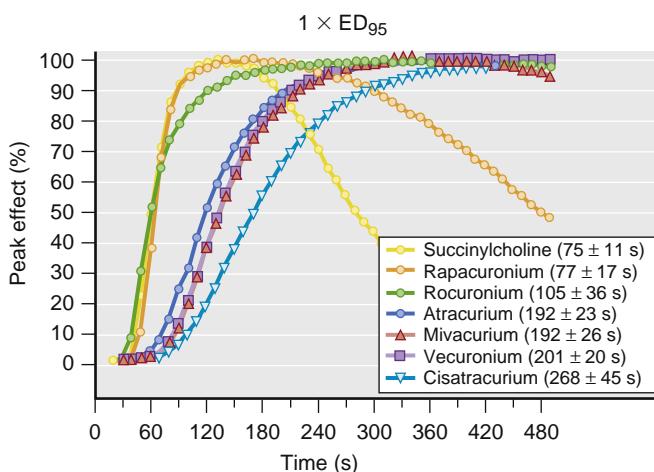


Fig. 27.10 Percentages of peak effect after a dose causing on average 95% suppression of neuromuscular response (ED_{95}) of succinylcholine, rocuronium, rapacuronium, vecuronium, atracurium, mivacurium, and cisatracurium at the adductor pollicis muscle. Times (mean \pm standard deviation) in seconds to 95% of peak effect are shown in parentheses. (Data from references 114, 133, and 135.)

concentration resulting in 50% twitch depression), the rate of equilibration between plasma and biophase (k_{e0}), the initial rate of plasma clearance, and probably other factors as well.¹³⁶ Notably, rocuronium has a molar potency (ED_{95}) of 0.54 μ M/kg, which is approximately 13% that of vecuronium and only 9% that of cisatracurium; this finding illustrates the expected faster onset of rocuronium at the adductor pollicis muscle, as opposed to vecuronium and cisatracurium. Donati and Meistelman proposed a model to explain this inverse potency-onset relationship.^{116a}

The times to 95% blockade at the adductor pollicis after administration of the ED_{95} dose of succinylcholine, rocuronium, vecuronium, atracurium, mivacurium, and cisatracurium are shown in Fig. 27.10.^{114,133,135} The illustration shows that the most potent compound, cisatracurium,

has the slowest onset, and the least potent compound, rocuronium, has the most rapid onset.^{114,133,135} Bevan also proposed that rapid plasma clearance is associated with a rapid onset of action.¹³⁷ The fast onset of succinylcholine's action is related to its rapid metabolism and plasma clearance.

The onset of neuromuscular blockade is much faster in the muscles that are relevant to obtaining optimal intubating conditions (laryngeal adductors, diaphragm, and masseter) than in the muscle that is typically monitored (adductor pollicis) (Fig. 27.11).¹²¹ Thus neuromuscular blockade develops faster, has a shorter maximum depth and duration of effect, and recovers more quickly in these central muscles (Table 27.7).^{120-122,138,139}

Paralysis following intravenous administration does not occur instantaneously even with large doses of muscle relaxants. Onset of blockade occurs 1 to 2 minutes earlier in the laryngeal muscles than at the adductor pollicis after administration of nondepolarizing NMBDs. The pattern of blockade (onset, depth, and speed of recovery) in the corrugator supercili muscle is similar to that in the larynx,¹¹⁹ the diaphragm, and the muscles of the abdominal wall. By monitoring the onset of neuromuscular blockade at the corrugator supercili, one can predict the quality of tracheal intubating conditions. Good to excellent intubating conditions are observed in more than 90% of patients after disappearance of the TOF responses (a TOF count of zero) at the corrugator supercili.¹³¹ The onset of maximal blockade in the larynx also corresponds with the point at which the adductor pollicis muscle begins to show palpable evidence of weakening.

Rapid Tracheal Intubation

Rocuronium in high dose (0.9-1.2 mg/kg) or succinylcholine 1.5 mg/kg can be used interchangeably for rapid tracheal intubation because they provide adequate intubating conditions within 60 to 90 seconds. Hence if succinylcholine is considered undesirable or contraindicated, high doses of rocuronium can be administered.¹⁴⁰ The onset of action of other nondepolarizing NMBDs can be accelerated by administering a priming dose of the NMBD¹⁴¹ or

TABLE 27.7 Time Course of Action and Peak Effect Data at the Laryngeal Adductors and Adductor Pollicis

Dose (mg/kg)	Anesthesia	LARYNGEAL ADDUCTORS			ADDUCTOR POLLICIS			Reference
		Onset Time (s)	Maximum Block (% Depression)	Clinical Duration (min)	Onset Time (s)	Maximum block (% Depression)	Clinical Duration (min)	
Succinylcholine, 1.0	Propofol-fentanyl	34 ± 12	100 ± 0	4.3 ± 1.6	56 ± 15	100 ± 0	8 ± 2	122
Rocuronium, 0.25	Propofol-fentanyl	96 ± 6	37 ± 8	—	180 ± 18	69 ± 8	—	121
Rocuronium, 0.4	Propofol-fentanyl	92 ± 29	70 ± 15	—	155 ± 40	99 ± 3	24 ± 7	122
Rocuronium, 0.5	Propofol-fentanyl	84 ± 6	77 ± 5	8 ± 3	144 ± 12	98 ± 1	22 ± 3	121
Vecuronium, 0.04	Propofol-fentanyl	198 ± 6	55 ± 8	—	342 ± 12	89 ± 3	11 ± 2	120
Vecuronium, 0.07	Propofol-fentanyl	198 ± 12	88 ± 4	9 ± 2	342 ± 18	98 ± 1	22 ± 2	120
Mivacurium, 0.14	Propofol-alfentanil	137 ± 20	90 ± 7	5.7 ± 2.1	201 ± 59	99 ± 1	16.2 ± 4.6	138
Mivacurium, 0.2	Propofol-alfentanil	89 ± 26	99 ± 4	10.4 ± 1.5	202 ± 45	99 ± 2	20.5 ± 3.9	139

Clinical duration is the time until the first twitch of train-of-four (T1) has recovered to 25% of its control value. Mean and standard deviation^{122,138,139} or standard error of the mean.^{120,121}

by using combinations of NMBDs.¹⁴² Although combinations of mivacurium and rocuronium can achieve rapid onset without undue prolongation of action and without undesirable side effects,¹⁴² combinations of compounds of different structures may result in a marked prolongation of neuromuscular blockade. Additionally, combining different NMBDs may not consistently result in a rapid onset of neuromuscular block.

Timing Technique. This technique entails administration of a single intubating dose (two times the ED₉₅) of a rapid-onset NMBD such as rocuronium to an awake patient, followed by the administration of the anesthetic induction agent at the onset of clinical signs of weakness such as ptosis or loss of ability to maintain the raised arm. Using this technique, 0.6 mg/kg rocuronium can provide good to excellent intubating conditions within 45 seconds after induction of anesthesia.^{142a} Because of the potential for unpleasant symptoms and recall associated with neuromuscular paralysis in awake patients, this technique is no longer used clinically.

Priming Technique. Since the introduction of rocuronium into clinical practice, the use of priming technique has almost disappeared. When priming, a small, subparalyzing dose of the nondepolarizer ($\approx 20\%$ of the ED₉₅ or $\approx 10\%$ of the intubating dose) is administered 2 to 4 minutes before the intubating dose of the compound.¹⁴¹ This procedure accelerates the onset of blockade for most nondepolarizing NMBDs only by 30 to 60 seconds, thereby indicating that intubation can be performed within 90 seconds of the second dose. However, the intubating conditions that occur after priming are only marginally improved and do not match those that occur after succinylcholine. The size of the priming dose is limited by its effects on the awake patient,

since the anesthetic induction agent is administered only immediately prior to the intubating dose of NMBD. Further, priming doses can cause subtle degrees of neuromuscular blockade and increase the patient's discomfort, the risks of aspiration, and difficulty swallowing and breathing.¹⁴³ This technique is contraindicated in patients with abnormal airway anatomy or increased sensitivity to NMBDs such as patients with myasthenia gravis or those taking magnesium.

Large-Dose Regimen for Rapid Tracheal Intubation. Large doses of NMBDs are usually recommended when intubation must be accomplished in less than 90 seconds. High-dose regimens are associated with considerably prolonged duration of action and potentially increased cardiovascular side effects, however (see Table 27.5).^{140,144} Increasing the dosage of rocuronium from 0.6 mg/kg (twice the ED₉₅) to 1.2 mg/kg (four times the ED₉₅) shortens the onset time of complete neuromuscular block from 89 to 55 seconds but essentially doubles the clinical duration of action of the compound (the recovery of the first twitch of TOF [T1] to 25% of baseline values) from 37 to 73 minutes.¹⁴⁰

Small-Dose Relaxants for Tracheal Intubation. Small doses of NMBDs can be used for routine tracheal intubation. The use of smaller doses of NMBDs has the following two possible advantages: (1) it shortens the time to recovery from neuromuscular blockade, and (2) it reduces the requirement for anticholinesterase drugs. Rocuronium has the shortest onset time of all the nondepolarizing NMBDs currently available.^{121,122} The maximal effect of either 0.25 or 0.5 mg/kg of rocuronium at the laryngeal muscles occurs after 1.5 minutes.¹²¹ This interval is shorter than the 3.3 minutes reported after administration of equipotent

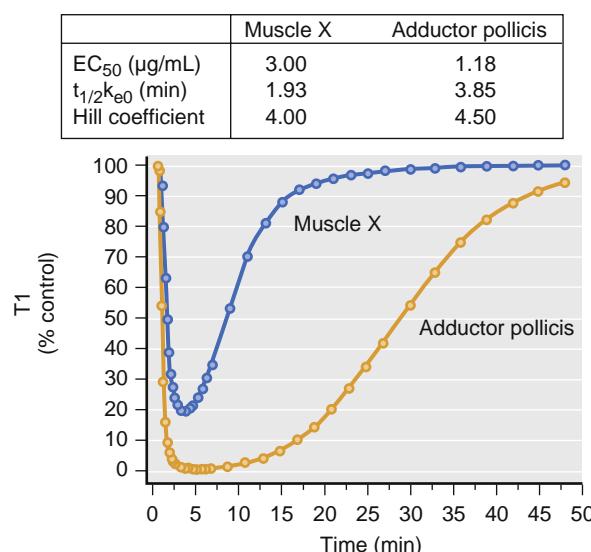


Fig. 27.12 A computer simulation based on Sheiner's model¹¹⁵ and data reported by Wierda and colleagues. The dose causing on average 95% suppression of neuromuscular response (ED₉₅) of rocuronium at the adductor pollicis from this model is 0.33 mg/kg. Rocuronium, 0.45 mg/kg is given as a bolus at time zero. Muscle X represents a muscle (e.g., the diaphragm or the laryngeal adductors) that is less sensitive to the effects of nondepolarizing relaxants than the adductor pollicis but has greater blood flow. In this example, the concentration of rocuronium producing 50% block (EC₅₀) of muscle X is 2.5 times that of the adductor pollicis, but the half-life of transport between the plasma and effect compartment ($t_{1/2}k_{el}$) of muscle X is only half as long. The rapid equilibration between plasma concentrations of rocuronium and muscle X results in the more rapid onset of blockade of muscle X than of the adductor pollicis. The greater EC₅₀ at muscle X explains the faster recovery of this muscle than of the adductor pollicis from neuromuscular blockade. Lower blood concentrations of rocuronium must be achieved at the adductor pollicis than at muscle X before recovery begins. T₁, First twitch of train-of-four. (From Naguib M, Kopman AF. Low dose rocuronium for tracheal intubation. *Middle East J Anesthesiol*. 2003;17:193–204, with permission from the *Middle East Journal of Anesthesiology*.)

doses of vecuronium (0.04 or 0.07 mg/kg),¹²⁰ and it is only slightly longer than the 0.9 minutes reported after 0.25 or 0.5 mg/kg of succinylcholine (see Table 27.7).¹²⁵

With a better understanding of the multiple factors that contribute to satisfactory conditions for intubation, it is now possible to administer NMBDs thoughtfully in this fashion. Intubating conditions are related more closely to the degree of neuromuscular blockade of the laryngeal adductor muscles than to the degree of blockade typically monitored at the adductor pollicis. Fig. 27.12 demonstrates this principle.¹³⁶ In the presence of an adequate depth of anesthesia, complete blockade at the larynx or diaphragm, or both, may not be a prerequisite for satisfactory intubating conditions. Kopman and colleagues noted that 0.5 mg/kg of rocuronium (1.5 times the ED₉₅) provided satisfactory conditions for intubation in patients anesthetized with 12.5 µg/kg of alfentanil and 2.0 mg/kg of propofol if laryngoscopy was delayed for 75 seconds after drug administration.¹⁴⁵ It was furthermore estimated that 1.5 times the ED₉₅ of rocuronium would produce at least 95% blockade in 98% of the population.¹⁴⁵ A similar or lower multiple of rocuronium's ED₉₅ was shown to have a faster onset and shorter duration of action than those of atracurium¹⁴⁶ or cisatracurium.¹⁰⁹ In most patients receiving 15 µg/kg of

alfentanil followed by 2.0 mg/kg of propofol and 0.45 mg/kg of rocuronium, good to excellent conditions for intubation are present 75 to 90 seconds after the completion of drug administration.

METABOLISM AND ELIMINATION

The specific pathways of the metabolism (biotransformation) and elimination of NMBDs are summarized in Table 27.8. Of the nondepolarizing NMBDs listed, pancuronium, pipercuronium, vecuronium, atracurium, cisatracurium, and mivacurium are the only drugs that are metabolized or degraded. Nearly all nondepolarizing NMBD molecules contain ester linkages, acetyl ester groups, and hydroxy or methoxy groups. These substitutions, especially the quaternary nitrogen groups, confer a high degree of water solubility with only slight lipid solubility. The hydrophilic nature of relaxant molecules enables easy elimination in the urine through glomerular filtration, with no tubular resorption or secretion. Therefore all nondepolarizing NMBDs show elimination of the parent molecule in the urine as the basic route of elimination; those with a long duration of action thus have a clearance rate that is limited by the glomerular filtration rate (1-2 mL/kg/min).

Steroidal Compounds

Long-Acting Neuromuscular Blocking Drugs. Pancuronium is cleared largely by the kidney¹⁴⁷ and, to a limited extent, by hepatic uptake and elimination. A small amount (15%-20%) is deacetylated at the 3 position in the liver, but this makes a minimal contribution to the total clearance. Deacetylation also occurs at the 17 position, but to such a small extent as to be clinically irrelevant. The three known metabolites have been individually studied in anesthetized humans.¹⁴⁸ The 3-OH metabolite is the most potent of the three, being approximately half as potent as pancuronium, and is the only one present in detectable concentrations in the plasma. This metabolite has pharmacokinetics and duration of action similar to those of pancuronium.¹⁴⁸ The 3-OH metabolite is most likely excreted largely by the kidney.¹⁴⁸ The parent compound and the 3-OH metabolite are also cleared in small amounts through a minor liver pathway. The total clearance is delayed, and the duration of action is significantly lengthened, by severe disorders of renal or hepatic function.¹⁴⁹⁻¹⁵¹

Intermediate-Acting Neuromuscular Blockers.

Vecuronium, the 2-desmethyl derivative of pancuronium, is more lipid soluble than pancuronium because of the absence of the quaternizing methyl group at the 2 position. It undergoes two to three times more metabolism than pancuronium. Vecuronium is taken up into the liver by a carrier-mediated transport system,¹⁵² and it is then deacetylated at the 3 position by liver microsomes. Approximately 12% of vecuronium clearance is through conversion to 3-desacetylvecuronium,¹⁵³ and 30% to 40% of the drug is cleared in the bile as the parent compound.¹⁵⁴ Although the liver is the principal organ of elimination for vecuronium, the drug also undergoes significant (up to 25%) renal excretion, and this combined organ elimination gives it a clearance rate of 3 to 6 mL/kg/min.^{153,155}

TABLE 27.8 Metabolism and Elimination of Neuromuscular Blocking Drugs

Drug	Duration	Metabolism (%)	ELIMINATION		Metabolites
			Kidney (%)	Liver (%)	
Succinylcholine	Ultrashort	Butyrylcholinesterase (98%-99%)	<2%	None	Monoester (succinyl monocholine) and choline; the monoester is metabolized much more slowly than succinylcholine
Gantacurium	Ultrashort	Cysteine (fast) and ester hydrolysis (slow)	?	?	Inactive cysteine adduction product, chloroformate monoester, and alcohol
Mivacurium	Short	Butyrylcholinesterase (95%-99%)	<5%	None	Monoester and quaternary alcohol; the metabolites are inactive and most likely are not metabolized any further
(Metabolites eliminated in urine and bile)					
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60%-90%)	10%-40%	None	Laudanosine, acrylates, alcohols, and acids; although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible
(Metabolites eliminated in urine and bile)					
Cisatracurium	Intermediate	Hofmann elimination (77%)	Renal clearance is 16% of total		Laudanosine and acrylates; ester hydrolysis of the quaternary monoacrylate occurs secondarily; because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are 5-10 times lower than in the case of atracurium, thus making this a nonissue in practice
Vecuronium	Intermediate	Liver (30%-40%)	40%-50%	50%-60% ≈60%	The 3-OH metabolite accumulates, particularly in renal failure; it has ≈80% the potency of vecuronium and may be responsible for delayed recovery in ICU patients
(Metabolites excreted in urine and bile) ≈40%					
Rocuronium	Intermediate	None	10%-25%	>70%	None
Pancuronium	Long	Liver (10%-20%)	85%	15%	The 3-OH metabolite may accumulate, particularly in renal failure; it is approximately two thirds as potent as the parent compound
<i>d</i> -Tubocurarine	Long	None	80% (?)	20%	None

3-OH, 3-hydroxy; ?, unknown; CNS, central nervous system; ICU, intensive care unit.

The principal metabolite of vecuronium, 3-desacetylvecuronium, is a potent NMBD ($\approx 80\%$ of the potency of vecuronium). The metabolite, however, has slower plasma clearance and longer duration of action than vecuronium.¹⁵³ 3-Desacetylvecuronium has a clearance rate of 3.5 mL/kg/min, and renal clearance accounts for approximately one sixth of its elimination.¹⁵³ In patients with renal failure in the ICU, 3-desacetylvecuronium can accumulate and produce prolonged neuromuscular blockade.¹⁵⁶ Other putative metabolites are 17-desacetylvecuronium and 3,17-bisdesacetylvecuronium, neither of which occurs in clinically significant amounts.

Rocuronium is eliminated primarily by the liver, with a small fraction ($\approx 10\%$) eliminated in the urine.¹⁵⁷ It is taken up into the liver by a carrier-mediated active transport system.¹⁵⁸ The putative metabolite, 17-desacetylrocuronium, has low (5%-10%) neuromuscular blocking activity of the parent drug and it has not been detected in significant quantities. The elimination of rocuronium occurs predominately through its biliary excretion. The organic anion transporting peptide 1A2 (OATP1A2) mediates the hepatocellular uptake of a variety of drugs, including rocuronium. The peptide is encoded by the *SLCO1A2* gene and is expressed in the bile duct cells (cholangiocytes) of the liver.^{158a} Genetic polymorphism of the *SLCO1A2* gene has recently been reported, and was shown to reduce the clearance of rocuronium in patients undergoing elective surgeries.^{158a} This reduction in the biliary excretion may partially explain the marked prolongation in the duration of action of rocuronium in some patients.^{158b}

Benzylisoquinolinium Compounds

Short-Acting Neuromuscular Blocking Drugs. Mivacurium is hydrolyzed in the plasma by butyrylcholinesterase to a monoester and an amino alcohol,⁹ which are excreted in urine and bile. They have less than 1% of the neuromuscular blocking activity of the parent compound. Less than 5% of mivacurium is excreted in the urine as the parent compound.

Mivacurium consists of three stereoisomers, and the clearances of the two most pharmacologically active isomers, the *cis-trans* and *trans-trans*, are approximately 100 and 50 to 70 mL/kg/min, respectively.^{94,159,160} These two isomers show elimination half-lives of 2 to 3 minutes.⁹⁴ The third stereoisomer, the *cis-cis*, is present as only 4% to 8% of the mivacurium mixture and has less than 10% of the neuromuscular blocking potency of the other two isomers.⁹⁴ Consequently, even though it has a much longer elimination half-life (55 minutes) and lower clearance (≈ 4 mL/kg/min) than the two other isomers, it does not contribute significantly to the duration of action of mivacurium.⁹⁴ This rapid enzymatic clearance of mivacurium accounts for its short duration of action.^{9,94} When butyrylcholinesterase activity is significantly decreased, however, as in the rare patient who is homozygous for genetically atypical enzymes, the duration of action of mivacurium is prolonged for up to several hours.¹⁶¹⁻¹⁶⁴

CW 1759-50 is an ultrashort-acting nondepolarizing NMBD that was developed to minimize the histaminoid side effects associated with gantacurium. In laboratory animals, the ED₉₅ of CW 1759-50 is 0.03 mg/kg (cat) and 0.069 mg/kg (rhesus monkey). Its total duration of action

(spontaneous recovery) is approximately 8 minutes, and it is minimally prolonged (12 minutes) after administration of doses four times its ED₉₅.^{11a,11b} It can be antagonized rapidly (2 minutes) by L-cysteine. Its development for clinical use is undergoing.

Intermediate-Acting Neuromuscular Blocking Drugs. Atracurium is metabolized through two pathways: Hofmann elimination and nonspecific ester hydrolysis. Hofmann elimination is a purely chemical process that results in loss of the positive charges by molecular fragmentation to laudanosine (a tertiary amine) and a monoquaternary acrylate, compounds that are thought to have no neuromuscular and little or no cardiovascular activity of clinical relevance.¹⁶⁵

Because it undergoes Hofmann elimination, atracurium is relatively stable at pH 3.0 and 4°C and becomes unstable when it is injected into the bloodstream. Early observations of the breakdown of the drug in buffer and plasma showed faster degradation in plasma, a finding suggesting a possible enzymatic hydrolysis of the ester groups. Further evidence suggested that ester hydrolysis may be more important than originally realized in the breakdown of atracurium.¹⁶⁶ By using a pharmacokinetics analysis, Fisher and associates concluded that a significant amount of clearance of atracurium may be by routes other than ester hydrolysis and Hofmann elimination.¹⁶⁷ Thus it appears that atracurium's metabolism is complicated and may not be completely understood.¹⁶⁷

Laudanosine, a metabolite of atracurium, has CNS-stimulating properties. Because it crosses the blood-brain barrier, laudanosine was thought to cause excitement and seizure activity. However, plasma concentrations of this metabolite are very low, and adverse effects are unlikely to occur with atracurium (or cisatracurium) use in either the operating room or the ICU.

Atracurium is a mixture of 10 optical isomers. Cisatracurium is the 1R *cis*-1'R *cis* isomer of atracurium.⁹⁰ Like atracurium, cisatracurium is metabolized by Hofmann elimination to laudanosine and a monoquaternary acrylate.^{168,169} In contrast, however, no ester hydrolysis of the parent molecule occurs. Hofmann elimination accounts for 77% of the total clearance of 5 to 6 mL/kg/min. Twenty-three percent of the drug is cleared through organ-dependent means, and renal elimination accounts for 16% of this.¹⁶⁹ Because cisatracurium is approximately four or five times as potent as atracurium, approximately five times less laudanosine is produced, and, as with atracurium, accumulation of this metabolite is not thought to be of any consequence in clinical practice.

Long-Acting Neuromuscular Blocking Drugs. dTc has no active metabolism and the kidney is the major pathway of elimination, with approximately 50% of a dose eliminated through renal pathways. The liver is likely a secondary route of elimination.

Asymmetric Mixed-Onium Fumarates

Gantacurium and CW 002 are degraded by two chemical mechanisms, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product and (2) slower hydrolysis of the ester

TABLE 27.9 Approximate Autonomic Margins of Safety of Nondepolarizing Neuromuscular Blockers

Drugs	Vagus*	Sympathetic Ganglia*	Histamine Release†
BENZYLISOQUINOLINIUM COMPOUNDS			
Mivacurium	>50	>100	3.0
Atracurium	16	40	2.5
Cisatracurium	>50	>50	None
<i>d</i> -Tubocurarine	0.6	2.0	0.6
STEROIDAL COMPOUNDS			
Vecuronium	20	>250	None
Rocuronium	3.0-5.0	>10	None
Pancuronium	3.0	>250	None

*In cats.

†In human subjects.

Definition: number of multiples of the dose causing on average 95% suppression of neuromuscular response (ED₉₅) for neuromuscular blockade required to produce the autonomic side effect (ED₅₀).

bond to presumably inactive hydrolysis products (see Fig. 27.7).^{11,170} CW 1759-50 is degraded nonenzymatically by endogenous L-cysteine at physiological pH and temperature, which accounts for its ultrashort duration of action.

In summary, the only short-acting nondepolarizing NMBD, mivacurium, is cleared rapidly and almost exclusively by metabolism by butyrylcholinesterase, thus resulting in much greater plasma clearance than that of any other nondepolarizing NMBD.⁹ NMBDs of intermediate duration, such as vecuronium, rocuronium, atracurium, and cisatracurium, have clearance rates in the range of 3 to 6 mL/kg/min because of multiple pathways of degradation, metabolism, and/or elimination. Atracurium is cleared two to three times more rapidly than the long-acting drugs.¹⁷¹⁻¹⁷⁴ Similar clearance values have been obtained for rocuronium¹⁷⁵⁻¹⁷⁹ and cisatracurium.^{168,169,180} The long-acting NMBDs undergo minimal or no metabolism, and they are eliminated largely unchanged, mostly by renal excretion. Hepatic pathways are less important in their metabolism.

ADVERSE EFFECTS OF NEUROMUSCULAR BLOCKING DRUGS

NMBDs seem to play a prominent role in the incidence of adverse reactions that occur during anesthesia. The Committee on Safety of Medicines in the United Kingdom reported that 10.8% (218 of 2014) of adverse drug reactions and 7.3% of deaths (21 of 286) were attributable to the NMBDs.¹⁸¹

Autonomic Effects

While NMBDs have little penetration through the blood-brain barrier, they may interact with nicotinic and muscarinic cholinergic receptors within the peripheral nervous system, in particular the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junction.

Dose-response ratios comparing the neuromuscular blocking potencies of these drugs (the ED₉₅) with their potencies in blocking vagal (parasympathetic) or sympathetic

ganglionic transmission (the ED₅₀) can be constructed (Table 27.9). These ratios are termed the autonomic margin of safety of the relaxant in question. The higher the dose ratio, the lower is the likelihood of, or the greater the safety ratio for, the occurrence of the particular autonomic effect. The side effect is considered absent (none) in clinical practice if the safety ratio is greater than 5; it is weak or slight if the safety ratio is 3 or 4, moderate if 2 or 3, and strong or prominent if the ratio is 1 or less.

These autonomic responses are not reduced by slower injection of the muscle relaxant. They are dose related and additive over time if divided doses are given. If identical to the original dose, subsequent doses will produce a similar response (i.e., no tachyphylaxis will occur). This is not the case, however, when the side effect of histamine release is in question. Cardiovascular responses secondary to histamine release are decreased by slowing the injection rate, and the response undergoes rapid tachyphylaxis. The autonomic effects of NMBDs are summarized in Table 27.10.

Histamine Release. Quaternary ammonium compounds (e.g., NMBDs) are generally weaker histamine-releasing substances than are tertiary amines such as morphine. Nevertheless, when large doses of certain NMBDs are administered rapidly, erythema of the face, neck, and upper torso may develop, as well as a brief decrease in arterial pressure and a slight to moderate increase in heart rate. Bronchospasm in this setting is very rare. The clinical effects of histamine are seen when plasma concentrations increase 200% to 300% of baseline values, and these effects involve chemical displacement of the contents of mast cell granules containing histamine, prostaglandin, and possibly other vasoactive substances.¹⁸² The serosal mast cell, located in the skin and connective tissue and near blood vessels and nerves, is principally involved in the degranulation process.¹⁸²

The side effect of histamine release is most often noted following administration of the benzylisoquinolinium class of muscle relaxants, although it has also been noted in steroid relaxants of low potency. The effect is usually of short duration (1-5 minutes), is dose related, and is

TABLE 27.10 Clinical Autonomic Effects of Neuromuscular Blocking Drugs

Drug Type	Autonomic Ganglia	Cardiac Muscarinic Receptors	Histamine Release
DEPOLARIZING SUBSTANCE			
Succinylcholine	Stimulates	Stimulates	Slight
BENZYLISOQUINOLINIUM COMPOUNDS			
Mivacurium	None	None	Slight
Atracurium	None	None	Slight
Cisatracurium	None	None	None
d-Tubocurarine	Blocks	None	Moderate
STEROIDAL COMPOUNDS			
Vecuronium	None	None	None
Rocuronium	None	Blocks weakly	None
Pancuronium	None	Blocks moderately	None

clinically insignificant in healthy patients. The hypotensive cardiovascular response to 0.6 mg/kg of dTc in humans is prevented both by antihistamines and by nonsteroidal anti-inflammatory drugs (e.g., aspirin).¹⁸³ The final step in dTc-induced hypotension is modulated by prostaglandins that are vasodilators.¹⁸³ This side effect can be reduced considerably by using a slower injection rate that results in lower peak plasma concentrations of dTc. It is also prevented by prophylaxis with combinations of histamine₁ and histamine₂ blockers.¹⁸⁴ If a minor degree of histamine release such as described earlier occurs after an initial dose of an NMBD, subsequent doses will generally cause no response at all, as long as they are no larger than the original dose. This is clinical evidence of tachyphylaxis, an important characteristic of histamine release. A much more significant degree of histamine release occurs during anaphylactoid or anaphylactic reactions, but these are very rare.

Clinical Cardiovascular Manifestations of Autonomic Mechanisms

HYPOTENSION. The hypotension seen with the use of atracurium and mivacurium results from histamine release, whereas dTc causes hypotension by histamine release and ganglionic blockade.^{185,186} The effects of dTc occur closer to the dose required to achieve neuromuscular blockade.¹¹³ The safety margin for histamine release is approximately three times greater for atracurium and mivacurium than it is for dTc.^{182,183,186} Rapid administration of atracurium in doses greater than 0.4 mg/kg and of mivacurium in doses greater than 0.15 mg/kg has been associated with transient hypotension secondary to histamine release (Fig. 27.13).

TACHYCARDIA. Pancuronium causes a moderate increase in heart rate and, to a lesser extent, in cardiac output, with little or no change in systemic vascular resistance.¹⁸⁷ Pancuronium-induced tachycardia has been attributed to the following: (1) vagolytic action,¹⁸⁷ probably from inhibition of M₂ receptors; and (2) sympathetic stimulation that involves both direct (blockade of neuronal uptake of norepinephrine) and indirect (release of norepinephrine from adrenergic nerve endings) mechanisms.¹⁸⁸ In humans a decrease in plasma norepinephrine

levels was surprisingly found after administration of either pancuronium or atropine.¹⁸⁹ The investigators postulated that the increase in heart rate or rate-pressure product occurs because pancuronium (or atropine) acts through baroreceptors to reduce sympathetic outflow.¹⁸⁹ More specifically, the vagolytic effect of pancuronium increases heart rate and hence blood pressure and cardiac output, in turn influencing the baroreceptors to decrease sympathetic tone. Support for this concept is provided by the finding that prior administration of atropine attenuates or eliminates the cardiovascular effects of pancuronium.¹⁸⁷ However, a positive chronotropic effect that places emphasis on the vagolytic mechanism has not been found in humans.¹⁹⁰ The tachycardia seen with benzylisoquinolinium compounds is the result of histamine release.

DYSRHYTHMIAS. Succinylcholine and dTc actually reduce the incidence of epinephrine-induced dysrhythmias.¹⁹¹ Possibly because of enhanced atrioventricular conduction,¹⁹² the incidence of dysrhythmias caused by pancuronium appears to increase during halothane anesthesia.¹⁸⁷ There are reports of rapid tachycardia (>150 beats/min) that progressed to atrioventricular dissociation in two patients anesthetized with halothane who also received pancuronium.¹⁹³ The only other factor common to those two patients was that both were taking tricyclic antidepressant drugs.

BRADYCARDIA. Several case reports described the occurrence of severe bradycardia and even asystole after vecuronium or atracurium administration.^{194,195} All these cases were also associated with opioid coadministration. Subsequent studies indicated that administration of vecuronium or atracurium alone does not cause bradycardia.¹⁹⁶ When combined with other drugs that do cause bradycardia (e.g., fentanyl), however, the nonvagolytic relaxants such as vecuronium, cisatracurium, and atracurium allow this mechanism to occur unopposed. Thus the moderate vagolytic effect of pancuronium is often used to counteract opioid-induced bradycardia.

Respiratory Effects. The muscarinic cholinergic system plays an important role in regulating airway function. Five muscarinic receptors have been cloned,¹⁹⁷ three of which (M₁ to M₃) exist in the airways.¹⁹⁸ M₁ receptors are under

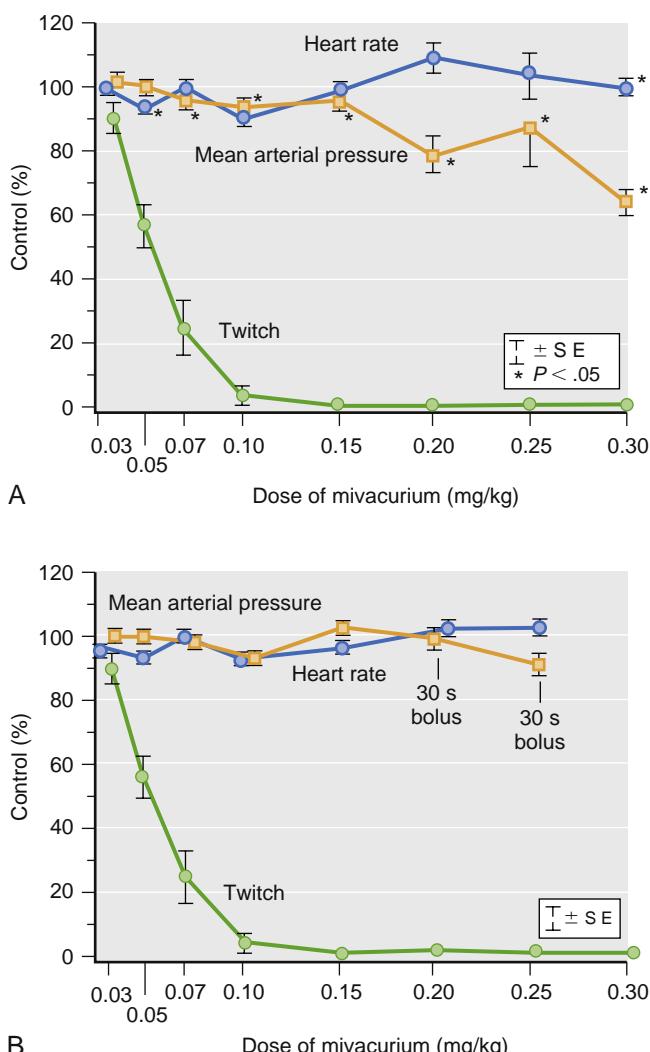


Fig. 27.13 Dose response to mivacurium in patients under nitrous oxide–oxygen–opioid anesthesia. Maximum changes at each dose are shown; $n = 9$ subjects per group. (A) With fast injection, a 15% to 20% decrease in arterial pressure occurred at 2.5 to 3 times the ED₉₅ (0.20–0.25 mg/kg). (B) The changes were less than 10% when slower injection (30 seconds) was done. (From Savarese JJ, Ali HH, Basta SJ, et al. The cardiovascular effects of mivacurium chloride [BW B1090U] in patients receiving nitrous oxide–opiate–barbiturate anesthesia. *Anesthesiology*. 1989;70:386–394.)

sympathetic control, and they mediate bronchodilation.¹⁹⁹ M₂ receptors are located presynaptically (Fig. 27.14), at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of acetylcholine. The M₃ receptors, which are located postsynaptically (see Fig. 27.14), mediate contraction of the airway smooth muscles (i.e., bronchoconstriction).¹⁹⁹ Nondepolarizing NMBDs have different antagonistic activities at both M₂ and M₃ receptors.²⁰⁰ For example, blockade of M₃ receptors on airway smooth muscle inhibits vagally induced bronchoconstriction (i.e., causes bronchodilation), whereas blockade of M₂ receptors results in increased release of acetylcholine that acts on M₃ receptors, thus causing bronchoconstriction.

The affinity of the compound rapacuronium to block M₂ receptors is 15 times higher than its affinity to block M₃ receptors.²⁰⁰ This explains the high incidence (>9%) of severe bronchospasm^{201–203} reported with this drug that

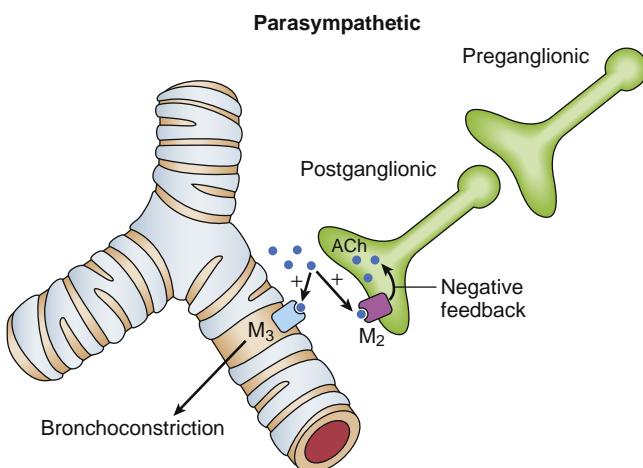


Fig. 27.14 The muscarinic (M₃) receptors are located postsynaptically on airway smooth muscle. Acetylcholine (ACh) stimulates M₃ receptors to cause contraction. M₂ muscarinic receptors are located presynaptically at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of ACh.

resulted in its withdrawal from the market. In laboratory animals (guinea pig), CW 1759-50 is reported to have five times greater safety at both M₂ and M₃ receptors than rapacuronium.^{11b}

The administration of benzylisoquinolinium NMBDs (with the exception of cisatracurium) is associated with histamine release, which may result in increased airway resistance and bronchospasm in patients with hyperactive airway disease.

Allergic Reactions. The frequency of life-threatening anaphylactic (immune-mediated) or anaphylactoid reactions occurring during anesthesia has been estimated at 1 in 10,000 to 20,000 anesthetic procedures, whereas it is estimated at 1 in 6500 administrations of NMBDs in some countries.^{204,205} In France, the most common causes of anaphylaxis in patients who experienced allergic reactions were reported to be NMBDs (60.6%), antibiotics (18.2%), dyes (5.4%), and latex (5.2%).^{206,206a} Patients were sensitized to 2 or more NMBDs in approximately 50% of the cases and no cross-sensitivity could be predicted without skin testing. Anaphylactic reactions are mediated through immune responses involving immunoglobulin E (IgE) antibodies fixed to mast cells. Anaphylactoid reactions are not immune mediated and represent exaggerated pharmacologic responses in very rare and very sensitive individuals.

However, anaphylaxis to nondepolarizing NMBDs is not uncommon in patients without any previous exposure to any nondepolarizing NMBDs. Cross-reactivity occurs between NMBDs and food, cosmetics, disinfectants, and industrial materials.²⁰⁷ Sensitization to nondepolarizing NMBDs may also be related to pholcodine, a cough-relieving medicine. Cross-reactivity is seen in 70% of patients with a history of anaphylaxis to an NMBD.²⁰⁶ Six years after the withdrawal of pholcodine from the Norwegian market, the prevalence of IgE sensitization to NMBDs (succinylcholine) decreased significantly.^{207a}

Steroidal compounds (e.g., rocuronium, vecuronium, or pancuronium) result in no significant histamine release.¹⁸⁶ For example, four times the ED₉₅ of rocuronium (1.2 mg/

kg) causes no significant histamine release.²⁰⁸ Nevertheless, rocuronium and succinylcholine are reportedly associated with a 43.1% and 22.6% incidence, respectively, of anaphylaxis in France.²⁰⁶ Rose and Fisher classified rocuronium and atracurium as having intermediate levels of risk for causing allergic reactions.²⁰⁹ These investigators also noted that the increased number of reports of anaphylaxis with rocuronium is in line with the market share of that drug's usage. Watkins stated, "The much higher incidence of rocuronium reactions reported in France is currently inexplicable and is likely to remain so if investigators continue to seek a purely antibody-mediated response as an explanation of all anaphylactoid reaction presentations."²¹⁰ All nondepolarizing NMBDs may elicit anaphylaxis. More recent publications have highlighted the need for standardization of diagnostic procedures of anaphylactic reactions. Biochemical tests should be performed rapidly after occurrence of an anaphylactic reaction. An early increase in plasma histamine is observed 60 to 90 minutes after anaphylactic reactions. Serum tryptase concentration typically reaches a peak between 15 and 120 minutes, depending on the severity of the reaction, and is much more specific than histamine as a marker of anaphylactic reaction. It is highly suggestive of mast cell activation. Skin testing remains the gold standard for detection of the culprit agent.^{77a} For many years, dilution thresholds have been debated. For instance, Laxenaire used a 1:10 dilution of rocuronium for interdermal skin testing,²¹² whereas Rose and Fisher used a 1:1000 dilution.²⁰⁹ Levy and associates showed that rocuronium in a 1:10 dilution can produce false-positive results in intradermal testing and suggested that rocuronium be diluted at least 100-fold to prevent such results.²¹³ The authors also reported that high concentrations ($\geq 10^{-4}$ M) of both rocuronium and cisatracurium were capable of producing a wheal-and-flare response to intradermal testing, which was associated with mild to moderate mast cell degranulation in the cisatracurium group only.²¹³ However, in contrast to control patients, skin tests with nondepolarizing NMBDs that were performed in patients who had an anaphylactic reaction were considered reliable. In the case of suspected anaphylactic reaction to any NMBD, it is mandatory to complete investigation for cross-reactivity with other commercially available NMBDs to identify safe alternative regimens.

All NMBDs can cause noncompetitive inhibition of histamine-N-methyltransferase, but the concentrations required for that inhibition greatly exceed those that would be used clinically, except in the case of vecuronium, with which the effect becomes manifest at 0.1 to 0.2 mg/kg.²¹⁴ This finding could explain the occurrence of occasional severe bronchospasm in patients after receiving vecuronium.²¹⁵ For goals of treatment of anaphylactic reactions, see Chapters 5 and 6.

DRUG INTERACTIONS AND OTHER FACTORS AFFECTING RESPONSE TO NEUROMUSCULAR BLOCKERS

A drug-drug interaction is an *in vivo* phenomenon that occurs when the administration of one drug alters the effects or kinetics of another drug. *In vitro* physical or chemical incompatibilities are *not* considered drug interactions.²¹⁶

Many drugs interact with NMBDs or their antagonists, or both, and it is beyond the scope of this chapter to review them all.^{216,217} Some of the more important drug interactions with NMBDs and their antagonists are discussed in the following sections.

Interactions Among Nondepolarizing Neuromuscular Blocking Drugs

Mixtures of two nondepolarizing NMBDs are considered to be either additive or synergistic. Antagonistic interactions have not been reported in this class of drugs. Additive interactions have been demonstrated after administration of chemically related drugs, such as atracurium and mivacurium,²¹⁸ or after coadministration of various pairs of steroid NMBDs.⁹⁸ Conversely, combinations of structurally dissimilar (e.g., a steroid with a benzylisoquinolinium) NMBDs, such as the combinations of pancuronium and dTc,²¹⁹ pancuronium and metocurine,²¹⁹ rocuronium and mivacurium,¹⁴² or rocuronium and cisatracurium,¹⁰⁹ produce a synergistic response. An additional advantage (rapid onset and short duration) is noted for mivacurium-rocuronium combinations.¹⁴² Although the precise mechanisms underlying a synergistic interaction are not known, hypotheses that have been put forward include the existence of multiple binding sites at the neuromuscular junction (presynaptic and postsynaptic receptors)²²⁰ and the nonequivalence of binding affinities of the two α subunits (α_H and α_L). Further, inhibition of butyrylcholinesterase by pancuronium results in decreased plasma clearance of mivacurium and marked potentiation of the neuromuscular blockade.²²¹

The pharmacodynamic response to the use of two different nondepolarizing NMBDs during the course of anesthesia depends not only on the specific drugs used but also on the sequence of their administration.^{222,223} Approximately three half-lives are required for a clinical change-over (so that 95% of the first drug has been cleared) and for the duration of the blockade to begin to take on the characteristics of the second drug. After the administration of pancuronium, recovery from the first two maintenance doses of vecuronium is reportedly prolonged, although this effect becomes negligible by the third dose.²²² Similarly, Naguib and colleagues noted that the mean duration of the first maintenance dose of mivacurium to 10% recovery of the first twitch was significantly longer after atracurium (25 minutes) than after mivacurium (14.2 minutes).²¹⁸ However, the duration of the second maintenance dose of mivacurium after atracurium (18.3 minutes) was similar to that of mivacurium after mivacurium (14.6 minutes).

The apparent prolongation of action of the first maintenance dose of mivacurium administered after atracurium,²¹⁸ and of those reported with vecuronium after pancuronium,^{222,223} is not related to synergism. Combinations of atracurium and mivacurium²¹⁸ and of vecuronium and pancuronium⁹⁸ are simply additive. However, this prolongation in the duration of action could be attributed to the relative concentrations of these drugs at the receptor site. Because most receptors remain occupied by the drug administered initially, the clinical profile depends on the kinetics or dynamics (or both) of the drug administered first, rather than on those of the second (maintenance)

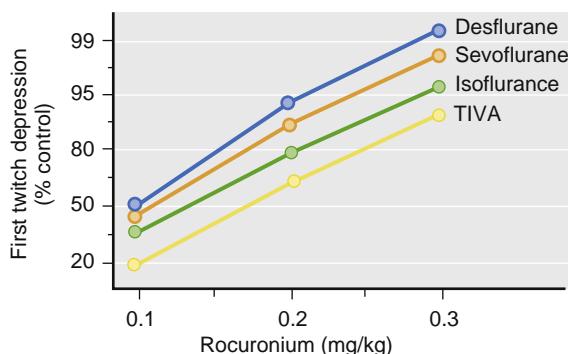


Fig. 27.15 Cumulative dose-response curves for rocuronium-induced neuromuscular blockade during 1.5 minimum alveolar concentration anesthesia with desflurane, sevoflurane, isoflurane, and total intravenous anesthesia (TIVA). (From Wulf H, Ledowski T, Linstedt U, et al. Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia. *Can J Anaesth*. 1998;45:526–532, with permission from the *Canadian Journal of Anaesthesia*.)

drug. However, with further incremental doses of the second drug, a progressively larger proportion of the receptors is occupied by that second drug, and its clinical profile becomes evident.

Interactions Between Succinylcholine and Nondepolarizing Neuromuscular Blocking Drugs

The interaction between succinylcholine and nondepolarizing NMBDs depends on the order of administration and the doses used.^{81,224,225} Small doses of different nondepolarizing NMBDs administered before succinylcholine to prevent fasciculations have an antagonistic effect on the development of subsequent depolarizing block produced by succinylcholine.^{27,81} Therefore it is recommended that the dose of succinylcholine be increased after the administration of a defasciculating dose of a nondepolarizing NMBD.²⁷

Studies of the effects of administering succinylcholine before nondepolarizing NMBDs have produced conflicting results. Several investigators reported potentiation of the effects of pancuronium,²²⁴ vecuronium, and atracurium²²⁵ by prior administration of succinylcholine. In contrast, other investigators found no significant influence of succinylcholine on subsequent administration of pancuronium, rocuronium, or mivacurium.^{81,226,227}

Interactions With Inhaled Anesthetics

Deep anesthesia induced with potent volatile anesthetics (in the absence of neuromuscular blockade) may cause a slight reduction of neuromuscular transmission, as measured by depression of sensitive indicators of clinical neuromuscular function, such as tetanus and TOF ratio.²²⁸ Inhaled anesthetics also enhance the neuromuscular blocking effects of nondepolarizing NMBDs. Inhaled anesthetics decrease the required dose of NMBDs, and prolong both the duration of action of the NMBD and recovery from neuromuscular block,²²⁹ depending on the duration of anesthesia,^{228,230,231} the specific inhaled anesthetic,²³² and the concentration (dose) given.²³³ The rank order of potentiation is desflurane > sevoflurane > isoflurane > halothane > nitrous oxide/barbiturate/opioid or propofol anesthesia (Fig. 27.15).^{234–236}

The greater clinical muscle-relaxing effect produced by less potent anesthetics is mainly caused by their larger aqueous concentrations.²³⁷ Desflurane and sevoflurane have low blood-gas and tissue-gas solubility, so equilibrium between the end-tidal concentration and the neuromuscular junction is reached more rapidly with these anesthetics than with older inhaled anesthetics.

The interaction between volatile anesthetics and NMBDs is one of pharmacodynamics, not pharmacokinetics.²³⁸ The proposed mechanisms behind this interaction include (1) a central effect on α motoneurons and interneuronal synapses,²³⁹ (2) inhibition of postsynaptic nAChR,²⁴⁰ and (3) augmentation of the antagonist's affinity at the receptor site.²³⁷

Interactions With Antibiotics

Most antibiotics can cause neuromuscular blockade in the absence of NMBDs. The aminoglycoside antibiotics, the polymyxins, and lincomycin and clindamycin primarily inhibit the prejunctional release of acetylcholine and also depress postjunctional nAChR sensitivity to acetylcholine.²⁴¹ The tetracyclines, in contrast, exhibit postjunctional activity only. When combined with NMBDs, the aforementioned antibiotics can potentiate neuromuscular blockade.²⁴² The cephalosporins and penicillins have not been reported to potentiate neuromuscular blockade. Because antagonism of neuromuscular blockade with neostigmine has been reported to be more difficult after the administration of aminoglycosides,²⁴³ ventilation should be controlled until the neuromuscular blockade terminates spontaneously. Ca^{2+} should not be used to hasten the recovery of neuromuscular function for two reasons: the antagonism it produces is not sustained, and it may prevent the antibacterial effect of the antibiotics.

Temperature

Hypothermia prolongs the duration of action of nondepolarizing NMBDs.^{244–246} The force of contraction of the adductor pollicis decreases by 10% to 16% per degree Celsius decrease in muscle temperature lower than 35.2°C.^{247,248} To maintain the muscle temperature at or higher than 35.2°C, the central temperature must be maintained above 36.0°C.²⁴⁴ The mechanical response recovery to 10% twitch height with 0.1 mg/kg of vecuronium increases from 28 minutes at a mean central temperature of 36.4°C to 64 minutes at 34.4°C.²⁴⁴ The mechanism or mechanisms underlying this prolongation may be pharmacodynamic or pharmacokinetic, or both.²⁴⁶ They include diminished renal and hepatic excretion, changing volumes of distribution, altered local diffusion receptor affinity, changes in pH at the neuromuscular junction, and the net effect of cooling on the various components of neuromuscular transmission.^{244,249} Hypothermia decreases the plasma clearance and prolongs the duration of action of rocuronium and vecuronium.²⁴⁶ Temperature-related differences in the pharmacodynamics of vecuronium have also been reported. The k_{el} decreases (0.023/min/°C) with lower temperature, a finding suggesting slightly delayed equilibration of drug between the circulation and the neuromuscular junction during hypothermia.²⁴⁶ The Hofmann elimination process of atracurium is slowed by a decrease in pH and especially by a decrease in temperature.²⁵⁰ In fact, atracurium's duration

of action is markedly prolonged by hypothermia.²⁴⁵ For instance, the duration of action of a dose of 0.5 mg/kg atracurium is 44 minutes at 37°C but 68 minutes at 34.0°C when evoked mechanical responses are monitored.

Changes in temperature also affect the interpretation of the results of monitoring neuromuscular blockade. For example, the duration of action of vecuronium measured in an arm cooled to a skin temperature of 27°C is prolonged, and monitoring by PTC in that arm is unreliable.²⁵¹ In the same patient, TOF responses are different if the arms are at different temperatures, and the correlation of responses in the two arms becomes progressively poorer as the temperature difference between the arms increases.²⁵²

The efficacy of neostigmine is not altered by mild hypothermia.²⁵³⁻²⁵⁵ Hypothermia does not change the clearance, maximum effect, or duration of action of neostigmine in volunteers.²⁵⁵ Mild hypothermia prolonged sugammadex reversal of deep rocuronium block by 46 seconds, a prolongation considered clinically acceptable.^{255a}

Interactions With Magnesium and Calcium

Magnesium sulfate, given for treatment of preeclampsia and eclamptic toxemia, potentiates the neuromuscular blockade induced by nondepolarizing NMBDs.^{256,257} After a dose of 40 mg/kg of magnesium sulfate, the ED₅₀ of vecuronium was reduced by 25%, the onset time was nearly halved, and the recovery time nearly doubled.²⁵⁷ Neostigmine-induced recovery is also attenuated in patients treated with magnesium.²⁵⁶ The mechanisms underlying the enhancement of nondepolarizing block by magnesium probably involve both prejunctional and postjunctional effects. High magnesium concentrations inhibit Ca²⁺ channels at the presynaptic nerve terminals that trigger the release of acetylcholine.¹⁶ Further, magnesium ions have an inhibitory effect on postjunctional potentials and cause decreased excitability of muscle fiber membranes. In patients receiving magnesium, the dose of nondepolarizing NMBDs must be reduced and carefully titrated using an objective monitor to ensure adequate recovery of neuromuscular function prior to tracheal extubation.

The interaction between magnesium and succinylcholine is controversial, with some reports suggesting that magnesium antagonizes the block produced by succinylcholine.²⁵⁸ Ca²⁺ triggers the release of acetylcholine from the motor nerve terminal and enhances excitation-contraction coupling in muscle.¹⁶ Increasing Ca²⁺ concentrations decreased the sensitivity to dTc and pancuronium in a muscle-nerve model.²⁵⁹ In hyperparathyroidism, hypercalcemia is associated with decreased sensitivity to atracurium and thus a shortened time course of neuromuscular blockade.²⁶⁰

Interactions With Lithium

Lithium is used for treatment of bipolar affective disorder (manic-depressive illness). The lithium ion resembles Na⁺, K⁺, magnesium, and Ca²⁺ ions, and therefore may affect the distribution and kinetics of all these electrolytes.²⁶¹ Lithium enters cells via Na⁺ channels and tends to accumulate within the cells.

By its activation of K⁺ channels, lithium inhibits neuromuscular transmission presynaptically and muscular contraction postsynaptically.²⁶² The combination of lithium and pipecuronium results in a synergistic inhibition of neuromuscular transmission, whereas the combination

of lithium and succinylcholine results in additive inhibition.²⁶² Prolongation of neuromuscular blockade was reported in patients taking lithium carbonate and receiving both depolarizing and nondepolarizing NMBDs.²⁶³ Only one report did not demonstrate prolongation of recovery from succinylcholine in patients receiving lithium.²⁶⁴ In patients who are stabilized on lithium therapy and undergoing surgery, NMBDs should be administered in incremental and reduced doses and titrated to the degree of blockade required.

Interactions With Local Anesthetic and Antidysrhythmic Drugs

Local anesthetics act on the presynaptic and postsynaptic part of the neuromuscular junction. In large intravenous doses, most local anesthetics block neuromuscular transmission; in smaller doses, they enhance the neuromuscular blockade produced by both nondepolarizing and depolarizing NMBDs.²⁶⁵ The ability of neostigmine to antagonize a combined local anesthetic-neuromuscular blockade has not been studied. Procaine also inhibits butyrylcholinesterase and may augment the effects of succinylcholine and mivacurium by decreasing their hydrolysis by the enzyme.

In small intravenous doses, local anesthetics depress posttetanic potentiation, and this is thought to be a neural prejunctional effect.²⁶⁶ With larger doses, local anesthetics block acetylcholine-induced muscular contractions, a finding suggesting that local anesthetics have a stabilizing effect on the postjunctional membrane.²⁶⁷ Procaine displaces Ca²⁺ from the sarcolemma and thus inhibits caffeine-induced contracture of skeletal muscle.²⁶⁸ Most of these mechanisms of action probably apply to all local anesthetics.

Several drugs used for the treatment of dysrhythmias augment the blockade induced by NMBDs. Single-fiber electromyography found that verapamil and amlodipine impair neuromuscular transmission in subjects without neuromuscular disease.²⁶⁹ Clinical reports suggested potentiation of neuromuscular block with verapamil²⁷⁰ and impaired reversal of vecuronium in a patient receiving disopyramide.²⁷¹ However, the clinical significance of these interactions is probably minor.

Interactions With Antiepileptic Drugs

Anticonvulsants have a depressant action on acetylcholine release at the neuromuscular junction.^{272,273} Patients receiving long-term anticonvulsant therapy demonstrated resistance to nondepolarizing NMBDs (except mivacurium²⁷⁴ and probably atracurium as well²⁷³), as evidenced by accelerated recovery from neuromuscular blockade and the need for increased doses to achieve complete neuromuscular blockade. Vecuronium clearance is increased two-fold in patients receiving long-term carbamazepine therapy.²⁷⁵ Other investigators, however, attribute this resistance to the increased binding (i.e., decreased free fraction) of the NMBDs to α_1 -acid glycoproteins or to upregulation of neuromuscular acetylcholine receptors (or to both mechanisms).²⁷⁶ The latter could also explain the hypersensitivity seen with succinylcholine.²⁷⁷ The slight prolongation of succinylcholine's action in patients taking anticonvulsants has few clinical implications. Conversely, the potential hyperkalemic response to succinylcholine in the presence of receptor upregulation is of concern.

Interactions With Diuretics

Early results showed that in patients undergoing renal transplantation, the intensity and duration of dTc neuromuscular blockade was increased after a dose of furosemide (1 mg/kg intravenously).²⁷⁸

Furosemide reduced the concentration of dTc required to achieve 50% twitch tension depression in the indirectly stimulated rat diaphragm and intensified the neuromuscular blockade produced by dTc and succinylcholine.²⁷⁹ Furosemide appears to inhibit the production of cyclic adenosine monophosphate. In addition, the breakdown of adenosine triphosphate is inhibited, resulting in reduced output of acetylcholine. Acetazolamide antagonized the effects of anticholinesterases in the rat phrenic-diaphragm preparation.²⁸⁰ However, in one report, 1 mg/kg of furosemide facilitated recovery of the evoked twitch response after pancuronium.²⁸¹ Long-term furosemide treatment had no effect on either dTc- or pancuronium-induced neuromuscular blockade.²⁸²

In contrast, mannitol appears to have no effect on a nondepolarizing neuromuscular blockade. Increasing urine output by the administration of mannitol or other osmotic or tubular diuretics has no effect on the rate at which dTc and presumably other NMBDs are eliminated in the urine.²⁸³

Interactions With Other Drugs

Dantrolene, a drug used for the treatment of malignant hyperthermia, prevents Ca^{2+} release from the sarcoplasmic reticulum and blocks excitation-contraction coupling. Although dantrolene does not block neuromuscular transmission, the mechanical response to stimulation is depressed, resulting in potentiation of nondepolarizing neuromuscular blockade.²⁸⁴

Azathioprine, an immunodepressant drug that is used in patients undergoing renal transplantation, has a minor antagonistic action on muscle relaxant-induced neuromuscular blockade.²⁸⁵

Steroids antagonize the effects of nondepolarizing NMBDs in both humans²⁸⁶ and animals.²⁸⁷ Possible mechanisms for this interaction include facilitation of acetylcholine release because of the effect of steroids on the presynaptic motor nerve terminal.²⁸⁸ Other reports, however, described a noncompetitive inhibition and channel blockade of the nAChR.²⁸⁹ Endogenous steroids act noncompetitively on nAChRs.²⁹⁰ Prolonged treatment with a combination of corticosteroids and NMBDs can result in prolonged weakness in patients receiving critical care (see the later section on NMBDs and weakness syndromes in critically ill patients).

Antiestrogenic drugs such as tamoxifen appear to potentiate the effects of nondepolarizing NMBDs.²⁹¹

Special Populations

PEDIATRIC PATIENTS

The development of the neuromuscular junction is not complete at birth.¹⁶ In humans, maturation of neuromuscular transmission occurs after the first 2 months of age, although immature junctions have been found up to 2 years of age. The main evolution during the first months of life is that the fetal receptors located outside the neuromuscular junction will disappear and will be replaced by mature receptors with ϵ

subunits instead of γ subunits. These changes suggest that the neonate's neuromuscular junction may exhibit evidence of its immaturity by changes in response to NMBDs, although NMBDs can be used safely in term and preterm infants.

The routine administration of succinylcholine to healthy children should be discontinued. In apparently healthy children, intractable cardiac arrest with hyperkalemia, rhabdomyolysis, and acidosis may develop after succinylcholine administration, particularly in patients with unsuspected muscular dystrophy of the Duchenne type²⁹² (see the section on complications of succinylcholine).

Significant age-related differences in the potency of nondepolarizing NMBDs exist in infants and children when compared with adults. Children require higher doses of nondepolarizing NMBDs than any other age group of patients. In infants less than 1 year old, the ED₉₅ at the adductor pollicis is approximately 30% less than in older children. It is not apparent from older studies whether the neonate is more sensitive than adults to nondepolarizing NMBDs,²⁹³ although most of the studies showed a wider range of dosage requirement in the neonate. These apparent discrepancies have been explained in studies by Fisher and associates on the pharmacokinetics and pharmacodynamics of NMBDs in infants, children, and adults.²⁹⁴⁻²⁹⁶ Neonates and infants are more sensitive than adults to the neuromuscular blocking effects of dTc.²⁹⁴ Plasma concentrations required to achieve a desired level of neuromuscular blockade are 57% and 32% lower in neonates and infants, respectively, when compared with children. However, the dosage should not be decreased as much because neonates and infants have a larger volume of distribution at steady state. This increased volume of distribution results from the increase in extracellular fluid volume during the first months of life. This increase, in association with a lower elimination clearance, contributes to a longer elimination half-life.^{294,297} In infants, less frequent dosing (longer dosing intervals) of nondepolarizing NMBDs may be required than in older children.

Atracurium, vecuronium, cisatracurium, rocuronium, and mivacurium are commonly administered to children because many surgical procedures are of short duration in children and are compatible with the duration of action of a single intubating dose. Onset time of neuromuscular block is faster in infants (30%) and children (40%) when compared with adults. This age-related effect is probably caused by circulatory factors such as the relative decrease in cardiac output and increase in circulation time with age.

As for long-acting NMBDs, the sensitivity of infants to vecuronium is greater than that of children (ED₉₅ 0.047 mg/kg vs. 0.081 mg/kg, respectively).^{298,299} An increased duration of action in infants is most likely secondary to the increased volume of distribution of vecuronium because its clearance is unchanged.^{295,297} An age-dependent prolongation of action has been demonstrated in infants. A dose of 0.1 mg/kg of vecuronium produces almost a complete neuromuscular block of approximately 60 minutes' duration in infants but of only 20 minutes' duration in children and adults. Vecuronium therefore acts as a long-acting muscle NMBD in the neonate.^{295,297}

In contrast, the duration of action of atracurium is not significantly different in the pediatric patient from that in the adult.³⁰⁰ As with vecuronium and dTc, the volume of distribution is increased in infants.²⁹⁶ However, the clearance of

atracurium is also more rapid.²⁹⁶ Therefore the same dose (0.5-0.6 mg/kg) can be used in infants, children, and adults for tracheal intubation without any major differences among the three groups in the drug's duration of action. Atracurium recovery from neuromuscular blockade is little affected by age in pediatric patients more than 1 month old. Histamine release and the occurrence of untoward reactions caused by atracurium are less frequent in children than in adults. In children, a dose of 0.1 µg/kg of cisatracurium has an onset just longer than 2 minutes and a clinical duration of approximately 30 minutes during balanced or halothane anesthesia.³⁰¹ The calculated ED₉₅ doses of cisatracurium in infants and children are 43 and 47 µg/kg, respectively.³⁰² The mean infusion rate necessary to maintain 90% to 99% neuromuscular blockade is also similar in infants and children.³⁰²

Rocuronium in adults is an intermediate-acting NMBD with a faster onset of action than other nondepolarizing NMBDs, and this is also true in infants and children.^{303,304} The ED₉₅ is approximately 0.4 mg/kg in children; it is approximately 20% to 30% greater than that in adults, but its onset is faster in adults.³⁰⁴ In children, 0.6 mg/kg of rocuronium produces better conditions for rapid tracheal intubation (approximately 60 seconds) than does 0.1 mg/kg of vecuronium (approximately 100 seconds) or 0.5 mg/kg of atracurium (approximately 180 seconds).³⁰³ Evidence indicates that, even during sevoflurane induction in infants, the addition of 0.3 mg/kg rocuronium significantly improves intubating conditions and significantly decreases the frequency of respiratory adverse events such as desaturation because of laryngospasm during induction.³⁰⁵ As with adults, for rapid sequence induction and intubation (60 seconds) in the presence of a full stomach, a 1.2 mg/kg dose of rocuronium is suggested to provide rapid, excellent intubating conditions in pediatric patients.

The rate of recovery of intermediate- or short-acting NMBDs is faster than that of long-acting drugs in children. A neostigmine dose of 30 µg/kg in children is quite comparable to the usual dose of 40 µg/kg in adults and provides satisfactory antagonism of nondepolarizing NMBD. Neostigmine-assisted recovery is dependent on age and is more rapid in children than either infants or adults.^{305a} Several studies have demonstrated that when children's tracheas were extubated using clinical criteria of recovery, the TOF ratio did not exceed 0.50 to 0.60, whereas a TOF ratio greater than 0.90 is required to guarantee full recovery from neuromuscular block. These results highlight the need for objective (quantitative) assessment of neuromuscular block, even in infants and children, because of their sensitivity and variability in their responsiveness to nondepolarizing NMBDs.

OLDER PATIENTS

The pharmacodynamics of NMBDs may be altered in older patients. Physiologic changes such as decreases in total body water and lean body mass, increases in total body fat, decreases in hepatic and renal blood flow and hepatic enzyme activity, and decreases in glomerular filtration rate ($\approx 20\%/\text{year}$ in adults) typically accompany the aging process. These changes may account for the altered responses of older adults to NMBDs. Some physiologic and anatomic changes at the neuromuscular junction also occur with aging. These include an increase in the distance between the junctional axon and the motor end plate, flattening of

the folds of the motor end plate, decreased concentration of acetylcholine receptors at the motor end plate, decrease in the amount of acetylcholine in each vesicle in the prejunctional axon, and decreased release of acetylcholine from the preterminal axon in response to a neural impulse.¹⁶

Several studies found no differences in the initial dose requirement for nondepolarizing muscle relaxants in older adults. The dose-response curves of atracurium, pancuronium, and vecuronium were shifted slightly to the right of the curves for the younger adult subjects; however, no significant differences were noted. After a bolus dose of pancuronium, no significant difference was observed in any of the plasma concentrations corresponding to a fixed degree of neuromuscular block. Such results confirm that nondepolarizing muscle relaxants are as potent in older as in young adult patients. The onset of neuromuscular block can be delayed and can be correlated with age.³⁰⁶ This age-related effect is probably caused by circulatory factors such as the decrease in cardiac output and increase in circulation time in older adults. These factors induce slower biophase equilibration with plasma. The onset of rocuronium neuromuscular block was prolonged to 3.7 from 3.1 minutes in older adults. Similarly, the onset of cisatracurium is delayed approximately 1 minute in this age group.

A prolongation of the duration of action of nondepolarizing muscle relaxants and a decrease in dose requirements for the maintenance of neuromuscular block have been observed with several currently available muscle relaxants in older adults. These results are explained by pharmacokinetic changes in this population. The distribution and elimination may be altered by any of the multitude of physiologic changes that accompany the aging process. The effect of aging alone, as opposed to disease states often associated with the aging process, may be difficult to distinguish in identifying mechanisms of altered NMBD action in older adults.

Pancuronium,³⁰⁷ vecuronium,^{295,308} and rocuronium¹⁷⁷ depend on the kidney or the liver (or both) for their metabolism and elimination. Therefore they all show altered pharmacodynamics and pharmacokinetics in older patients. Pancuronium has delayed recovery in older adults because of decreased plasma clearance secondary to delayed urinary excretion. Vecuronium dose requirements to maintain a constant neuromuscular block are decreased by approximately 36% in patients older than 60 years, and spontaneous recovery is significantly longer in older patients.²⁵ Plasma clearance is reduced by more than 50% and elimination half-life prolonged by 60% in older patients.³⁰⁸ The prolongation of vecuronium action appears to be secondary to decreased drug elimination consistent with age-associated decreases in hepatic and renal blood flows. The duration of action of rocuronium and the recovery index are also increased in older adults. The prolongation of action can be explained by a 27% decrease in plasma clearance.

In the case of drugs whose elimination is independent of hepatic or renal blood flow, pharmacokinetics and pharmacodynamics should not be altered significantly by age. Atracurium has multiple routes of elimination. Degradation by Hofmann elimination and ester hydrolysis is independent of the liver and the kidney and is not affected by age. The only pharmacokinetic change is a slight increase of the volume of distribution at steady state leading to a modestly increased

elimination half-life. Consequently, the duration of action, the recovery index, and the dose requirement during a continuous infusion are independent of age. Cisatracurium is mainly eliminated by Hofmann elimination, and unlike atracurium, cisatracurium does not undergo hydrolysis by specific esterases. It exhibits a slightly delayed onset of effect in older patients because of slower biophase equilibration. Clearances are not decreased in patients of advanced age. The slight prolongation of the elimination half-life of the drug in older adults is secondary to an increased volume of distribution at steady state (+10%). These minor pharmacokinetic changes are not associated with changes in the recovery profile in older patients.

Butyrylcholinesterase activity in older adults, although still in the normal range, is approximately 26% lower than that in young adults.³⁰⁹ Because mivacurium is metabolized by butyrylcholinesterase, its clearance is likely to be slightly reduced in older patients, thus resulting in a 20% to 25% longer duration of action,³¹⁰ as well as a decreased infusion requirement to maintain a stable depth of block. Succinylcholine metabolism is unaffected by these changes.

In general, when maintaining neuromuscular blockade with nondepolarizing NMBDs in older patients, one can expect that, with the exception of atracurium and cisatracurium, the dosing interval will be increased to maintain the desired depth of neuromuscular blockade. The choice of drug and monitoring the depth of blockade are exceptionally important in this population because recovery of neuromuscular function is generally delayed in older patients. Inadequate or incomplete recovery of muscle strength after the use of pancuronium is associated with an increased incidence of perioperative pulmonary complications in this patient population.¹²⁹ The clear relationship between incomplete recovery from neuromuscular block and occurrence of critical respiratory events in the PACU highlights the need for objective monitoring to ensure recovery of neuromuscular block in older patients.

OBESIVE PATIENTS

The level of plasma pseudocholinesterase activity and the volume of extracellular fluid, which are the main determinants of the duration of action of succinylcholine, are increased in obese patients. For complete neuromuscular paralysis and predictable intubating conditions, a 1-mg/kg dose based on total-body weight (TBW) is recommended.³¹¹

Initial studies showed that obese subjects needed significantly more pancuronium than nonobese patients to maintain a constant 90% depression of twitch height. However, when corrected for body surface area (BSA), no significant difference was noted in dose requirement to maintain neuromuscular block.

The use of NMBDs with an intermediate duration of action should be preferred. Vecuronium doses based on TBW induce a prolonged duration of action in obese patients, although vecuronium pharmacokinetics is unaltered by obesity. The prolonged recovery in obese patients can be explained by the larger total dose of vecuronium administered to these patients. With larger doses, when administration is based on TBW, recovery occurs during the elimination phase when plasma concentration decreases more slowly than during the distribution phase.³¹² The

pharmacokinetics of rocuronium is not altered by obesity. In the same way, the duration of action of rocuronium is significantly prolonged when the dose is calculated according to TBW. In contrast, when rocuronium is dosed according to ideal body weight (IBW), the clinical duration is less than half.^{313,314}

A correlation exists between the duration of action of atracurium and TBW when the dose is given as milligrams per kilogram of TBW. The clinical duration of action is doubled when the drug is given based on TBW versus IBW. There is little difference between obese and normal-weight patients in atracurium elimination half-life (19.8 vs. 19.7 minutes), volume of distribution at steady state (8.6 vs. 8.5 L), and total clearance (444 vs. 404 mL/min).³¹⁵ The finding that IBW avoids prolonged recovery of atracurium-induced blockade can be explained by an unchanged muscle mass and an unchanged volume of distribution in morbidly obese patients compared with normal-weight patients.³¹⁶ The duration of cisatracurium is also prolonged in obese patients when the drug is given on the basis of TBW versus IBW.

In summary, nondepolarizing NMBDs should be given to obese patients on the basis of IBW rather than on their actual body weight, to ensure that these patients are not receiving relative overdoses and to avoid prolonged recovery. When using maintenance doses, objective monitoring is strongly recommended to avoid accumulation.

SEVERE RENAL DISEASE

NMBDs contain quaternary ammonium groups that make them very hydrophilic. They are therefore usually completely ionized at a pH of 7.4 and are poorly bound to plasma proteins. The predominant pathway of elimination of steroid muscle relaxants is ultrafiltration by the glomeruli before urinary excretion. Renal failure influences the pharmacologic characteristics of nondepolarizing NMBDs by producing either decreased renal elimination of the drug or its metabolites. Only atracurium, cisatracurium, and, to some extent, vecuronium are independent of renal function. Succinylcholine elimination is mainly independent of kidney function. However, succinylcholine is metabolized by plasma cholinesterases, and concentrations may be slightly decreased in patients with severe renal failure (Table 27.11). The decrease in plasma cholinesterase activity is always moderate (30%) and does not result in prolongation of succinylcholine-induced neuromuscular block. Succinylcholine induces a transient increase in plasma K⁺ concentration (<0.5 mmol/L). Therefore succinylcholine is not contraindicated in severe renal failure when plasma K⁺ concentrations are within the normal range. The duration of action of NMBDs may be prolonged in patients with renal failure.

Renal failure does not alter the sensitivity (dose response) of patients to the neuromuscular blocking action of pancuronium,³¹⁷ atracurium,³¹⁸ vecuronium,³¹⁹ or rocuronium.³²⁰ All long-acting muscle relaxants are eliminated predominantly through the kidney, and renal failure is associated with reduced plasma clearance and increased elimination half-life for these drugs as well.¹⁰³ The elimination half-life of pancuronium is increased by 500% in patients with severe renal failure. As a consequence of these

TABLE 27.11 Pharmacokinetics of Neuromuscular Blocking Drugs in Patients With Normal Renal Function or Renal Failure

	PLASMA CLEARANCE (ML/KG/MIN)		VOLUME OF DISTRIBUTION (ML/KG)		ELIMINATION HALF-LIFE (MIN)		References
	Normal Function	Renal Failure	Normal Function	Renal Failure	Normal Function	Renal Failure	
SHORT-ACTING DRUGS							
Mivacurium isomers							160
<i>Cis-trans</i>	106	80	278	475	2.0	4.3	
<i>Trans-trans</i>	57	48	211	270	2.3	4.3	
<i>Cis-cis</i>	3.8	2.4*	227	244	68	80	
INTERMEDIATE-ACTING DRUGS							
Atracurium	6.1	6.7	182	224	21	24	172
	5.5	5.8	153	141	19	20	173*,†
	10.9	7.8	280	265	17.3	19.7	322
Cisatracurium	5.2	—	31	—	—	—	169
Vecuronium	3.0	2.5	194	239	78	97	324
	5.3	3.1*	199	241	53	83*	325
Rocuronium	2.9	2.9	207	264*	71	97*	175
LONG-ACTING DRUGS							
<i>d</i> -Tubocurarine	2.4	1.5	250	250	84	132	115
Pancuronium	74	20*	148	236*	97	475*	149†
	1.7	0.9	261	296*	132	257*	380

*Significant difference between normal renal function versus renal failure.

†Values expressed as mL/min, not weight adjusted.

pharmacokinetic changes, the duration of neuromuscular blockade produced by these drugs is longer and more variable than in patients with normal renal function. Because of the potential for prolonged blockade and the availability of intermediate- and short-acting NMBDs, long-acting NMBDs should not be used in patients with renal failure.

The pharmacokinetics and duration of action of atracurium are unaffected by renal failure.^{321,322} This lack of effect is in part because Hofmann elimination and ester hydrolysis¹⁷³ account for 50% of its total clearance.¹⁶⁷ Laudanosine, the principal metabolite of atracurium, is eliminated unchanged by the kidney. The elimination half-life of laudanosine increases in renal failure.³²² Even during continuous administration of atracurium, laudanosine plasma concentrations are 10 times lower than concentrations associated with seizures in dogs.

In patients with chronic renal failure, the duration of action of cisatracurium is not prolonged.³²³ Hofmann elimination accounts for 77% of the total clearance of cisatracurium,¹⁶⁹ and renal excretion accounts for 16% of its elimination.¹⁶⁹ The peak plasma laudanosine concentration is 10 times lower than after equipotent doses of atracurium. In patients with end-stage renal failure, the volume of distribution is unchanged, but there is a 13% reduction in clearance and an increase from 30 to 34 minutes in elimination half-life.

Vecuronium relies principally on hepatic mechanisms for its elimination. However, its clearance is reduced and its elimination half-life is increased in patients with renal failure.^{324,325} In one study, the duration of action of 0.1 mg/

kg of vecuronium was both longer and more variable in patients with renal failure than in those with normal renal function.³²⁵ In three other studies, the duration of action of 0.05 to 0.14 mg/kg of vecuronium was not prolonged by renal failure, but this result was likely caused by the use of relatively small doses or inadequate sample sizes.³²⁴ The principal metabolite of vecuronium, 3-desacetylvecuronium, has 80% of the neuromuscular blocking activity of vecuronium¹⁵³; it may cause prolonged paralysis in patients with renal failure in the ICU.¹⁵⁶ In patients with renal failure, the duration of action and the rate of recovery from vecuronium- or atracurium-induced neuromuscular blockade during surgery are similar.³²⁶

The major routes of elimination of rocuronium are biliary and urinary excretion. Rocuronium is taken up by the liver and metabolized, excreted, or both, in bile and feces in high concentrations. After 0.6 mg/kg rocuronium, up to one fifth of the dose is recovered unchanged from the urine within 24 hours, and no active metabolites can be found in humans. Pharmacokinetic studies showed that the clearance of rocuronium was reduced by 33% to 39% in patients with renal failure.^{326a} The distribution volume of this drug remained unchanged or slightly increased.¹⁷⁵ The elimination half-life was 70 and 57 minutes in patients with and without renal failure, respectively. The duration of action of single and repeated doses, however, was not affected significantly.³²⁰

In renal failure, there is no significant change in the volume of distribution of neostigmine. The clearance is decreased by two thirds and the elimination half-life is

TABLE 27.12 Pharmacokinetics of Neuromuscular Blocking Drugs in Patients With Normal Liver Function or Hepatobiliary Disease

	PLASMA CLEARANCE (ML/KG/MIN)		VOLUME OF DISTRIBUTION (ML/KG)		ELIMINATION HALF-LIFE (MIN)		Hepatic Pathology	References
	Normal	Disease	Normal	Disease	Normal	Disease		
SHORT-ACTING DRUGS								
Mivacurium isomers							Cirrhosis	159
<i>Cis-trans</i>	95	44*	210	188	1.53	2.48*		
<i>Trans-trans</i>	70	32*	200	199	2.32	11.1*		
<i>Cis-cis</i>	5.2	4.2	266	237	50.3	60.8		
INTERMEDIATE-ACTING DRUGS								
Atracurium	5.3	6.5	159	207*	21	22	Hepatorenal	318
	6.6	8.0*	202	282*	21	25	Cirrhosis	174
Cisatracurium	5.7	6.6*	161	195*	23.5	24.4	Transplantation	
<i>Vecuronium</i>	4.26	2.73*	246	253	58	84*	Cirrhosis	154
	4.30	2.36*	247	206	58	98*	Cholestasis	381
	4.5	4.4	180	220	58	51	Cirrhosis	155
<i>Rocuronium</i>	2.79	2.41	184	234	87.5	96.0	Cirrhosis	176
	217	217	16.4	23.4*	76.4	111.5*	Mixed	178†
	296	189	151	264*	56	98*	Cirrhosis	326c†
	3.70	2.66*	211	248	92	143*	Cirrhosis	179
LONG-ACTING DRUGS								
<i>Pancuronium</i>	123	59*	261	307*	133	267*	Cholestasis	151†
	1.86	1.45*	279	416*	114	208*	Cirrhosis	150
	1.76	1.47	284	425*	141	224*	Cholestasis	383

*Significant difference between normal hepatic function versus hepatobiliary disease.

†Values expressed as mL/min, or L, not weight adjusted.

prolonged from 80 to 183 minutes in patients with renal failure. The clearance of edrophonium is also significantly reduced and its elimination half-life significantly prolonged in patients with end-stage renal failure.

HEPATOBILIARY DISEASE

In comparison with renal elimination, liver function is a modest determinant of the pharmacokinetics of nondepolarizing muscle relaxants. The influence of hepatobiliary disease on the pharmacokinetics of NMBDs can be complex because of the different types of liver failure (Table 27.12). Cirrhosis is associated with an increased extracellular water compartment, edema, and, often, kidney dysfunction. Cholestasis induces decreased biliary excretion but is not associated with significant liver failure, contrary to acute hepatic failure.

A delayed onset of action and an apparent resistance to nondepolarizing muscle relaxants occur in patients with cirrhosis, although studies demonstrated that the sensitivity of the neuromuscular junction was unaltered. This is the consequence of the increased volume of distribution, which induces greater dilution of muscle relaxants in cirrhotic patients. The increase of terminal half-life can be secondary

to either the increased volume of distribution or decreased biliary excretion for muscle relaxants dependent on hepatic function for elimination.¹⁵⁴ Following a single dose of nondepolarizing muscle relaxant, in most of the cases, no prolongation of the duration of action occurs because it is dependent on distribution. However, for muscle relaxants dependent on hepatic elimination, prolongation of neuromuscular block can be observed following repeated doses or continuous infusion.

Pancuronium is mainly eliminated through the kidney, although one third of the dose is metabolized and excreted through the liver. The elimination half-life increases from 114 to 208 minutes in cirrhotic patients.¹⁵⁰ This is the consequence of a 50% increase of the volume of distribution in conjunction with a 22% decrease in plasma clearance.¹⁵⁰ Cholestasis induces a 50% decrease in pancuronium clearance leading to a prolonged elimination half-life of 270 minutes. Severe acute hepatic failure also induces reduced plasma clearance and a prolonged elimination half-life.

Vecuronium elimination is mainly through the bile.^{326b} Only a small fraction is metabolized to 3-hydroxyvecuronium, which still has 60-80% of the potency of vecuronium. This metabolic process is

presumed to occur in the liver because 40% of the total dose of vecuronium is found in the liver and bile as both parent drug and metabolite.¹⁴⁷ The elimination half-life is increased in mildly decompensated cirrhotic patients as the result of a decreased clearance,¹⁵⁴ whereas the volume of distribution of the central compartment and the volume of distribution at steady state can be increased. In cirrhotic patients, the duration of action of vecuronium is related to the dose. A dose of 0.1 mg/kg has a slower onset of action and a shorter duration of action because the volume of distribution is increased. In contrast, after 0.2 mg/kg vecuronium, the duration of action is increased from 65 minutes to 91 minutes in cirrhotic patients because elimination is impaired. Cholestasis can increase plasma concentration of bile salts and thus reduce the hepatic uptake of vecuronium,¹⁴⁷ as well as pancuronium. This may explain the decreased clearance observed by some investigators. The duration of action of vecuronium is increased by 50% in patients with biliary obstruction.

Rocuronium is mainly excreted into the bile. The volume of both the central compartment (+33%) and the volume of distribution at steady state (+43%) are increased in cirrhotic patients, whereas clearance may be decreased.^{326c} The duration of action is prolonged in patients with hepatic disease, and a correlation exists between the increased volume of distribution and the slower onset of action when compared with controls.¹⁷⁶

Atracurium and cisatracurium share organ-independent modes of elimination.^{165,168,169} As a consequence, their clearance should be little affected by hepatic disease. In fact, and in contrast to all other NMBDs, the plasma clearances of atracurium and cisatracurium are slightly increased in patients with liver disease (see Table 27.12).^{174,180} Because elimination of atracurium and cisatracurium occurs outside of, as well as from within, the central compartment, investigators have suggested that a larger distribution volume should be associated with greater clearance.¹⁶⁹ In two studies,^{174,180} volumes of distribution and clearances of the drugs increased with liver disease, thereby lending support to this hypothesis.¹⁶⁹ The increased clearance of the relaxant in patients with liver disease is not reflected in a decrease in the drug's duration of action.^{174,180}

One concern raised about administering atracurium to patients with hepatic disease is the possible accumulation of laudanosine. Although laudanosine relies principally on hepatic mechanisms for its elimination, the concentrations encountered during liver transplantation are unlikely to be associated with clinical sequelae.³²⁷

Because of the wide interindividual variations seen in the response to nondepolarizing muscle relaxants in patients with hepatic disease, quantitative monitoring of neuromuscular block is required, with careful titration of doses.

In patients with severe liver disease, butyrylcholinesterase activity is decreased because of decreased synthesis of the hepatic enzymes. Consequently, the plasma clearance of the isomers of mivacurium is decreased by approximately 50% (see Table 27.12),¹⁵⁹ and the drug's duration of action is prolonged and may be almost tripled.¹⁵⁹

TABLE 27.13 Conditions Associated With Upregulation and Downregulation of Acetylcholine Receptors

nAChR Upregulation	nAChR Downregulation
Spinal cord injury	Myasthenia gravis
Stroke	Anticholinesterase poisoning
Burns	Organophosphate poisoning
Prolonged immobility	
Prolonged exposure to neuromuscular blockers	
Multiple sclerosis	
Guillain-Barré syndrome	

nAChR, Nicotinic acetylcholine receptor.

BURNS

In patients with burn injuries, muscle relaxants can be used to facilitate mechanical ventilation, which can be associated with sustained improvement in oxygenation. After a period of immobilization, burn injury causes upregulation of both fetal ($\alpha_2\beta\gamma\delta$) and mature ($\alpha_2\beta\epsilon\delta$) nAChRs.³²⁸ This upregulation of nAChRs usually is associated with resistance to nondepolarizing NMBDs and increased sensitivity to succinylcholine.³²⁹ Causes of upregulation of nAChRs are listed in Table 27.13. A significant increase in the quantal content of evoked acetylcholine release is typically noted by 72 hours after scald injury in rats.³³⁰ This increase also contributes to the resistance to NMBDs in patients with burn injuries. In mice, thermal injury induces changes in diaphragm acetylcholinesterase with respect to total content and specific molecular forms.³³¹

Resistance to the effects of nondepolarizing NMBDs is usually seen in patients with burns over at least 25% of their total BSA.^{329,332,333} Recovery of neuromuscular function to preburn levels may take several months or even years after the burn injury.³³⁴ The increase in serum K⁺ concentration that normally follows succinylcholine administration is markedly exaggerated in burned patients and may be lethal.³³⁵ K⁺ concentrations as high as 13 mEq/L, resulting in ventricular tachycardia, fibrillation, and cardiac arrest, have been reported.³³⁵ The magnitude of the hyperkalemic response does not appear to correlate closely with the magnitude of the burn injury. Potentially lethal hyperkalemia was seen in a patient with only an 8% total BSA burn.³³⁶ Succinylcholine has been safely administered within 24 hours of a burn injury. It can be used for prehospital or emergency room intubation. After an initial 24-hour interval, however, sufficient alteration in muscle response may have occurred. Because of the unpredictability of occurrence of hyperkalemia, the use of succinylcholine is best avoided after 24 hours following a burn injury.

The time course of abnormal muscle membrane function corresponds with that of the healing process. Once normal skin has regrown and any infection subsides, the normal acetylcholine receptor populations appear to return.³³⁴ Although normal responses to succinylcholine have been demonstrated in burned patients studied 3 years after injury,³³⁴ the actual length of time during which a patient

BOX 27.1 Reported Indications for the Use of Muscle Relaxants in the Intensive Care Unit

- Facilitation of mechanical ventilation
- Facilitation of endotracheal intubation
- Enabling patient to tolerate mechanical ventilation
- High pulmonary inflation pressures (e.g., acute respiratory distress syndrome)
- Hyperventilation for increased intracranial pressure
- Facilitation of therapeutic or diagnostic procedures
- Tetanus
- Status epilepticus
- Reduction of oxygen consumption
- Abolishing shivering
- Reduction of work of breathing

with a burn injury may be at risk for the hyperkalemic response is not well defined. A conservative guideline therefore would be to avoid the use of succinylcholine in patients 24 hours after a thermal injury and for at least 1 or 2 years after the burned skin has healed.

USE OF NEUROMUSCULAR BLOCKING DRUGS AND WEAKNESS SYNDROMES IN CRITICALLY ILL PATIENTS

NMBDs are frequently used in conjunction with sedatives and analgesics in ICUs. The indications for the use of NMBDs in the ICU are outlined in *Box 27.1*. Few available data support their use, and evidence for a beneficial effect on pulmonary function or patient oxygenation is inconclusive.³³⁷ However, a multicenter, double-blind trial showed that, in a subset of patients with acute respiratory distress syndrome, early and short-term administration of cisatracurium for 48 hours could be beneficial.³³⁸ Half of the patients in the placebo group in that study received one or more doses of cisatracurium. The study was underpowered, and the effect on mortality was statistically borderline, with no between-group difference in crude mortality rate. Yet, non-depolarizing NMBDs are sometimes used in ICU patients. Of particular concern in intensive-care settings is the risk that paralyzed patients receive inadequate analgesia and sedation.³³⁹ This reason for this concern may be that ICU nurses and physicians are unfamiliar with the pharmacology of the NMBDs.^{339,340} For instance, pancuronium was thought to be an anxiolytic by 50% to 70% of ICU nurses and house staff, and 5% to 10% thought it was an analgesic.³³⁹ In the United Kingdom, the erroneous use of NMBDs as sedatives in intensive care was not uncommon in the 1980s.³⁴¹ Approximately 96% of ICU patients received NMBDs to aid mechanical ventilation in 1980. By 1986, their use had decreased to 16% of ventilated patients.³⁴¹ Currently, intensivists are aware of the side effects and generally avoid administration of NMBDs to critically ill ICU patients. Clinical practice guidelines for management of critically ill adults who require neuromuscular paralysis have been published.^{341a} Specific indications for the use of NMBDs in the ICU setting include severe, refractory hypoxemia; suppression of shivering during therapeutic hypothermia after cardiac arrest; elimination of unwanted movement

BOX 27.2 Complications of Muscle Paralysis in the Intensive Care Unit

- Short-term use
 - Specific, known drug side effects
 - Inadequate ventilation in the event of a ventilator failure or circuit disconnection
 - Inadequate analgesia and/or sedation
- Long-term use
 - Complications of immobility
 - Deep vein thrombosis and pulmonary embolus
 - Peripheral nerve injuries
 - Decubitus ulcers
 - Inability to cough
 - Retention of secretions and atelectasis
 - Pulmonary infection
 - Dysregulation of nicotinic acetylcholine receptors
 - Prolonged paralysis after stopping relaxant
 - Persistent neuromuscular blockade
 - Critical illness myopathy
 - Critical illness polyneuropathy
 - Combination of the above
 - Unrecognized effects of drug or metabolites
 - Succinylcholine and metabolic acidosis or hypovolemia
 - 3-Desacetylvecuronium and neuromuscular blockade
 - Laudanosine and cerebral excitation

in patients with status asthmaticus, high intracranial or intraabdominal pressure, massive hemoptysis, or to facilitate short procedures such as bronchoscopy or endoscopy; and acute respiratory failure in patients who require emergent tracheal intubation.^{341a}

A prolonged ICU stay during critical illness is associated with disorders of neuromuscular function that contribute to morbidity, length of hospital stay, weaning difficulties, and prolonged rehabilitation.³⁴² The complications of long-term administration of NMBDs in the ICU are outlined in *Box 27.2*. In the ICU, duration of mechanical ventilation, sepsis, the dysfunction of two or more organs, female sex, administration of steroids, and hypercapnia are known risk factors for developing neuromuscular dysfunction. Syndromes of weakness in critically ill patients are relatively common and likely polymorphic in origin. In a retrospective study of 92 critically ill patients with clinically diagnosed weakness, electromyographic studies indicated that acute myopathy (critical illness myopathy [CIM]) is three times as common as acute axonal neuropathy (critical illness neuropathy): 43% versus 13%, respectively.³⁴² The additional healthcare cost of a single case of persistent weakness was estimated at approximately \$67,000.³⁴³ Conditions to consider when making a differential diagnosis of neuromuscular weakness in the ICU are listed in *Box 27.3*.

Critical Illness Myopathy

Lacomis and colleagues suggested using the term CIM,³⁴⁴ instead of the current terms used in the literature, such as acute quadriplegic myopathy,³⁴⁵ acute (necrotizing) myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, and critical care myopathy.

Initial published reports of CIM in the ICU focused on patients with status asthmaticus³⁴⁶ who typically had been treated with corticosteroids and nondepolarizing NMBDs.

BOX 27.3 Causes of Generalized Neuromuscular Weakness in the Intensive Care Unit

Central nervous system
Septic or toxic-metabolic encephalopathy
Brainstem stroke
Central pontine myelinolysis
Anterior horn cell disorders (e.g., amyotrophic lateral sclerosis)
Peripheral neuropathies
Critical illness polyneuropathy
Guillain-Barré syndrome
Porphyria
Paraneoplasia
Vasculitis
Nutritional and toxic neuropathies
Neuromuscular junction disorders
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Botulism
Prolonged neuromuscular junction blockade
Myopathies
Critical illness myopathy
Cachectic myopathy
Rhabdomyolysis
Inflammatory and infectious myopathies
Muscular dystrophies
Toxic myopathies
Acid maltase deficiency
Mitochondrial
Hypokalemia
Hypermetabolic syndromes with rhabdomyolysis (e.g., neuroleptic malignant syndrome)

From Lacomis D. Critical illness myopathy. *Curr Rheumatol Rep.* 2002;4:403–408.

Nevertheless, myopathy has also been documented in asthmatic patients and in patients with chronic lung disease without paralysis who received corticosteroids,³⁴⁷ as well as in critically ill patients with sepsis who received neither corticosteroids nor nondepolarizing NMBDs.³⁴⁸ The primary cause of this condition is a loss of myosin in myocytes with subsequent loss of contractile capacity. Animal studies also reveal that the number of cytosolic corticosteroid receptors is increased in immobilized muscles relative to that in contralateral controls.³⁴⁹ It seems—at least in some patients—that prolonged immobility may be the key risk factor for myopathy in corticosteroid-treated patients,³⁵⁰ and selective muscle atrophy is a result of changes in glucocorticoid sensitivity.³⁴⁹

Sepsis, immobility, and the catabolism associated with negative nitrogen balance may also result in myopathy.¹⁶ Skeletal muscle hypoperfusion is noted in patients with severe sepsis despite normal or elevated whole blood oxygen delivery.³⁵¹ Antibodies to nAChRs were demonstrated in a rodent model of sepsis.³⁵² Thus myasthenia-like syndrome is also seen in critically ill patients. Evidence for local immune activation by cytokine expression in the skeletal muscle was reported in patients with CIM.³⁵³

The major feature of CIM is flaccid weakness that tends to be diffuse and sometimes also includes the facial muscles and diaphragm.³⁴⁴ The clinical features of CIM overlap with those of critical illness polyneuropathy (CIP) and prolonged

neuromuscular blockade.³⁴⁴ Electrophysiologic studies and increases in serum creatine kinase concentrations may differentiate neuropathy from myopathy.³⁴⁴ Lacomis and colleagues stated, “muscle biopsy should be considered if another myopathic process such as an inflammatory myopathy is suspected or if the histologic findings would affect management.”³⁴⁴

Critical Illness Polyneuropathy

CIP is the polyneuropathy seen in critically ill patients. It affects both sensory and motor nerves and occurs in 50% to 70% of patients with multisystem organ failure and systemic inflammatory response syndrome.³⁵⁴ Investigators have postulated that systemic inflammatory response syndrome contributes to CIP by releasing cytokines and free radicals that damage the microcirculation of the central and peripheral nervous systems.³⁵³ Dysregulation of the microcirculation may render the peripheral nervous system susceptible to injury.

Although no pharmacologic treatment for muscle weakness syndromes in the critically ill patient currently exists, increasing evidence indicates the positive effects of early physical rehabilitation during ICU stay. Previously, intensive insulin therapy during critical illness was found to decrease the risk of CIP, and the maintenance of blood glucose at or below 110 mg/mL in critically ill patients may reduce the risk of CIP.

The outcomes from CIM and CIP appear to be similar. The reported mortality rate of patients with CIP syndrome is approximately 35%. In one study, 100% (13 of 13) of the patients who survived had abnormal clinical or neurophysiologic findings 1 to 2 years after the onset of the CIP syndrome, and quality of life was markedly impaired in all patients.³⁵⁵

Clinical Implications

Nondepolarizing NMBDs are the most common chemical agents producing immobilization and inducing a denervation-like state. In such circumstances, besides the mature or junctional nAChR formed of two α and one each of β , ϵ , and δ subunits, two other isoforms, the immature AChR or γ AChR and the neuronal α 7AChR, are expressed in the muscle. The immature AChR is also referred to as extrajunctional because it is expressed mostly in the extrajunctional part of the muscle. Upregulation of nAChRs was noted in the muscles of deceased critically ill adults who had received long-term infusions of vecuronium.³⁵⁶ Upregulation refers to changes in the number of available receptors, but these changes usually do not involve a change in isoform configuration. These three types of receptors can coexist in the muscle.

Should Succinylcholine Be Used in Patients in the Intensive Care Unit?

It is likely that upregulation of nAChRs induced by immobilization and by prolonged administration of nondepolarizing NMBDs contributes to (1) the higher incidence of cardiac arrest associated with the use of succinylcholine in ICU patients³⁵⁶ and (2) increased requirements for nondepolarizing NMBDs in ICU patients.³⁵⁷ Even more important, succinylcholine more easily depolarizes immature nAChRs that may induce profound outward K^+ flux, with subsequent hyperkalemia. Moreover, the α 7AChR can also be depolarized by succinylcholine, thus contributing to the K^+ efflux from the cell to the extracellular space. Therefore

succinylcholine should be avoided in ICU patients in whom total body immobilization exceeds 24 hours.¹⁶

Should Nondepolarizing Neuromuscular Blocking Drugs Be Used in Patients in the Intensive Care Unit?

NMBD-associated persistent weakness appears to be a distinct pathologic entity and is not simply a manifestation of weakness syndromes in critically ill patients. In a prospective study, there was a 70% incidence of persistent weakness in ICU patients who received NMBDs for more than 2 days, compared with a 0% incidence in similar ICU patients who received no NMBD.³⁵⁸ This is compelling evidence for the effects of nondepolarizing NMBDs in this complication.

Long-term weakness has been described after nondepolarizing NMBDs.^{156,359,360} Approximately 20% of patients who received NMBDs for more than 6 days,³⁵⁹ 15% to 40% of asthmatic patients who also received high-dose steroids,³⁴⁶ and 50% of patients with renal failure who received vecuronium developed prolonged weakness.¹⁵⁶ Clinically, it appears that prolonged recovery from neuromuscular blockade occurs more frequently when steroid NMBDs are used.^{156,359}

However, prolonged weakness was also noted after the use of atracurium in ICU patients.³⁶⁰ Further, the use of atracurium has raised concerns about its metabolite, laudanosine. Laudanosine, also detected in the cerebrospinal fluid (CSF) of ICU patients given atracurium,³⁶¹ is an analeptic and can trigger seizures in animals.³⁶² The toxic dose in humans is not known, but case reports have noted patients having seizures while receiving atracurium, and laudanosine has not been ruled out as a cause of these seizures.³⁶³⁻³⁶⁵ Evidence also indicates that laudanosine can activate neuronal nicotinic receptors.³⁶⁶ Cisatracurium is a single isomer of atracurium, and because it is four to five times more potent than atracurium, it is given in smaller total doses. Therefore the risk of laudanosine-related adverse effects should be minimal.³⁶⁷

Nondepolarizing NMBDs are polar molecules and do not readily cross the blood-brain barrier, but vecuronium and its long-acting active metabolite, 3-desacetylvecuronium, have been detected in the CSF of patients in the ICU. The CNS effects of NMBDs and their metabolites in humans have not been well studied, but in rats, atracurium, pancuronium, and vecuronium injected into the CSF caused dose-related cerebral excitation culminating in seizures.³⁶² Cerebral excitation with consequent increased cerebral oxygen demand is undesirable in ICU patients at risk of cerebral ischemia. Investigators have also suggested that nondepolarizing NMBDs can gain access to nerves during systemic inflammatory response syndrome, thus resulting in direct neurotoxicity.³⁶⁸

When nondepolarizing NMBDs are necessary, the use of an objective neuromuscular monitor is recommended, and periodic return of muscle function should be allowed. Adjusting the dosage of NMBDs by peripheral nerve stimulation versus standard “clinical dosing” in critically ill patients reduces drug requirements, produces faster recovery of neuromuscular function, and is cost-effective.³⁶⁹ Daily interruption of sedative-drug infusions decreases the duration of mechanical ventilation and the length of stay in the ICU.³⁷⁰ The effect of such an

BOX 27.4 Recommendations for the Use of Neuromuscular Blockers in the Intensive Care Unit

- Avoid the use of neuromuscular blockers by
 - Maximal use of analgesics and sedatives
 - Manipulation of ventilatory parameters and modes
- Minimize the dose of neuromuscular blocker
 - Use a peripheral nerve stimulator with train-of-four monitoring
 - Do not administer for more than 2 days continuously
 - Administer by bolus rather than infusion
 - Administer only when required and to achieve a well-defined goal
 - Continually allow recovery from paralysis
 - Consider alternative therapies

approach on the weakness syndromes in the ICU patient is unknown. When nondepolarizing NMBDs are used, the guidelines in **Box 27.4** may help minimize the incidence of complications. As stated in the clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient,³³⁷ “Independent of the reasons for using neuromuscular blockers, we emphasize that all other modalities to improve the clinical situation must be tried, using neuromuscular blockers only as a last resort. To this admonition, we would add a plea that clinicians use objective monitors, whenever possible, to guide NMBD administration and assess readiness for tracheal extubation, whether in the operating room or ICU settings. The unquestionable benefits of quantitative neuromuscular monitoring are described in **Chapter 43**.

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 Complete references available online at expertconsult.com.

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GLENN MURPHY, HANS D. DE BOER, LARS I. ERIKSSON, AND RONALD D. MILLER

KEY POINTS

- Appropriate reversal of a nondepolarizing neuromuscular blockade is essential to avoid adverse patient outcomes. Complete recovery of muscle strength should be present, and the residual effects of neuromuscular blocking drugs (NMBDs) should be fully pharmacologically reversed (or spontaneously recovered).
- Sufficient recovery from neuromuscular blockade for tracheal extubation can be confirmed by an adductor pollicis train-of-four (TOF) ratio of at least 0.90 (or 1.0 if accelerometry [AMG] is used). Quantitative neuromuscular monitoring is the only method of assessing whether a safe level of recovery of muscular function has occurred.
- Residual neuromuscular blockade is not a rare event in the postanesthesia care unit (PACU). Approximately 30% to 50% of patients can have TOF ratios less than 0.90 following surgery.
- Patients with TOF ratios less than 0.90 in the PACU are at increased risk for hypoxemic events, impaired control of breathing during hypoxia, airway obstruction, postoperative pulmonary complications, symptoms of muscle weakness, and prolonged PACU admission times. Appropriate management of neuromuscular blockade can decrease the incidence of, or eliminate, residual blockade, which will reduce the risks of these adverse postoperative events.
- Neostigmine, pyridostigmine, and edrophonium inhibit the breakdown of acetylcholine, resulting in an increase in acetylcholine in the neuromuscular junction. However, there is a “ceiling” effect to the maximal concentration of acetylcholine that can be achieved with these drugs. Reversal of neuromuscular blockade with anticholinesterases should not be attempted until some evidence of spontaneous recovery is present. Neostigmine in the dose range of 30 to 70 µg/kg body weight antagonizes moderate to shallow levels of neuromuscular blockade. However, if these reversal drugs are given in the presence of full neuromuscular recovery, paradoxical muscle weakness theoretically may be induced.
- Sugammadex is a modified γ -cyclodextrin that shows a high affinity for the steroidal NMBDs rocuronium and vecuronium. Sugammadex is able to form a tight inclusion complex with either of these steroidal NMBDs, thereby inactivating the effects of rocuronium and vecuronium, resulting in rapid reversal of neuromuscular blockade.
- Sugammadex is able to reverse a moderate/shallow and a profound neuromuscular blockade with a dose of 2.0 mg/kg and 4.0 mg/kg, respectively. An immediate reversal of neuromuscular blockade induced by rocuronium is possible with a dose of sugammadex 16 mg/kg. Reversal of neuromuscular blockade by sugammadex is rapid and without many of the side effects encountered with anticholinesterase drugs.
- Fumarates (gantacurium [GW280430A, AV430A], CW002, and CW011) represent a new class of NMBDs in development that are inactivated primarily via adduction of cysteine to the double bond of the compounds, resulting in inactive breakdown products. Laboratory studies have shown that the administration of exogenous L-cysteine results in complete reversal of deep neuromuscular blockade within 2 to 3 minutes.

History

The paralytic effects of curare have been recognized since the time of Sir Walter Raleigh's voyage on the Amazon in 1595.¹ In 1935, the name *d*-tubocurarine was assigned to an alkaloid isolated from a South American vine (*Chondrodendron tomentosum*). At approximately the same time, experiments from pharmacology and physiology laboratories in London suggested that acetylcholine was the chemical neurotransmitter at motor nerve endings.²

Investigations from these same laboratories demonstrated that eserine (physostigmine)-like substances could reverse the effects of curare at the neuromuscular junction of frog nerve-muscle preparations.² In the clinical setting, Bennett (1940) described the use of curare in the prevention of traumatic complications during convulsive shock therapy.³ In 1942, Griffith and colleagues reported on the effects of an extract of curare in 25 surgical patients; all patients appeared to recover fully without administration of an antagonist such as neostigmine.⁴

The importance of pharmacologic reversal of neuromuscular blockade was suggested in 1945. Specifically, use of neostigmine or physostigmine to antagonize curare was recognized and was recommended to be available whenever muscle relaxants were given in the operating room.⁵ The first large case series examining the use of curare was published by Cecil Gray in 1946.¹ A crystalline extract, *d*-tubocurarine chloride, was administered in 1049 general anesthesia cases. No postoperative complications directly attributable to *d*-tubocurarine were noted, and physostigmine was administered to only two patients in the series. However, in a later review article (1959) from the same anesthesia department, the authors concluded that "it is safer to always use neostigmine when nondepolarizing relaxants have been administered."⁶ By the mid-1960s, significant differences in neuromuscular management existed between the United States and Europe. As noted in an editorial from this time, "In Great Britain the majority of anesthetists have arbitrarily adopted the attitude that the dangers of reversal are far less than those of latent paresis, so that most patients receive at least some anticholinesterase drug at the end of anesthesia." In the United States, however, where smaller doses of curare were used, the emphasis was more on the mortality and morbidity associated with reversal drugs. Of greater importance was the use of muscle relaxants in smaller doses so that reversal drugs were not necessary.⁷ In fact, in the senior author's training (Miller), the prevailing thinking was that emphasis in anesthesia should be on "properly anesthetizing rather than paralyzing" a patient; it was commonly said that "curare is not an anesthetic."

Despite more than seven decades of research, significant differences in opinion still exist regarding management of neuromuscular blockade at the conclusion of surgery and anesthesia. On a routine basis, some clinicians pharmacologically antagonize a nondepolarizing neuromuscular blocking drug (NMBD), whereas others antagonize neuromuscular blockade only when obvious clinical muscle weakness is present. The issue is whether clinically important weakness exists when it is not clinically apparent. Will monitoring of neuromuscular blockade improve patient care? The aim of this chapter is to review the consequences of incomplete neuromuscular recovery, the use of anticholinesterase drugs in clinical practice (benefits, risks, and limitations), and the recent developments in novel drugs to reverse/antagonize residual neuromuscular blockade.

Antagonism of Neuromuscular Blockade: Current Management Practices

A number of survey studies have been conducted to determine how clinicians evaluate and manage neuromuscular blockade in the perioperative period. In the late 1950s, a survey was sent to anesthetists in Great Britain and Ireland.⁶ Forty-four percent of the respondents used neostigmine "always" or "almost always" when *d*-tubocurarine chloride or gallamine was used. Two thirds of respondents administered 1.25 to 2.5 mg when antagonizing these NMBDs.⁶ Despite accumulating data demonstrating

a continued frequent incidence of residual neuromuscular blockade, more-recent surveys indicate that attitudes toward reversal of neuromuscular blockade have changed little over the intervening decades. A questionnaire sent to German anesthesiologists in 2003 revealed routine reversal with neostigmine at the end of surgery was not practiced in 75% of anesthesia departments.⁸ A similar survey of 1230 senior anesthetists in France reported that pharmacologic antagonism of neuromuscular blockade was "systematic" or "frequent" in only 6% and 26% of surgical cases, respectively.⁹ In contrast, reversal of nondepolarizing NMBDs was routinely performed in Great Britain.¹⁰

A large-scale, comprehensive survey of neuromuscular management practices in the United States and Europe was conducted in order to better understand attitudes about doses of NMBDs, monitoring, and pharmacologic reversal.¹¹ Only 18% of European respondents and 34.2% of respondents from the United States "always" administered an anticholinesterase drug when a nondepolarizing relaxant was used. The findings from these surveys suggest that there is little agreement about best practices related to reversal of neuromuscular blockade. Despite perioperative guidelines from several international and national organizations, surveys from many countries reveal that most clinicians do not monitor or reverse a neuromuscular blockade in the operating room. Surprisingly, most anesthesiologists have not witnessed obvious adverse events directly attributable to incomplete recovery from neuromuscular blockade.¹¹ Therefore the potential hazards of reversal of neuromuscular blockade using an anticholinesterase drug (see later) are likely estimated to be more frequent than the risks of residual neuromuscular blockade. In the following sections, the definitions, incidence, and clinical implications of residual neuromuscular blockade are reviewed.

RESIDUAL NEUROMUSCULAR BLOCKADE

Assessment of Residual Neuromuscular Blockade

In order to optimize patient safety, tracheal extubation in the operating room should not occur until complete recovery of muscle strength is present and the residual effects of NMBDs have been fully reversed (or spontaneously recovered). Therefore methods to detect and treat residual muscle weakness are essential in improving postoperative outcomes. Three methods are commonly used in the operating room to determine the presence or absence of residual neuromuscular blockade: clinical evaluations for signs of muscle weakness, qualitative neuromuscular monitors (peripheral nerve stimulators), and quantitative (objective) neuromuscular monitors. A more detailed description of the types of neuromuscular monitors used perioperatively is provided in Chapter 43.

Clinical Evaluation for Signs of Muscle Weakness. Following the introduction of *d*-tubocurarine into clinical practice, residual paralysis and the need for neostigmine was determined primarily by the observation of "shallow, jerky movements of the diaphragm" at the end of surgery.¹² In the absence of any clinically observable respiratory impairment, neuromuscular function was assumed to be adequate, and no reversal drugs were administered. A peripheral nerve stimulator to assess neuromuscular

TABLE 28.1 Sensitivity, Specificity, Positive, and Negative Predictive Values of an Individual Clinical Test for a Train-of-Four <90% in 640 Surgical Patients

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Inability to smile	0.29	0.80	0.47	0.64
Inability to swallow	0.21	0.85	0.47	0.63
Inability to speak	0.29	0.80	0.47	0.64
General weakness	0.35	0.78	0.51	0.66
Inability to lift head for 5 s	0.19	0.88	0.51	0.64
Inability to lift leg for 5 s	0.25	0.84	0.50	0.64
Inability to sustain hand grip for 5 s	0.18	0.89	0.51	0.63
Inability to perform sustained tongue depressor test	0.22	0.88	0.52	0.64

The sensitivity of a test is the number of true positives \div the sum of true positives + false negatives; the specificity is the number of true negatives \div the sum of true negatives + false positives. True positives are patients scoring positive for a test and having a train-of-four (TOF) <90%. False negatives are patients with a negative test result but a TOF <90%. True negatives have a negative test score and a TOF not <90%; false positives score positively but have a TOF not <90%. A positive test result means *inability* to smile, swallow and speak, general muscular weakness, and so on.

From Cammu G, De Witte J, De Veylder J, et al. Postoperative residual paralysis in outpatients versus inpatients. *Anesth Analg*. 2006;102:426–429.

blockade was first used in the 1960s by Harry Churchill-Davidson in the United Kingdom and later in the United States. However, routine use of a peripheral nerve stimulator did not occur. In fact, several decades later, the most commonly applied technique for evaluation of recovery of neuromuscular function continues to be the use of clinical tests for signs of apparent muscle weakness.¹³ Furthermore, one of the primary factors that determines whether clinicians elect to administer a reversal drug at the end of surgery is the presence of signs of muscle weakness.¹¹ However, for decades an array of clinical studies from different countries have consistently shown that tests of muscle strength are not sensitive or reliable indices of adequate neuromuscular recovery. The most commonly applied criteria used to determine suitability for extubation of the trachea are a “normal” pattern of ventilation and a sustained head lift.¹³ Unfortunately, the sensitivity of each test in detecting residual blockade is poor. At a level of neuromuscular recovery that allows for adequate ventilation in a patient whose trachea is intubated, the muscles responsible for maintaining airway patency and protection are significantly impaired.¹⁴ Other investigators have observed that the majority of subjects could maintain a 5-second head lift at a train-of-four (TOF) ratio of 0.50 or less.^{15,16} Additional clinical tests of muscle strength, such as sustained hand-grip, leg-lift, or eye opening, have been demonstrated to have a low sensitivity in predicting recovery of neuromuscular function (Table 28.1).^{17,18}

Qualitative Neuromuscular Monitoring. Qualitative neuromuscular monitors—or more accurately, peripheral nerve stimulators—deliver an electrical stimulus to a peripheral nerve, and the response to nerve stimulation is subjectively assessed by clinicians either visually or tactilely (i.e., placing a hand on the thumb to detect the muscle contraction after ulnar nerve stimulation) (Fig. 28.1). Three patterns of nerve stimulation are used in the clinical setting to assess patients for residual blockade: TOF, tetanic, and double-burst stimulation. TOF stimulation delivers four supramaximal stimuli every 0.5 seconds, tetanic stimulation consists of a series of extremely rapid (usually 50 or 100 Hz) stimuli typically

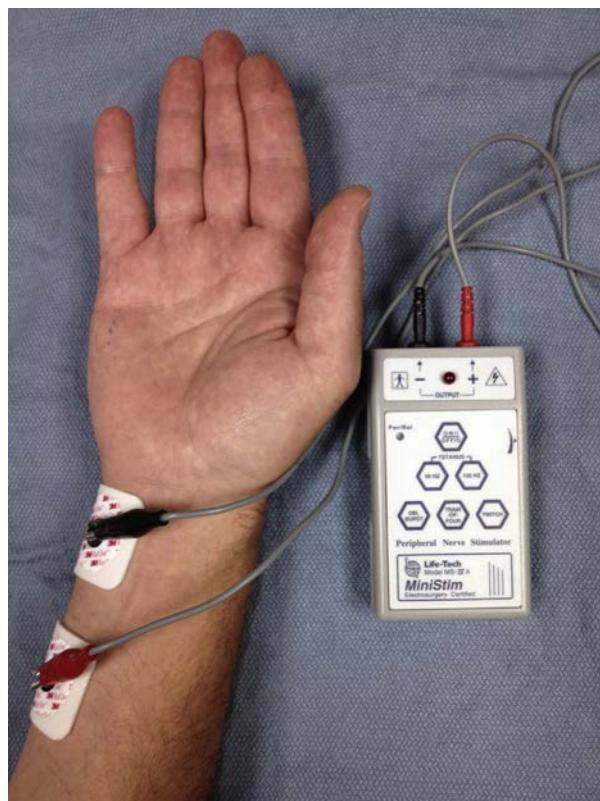


Fig. 28.1 Example of a qualitative neuromuscular monitor (or more appropriately, a peripheral nerve stimulator). (MiniStim, Halyard Health, Roswell, GA) A peripheral nerve is stimulated, and the response to nerve stimulation is subjectively (qualitatively) assessed using either visual or tactile (hand placed on the muscle) means. In this illustration, the ulnar nerve is stimulated, and movement of the thumb subjectively evaluated.

applied over 5 seconds, and double-burst stimulation delivers two short bursts of 50-Hz tetanic stimuli separated by 750 ms. The presence of fade with these patterns of nerve stimulation indicates incomplete neuromuscular recovery. Although qualitative monitoring may guide management during early recovery from neuromuscular blockade, the sensitivity of these devices in detecting small degrees of

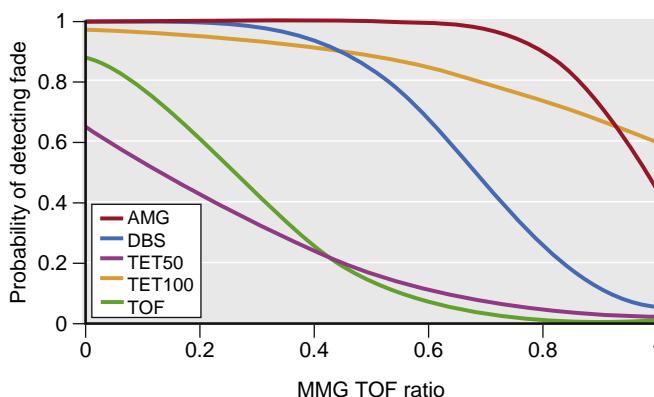


Fig. 28.2 Detection of fade with various neuromuscular monitoring techniques. Residual neuromuscular blockade was evaluated using acceleromyography (AMG), tactile assessment of train-of-four (TOF), double-burst stimulation (DBS), 50-Hz tetanic (TET50), or 100-Hz tetanic (TET100). The mechanomyographic (MMG) adductor pollicis TOF ratio was measured at one extremity. During recovery, a blinded observer estimated tactile fade in the other extremity. Probability of detection of fade by logistic regression is presented. (From Capron F, Fortier LP, Racine S, Donati F. Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanic, 100-hertz tetanic, and acceleromyography. *Anesth Analg*. 2006;102:1578–1584.)

residual paresis (TOF ratios between 0.50 and 1.0) is limited (Fig. 28.2). When using TOF stimulation, investigators have consistently observed that clinicians are unable to detect fade when TOF ratios exceed 0.30 to 0.40.^{19–21} Similarly, the observation of fade during a 5-second, 50-Hz tetanic stimulation is difficult when TOF ratios are greater than 0.30.^{21,22} The ability of clinicians to detect fade is improved with double-burst stimulation; the threshold for detection of fade is approximately 0.6 to 0.7 using this mode of stimulation.^{20,21,23} However, regardless of the mode of nerve stimulation used, residual neuromuscular blockade cannot always be reliably excluded using qualitative monitoring.

Quantitative Neuromuscular Monitoring. Quantitative neuromuscular monitors are instruments that permit both stimulation of a peripheral nerve and the quantification and recording of the evoked response to nerve stimulation. Quantitative monitors allow an accurate assessment of the degree of muscle weakness using either TOF stimulation (TOF ratio displayed) or single-twitch stimulation (response compared with control “twitch” as a percentage). Although five different methods of quantifying neuromuscular function in the operating room have been developed, only one technology, acceleromyography (AMG, available as the Stimpod, Xavant Technology, Pretoria, South Africa), is commercially obtainable as a stand-alone monitor. The portable TOF-Watch AMG monitor (Bluestar Enterprises, San Antonio, Texas), which has been used in the majority of published clinical trials, is no longer sold in the United States (Fig. 28.3). In a study comparing AMG with standard qualitative tests (tactile fade to TOF, double-burst, 5-Hz tetanic, and 100-Hz tetanic stimulation), AMG was the most accurate technique in detecting residual paralysis (see Fig. 28.2).²¹ In addition, the use of AMG in the operating room has been demonstrated to reduce the risk of residual neuromuscular blockade in the postanesthesia care unit (PACU)^{24–27} and to decrease adverse respiratory events and

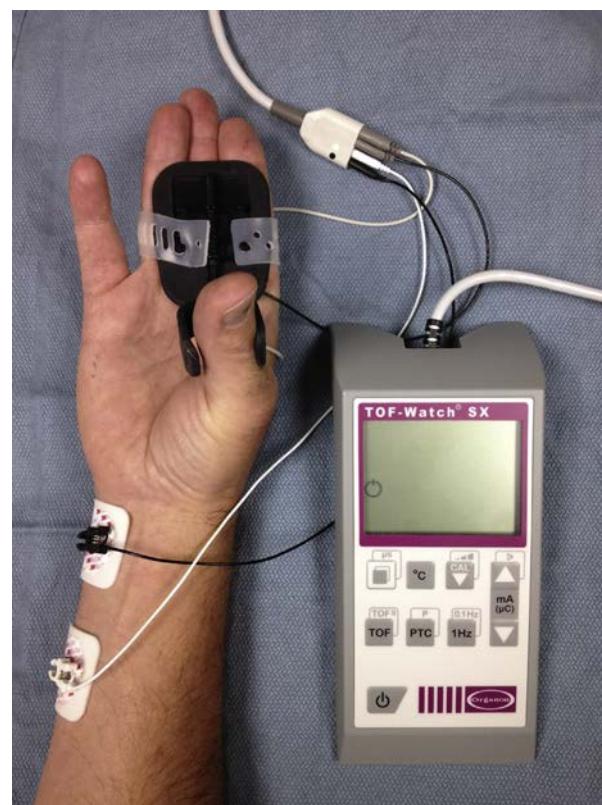


Fig. 28.3 Example of a quantitative neuromuscular monitor (acceleromyography). (TOF-Watch AMG, Bluestar Enterprises, San Antonio, TX) Ulnar nerve stimulation results in thumb movement, which is sensed by a piezoelectric sensor attached to the thumb. To improve the consistency of responses, a hand adapter applies a constant preload. Acceleration of the thumb is sensed by the piezoelectric sensor, and is proportional to the force of muscle contraction.

symptoms of muscle weakness associated with incomplete neuromuscular recovery.^{26,27} In clinical practice, AMG is a valuable monitor in determining whether full recovery of neuromuscular function has occurred before tracheal extubation, and provides objective data to guide dosing of reversal drugs at the conclusion of surgery (see later).

A careful evaluation of the degree of residual blockade at the conclusion of a general anesthetic is essential in order to avoid the potential hazards of incomplete neuromuscular recovery following tracheal extubation. However, the methods used by most clinicians (ability to perform a head lift or maintain a stable pattern of ventilation; no fade observed to TOF or tetanic nerve stimulation) are insufficient in assuring safe recovery. At the present time, quantitative neuromuscular monitoring is the only method of determining whether full recovery of muscular function has occurred and reversal drugs safely avoided. In order to exclude with certainty the possibility of residual paresis, quantitative monitoring should be used. For a more comprehensive description of neuromuscular monitoring see Chapter 43.

Definitions of Residual Neuromuscular Blockade

QUANTITATIVE NEUROMUSCULAR MONITORING: TOF RATIO LESS THAN 0.70 AND LESS THAN 0.90 Traditionally, residual neuromuscular blockade has been defined using quantitative neuromuscular monitoring. Although peripheral nerve stimulation was used in the 1960s, Ali and colleagues

first described the application of peripheral nerve stimulation for neuromuscular monitoring using the ulnar nerve–adductor pollicis unit as the site of monitoring in the early 1970s.^{28,29} By comparing the amplitude of the fourth (T4) to the first (T1) evoked mechanical or electromyographic response (TOF response), the degree of neuromuscular recovery could be measured. Shortly thereafter, these same investigators performed several studies examining the association between the degree of residual blockade in the hand (defined using quantified T4/T1 ratio, i.e., TOF ratio) with symptoms of peripheral muscle weakness and spirometry measurements.^{30–32} At adductor pollicis TOF ratios less than 0.60, signs of muscle weakness, tracheal tug, and ptosis were observed. When TOF ratios recovered to 0.70, the majority of patients were able to sustain head lift, eye opening, hand grasp, tongue protrusion, and a vital capacity exceeding 15 mL/kg. On the basis of these data, a TOF ratio of 0.70 was previously agreed on to represent acceptable neuromuscular recovery at the end of a general anesthetic that included administration of nondepolarizing NMBDs. Yet, more recently, clinically significant muscle weakness and impaired respiratory control have been observed at TOF ratios of up to 0.90. At TOF ratios less than 0.90, awake volunteers exhibit impaired pharyngeal function, airway obstruction, an increased risk of aspiration of gastric contents, an impaired hypoxic ventilatory control, and unpleasant symptoms of muscle weakness.^{33–37} In surgical patients, an association between TOF ratios less than 0.90 and adverse respiratory events and prolonged PACU length of stay has been observed.^{38,39} At the present time, it is generally agreed that adequate recovery of neuromuscular function is represented by an adductor pollicis TOF ratio of at least 0.90 (or even 1.0 when AMG is used).

CLINICAL SIGNS AND SYMPTOMS. A variety of clinical signs may be present in patients with residual neuromuscular blockade, including the following: inability to perform a head lift, hand grip, eye opening, or tongue protrusion; inability to clench a tongue depressor between the incisor teeth; inability to smile, swallow, speak, cough, track objects with eyes; or inability to perform a deep or vital capacity breath.⁴⁰ Symptoms of residual blockade that have been reported include subjective difficulty performing the aforementioned tests, as well as blurry vision, diplopia, facial weakness, facial numbness, and general weakness.^{37,40} Although the majority of patients with TOF ratios of 0.90 to 1.0 will have recovered satisfactory strength in

most muscle groups, signs and symptoms of muscle weakness may be present in some of these patients. In contrast, a few patients with significant residual blockade (TOF ratios < 0.70) may exhibit no apparent muscle weakness. The most inclusive and precise definition of residual neuromuscular blockade should include not only objective and quantifiable monitoring data (a TOF ratio < 0.90 demonstrated with AMG, mechanomyography [MMG], or electromyography [EMG]) but also clinical evidence of impaired neuromuscular recovery (swallowing impairment, inability to speak or perform a head lift, diplopia, and/or general weakness).

Incidence of Residual Neuromuscular Blockade

Residual neuromuscular blockade is not a rare event in the PACU. In 1979, Viby-Mogensen examined the efficacy of neostigmine in reversing *d*-tubocurarine, gallamine, or pancuronium blockade.⁴¹ On arrival to the PACU, 42% of patients had a TOF ratio less than 0.70, and 24% were unable to perform a 5-second head lift (the majority of these subjects had TOF ratios < 0.70). The authors concluded that the average dose of neostigmine given (2.5 mg) was insufficient for reversing neuromuscular blockade. Subsequent studies demonstrated a similarly frequent incidence of residual blockade in patients receiving long-acting NMBDs; 21% to 50% of patients in the early postoperative period had TOF ratios less than 0.70.^{42–44} Subsequently, the risk of postoperative residual blockade was reduced if intermediate-acting NMBDs were used instead of long-acting drugs.^{44–46} As the use of long-acting NMBDs began to decrease in clinical practices, many investigators hoped that residual blockade would become an uncommon occurrence in the PACU. However, incomplete neuromuscular recovery continues to be a common postoperative event. Large-scale studies (150–640 subjects) have demonstrated that approximately 31% to 50% of patients have clinically significant residual neuromuscular blockade with adductor pollicis TOF ratios less than 0.90 following surgery.^{17,47,48} A recent multicenter investigation enrolling 1571 patients from 32 centers documented that 58% of patients had TOF ratios less than 0.90 at the time of tracheal extubation, despite the use of neostigmine reversal in 78% of subjects.⁴⁹ In a metaanalysis of data from 24 clinical trials, Naguib and colleagues calculated the incidence of residual blockade by NMBD type and TOF ratio.⁴⁴ The pooled rate of residual blockade, defined as a TOF ratio less than 0.90, was 41% when studies using intermediate-acting NMBDs were analyzed (Table 28.2). In conclusion, a frequent incidence

TABLE 28.2 Pooled Estimated Incidence of Residual Neuromuscular Blockade by Muscle Relaxant Type and Train-of-Four Ratio

Sub-Population	Pooled Rate of RNMB*	Confidence Interval	HETEROGENEITY	
			P-value	Inconsistency [†] (%)
Long-acting MR (TOF <0.70)	0.351	(0.25–0.46)	<.001	86.7
Intermediate-acting MR (TOF <0.70)	0.115	(0.07–0.17)	<.001	85.9
Long-acting MR (TOF <0.90)	0.721	(0.59–0.84)	<.001	88.1
Intermediate-acting MR (TOF <0.90)	0.413	(0.25–0.58)	<.001	97.2

*Pooled rate of RNMB is the weighted average. The weight in the random-effect model takes into account both between and within studies variation.

[†]Inconsistency is the proportion of between studies variability that cannot be explained by chance.

MR, Muscle relaxant; RNMB, residual neuromuscular blockade; TOF, train-of-four.

From Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth*. 2007;98:302–316.

of residual neuromuscular blockade still occurs worldwide in the immediate postoperative period; with current practice and inadequate monitoring, the incidence of this complication is not decreasing over time.

The observed incidence of postoperative residual blockade varies widely between studies, ranging from 5% to 93%.⁴⁴ A number of factors may influence the degree of neuromuscular recovery measured following tracheal extubation, accounting for the reported variability in the incidence of residual blockade (Box 28.1). The observed incidence of residual blockade is more frequent if a threshold definition of 0.90 is used (vs. the previous threshold of 0.70) (see Table 28.2). Similarly, a frequent incidence of residual paralysis is observed if there is a short time interval between reversal of NMBDs and quantification of TOF ratios (TOF ratios measured at the time of extubation vs. measurement in the PACU).⁵⁰ Furthermore, the technology used to quantify neuromuscular recovery may influence the percentage of patients with TOF ratios less than 0.90 following surgery. For example, when compared with MMG, AMG frequently overestimates the degree of neuromuscular recovery.²¹ Additional factors influencing the degree of residual paralysis are discussed later.

Adverse Effects of Residual Blockade

Many investigations have demonstrated that approximately one half of patients will be admitted to the PACU with TOF ratios less than 0.90, as measured with AMG, MMG, or EMG.⁴⁴ The impact of this residual muscle weakness on clinical outcomes has been less well documented.

Yet even minimal levels of neuromuscular blockade may have clinical consequences. The following section reviews the effects of residual blockade in both awake volunteer studies and in postoperative surgical patients.

Adverse Effects of Residual Blockade—Awake Volunteer Studies. Surgical patients receive a variety of anesthetics in the perioperative period, which complicates an assessment of the particular effect of residual neuromuscular blockade on clinical outcomes. Conducting awake volunteer trials allows investigators to more precisely quantify the impact of NMBDs and various degrees of neuromuscular blockade on physiologic systems in the absence of anesthetics. In general, these studies have titrated NMBDs to various TOF ratios in awake subjects and measured the effects on the respiratory system and on signs and symptoms of muscle weakness.

Early volunteer investigations concluded that respiratory impairment was minimal at TOF ratios of 0.60 to 0.70.³² Respiratory frequency, tidal volume, vital capacity, and peak expiratory flow rates were not altered during the study, although vital capacity and inspiratory force were both significantly reduced compared with control values at a TOF ratio of 0.60.³² The authors concluded that these changes were of minor clinical importance. Subsequent investigations have revealed that pharyngeal and respiratory function is impaired at TOF ratios as high as 0.90 to 1.0. Return of pharyngeal muscle function is essential for airway control following tracheal extubation. In series of human studies from the Karolinska Institutet, Sweden, a

BOX 28.1 Factors Influencing the Measured Incidence of Postoperative Residual Neuromuscular Blockade

Preoperative Factors

1. Definition of residual neuromuscular blockade
 - TOF ratio < 0.70 (before 1990)
 - TOF ratio < 0.90 (after 1990)
 - Presence of signs or symptoms of muscle weakness
2. Patient factors
 - Age (higher risk in older adults)
 - Gender
 - Preexisting medical conditions (renal or liver dysfunction, neuromuscular disorders)
 - Medications known to affect neuromuscular transmission (antiseizure medications)

Intraoperative Anesthetic Factors

1. Type of NMBD administered intraoperatively
 - Intermediate-acting NMBD (lower risk)
 - Long-acting NMBD (higher risk)
2. Dose of NMBD used intraoperatively
3. Use of neuromuscular monitoring
 - Qualitative monitoring (studies inconclusive)
 - Quantitative monitoring (lower risk)
4. Depth of neuromuscular blockade maintained
 - “Deeper blockade” (TOF count of 1-2) (higher risk)
 - “Lighter blockade” (TOF count of 2-3) (lower risk)
5. Type of anesthesia used intraoperatively
 - Inhalational agents (higher risk)
 - TIVA (lower risk)

Factors Related to Antagonism of Residual Blockade

1. Use of reversal agents (lower risk)
 - Neostigmine
 - Pyridostigmine
 - Edrophonium
 - Sugammadex
2. Dosage of reversal agent used
3. Time interval between reversal agent administration and quantification of residual blockade

Factors Related to Measurement of Residual Blockade

1. Method of objective measurement of residual neuromuscular blockade
 - Mechanomyography (MMG)
 - Electromyography (EMG)
 - Acceleromyography (AMG)
 - Kinemyography (KMG)
 - Phonemyography (PMG)
2. Time of measurement of residual neuromuscular blockade
 - Immediately

Postoperative Factors

1. Respiratory acidosis and metabolic alkalosis (higher risk)
2. Hypothermia (higher risk)
3. Drug administration in the PACU (antibiotics, opioids) (higher risk)

functional assessment of the pharynx, upper esophageal muscles, and the integration of respiration with swallowing was performed during various levels of neuromuscular blockade.³³⁻³⁴ At adductor pollicis TOF ratios less than 0.90, pharyngeal dysfunction was observed in 17% to 28% of young adult volunteers (Fig. 28.4),³³ increasing more than twofold in patients older than 60 years and associated with reduced upper esophageal sphincter resting tone and misdirected swallowing and aspiration (laryngeal penetration) of oral contrast material.^{33,34,51} Eikermann and colleagues conducted a series of investigations examining the effect of residual paresis on respiratory muscle function in awake volunteers. Awake subjects were administered

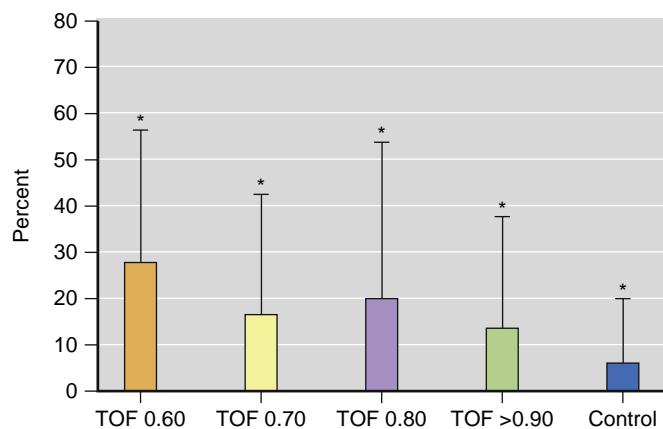


Fig. 28.4 Incidence of pharyngeal dysfunction during atracurium-induced partial neuromuscular blockade corresponding to steady-state adductor pollicis TOF ratio of 0.60, 0.70, 0.80, >0.90, and control in young volunteers. TOF, Train-of-four. (Modified from Sundman E, Witt H, Olsson R, et al. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans. *Anesthesiology*. 2000;92:977-984.)

a rocuronium infusion, which was titrated to a TOF ratio 0.50 to 1.0. At a minimal level of residual blockade (approximately 0.80), the authors observed impaired inspiratory air flow and upper airway obstruction,³⁵ a marked decrease in upper airway volumes and upper airway dilator muscle function,⁵² and increased upper airway closing pressure and collapsibility (Fig. 28.5).⁵³ In addition, evidence from human studies of respiratory control suggest that residual blockade inhibits hypoxic ventilatory control while leaving the ventilatory control during hypercapnia unaffected. In human volunteers, the hypoxic ventilatory response was attenuated by 30% after administration of either atracurium, vecuronium, or pancuronium at an adductor pollicis TOF ratio of 0.70, returning to normal after spontaneous recovery to a TOF ratio of greater than 0.90 (Fig. 28.6).⁵⁴ An increase in ventilatory drive during hypoxia is primarily mediated by afferent input from peripheral chemoreceptors in the carotid bodies located bilaterally at the carotid artery bifurcation, whereas ventilatory regulation during hypercapnia is mediated via CO_2 interaction with brainstem chemoreceptors. In experimental animals, the firing frequencies of carotid body chemoreceptors are almost abolished by the administration of a nondepolarizing NMBD via blockade of cholinergic neuronal subtype receptors within the carotid body oxygen signaling pathway.⁵⁵

Awake volunteer studies have also revealed that unpleasant symptoms of muscle weakness are present in subjects with small degrees of residual neuromuscular blockade. Conscious subjects given a small “priming” dose of pancuronium noted blurred vision, difficulty swallowing, and keeping their eyes open, and jaw weakness at a TOF ratio of 0.81.⁵⁶ Symptoms of diplopia, dysarthria, and subjective difficulty swallowing were reported by subjects at TOF ratios of 0.60 and 0.70.³⁴ Reduced clarity of vision was described in all subjects receiving a mivacurium infusion at a TOF ratio of 0.81.⁵⁷ Kopman and associates examined 10 volunteers

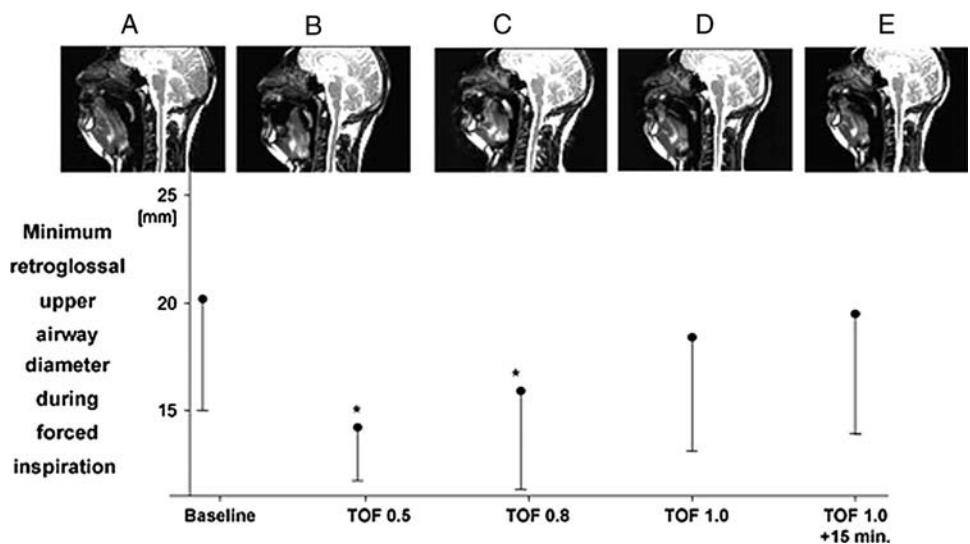


Fig. 28.5 An investigation examining the effect of residual neuromuscular blockade on respiratory muscle function in awake volunteers. Subjects were administered a rocuronium infusion, which was titrated to a train-of-four (TOF) ratio 0.5 to 1.0. Supraglottic airway diameter and volume was measured by respiratory-gated magnetic resonance imaging. Minimum retroglossal upper airway diameter during forced inspiration (A) before neuromuscular blockade (baseline), at a steady-state TOF ratio of (B) 0.50 and (C) 0.80, (D) after recovery of the TOF ratio to 1.0, and (E) 15 minutes later. Images from the volunteer show that a partial paralysis evokes an impairment of upper airway diameter increase during forced inspiration. $P < .05$ versus baseline. (From Eikermann M, Vogt FM, Herbstreich F, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Respir Crit Care Med*. 2007;175:9-15.)

for symptoms and signs of residual paralysis at various TOF ratios.³⁷ Testing was performed at baseline (before an infusion of mivacurium), at a TOF ratio of 0.65 to 0.75, at 0.85 to 0.95, and at full recovery (1.0). All subjects had significant signs and symptoms at a TOF ratio of 0.70 (inability to maintain incisor teeth apposition, sit without assistance, drink from a straw, visual disturbances, facial numbness, difficulty speaking and swallowing, general weakness), and in seven subjects, visual symptoms persisted for up to 90 minutes after the TOF ratio had recovered to unity.

Adverse Effects of Residual Blockade—Postoperative Surgical Patients. Awake volunteers have impairment of respiratory function and a variety of symptoms of muscle weakness at TOF ratios of 0.50 to 0.90. Similar adverse events have been observed in postoperative surgical patients with TOF ratios less than 0.90 measured in the PACU. Incomplete neuromuscular recovery is a risk factor for hypoxic events, airway obstruction, unpleasant symptoms of muscle weakness, delayed PACU length of stay, and pulmonary complications during the early postoperative period.

Clearly, an association exists between neuromuscular management characteristics and postoperative morbidity and mortality. Beecher and colleagues collected data from 10 university hospitals between the years 1948 to 1952 to determine anesthetic-related causes of mortality.⁵⁸ Risk of death related to anesthesia was six times more frequent in patients receiving NMBDs (primarily tubocurarine and decamethonium) compared with those administered no NMBDs (1:370 vs. 1:2100). Although the authors conclude that there is "an important increase in anesthesia death rate when muscle relaxants are added"⁵⁸ to an anesthetic, the use or omission of pharmacologic reversal in patients receiving NMBDs was not reported or analyzed. In another large-scale study, mortality data associated with anesthesia were collected over a 10-year period (1967-1976) at a single institution in South Africa.⁵⁹ An analysis of 240,483 anesthetics revealed that "respiratory inadequacy following myoneural blockade" was the second-most common cause of death. Again, data relating to the use of pharmacologic

reversal drugs were not provided. A study from the Association of Anaesthetists of Great Britain and Ireland examined deaths that were judged "totally due to anesthesia" and reported that postoperative respiratory failure secondary to neuromuscular management was a primary cause of mortality.⁶⁰ Rose and associates examined patient, surgical, and anesthetic factors associated with critical respiratory events in the PACU.⁶¹ Of the anesthetic management factors assessed, the most frequent rate of critical respiratory events was observed in patients receiving large doses of NMBDs (the use of reversal drugs was not analyzed). Two investigations of anesthetic complications resulting in admissions to the intensive care unit determined that "failure to reverse after muscle relaxants" and "ventilatory inadequacy after reversal of muscle relaxants" were the most common causes of admission.^{62,63} Sprung and colleagues reviewed the medical records of patients who experienced a cardiac arrest over a 10-year period (223 of 518,284 anesthetics).⁶⁴ The most important category was the use of NMBDs, involving either hypoxia caused by inadequate pharmacologic reversal or asystole induced by anticholinesterase drugs. A large case-control investigation was performed of all patients undergoing anesthesia over a 3-year period ($n = 869,483$) in The Netherlands assessing the impact of anesthetic management characteristics on the risk of coma or death within 24 hours of surgery.⁶⁵ Reversal of the effects of NMBDs was associated with a significant reduction (odds ratio, 0.10; 95% confidence interval [CI], 0.03-0.31) in the risk of these complications. Two studies published in 2016 and 2017 examined the association between failure to reverse neuromuscular blockade and postoperative pneumonia.^{66,67} In an investigation examining 13,100 surgical patients, Bulka and associates observed that the risk of postoperative pneumonia was 2.26 times more likely in patients that did not receive reversal with neostigmine.⁶⁶ Similarly, a retrospective study of 11,355 noncardiac patients revealed that the risk of respiratory complications (failure to wean from the ventilator, reintubation, or pneumonia) was significantly higher (odds ratio 1.75) in patients who were administered an NMBD without neostigmine compared to those given neostigmine.⁶⁶

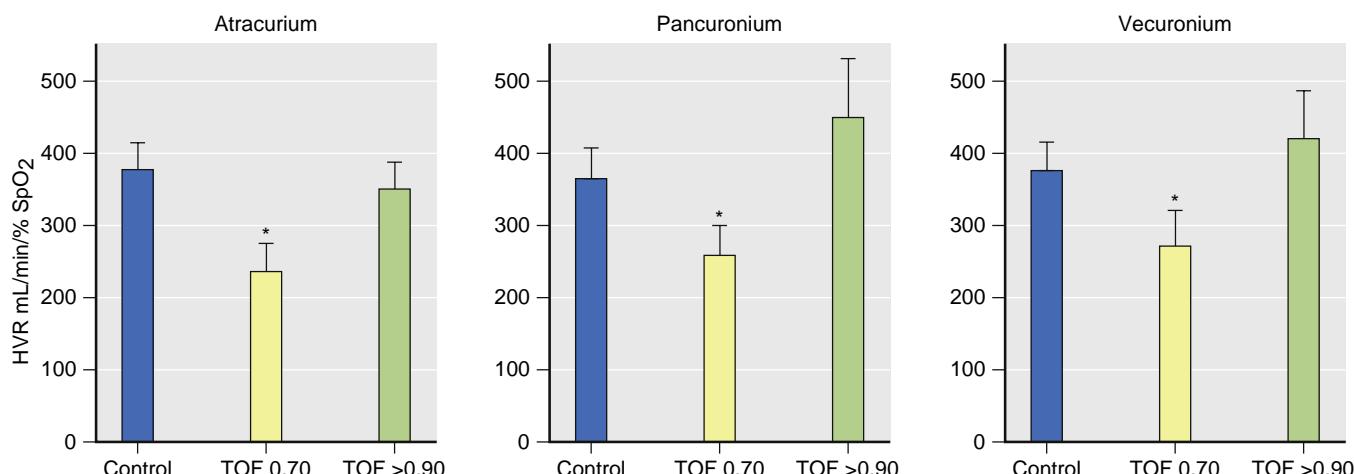


Fig. 28.6 Hypoxic ventilatory response (HVR) before (control); during steady-state infusion at train-of-four (TOF) ratio 0.70 of atracurium, pancuronium, and vecuronium; and after recovery (TOF ratio > 0.90). Data presented as means \pm SD. * = $P < .01$. SpO_2 , Saturation of arterial blood with oxygen. (From Eriksson LI. Reduced hypoxic chemosensitivity in partially paralysed man: a new property of muscle relaxants. *Acta Anaesthesiol Scand*. 1996;40:520-523.)

Epidemiologic studies thus suggest an association between incomplete neuromuscular recovery and adverse events in the early postoperative period. Notably, an important limitation of these outcome studies is that residual paresis was not quantified at the end of surgery. Therefore causality (residual blockade results in postoperative complications) can only be suggested but not proven.

In order to address these limitations, more recent studies have quantified TOF ratios in the PACU and documented a relationship between residual blockade and adverse outcomes. Several clinical investigations have documented an association between postoperative residual blockade and adverse respiratory events. In an observational study by Bissinger and colleagues, patients with TOF ratios less than 0.70 in the PACU had a more frequent incidence of hypoxemia (60%) compared with patients with TOF ratios 0.70 or greater (10%, $P < .05$).⁶⁸ Another small study of orthopedic surgical patients randomized to receive either pancuronium or rocuronium revealed that patients with TOF ratios less than 0.90 on arrival to the PACU were more likely to develop postoperative hypoxemia (24 of 39 patients) than those with TOF ratios greater than 0.90 (7 of 30 patients, $P = .003$).⁶⁹ Murphy and associates conducted a case-control study examining the incidence and severity of residual blockade in patients who developed critical respiratory events in the PACU.³⁸ Seventy-four percent of patients in the group with critical respiratory events had TOF ratios less than 0.70, compared with 0% in the matched control group (matched for age, sex, and surgical procedure). Because the two cohorts did not differ in any perioperative characteristics with the exception of neuromuscular recovery, these findings suggest that unrecognized residual paralysis is an important contributing factor to postoperative adverse respiratory events. Another investigation by this same group examined the effect of AMG monitoring on postoperative respiratory events.²⁶ Few patients randomized to AMG monitoring had postoperative TOF ratios less than 0.90, and a less frequent incidence of early hypoxemia and airway obstruction was observed in this group (compared with patients randomized to standard qualitative monitoring). A study of 114 patients randomized to neostigmine reversal or placebo (saline) documented a significantly more frequent incidence of both postoperative residual blockade and hypoxemia in the placebo group.⁷⁰ Residual blockade in the PACU may also result in pulmonary complications within the first postoperative week. Berg and colleagues randomized 691 patients to receive pancuronium, atracurium, or vecuronium.⁷¹ TOF ratios were quantified in the PACU, and subjects were followed for 6 days for pulmonary complications. In the pancuronium group, significantly more patients with TOF ratios less than 0.70 developed a pulmonary complication (16.9%) compared with patients with TOF 0.70 or greater (4.8%). Notably, the study also demonstrated a continuously increased risk for postoperative pulmonary complications with increased age, a finding of significant clinical relevance for older adult patients, a growing part of the surgical patient population. Norton and colleagues assessed recovery characteristics in 202 consecutive patients arriving in the PACU. Thirty percent of patients had TOF ratios greater than 0.9; subjects with residual block had a significantly higher incidence of critical respiratory events, airway obstruction, hypoxemia,

and respiratory failure.⁷² An observational study enrolling 150 patients ages 18 to 50 and 150 patients more than 70 years old assessed the association between incomplete neuromuscular recovery ($TOF < 0.9$) and adverse events from the time of tracheal extubation until hospital discharge.⁷³ Elderly subjects had a higher risk of residual block (58% vs. 30%), and those elderly with TOF ratios less than 0.9 had a significantly higher incidence of airway obstruction episodes and hypoxemic events, as well as signs and symptoms of muscle weakness.⁷³ A multicenter study from Spain enrolling 763 patients from 26 centers reported that 27% of patients had TOF ratios less than 0.9 and that these subjects had a higher incidence of adverse respiratory events (odds ratio 2.57) and an increased risk of reintubation.⁷⁴ An additional study (340 patients) noted that patients with residual block had a greater than sixfold increase in postoperative adverse respiratory events.⁷⁵

Residual blockade causes unpleasant symptoms of muscle weakness. This symptom of “general weakness” was the most sensitive “test” for determining whether patients had a TOF ratio of less than 0.90 in the PACU.¹⁷ Orthopedic surgical patients given pancuronium had a more frequent risk of exhibiting both TOF ratios less than 0.90 and symptoms of blurry vision and general weakness during the PACU admission, compared with patients randomized to receive rocuronium.⁶⁹ Similar findings were observed in a cardiac surgical patient population not receiving anticholinesterase drugs.⁷⁶ The subjective experience of residual neuromuscular blockade after surgery was determined by examining 155 patients for 16 symptoms of muscle weakness during the PACU admission.²⁷ The presence of symptoms of muscle weakness was predictive of a TOF ratio less than 0.90 (good sensitivity and specificity).

The residual effects of NMBDs on postoperative muscle strength may impair clinical recovery and prolong PACU discharge times. In a small study of patients randomized to receive either pancuronium or rocuronium, the times required to meet and achieve discharge criteria were significantly longer in the pancuronium group, and patients in the cohort as a whole with postoperative TOF ratios less than 0.90 were more likely to have a prolonged PACU stay compared with those with TOF ratios greater than 0.90.⁶⁹ A larger investigation measured TOF ratios in 246 consecutive patients on arrival to the PACU.³⁹ The PACU length of stay was significantly longer in patients with TOF ratios less than 0.90 (323 minutes) compared with patients with adequate recovery of neuromuscular function (243 minutes). Multiple regression analysis revealed that only age and residual blockade were independently associated with PACU length of stay.

In conclusion, a number of studies conducted over the past five decades have documented the effects of small degrees of residual blockade in human volunteers and surgical patients. Awake volunteer investigations have demonstrated that subjects with TOF ratios less than 0.90 have reduced upper airway tone and diameters, upper airway obstruction, pharyngeal dysfunction with impaired airway integrity, decreased upper esophageal tone, and an increased risk of aspiration, impaired hypoxic ventilatory control, and unpleasant symptoms of muscle weakness. Epidemiologic outcome investigations have suggested an association between incomplete neuromuscular recovery

and major morbidity and mortality. Prospective clinical trials have revealed that patients with TOF ratios less than 0.90 in the PACU are at increased risk for hypoxic events, airway obstruction, postoperative pulmonary complications, symptoms of muscle weakness, and prolonged PACU admission times. These data suggest that residual blockade is an important patient safety issue in the early postoperative period. Therefore appropriate management of reversal of neuromuscular blockade and assessment of recovery from neuromuscular blockade are two essential clinical components to optimize patient outcomes.

Drugs Used to Antagonize (Reverse) Neuromuscular Blockade

Reversal of neuromuscular blockade is theoretically possible by three principal mechanisms: (1) an increase in presynaptic release of acetylcholine; (2) a decrease in enzymatic metabolism of acetylcholine by cholinesterase, thereby increasing receptor binding competition; and (3) a decrease in the concentration of the NMBD at the effect-site, freeing the postsynaptic receptors.

ANTICHOLINESTERASE REVERSAL OF NEUROMUSCULAR BLOCKADE

Nondepolarizing NMBDs inhibit neuromuscular transmission primarily by competitively antagonizing or blocking the effect of acetylcholine at the postjunctional nicotinic acetylcholine receptor (nAChR). Binding of nondepolarizing NMBDs to the nAChR occurs in a competitive fashion. If larger concentrations of acetylcholine are present at the neuromuscular junction, acetylcholine will attach to the postsynaptic receptor and facilitate neuromuscular transmission and muscle contraction. Conversely, if larger concentrations of a nondepolarizing NMBD are present at the neuromuscular junction, binding to α subunits of the receptor will preferentially occur, preventing central pore opening and muscle depolarization from occurring. A more detailed description of the neuromuscular junction is provided in [Chapter 12](#).

One mechanism of reversing the effects of NMBDs is by an increase in the concentration of acetylcholine at the neuromuscular junction. This can be accomplished using an inhibitor of cholinesterase, which constrains the enzyme that breaks down acetylcholine at the neuromuscular junction (acetylcholinesterase). Three anticholinesterase drugs are commonly used in clinical practice: neostigmine, edrophonium, and pyridostigmine. Neostigmine is likely the most commonly administered drug. Over the prior six decades, anticholinesterases have been the only drugs used clinically to reverse neuromuscular blockade (until the recent introduction of sugammadex).

Mechanism of Action of Anticholinesterases

Acetylcholine is the primary neurotransmitter that is synthesized, stored, and released by exocytosis at the distal motor nerve terminal. Acetylcholinesterase is the enzyme responsible for the control of neurotransmission at the

neuromuscular junction by hydrolyzing acetylcholine. Rapid hydrolysis of acetylcholine removes excess neurotransmitter from the synapse, preventing overstimulation and tetanic excitation of the postsynaptic muscle. Nearly half of the acetylcholine molecules released from the presynaptic nerve membrane are hydrolyzed by acetylcholinesterase before reaching the nAChR.⁷⁷ The action of acetylcholinesterase is quite rapid; acetylcholine molecules are hydrolyzed in approximately 80 to 100 μ s (microseconds). Acetylcholinesterase is concentrated at the neuromuscular junction, and there are approximately 10 enzyme-binding sites for each molecule of acetylcholine released.⁷⁸ However, lower concentrations of acetylcholinesterase are present along the length of the muscle fiber. Each molecule of acetylcholinesterase has an active surface with two important binding sites, an anionic site and an esteratic site. The negatively charged anionic site on the acetylcholinesterase molecule is responsible for electrostatically binding the positively charged quaternary nitrogen group on the acetylcholine molecule. The esteratic site forms covalent bonds with the carbamate group at the opposite end of the acetylcholine molecule and is responsible for the hydrolytic process ([Fig. 28.7](#)).⁷⁸ In addition, a secondary or peripheral anionic site has been proposed. Binding of ligands to the peripheral anionic site results in inactivation of the enzyme.

The anticholinesterase drugs used by anesthesiologists interact with the anionic and esteratic sites of acetylcholinesterase. These drugs are characterized as either prosthetic inhibitors (edrophonium) or oxydiaphoretic (acid-transferring) inhibitors (neostigmine, pyridostigmine) of the enzyme. Edrophonium rapidly binds to the anionic site via electrostatic forces and to the esteratic site by hydrogen bonding.^{77,78} Rapid binding may account for the short onset of action of edrophonium in clinical practice. During the time edrophonium is bound, the enzyme is inactive and edrophonium is not metabolized. However, the interaction between edrophonium and acetylcholinesterase is weak and short-lived. The dissociation half-life of this interaction is approximately 20 to 30 seconds, and the interaction between drug and enzyme is competitive and reversible. Because the nature of the binding is relatively brief, the efficacy of edrophonium in reversing neuromuscular blockade may be limited. Neostigmine and pyridostigmine are oxydiaphoretic inhibitors of acetylcholinesterase, which also

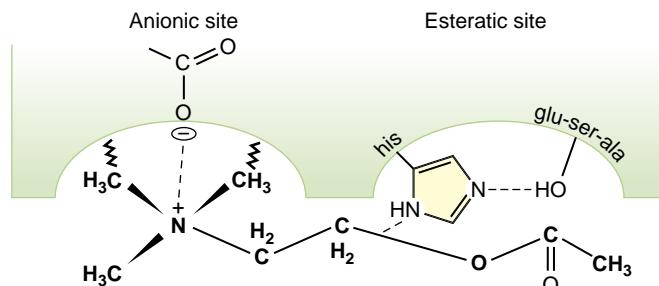


Fig. 28.7 Active binding sites on acetylcholinesterase. The positively charged quaternary nitrogen group on acetylcholine (Ach) binds by electrostatic forces to the negatively charged anionic site on the enzyme. The carbamate group at the opposite end of the Ach molecule forms covalent bonds with and is metabolized at the esteratic site. (From Caldwell JE. Clinical limitations of acetylcholinesterase antagonists. *J Crit Care*. 2009;24:21–28.)

bind to the anionic site. In addition, these drugs transfer a carbamate group to acetylcholinesterase, creating a covalent bond at the esteratic site.^{77,78} This reaction results in an inactivation of the enzyme, as well as the hydrolysis of the drug. The stronger interaction between neostigmine and enzyme results in dissociation half-life of approximately 7 minutes.⁷⁸ Therefore the duration of enzyme inhibition is longer with neostigmine and pyridostigmine compared with edrophonium. These interactions at the molecular level likely have little impact on the duration of action in clinical practice. Duration of clinical effect is primarily determined by removal of anticholinesterase from the plasma.⁷⁹

The administration of anticholinesterases has also been reported to produce presynaptic effects.⁷⁹ Laboratory investigations have demonstrated that these prejunctional effects may actually facilitate neuromuscular transmission. Anticholinesterases produce a reversible increase in the duration of the action potential and refractory period of the nerve terminal. Because the quantity of acetylcholine released is a function of the extent and duration of the depolarization of the terminal membrane, the period of acetylcholine release in response to nerve stimulation may be increased by anticholinesterase agents.⁷⁹ Excessive release of acetylcholine, coupled with decreased hydrolysis due to acetylcholinesterase inhibition, results in prolonged end-plate potentials and repetitive firing of muscle fibers. These prejunctional effects appear to account for the observations that spontaneous contractions of muscles can occur when anticholinesterases are given in the absence of NMBDs.⁷⁹

Although neostigmine, pyridostigmine, and edrophonium inhibit the breakdown of acetylcholine, resulting in an increase in acetylcholine in the neuromuscular junction, there is a clinically relevant “ceiling” effect to the maximal concentration of acetylcholine. As concentrations of acetylcholine increase, some of the neurotransmitter diffuses away from the neuromuscular junction, while additional acetylcholine undergoes reuptake into motor nerve terminals. As the processes of diffusion and reuptake reach equilibrium with augmented release by enzyme inhibition, a “peak” level at the neuromuscular junction is reached.⁷⁸ Once the acetylcholinesterase enzyme is maximally inhibited by an anticholinesterase agent and peak concentrations of acetylcholine are present, the administration of additional drug will not further increase acetylcholine levels or enhance recovery of neuromuscular blockade. This “ceiling” effect of anticholinesterases is an important limitation of all clinically used agents; neuromuscular blockade cannot be adequately reversed if high concentrations of NMBDs are present at the neuromuscular junction.

Pharmacokinetic and Pharmacodynamic Properties of Anticholinesterases

A large number of clinical studies have examined the pharmacokinetic and pharmacodynamic characteristics of neostigmine, pyridostigmine, and edrophonium.

The pharmacokinetic profiles of neostigmine, pyridostigmine, and edrophonium are presented in Table 28.3. Most studies have used a two-compartment model to establish pharmacokinetic characteristics of each agent. Following a bolus administration, plasma concentrations peak rapidly and decline significantly within the first 5 to 10 minutes. This is followed by a slower decline in plasma concentrations

TABLE 28.3 Pharmacokinetics of Neostigmine, Pyridostigmine, and Edrophonium in Patients Without and With Renal Failure

	WITHOUT RENAL FAILURE			WITH RENAL FAILURE		
	N	P	E	N	P	E
Distribution half-life (T _{1/2α} , min)	3.4	6.7	7.2	2.5	3.9	7.0
Elimination half-life (T _{1/2β} , min)	77	113	110	181	379	304
Volume of central compartment (L/kg)	0.2	0.3	0.3	0.3	0.4	0.3
Total plasma clearance (mL/kg/min)	9.1	8.6	9.5	4.8	3.1	3.9

Data from references 73–76.

From Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, ed. *Miller's Anesthesia*. 7th ed. Philadelphia: Saunders; 2010.

due to the elimination phase.⁷⁹ In general, the pharmacokinetic profiles of all three anticholinesterases are similar. Early studies suggested that the duration of edrophonium was too short for clinical use. However, studies using larger doses (0.5 or 1.0 mg/kg) demonstrated that the elimination half-life of edrophonium was not significantly different from that of neostigmine or pyridostigmine and that edrophonium could produce prompt and sustained reversal of neuromuscular blockade.^{80,81} The longer elimination half-life of pyridostigmine likely accounts for the longer duration of action compared with the other anticholinesterase drugs.⁸²

The pharmacokinetics of anticholinesterases can be influenced by renal function, age, and body temperature. The elimination half-life of all three agents is altered by the presence of renal insufficiency or failure (see Table 28.3). Renal excretion accounts for approximately 50% of plasma clearance of neostigmine; elimination half-life is significantly prolonged and serum clearance decreased in anephric patients.⁸³ Similarly, renal function accounts for 70% to 75% of serum clearance of pyridostigmine and edrophonium.^{82,84} The reduced plasma clearance of the anticholinesterases in renal failure patients provides a “margin of safety” against the risk of postoperative “recurarization” (the effects of the NMBD persist longer than that of the reversal agent, resulting in a worsening of residual paresis). The pharmacokinetics of edrophonium have been examined in older adult (age > 70 years) patients. When compared with a younger cohort, older adult patients exhibited a significant decrease in plasma clearance (5.9 ± 2 vs. 12.1 ± 4 mL/kg/min) and a prolonged elimination half-life (84.2 ± 17 vs. 56.6 ± 16 minutes).⁸⁵ Mild hypothermia (reduction in core temperature of 2°C) more than doubles the duration of action of intermediate-acting NMBDs.⁸⁶ In a study of human volunteers cooled to 34.5°C, the central volume of distribution of neostigmine decreased 38% and the onset time of maximal blockade increased from 4.6 to 5.6 minutes.⁸⁷ However, the clearance, maximal effect, and duration of action of neostigmine were not altered by a reduction in body temperature. Therefore if hypothermia influences the degree of neuromuscular recovery, it is likely

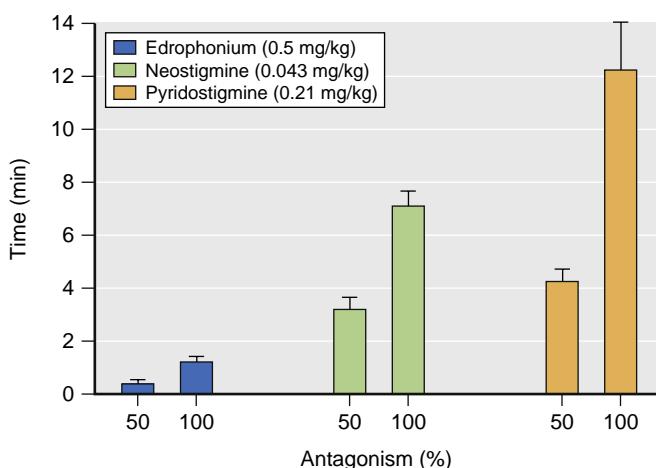


Fig. 28.8 Comparison of onset of action for edrophonium, neostigmine, and pyridostigmine. Values plotted are means \pm SE. Edrophonium's onset was significantly faster than neostigmine or pyridostigmine. (From Cronnelly R, Morris RB, Miller RD. Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology*. 1982;57:261–266.)

secondary to an effect on the pharmacology of NMBDs (not the anticholinesterase).

Onset of action may be more rapid with edrophonium than with either neostigmine or pyridostigmine. When *d*-tubocurarine neuromuscular blockade was reversed with approximately equipotent doses of the three clinically used anticholinesterases, the peak effect of antagonism was reached significantly faster with edrophonium (0.8–2.0 minutes) than with neostigmine (7–11 minutes) or pyridostigmine (12–16 minutes) (Fig. 28.8).⁸⁰ Similar findings have been observed in patients receiving other long- and intermediate-acting NMBDs. When larger doses (0.5–1.0 mg/kg) of edrophonium are administered during moderate levels of neuromuscular blockade (10% recovery of single-twitch height after pancuronium or atracurium), the onset time of edrophonium was faster than neostigmine.^{88,89} During deeper levels of blockade (<10% recovery of single twitch), edrophonium 1.0 mg/kg and neostigmine 0.04 mg/kg had similar onset times when vecuronium was used (and both were faster than edrophonium 0.5 mg/kg).⁹⁰ When pancuronium was antagonized during deep blockade, edrophonium 1.0 mg/kg had a shorter onset time than neostigmine 0.04 mg/kg.⁹⁰ These findings suggest that onset time of antagonism is influenced by the type and dose of anticholinesterase used, the choice of NMBD administered intraoperatively, and the depth of neuromuscular blockade at the time of antagonism.

The duration of action of anticholinesterases is determined not only by the pharmacokinetic properties of the drugs, but also by the concentration of NMBD present at the neuromuscular junction at the time of reversal. Duration of neuromuscular blockade will naturally decrease over time as a result of metabolism and elimination of NMBDs. To accurately assess the duration of action of anticholinesterases during a stable, constant level of neuromuscular blockade, investigators have administered these agents to patients receiving an infusion of *d*-tubocurarine titrated to a 90% depression of single-twitch height.⁸⁰ The investigators observed that the duration of action of equipotent doses

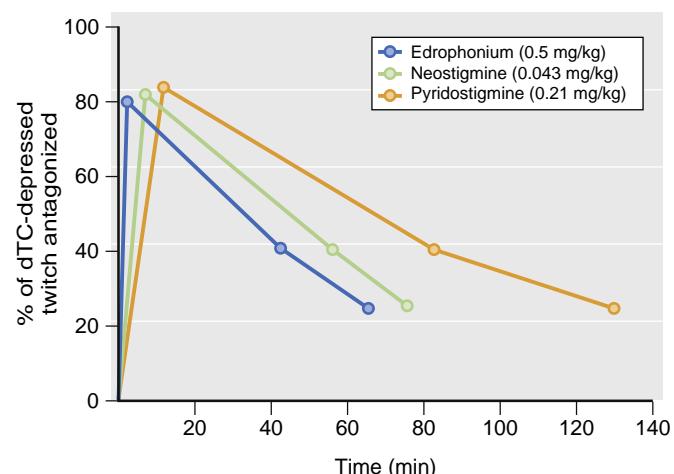


Fig. 28.9 Duration of antagonism compared at equipotent doses of neostigmine, pyridostigmine, and edrophonium. Values plotted are means. Edrophonium did not differ from neostigmine in duration; however, both were shorter than pyridostigmine. *dTC*, *d*-tubocurarine. (From Cronnelly R, Morris RB, Miller RD. Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology*. 1982;57:261–266.)

of neostigmine (0.043 mg/kg) and edrophonium (0.5 mg/kg) were similar (Fig. 28.9). The duration of both drugs, however, was significantly less than with pyridostigmine (0.21 mg/kg).

The comparative potencies of clinically used anticholinesterases have been calculated by constructing dose-response curves. In general, neostigmine is more potent than pyridostigmine, which is more potent than edrophonium. Neostigmine-to-pyridostigmine potency ratios of 4.4 to 6.7 have been reported (neostigmine is 4.4–6.7 times more potent than pyridostigmine).^{80,91} Neostigmine is even more potent than edrophonium, with potency ratios of 5.7 to 19.5 estimated from dose-response curves.^{80,91,92} The great variability in potency ratios described in the literature is related to several factors, which include the type of NMBD used in the studies, the endpoint selected to represent neuromuscular recovery, and the depth of blockade at the time of anticholinesterase administration.

In conclusion, pharmacokinetic and pharmacodynamic studies suggest that neostigmine, pyridostigmine, and edrophonium are all effective in reversing neuromuscular blockade when used in appropriate and equipotent doses. The following section will review factors that determine the efficacy of these agents in reversing neuromuscular blockade in the clinical setting.

Factors Determining the Adequacy of Recovery Following Administration of Anticholinesterases

Depth of Neuromuscular Blockade or Train-of-Four Count at the Time of Reversal. The primary anesthetic management variable determining the effectiveness of anticholinesterase agents in completely antagonizing neuromuscular blockade at the end of surgery is the depth of neuromuscular blockade at the time of reversal. As opposed to sugammadex (see later in this chapter), reversal of blockade by anticholinesterases should not be attempted until some evidence of spontaneous recovery is present. Kirkegaard-Nielsen and associates examined the optimal time for

TABLE 28.4 Time (min) from Neostigmine Administration to a Train-of-Four Ratio 0.70, 0.80, and 0.90 When Given at a Train-of-Four Count of 1-4

TOF Ratio	GROUP*			
	I	II	III	IV
0.70				
Median	10.3 [†]	7.6 [‡]	5.0	4.1
Range	5.9-23.4	3.2-14.1	2.0-18.4	2.4-11.0
0.80				
Median	16.6 [†]	9.8 [‡]	8.3	7.5
Range	8.9-30.7	5.3-25.0	3.8-27.1	3.0-74.5
0.90				
Median	22.2	20.2	17.1	16.5
Range	13.9-44.0	6.5-70.5	8.3-46.2	6.5-143.3

TOF, Train-of-four.

*Group I was reversed at a TOF count of 1, group II was reversed at a TOF count of 2, group III was reversed at a TOF count of 3, and group IV was reversed at a TOF count of 4.

[†] $P < .05$, group I > group II, III, and IV.

[‡] $P < .05$, group II > group IV.

From Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. *Anesthesiology*. 2002;96:45-50.

neostigmine reversal of an atracurium blockade.⁹³ Administration of neostigmine 0.07 mg/kg during deep blockade (before the first twitch height reached 8%) resulted in significant prolongation of reversal times. In a similar investigation, atracurium was antagonized with neostigmine during intense blockade (posttetanic count [PTC] of 1 to >13).⁹⁴ Early administration of neostigmine did not shorten total recovery time and offered no clinical advantages. Similar findings have been observed during reversal of deep vecuronium blockade.⁹⁵ The total time to achieve a TOF ratio of 0.75 was the same whether neostigmine (0.07 mg/kg) was given 15 minutes after an intubating dose of vecuronium or whether single-twitch height had recovered to 10% of control.

The time required to achieve a TOF ratio of 0.90 after anticholinesterase administration is significantly shorter when a higher TOF count is present at reversal. Two studies have examined the efficacy of antagonizing residual blockade at varying TOF counts. Kirkegaard and colleagues randomized patients receiving cisatracurium to reversal with neostigmine (0.07 mg/kg) at the reappearance of the first, second, third, and fourth tactile TOF response (TOF count 1-4).⁹⁶ The median (range) time required to achieve a TOF ratio of 0.90 was 22.2 (13.9-44.0) minutes when reversal was attempted at a TOF count of 1. However, even when four responses were present, the time needed to attain a TOF ratio of 0.90 was 16.5 (6.5-143.3) minutes (Table 28.4). Kim and associates performed a similar study in which patients administered rocuronium were randomized to be reversed at the first through fourth tactile TOF responses.⁹⁷ In those patients receiving sevoflurane for anesthetic maintenance, the median (range) time required to achieve a TOF ratio of 0.90 was 28.6 (8.8-75.8) minutes when reversed at a TOF count of 1 and 9.7 (5.1-26.4) minutes when reversed at a TOF count of 4. In both

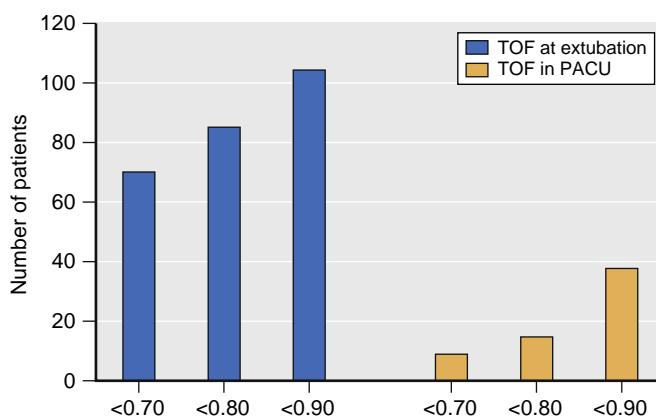


Fig. 28.10 Train-of-four (TOF) ratios measured immediately before tracheal extubation and again on admission to the postanesthesia care unit (PACU). The graphs illustrate the number of patients (of a total of 120) with TOF ratios <0.70, <0.80, and <0.90 at each measurement interval. (From Murphy GS, Szokol JW, Marymont JH, et al. Residual paralysis at the time of tracheal extubation. *Anesth Analg*. 2005;100:1840-1845.)

investigations, a large interindividual variability in reversal times was observed.^{96,97} This is likely a reflection of the individual response to the NMBD administered. The reason for marked prolongation of reversal times in some patients (up to 143 minutes) was not determined, but may be due to the “ceiling effect” with respect to the blockade (peak effect of the antagonist is followed by a plateau phase in which the balance between diminishing anticholinesterase activity and spontaneous recovery determines the slope of the recovery curve).⁹⁶ Both studies demonstrated that it was not possible to reliably achieve full neuromuscular recovery (TOF ratio of >0.90) in the majority of patients within 10 minutes of anticholinesterase administration. On the basis of data, expert opinion suggests that neostigmine should not be administered until the fourth “twitch” of the TOF count has returned.⁹⁸

Time Interval Between Anticholinesterase Administration and Tracheal Extubation. Studies have suggested that if four responses to TOF nerve stimulation are present, approximately 15 minutes are needed to reach a TOF ratio of 0.90 in most patients.^{96,97} Achieving a TOF ratio of 0.90 will require a significantly longer time (20–30 minutes) if a TOF count of 1 to 3 is observed at the time of reversal. To allow adequate neuromuscular recovery and ensure patient safety, anticholinesterase drugs should be given, on average, 15 to 30 minutes before clinicians anticipate removal of the endotracheal tube in the operating room. In many clinical situations, however, anticholinesterases are often administered at the conclusion of surgical closure, with tracheal extubation performed shortly thereafter. A survey of anesthesiologists from Europe and the United States revealed that approximately one half of respondents allowed only 5 minutes or less between anticholinesterase administration and tracheal extubation.¹¹ In a study of 120 surgical patients, TOF ratios were quantified at the time of tracheal extubation when clinicians had determined that full recovery of neuromuscular function had occurred using clinical criteria and qualitative neuromuscular monitoring (Fig. 28.10).⁷³ Mean TOF ratios of 0.67 were observed immediately before extubation, with

88% of patients exhibiting TOF less than 0.90. Of note, the median TOF count at reversal was 4, and the average time interval between neostigmine administration and tracheal extubation was only 8 minutes. The frequent incidence of residual blockade reported in multiple studies is likely attributable to the fact that anticholinesterases are not given early enough during the intraoperative anesthetic to ensure full neuromuscular recovery.

Type of Neuromuscular Blocking Drug Used Intraoperatively (Long-Acting Versus Intermediate-Acting).

Two separate processes contribute to recovery of neuromuscular function following anticholinesterase administration. The first is the inhibition of acetylcholinesterase at the neuromuscular junction produced by neostigmine, pyridostigmine, or edrophonium. The second is the spontaneous process of decrease in the concentration of the NMBD at the neuromuscular junction over time due to redistribution and elimination. Therefore NMBDs that are redistributed and eliminated more rapidly from the plasma should be associated with more rapid recovery profiles after anticholinesterase use. Not surprisingly, the probability of satisfactorily antagonizing neuromuscular blockade is a function of the properties of the NMBD used to provide muscle relaxation. The ability of edrophonium (0.75 mg/kg) and neostigmine (0.05 mg/kg) to antagonize neuromuscular blockade produced by atracurium, vecuronium, and pancuronium following termination of steady-state infusions (single-twitch depression 10% of control) has been examined.⁹⁹ TOF ratios 20 minutes postreversal were 0.80 and 0.95 (atracurium with edrophonium or neostigmine), 0.76 and 0.89 (vecuronium with edrophonium or neostigmine), and 0.44 and 0.68 (pancuronium with edrophonium or neostigmine). Another clinical study investigated recovery of neuromuscular function in patients randomized to receive either intermediate-acting (rocuronium, vecuronium, atracurium) or long-acting (pancuronium) NMBDs.¹⁰⁰ Neostigmine (0.04 mg/kg) was given at 25% recovery of control twitch height, and TOF ratios were measured for 15 minutes. Mean TOF ratios had recovered to 0.88 to 0.92 in patients receiving intermediate-acting NMBDs, versus only 0.76 in the pancuronium group (Fig. 28.11).

A number of clinical investigations have examined the incidence of residual blockade in the PACU in patients receiving either intermediate- or long-acting NMBDs. These studies have consistently demonstrated that fewer patients given intermediate-acting NMBD have residual blockade compared with those receiving long-acting agents. A meta-analysis of 24 clinical trials examined the pooled estimated incidence of residual blockade (defined as a TOF ratio < 0.90) by muscle relaxant type.⁴⁴ The risk of residual blockade was significantly less in patients given intermediate-acting NMBDs (41%) versus long-acting NMBDs (72%). In conclusion, the probability of incomplete neuromuscular recovery in the early postoperative period is decreased when shorter-acting NMBDs are used intraoperatively.

Type and Dose of Anticholinesterase. Complete recovery of neuromuscular function within 10 to 15 minutes with neostigmine, edrophonium, or pyridostigmine is difficult to achieve when profound neuromuscular blockade is present. Some investigations have suggested that edrophonium is

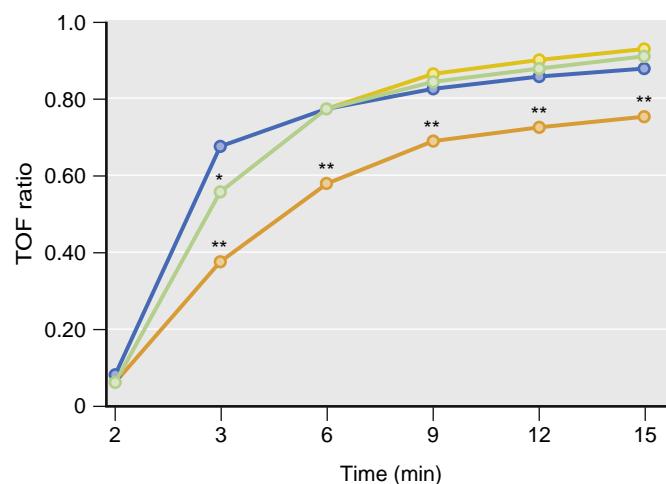


Fig. 28.11 Evolution of the train-of-four (TOF) ratio (mean) recorded at 3-minute intervals after administration of neostigmine 40 µg/kg when twitch height had returned to 25% of its initial value in groups of Roc (green), Vec (blue), Atr (yellow), and Pan (orange). * $P < .05$, one-way analysis of variance and Duncan multiple classification range tests (group Vec vs. groups Roc and Atr). ** $P < .01$, one-way analysis of variance and Duncan multiple classification range tests (group Pan versus groups Vec, Roc, Atr). (From Baurain MJ, Hoton F, D'Hollander AA, et al. Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium? *Br J Anaesth*. 1996;77:496–499.)

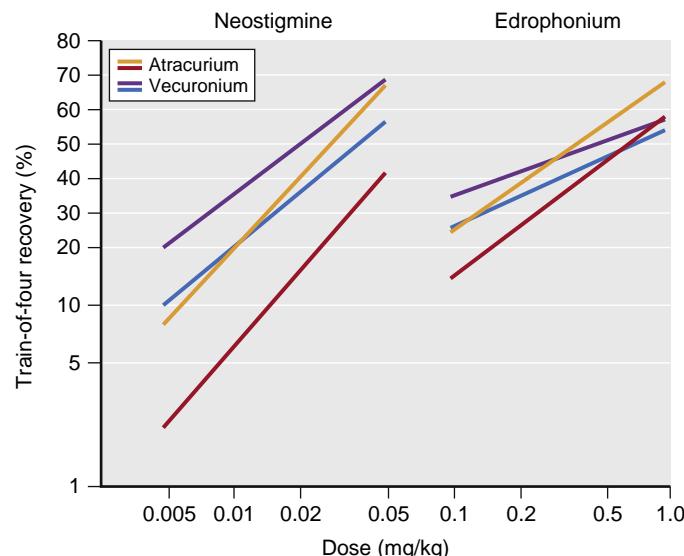


Fig. 28.12 Dose-response relationships of train-of-four assisted recovery evaluated 5 minutes (blue lines) or 10 minutes (purple lines) after administration of the antagonist as a function of the dose of neostigmine or edrophonium. The slopes of the curves obtained with edrophonium were usually flatter than the corresponding curves for neostigmine. (From Smith CE, Donati F, Bevan DR. Dose-response relationships for edrophonium and neostigmine as antagonists of atracurium and vecuronium neuromuscular blockade. *Anesthesiology*. 1989;71:37–43.)

less effective than neostigmine when reversing deep blockade; this may occur because the slopes of the dose-response relationships of neostigmine and edrophonium are not parallel (flatter dose-response curves are observed with edrophonium; Fig. 28.12).^{90,92} In contrast, the recovery profile of edrophonium with larger doses (approximately 1.0 mg/kg) does not differ from neostigmine and pyridostigmine, and

edrophonium can produce rapid and sustained reversal of neuromuscular blockade.^{88,90} At moderate levels of neuromuscular blockade all three agents appear to be similarly effective in reversing blockade, although the onset of edrophonium may occur more quickly.

In general, larger doses of anticholinesterases result in more rapid and complete reversal of neuromuscular blockade than smaller doses. This relationship remains true until the maximal dose of anticholinesterase has been administered. At this point, acetylcholinesterase is maximally inhibited, and additional amounts of anticholinesterase will result in no further antagonism. Maximal effective doses of neostigmine and edrophonium have not been clearly defined, but likely vary in relation to depth of blockade and type of NMBD used intraoperatively. Providing additional anticholinesterase beyond these maximum dose limits (neostigmine 60–80 µg/kg, edrophonium 1.0–1.5 mg/kg) provides no further benefit. When administered during deep neuromuscular blockade, a second dose of neostigmine (70 µg/kg) usually does not enhance recovery times beyond that observed with a single dose.⁹⁵

AGE

INFANTS AND CHILDREN. The dose of neostigmine producing 50% antagonism of a *d*-tubocurarine neuromuscular blockade was slightly smaller in infants (13 µg/kg) and children (15 µg/kg) compared with adults (23 µg/kg).¹⁰¹ The times to peak antagonism and duration of antagonism did not differ between infants, children, and adults. Pharmacokinetic modeling revealed that distribution half-lives and volumes were similar in all three cohorts, although elimination half-life was shorter in infants and children than adults. As in adults, the depth of neuromuscular blockade at the time of antagonism was a primary factor determining adequacy of recovery.^{102,103} Spontaneous recovery from neuromuscular blockade is more rapid in children compared with adults.¹⁰³ However, when neostigmine was administered at various levels of blockade, the times to achieve neuromuscular recovery were similar in children and adults (the times to reach a TOF ratio of 0.90 were reduced by 30%–40% compared with spontaneous recovery).¹⁰³ Thus in the clinical setting, reversal of neuromuscular blockade does not appear to differ significantly between children and adults.

OLDER ADULTS. Physiologic changes occur during the aging process that result in alterations in the response of older patients to NMBDs. These changes include an increase in body fat, a decrease in total body water, and declines in cardiac, hepatic, and renal function. In addition, anatomic alterations occur at the neuromuscular junction in older adults, such as a decrease in the concentration of nAChRs at the motor end plate and a reduction in the release of acetylcholine from the preterminal axon. All of these factors contribute to a prolongation of effect of most NMBDs in older patients. In a study comparing older adults (age > 70) to younger controls, plasma clearance of edrophonium was decreased and elimination half-life prolonged in the aged cohort. Despite higher plasma concentrations of edrophonium, however, duration of antagonism was not increased. In contrast, Young and colleagues observed that the duration of action of both neostigmine and pyridostigmine was significantly longer in older adults (age > 60) compared with younger

subjects.¹⁰⁴ These findings suggest that plasma concentrations and/or duration of action of both NMBDs and anticholinesterases (neostigmine and pyridostigmine) are prolonged in older patients, which should reduce the risk of recurarization. The risk of postoperative residual block in elderly patients (age > 70 years) who have received neostigmine is significantly higher than in a younger cohort receiving similar doses of this drug (ages 18–50, 58% vs. 30%, respectively).⁷³

TYPE OF ANESTHESIA. Volatile anesthetics intensify the action of nondepolarizing NMBDs when compared with intravenous anesthetics. Furthermore, volatile anesthetics interfere with the antagonism of neuromuscular blockade.¹⁰⁵ Kim and colleagues randomized patients to receive a propofol or sevoflurane anesthetic (Table 28.5).⁹⁷ The times required to achieve a TOF ratio of 0.70, 0.80, and 0.90 were significantly longer in patients given the sevoflurane-based anesthetic compared with the propofol-based technique. Similar findings have been observed in patients randomized to receive either isoflurane or propofol (neuromuscular recovery was delayed when a volatile anesthetic was used).^{105,106} These findings suggest that the probability of achieving a TOF ratio greater than 0.90 within 10 to 15 minutes of anticholinesterase administration is increased if a total intravenous anesthetic technique is administered as opposed to a volatile anesthetic.

CONTINUOUS INFUSION VERSUS BOLUS ADMINISTRATION OF NEUROMUSCULAR BLOCKING DRUGS. Recovery from neuromuscular blockade may also be influenced by mode of NMBD administration. Jellish and colleagues examined recovery characteristics of rocuronium and cisatracurium when given as either a bolus or continuous infusion.¹⁰⁶ The time required to reach a TOF ratio of 0.75 in the cisatracurium group was similar whether bolus or infusion techniques were used, whereas recovery was delayed when rocuronium was given as an infusion.¹⁰⁶ The authors conclude that cisatracurium may be the agent of choice for prolonged procedures since its recovery is not affected by length of infusion.

RENAL FUNCTION. As previously noted, renal excretion accounts for 50% to 75% of plasma clearance of neostigmine, pyridostigmine, and edrophonium. In anephric patients, elimination half-life of all three anticholinesterases is prolonged, and total plasma clearance of these agents is decreased (see Table 28.3). Similar changes in the pharmacokinetic characteristics of nondepolarizing NMBDs have been noted in patients with renal failure. Therefore management of anticholinesterase reversal should be similar in patients with normal and impaired renal function. Postoperative residual neuromuscular blockade in patients with renal failure is more likely secondary to improper titration of NMBDs intraoperatively rather than to inappropriate dosing of anticholinesterase agents.

ACID-BASE STATUS. The influence of metabolic status and respiratory acid-base balance on reversal of neuromuscular blockade has been investigated in the laboratory setting. Miller and associates noted that respiratory alkalosis and metabolic acidosis did not alter the dose of neostigmine needed to reverse a *d*-tubocurarine or pancuronium blockade. However, during respiratory acidosis and metabolic alkalosis, the dose of neostigmine needed to produce a comparable level of neuromuscular recovery was nearly twice

TABLE 28.5 Time (min) from Neostigmine Administration to a Train-of-Four Ratio of 0.70, 0.80, and 0.90 During Propofol- or Sevoflurane-Based Anesthesia

TOF Ratio	GROUP*			
	I	II	III	IV
PROPOFOL				
0.70	4.7 (2.5-7.8)†	4.0 (1.5-7.5)	3.4 (0.9-5.5)	2.1 (0.6-3.8)‡,§
0.80	6.4 (3.1-10.8)	5.5 (2.2-9.3)	4.4 (0.9-7.1)‡	3.3 (0.7-4.9)‡,§
0.90	8.6 (4.7-18.9)	7.5 (3.4-11.2)	5.4 (1.6-8.6)‡	4.7 (1.3-7.2)‡,§
SEVOFLURANE				
0.70	10.9 (3.6-28.9)¶	8.3 (2.5-22.3)¶	6.6 (2.4-18.5)‡,¶	5.4 (2.2-14.3)‡,§,¶
0.80	16.4 (5.9-47.5)¶	13.5 (5.1-37.2)¶	10.8 (4.2-29.2)‡,¶	7.8 (3.5-19.3)‡,§,¶
0.90	28.6 (8.8-75.8)¶	22.6 (8.3-57.4)¶	15.6 (7.3-43.9)‡,¶	9.7 (5.1-26.4)‡,§,¶

*Group I was reversed at a TOF count of 1, group II was reversed at a TOF count of 2, group III was reversed at a TOF count of 3, and group IV was reversed at a TOF count of 4.

†Values are median and (range).

‡ $P < .05$ compared with group I.

§ $P < .05$ compared with group II.

¶ $P < .0001$ compared with propofol groups.

TOF, Train-of-four.

From Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. *Anesth Analg*. 2004;99:1080-1085.

as large.^{107,108} Although clinical studies have not been performed, the findings from laboratory investigations suggest that complete reversal of neuromuscular blockade may be difficult in the presence of respiratory acidosis and metabolic alkalosis. In particular, clinicians should be aware of the risk of residual blockade in the setting of respiratory acidosis. A number of anesthetics (opioids, benzodiazepines, volatile anesthetics) can potentially depress the ventilatory drive in the early postoperative period. This respiratory depression may result in respiratory acidosis, which limits the ability of anticholinesterases to reverse neuromuscular blockade. The resultant residual blockade may further depress the respiratory muscle strength and ventilatory drive and increase the risk of adverse postoperative events.

NEUROMUSCULAR MONITORING. Qualitative and quantitative neuromuscular monitoring should be used to guide dosing of both NMBDs and their reversal in the operating room. In general, if deeper levels of neuromuscular blockade are present at the end of surgery (1-2 responses to TOF stimulation), larger doses of anticholinesterases should be given. In these clinical scenarios, maximal doses of neostigmine (70 $\mu\text{g}/\text{kg}$), edrophonium (1.0-1.5 mg/kg), or pyridostigmine (350 $\mu\text{g}/\text{kg}$) should be considered. If three to four responses to TOF stimulation are present with observable fade of the fourth response, moderate doses of anticholinesterase should be administered (40-50 $\mu\text{g}/\text{kg}$ of neostigmine, 0.5 mg/kg of edrophonium, 200 $\mu\text{g}/\text{kg}$ pyridostigmine). If four responses are present with no fade, low doses of anticholinesterases can be considered (e.g., 20 $\mu\text{g}/\text{kg}$ of neostigmine; see later).

Quantitative monitoring is also useful in guiding the dosing of anticholinesterases. Fuchs-Buder and colleagues investigated the dose-response relationship of neostigmine using AMG-based monitoring to guide neostigmine reversal (10, 20, or 30 $\mu\text{g}/\text{kg}$) given at TOF ratios of either 0.40 or 0.60 (Fig. 28.13).¹⁰⁹ All patients were able to achieve a TOF ratio of 0.90 within

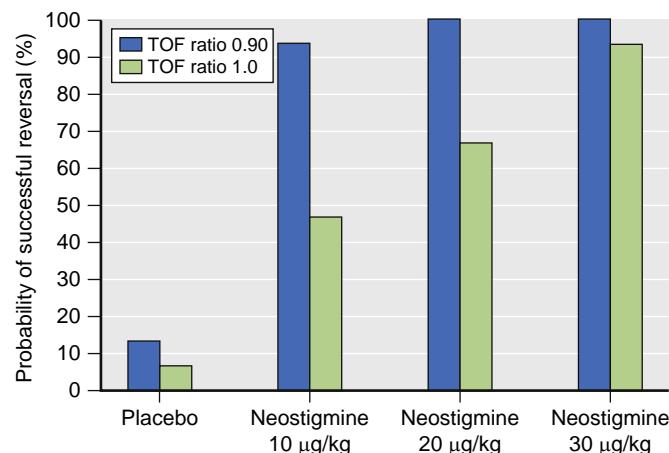


Fig. 28.13 Probability of successful reversal within 10 minutes after different doses of neostigmine or placebo. Neostigmine or placebo was given at a train-of-four ratio of 0.40. TOF, Train-of-four. (From Fuchs-Buder T, Meistelman C, Alla F, et al. Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine. *Anesthesiology*. 2010;112:34-40.)

10 minutes of receiving 20 $\mu\text{g}/\text{kg}$ of neostigmine. These findings demonstrate that small doses of neostigmine can be safely used if neuromuscular recovery is measured with quantitative monitoring. If muscle function is monitored manually with a peripheral nerve stimulator and no fade is detected manually with TOF stimulation, the TOF ratio is likely at least 0.40, but may be as high as 0.90 or 1.0. In the setting of full neuromuscular recovery, neostigmine administration may produce paradoxical muscle weakness (see later). This potential risk should be considered if neostigmine is used to reverse shallow blockade based on the results of qualitative neuromuscular monitoring.

In many clinical settings neuromuscular monitoring is unfortunately not used and decisions relating to the

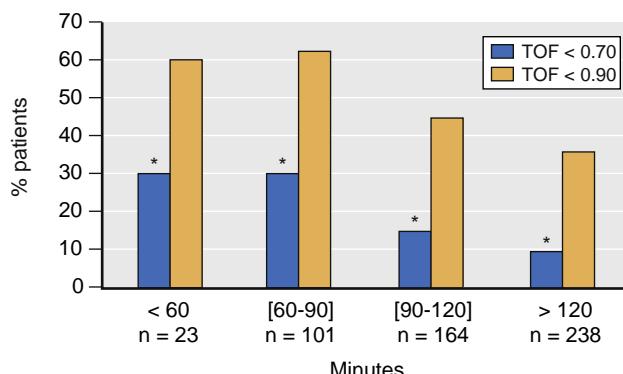


Fig. 28.14 The incidence of residual neuromuscular blockade after a single intubating dose of intermediate-duration nondepolarizing relaxant (rocuronium, vecuronium, or atracurium). Partial paralysis rate (percent) according to the delay between the administration of muscle relaxant and the arrival in the postanesthesia care unit. Partial paralysis was defined as a train-of-four (TOF) ratio less than 0.70 or less than 0.90. *n*, number of patients. *Significantly different from TOF < 0.90. (From Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology*. 2003;98:1042–1048.)

administration of anticholinesterases are based on the time that has elapsed between the last dose of NMBD and the conclusion of the anesthetic. Clinical studies do not support this practice. In a study of patients receiving a single intubating dose of vecuronium (0.1 mg/kg), 8.4% of patients had TOF ratios less than 0.80 4 hours after NMBD administration.¹¹⁰ Debaene and colleagues examined the incidence of residual blockade in a large cohort of patients given a single intubating dose of vecuronium, rocuronium, or atracurium.⁴⁷ Of the 239 patients who were tested 2 or more hours after administration of the NMBD, 37% had a TOF ratio less than 0.90 (Fig. 28.14). Murphy and associates administered a single 1 × ED 95 dose of rocuronium (average dose 25 mg) to 120 patients.¹¹¹ Despite an average case duration of 161 minutes, 21% of patients had not achieved a TOF ratio of 0.90 at the end of surgery. These investigations, as well as a number of pharmacokinetic and pharmacodynamic studies, demonstrate that the time course of spontaneous neuromuscular recovery is extremely variable from patient to patient. In order to detect and appropriately manage patients in whom delayed neuromuscular recovery may be present, quantitative neuromuscular monitoring is required.

PATIENTS WITH CHOLINESTERASE DEFICIENCY. The duration of neuromuscular blockade following the administration of either succinylcholine or mivacurium is primarily determined by their rate of hydrolysis by plasma cholinesterase. Patients with abnormal plasma cholinesterase phenotypes and activity can demonstrate significant prolongation of clinical effect of these NMBDs. Mivacurium is four to five times more potent in patients phenotypically homozygous for the atypical plasma cholinesterase gene than in patients with normal cholinesterase activity.¹¹² Following standard intubating doses of mivacurium, recovery of neuromuscular function may require up to 4 to 8 hours in patients with cholinesterase deficiency.¹¹³ Similar prolonged recovery times have been observed in patients administered succinylcholine who have atypical plasma cholinesterase genes.¹¹⁴

Human plasma cholinesterase has been used clinically to reverse neuromuscular blockade in patients with atypical serum cholinesterase. In 1977, Scholler and associates reported data on 15 patients with unexpected prolonged apnea lasting several hours after a dose of succinylcholine.¹¹⁵ Adequate spontaneous ventilation was restored within an average time of 10 minutes in all subjects following the administration of human serum cholinesterase. Naguib and associates reported successful reversal of a profound mivacurium-induced neuromuscular blockade with three doses of a purified human plasma cholinesterase preparation and, in a subsequent study, established a dose-response relationship for plasma cholinesterase as a reversal agent for mivacurium in normal subjects.^{113,116} The efficacy of exogenously administered plasma cholinesterase in antagonism of a mivacurium neuromuscular blockade was assessed in 11 patients phenotypically homozygous for atypical plasma cholinesterase.¹¹⁷ A purified concentrate of cholinesterase (2.8–10 mg/kg) was administered 30 or 120 minutes after an intubating dose of mivacurium. Administration of cholinesterase restored plasma cholinesterase to normal levels, resulting in a 9- to 15-fold increased clearance and a shorter elimination half-life of mivacurium. The first response to TOF stimulation was observed in 13.5 minutes, and the time to achieve a TOF ratio of 0.80 ranged from 30 to 60 minutes. These data suggest that prolonged neuromuscular blockade secondary to low or abnormal plasma cholinesterase activity can be successfully managed with purified human plasma cholinesterase. Decisions relating to management of prolonged neuromuscular blockade in patients with atypical plasma cholinesterase should be based on the availability and cost of human plasma cholinesterase versus delaying tracheal extubation until spontaneous neuromuscular recovery has occurred.

Box 28.2 summarizes clinical management strategies that can be used by clinicians to reduce the risk of residual blockade when NMBDs are antagonized with anticholinesterases.

Complications Associated With Inhibitors of Acetylcholinesterase

ANTICHOLINESTERASE-ASSOCIATED MUSCLE WEAKNESS. Anticholinesterases can antagonize moderate to shallow levels of neuromuscular blockade. However, if given when neuromuscular function is completely recovered, paradoxical muscle weakness theoretically may be induced. Large doses of neostigmine, pyridostigmine, and edrophonium may result in cholinergic hyperactivity and more intense fade in response to multiple nerve stimuli (decrease in TOF ratio) in an *in vitro* model.¹¹⁸ The administration of a second dose of neostigmine (2.5 mg) to patients with small degrees of residual blockade resulted in a decrease in TOF ratios, tetanic height, and tetanic fade.^{119,120} Caldwell examined neostigmine reversal (20 or 40 µg/kg) of residual neuromuscular blockade 1 to 4 hours after a single dose of vecuronium.¹¹⁰ TOF ratios increased in 52 patients and decreased in 8 patients; TOF ratio decreases were only observed in patients with TOF ratios 0.90 or greater at the time of reversal (with 40 µg/kg doses of neostigmine but not 20 µg/kg dosing).

The clinical implications of administration of neostigmine after neuromuscular recovery has occurred have been

BOX 28.2 Clinical Management Strategies to Reduce the Risk of Residual Neuromuscular Blockade When Anticholinesterase Reversal Agents Are Used

Quantitative Monitoring Used (e.g., Acceleromyography)

1. TOF count of 1 or no TOF response—delay reversal until neuromuscular recovery is more complete (TOF count of 2 or greater).
2. TOF count of 2 or 3—administer doses of anticholinesterases (neostigmine [70 µg/kg], edrophonium [1.0–1.5 mg/kg], or pyridostigmine [350 µg/kg]). Extubate when the adductor pollicis TOF ratio has reached 0.90.
3. TOF ratio ≥ 0.40 —administer moderate pharmacologic reversal doses of anticholinesterases (neostigmine [40–50 µg/kg], edrophonium [0.5 mg/kg], or pyridostigmine [200 µg/kg]). Extubate when the adductor pollicis TOF ratio has reached 0.90.
4. TOF ratio between 0.40 and 0.70—administer pharmacologic reversal, consider a low dose of neostigmine (20 µg/kg).
5. TOF ratio > 0.70 —avoid anticholinesterase reversal; risk of anticholinesterase-induced muscle weakness if given.

Qualitative Monitoring Used (Peripheral Nerve Stimulator)

1. TOF count of 1 or no TOF response—delay reversal until neuromuscular recovery is detectable (TOF count of 2 or greater)
2. TOF count of 2 or 3 at the end of surgery—administer anticholinesterases (neostigmine [70 µg/kg], edrophonium [1.0–1.5 mg/kg], or pyridostigmine [350 µg/kg]). Allow at least 15–30 minutes before tracheal extubation is performed.
3. TOF count of 4 with observable fade at the end of surgery (likely

adductor pollicis TOF ratio < 0.40)—administer anticholinesterases (neostigmine [40–50 µg/kg], edrophonium [0.5 mg/kg], or pyridostigmine [200 µg/kg]). Allow at least 10–15 minutes before tracheal extubation is performed.

4. TOF count of 4 with no perceived fade at the end of surgery (likely adductor pollicis TOF ratio ≥ 0.40)—administer pharmacologic reversal, consider a low dose of neostigmine (20 µg/kg).

No Neuromuscular Monitoring Used

1. Anticholinesterases should be considered. Spontaneous recovery of neuromuscular function may require several hours in a significant percentage of patients, even after a single intubating dose of an intermediate-acting NMBD.
2. Anticholinesterases should not be given until some evidence of recovery of muscle strength is observed since administration of an anticholinesterase during deep levels of paralysis may delay neuromuscular recovery.
3. Decisions relating to the use or avoidance of anticholinesterases should not be based upon clinical tests of muscle strength (5-second head lift). Many patients can perform these tests even in the presence of profound neuromuscular blockade (TOF ratio < 0.50). Other muscle groups may be significantly impaired (pharyngeal muscles) at the time when patients can successfully perform these tests.

NMBD, Neuromuscular blocking drug; TOF, train-of-four.

Modified from Brull SJ, Murphy GS. Residual neuromuscular block. Lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesth Analg*. 2010;111:129–140.

examined in studies by Eikermann and colleagues. Rats were administered neostigmine after TOF ratios recovered to 1.0. Neostigmine administration resulted in decreases in upper airway dilator muscle tone and volume, impairment of diaphragmatic function, and reductions in minute ventilation.^{121,122} In healthy volunteers given rocuronium, the administration of neostigmine after the recovery of the TOF to 1.0 induced genioglossus muscle impairment and increased upper airway collapsibility.¹²³ The adverse physiologic effects of neostigmine in the setting of complete neuromuscular recovery can potentially have negative respiratory consequences in postoperative surgical patients. The mechanisms proposed for this effect include sensitivity of the upper airway muscles to an overabundance of acetylcholine with desensitization of the ACh receptor, depolarizing blockade, or an open channel blockade. In contrast, Murphy and colleagues randomized 90 surgical patients to receive either 40 µg/kg of neostigmine or saline when TOF ratio of 0.90 to 1.0 was achieved at the end of surgery.¹¹¹ No decreases in TOF ratios were observed in any subjects given neostigmine, and no differences between groups were observed in the incidences of airway obstruction, hypoxic events, or signs and symptoms of muscle weakness. Studies suggest that sugammadex does not appear to produce adverse effects on upper airway tone or normal breathing when given after neuromuscular recovery.¹²¹

NAUSEA AND VOMITING. The impact of anticholinesterases on the incidence of postoperative nausea and vomiting remains controversial. Systemic anticholinesterases produce effects outside of the neuromuscular junction that may influence the risk of unwanted side effects following anesthesia and surgery. In addition to the action

within the neuromuscular junction, anticholinesterase drugs result in muscarinic effects on the gastrointestinal tract, resulting in stimulation of secretion of gastric fluid and increases in gastric motility. The use of smaller doses of neostigmine in combination with atropine decreases lower esophageal sphincter tone.¹²⁴ Furthermore, neostigmine may produce nausea and vomiting via a central effect. Intrathecal neostigmine increases the incidence of nausea and vomiting, likely through a direct effect on the brainstem.

Anticholinergic drugs (e.g., atropine, glycopyrrolate) are routinely administered with anticholinesterases in order to attenuate the undesirable muscarinic effects of these reversal agents. Perhaps anticholinergic drugs have antiemetic properties.¹²⁵ When given to children receiving sedation (in the absence of anticholinesterases), atropine was associated with significantly less vomiting (5.3%) than either glycopyrrolate (10.7%) or no anticholinergic (11.4%).¹²⁶ Similarly, surgical patients who were randomized to receive atropine had significantly less nausea than those given glycopyrrolate.¹²⁷ Atropine is a tertiary amine that can readily cross the blood-brain barrier and produce central effects, whereas glycopyrrolate is a quaternary amine that does not penetrate the blood-brain barrier. The beneficial effects of atropine on nausea and vomiting are likely secondary to a central nervous system effect.

Several randomized clinical trials have been performed to determine whether anticholinesterase administration results in an increase in the incidence of postoperative nausea and vomiting. Unfortunately, most study populations were small (39–120 patients). Two systematic reviews have been conducted to address this limitation. Tramer

TABLE 28.6 Early and Delayed Postoperative Nausea and Vomiting With Neostigmine Versus Control—Results of a Metaanalysis

Outcome	Anticholinergics	Number of Studies	Number of Participants	Relative Risk (95% CI)
Early nausea (0-6 h)	Atropine and Glycopyrrolate	6	584	1.24 (0.86-1.80)
	Atropine	1	79	0.67 (0.36-1.26)
	Glycopyrrolate	5	505	1.39 (0.97-1.99)
Early vomiting (0-6 h)	Atropine and Glycopyrrolate	8	768	1.05 (0.72-1.55)
	Atropine	2	199	0.75 (0.52-1.08)
	Glycopyrrolate	6	568	1.35 (0.88-2.06)
Delayed nausea (6-24 h)	Glycopyrrolate	4	337	1.09 (0.76-1.57)
Delayed vomiting (6-24 h)	Glycopyrrolate	4	337	1.01 (0.58-1.78)

CI, Confidence interval.

From Cheng CR, Sessler DI, Apfel CC. Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting? *Anesth Analg*. 2005;101:1349-1355.

and Fuchs-Buder analyzed eight trials with data on 1134 patients that compared reversal with neostigmine or edrophonium with spontaneous recovery from long- or intermediate-acting NMBDs.¹²⁸ An analysis of the neostigmine data across all trials and doses revealed no evidence of an increased risk of early and late nausea and vomiting when neostigmine was administered. However, some evidence in adults suggested that antagonism with larger doses of neostigmine (2.5 mg) might increase the incidence of these events. No evidence was found for this effect with edrophonium. A later systematic review evaluated the effect of neostigmine on postoperative nausea and vomiting while considering the different anticholinergics as confounding variables.¹²⁵ Ten randomized trials (933 patients) that compared neostigmine to inactive control were included. The combination of neostigmine with either glycopyrrolate or atropine did not increase the incidence of nausea or vomiting, nor was there an increased risk when large doses of neostigmine were compared with smaller doses (Table 28.6). Atropine was associated with a reduction in the risk of vomiting, but glycopyrrolate was not. In conclusion, there is at present insufficient evidence to conclude that neostigmine or edrophonium is associated with an increased risk of postoperative nausea and vomiting.

CARDIOVASCULAR EFFECTS. Pronounced vagal effects are observed following the administration of anticholinesterases—bradycardia and other bradyarrhythmias, such as junctional rhythms, ventricular escape beats, complete heart block, and asystole, have been reported. The time course of these bradyarrhythmias parallels the onset of action of the anticholinesterases, with the most rapid onset observed with edrophonium, slower for neostigmine, and slowest for pyridostigmine.⁹⁰ In order to counteract these cardiovascular effects, atropine and glycopyrrolate are administered concurrently with anticholinesterases. Atropine and glycopyrrolate have muscarinic (parasympathetic) blocking effects, but do not block nicotinic receptors. Atropine has a more rapid onset of action (approximately 1 minute) compared with glycopyrrolate (2-3 minutes), although the duration of action of both agents is similar (30-60 minutes). Despite the concurrent administration of anticholinergic drugs, a high incidence of bradyarrhythmias is observed following anticholinesterase reversal (up

to 50%-60% of patients in some studies).¹²⁹ The risk of arrhythmias is influenced by the type of anticholinesterase and anticholinergic used, the dose of anticholinesterase and anticholinergic administered, and background anesthetic used (opioid-based vs. volatile anesthetic and type of NMBD).

Several investigations have examined the heart rate and rhythm responses to various anticholinesterase/anticholinergic combinations. In general, it is preferable to use atropine with edrophonium because the onset of action of both drugs is rapid. Edrophonium-atropine mixtures induced small increases in heart rate, whereas edrophonium-glycopyrrolate mixtures caused decreases in heart rate and occasionally severe bradycardia.¹³⁰ Similarly, the onset of cholinergic effects of neostigmine coincides with the onset of the anticholinergic effects of glycopyrrolate; glycopyrrolate is superior to atropine in protecting against neostigmine-induced bradyarrhythmias.¹³¹ When atropine is given with edrophonium (0.5-1.0 mg/kg), doses of 5 to 7 µg/kg are recommended, although larger doses may be used in certain circumstances.^{130,132} If glycopyrrolate is given with neostigmine, minimal changes in heart rate are observed if a dose equivalent of one fourth the dose of neostigmine is used (e.g., 1 mg glycopyrrolate with 4 mg of neostigmine).¹³¹ Because the onset of action is slow with pyridostigmine, tachycardia may be observed when either atropine or glycopyrrolate is coadministered.

More recent investigations have examined the impact of atropine and glycopyrrolate, given with neostigmine, on autonomic control in the postoperative period. During physiologically stressful events, control of heart rate and arterial blood pressure is regulated by the sympathetic and parasympathetic nervous systems. Anticholinergic drugs attenuate the efferent parasympathetic regulation of heart rate and suppress cardiac baroreflex sensitivity and heart rate variability. This suppression of the parasympathetic system may predispose patients to cardiac arrhythmias following surgery. Marked decreases in baroreflex sensitivity and high-frequency heart rate variability have been observed in healthy volunteers given either atropine (20 µg/kg) or glycopyrrolate (7 µg/kg).¹³³ Although the times required to return to baseline values were prolonged in both groups, recovery times were significantly longer in the