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The Role of Pharmacokinetics in Anaesthesia: Application to Intravenous Infusions

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SUMMARY

Pharmacokinetic concepts describe the relationship between drug dose and resulting plasma concentration. A drug's pharmacokinetic profile can be described by distribution and elimination half-lives, initial volume of distribution, steady-state distribution volume, and metabolic and distributional clearance. After initiating a fixed rate of drug infusion, four to five terminal elimination half-lives are required to reach a steady state of constant plasma concentration. If a loading dose is given, a steady state can be achieved more rapidly. The most rapid method of achieving a constant plasma concentration involves using a variable rate of drug infusion that adjusts for the metabolic clearance and distribution of the drug. Computer-driven infusion pumps can be used to rapidly achieve, then maintain, constant plasma concentrations of a drug.

Key Words: PHARMACOKINETICS: distribution, elimination, infusion, steady-state

The safe use of intravenously administered drugs in clinical anaesthesia requires an understanding of the physiological and pharmacological processes that distribute drugs and eliminate them from the body. The discipline of pharmacokinetics pertains to the mathematical description of the processes and rates of drug movement from the sites of administration into the blood, distribution into the tissues, and elimination or excretion from the body. Pharmacokinetic concepts can be used to design drug administration regimens to achieve therapeutic goals (i.e. constant plasma concentrations). This article will first develop the basic principles of drug pharmacokinetics. The pharmacokinetic profiles of two intravenous anaesthetics (thiopentone, methohexitone) will be presented as examples of pharmacokinetic data analysis. Finally, the pharmacokinetic principles that govern infusions will be developed. The different approaches to achieving constant plasma concentrations will be presented.

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PHYSIOLOGICAL *VS* PHARMACOKINETIC MODELS

Anesthesiologists have classically conceptualised the distribution and elimination of intravenous drugs using models that were developed for the inhalational anaesthetics. These models are termed physiologic or perfusion models because they attempt to characterise drug behaviour in the body using drug partitioning coefficients, tissue sizes, and tissue-blood flow. Body tissues such as the vessel-rich group or the vessel-poor group are combined into 'compartments' on the basis of similar perfusion and drug partitioning characteristics. Price *et al.*[1] and Saidman and Eger[2] used these concepts to explain the fate of thiopentone in the human body. These perfusion models have major limitations

because of the many assumptions they incorporate.[3] For example, organ size and blood flows are assumed to be average, ignoring the wide variability that exists among normal individuals and the possible effects of concurrently administered anaesthetics or existing disease states.

Pharmacokinetic models

An alternative approach has been developed that characterises drug distribution and elimination using only plasma concentration and time data.[4-6] For most drugs, a plot of their plasma concentration (on a log scale) after a bolus intravenous injection *vs* time resembles that in Figure 1. It is possible to distinguish two distinct phases in the decline of drug concentration in plasma. The first phase is the distribution phase, which begins immediately after the bolus intravenous injection. In the distribution phase, there is rapid equilibration of drug between the rapidly equilibrating, vessel-rich tissues and the blood. The distribution phase involves drug movement from these tissues to less well-perfused tissues such as muscle and skin. When this phase is completed, the elimination phase begins, and the plasma concentration of the drug decreases less rapidly. The rate of drug elimination from the body can be characterised by the slope of the line representing the log plasma concentration plotted against time during the elimination phase. The numerical value of the slope of the elimination phase is termed 'beta' (β) and is called a first-order rate constant.

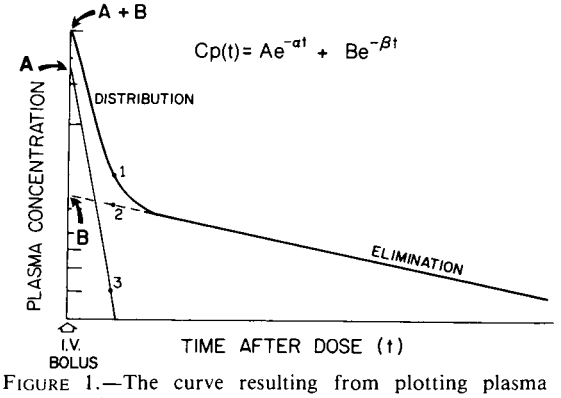

FIGURE 1.—The curve resulting from plotting plasma concentrations (on a log scale) against time (t) after an intravenous bolus injection of a drug. The plasma concentration (Cp) at time t can be characterised by a bi-exponential equation in which A and B represent the scale, α and β represent the rate of exponential fall of the plasma concentration, and e is the base of natural logs (e = 2.718 . . .).

A first-order process occurs when the rate of change of a variable is directly proportional to the magnitude of the variable. In contrast, for zero-order process the rate of change is constant at all magnitudes of the variable. The distribution and elimination of most drugs in the human body are governed by first-order processes. The actual amount of drug affected by the first-order process is determined by the numerical value of the rate constant. For example, in Figure 1 the slope of the elimination phase (rate constant) of 0.1/min would indicate a 10% rate of change in the plasma concentration per minute. Therefore, if the plasma concentration was 100 μg/ml at the start of the first minute, it would decline to 90 μg/ml at the end of the minute. Likewise, a plasma concentration of 10 μg/ml would decline to 9 μg/ml in one minute. Although the amount of drug eliminated in one minute is greater at 100 μg/ml (because 10 μg/ml is removed) than at 10 μg/ml (when 1 μg/ml is removed), the fraction of drug removed is the same (10/100 = 0.1; 1/10 = 0.1), indicating a first-order process.

The concept of elimination half-life is used, however, more frequently than the rate constant. The half-life is the time necessary for the drug concentration in plasma to decline by one-half. After four to five elimination half-lives, this concentration has declined by approximately 94% of the original value. The terminal elimination half-life is derived from the elimination rate constant (β) by the following equation:

$$\text{Elimination half-life} = \frac{\text{natural log of 2}}{\beta} = \frac{0.693}{\beta} \quad \text{(Eq. 1)}$$

It is also possible to estimate the distribution half-life. During the distribution phase, although drug elimination is also occurring, the distribution process predominates. The distribution half-life is estimated using a 'residuals' technique: the elimination phase line is extrapolated back into the distribution phase (Figure 1), and the predicted plasma concentration on the elimination phase line (point 1) is subtracted from the drug plasma concentration during the distribution phase (point 1). The residual (point 3) is then plotted. This process is repeated at several time

intervals. The slope of the residual line determines the rate constant alpha (α) that characterises the rate of drug distribution. The distribution and elimination phases have made possible the conceptualization of the body into two compartments (Figure 2). The central compartment represents the blood and rapidly equilibrating tissues such as liver, kidney, heart, lung and brain. The drug is intravenously administered into this compartment. The distribution phase represents equilibration of the central compartment with less rapidly equilibrating (generally because of lower perfusion) tissues such as muscle, skin and fat and is termed the peripheral compartment. These compartments represent theoretical spaces, postulated to account for the fact that drug is distributed into different tissues at different rates. One must be very careful in speculating which tissues compose the various compartments of a pharmacokinetic model. The examples mentioned are generalisations based upon an understanding of drug distribution gathered from physiological models. To accurately identify the tissues composing the various compartments, actual tissue sampling is necessary. This, however, is not possible in humans. Some drugs have two distribution phases, one rapid and one slow, followed by the elimination phase. This type of pharmacokinetic behaviour can be characterised using a three-compartment model. The central compartment is attached to two peripheral compartments: one rapidly equilibrating (shallow compartment) and a second, less rapidly equilibrating compartment (deep compartment).

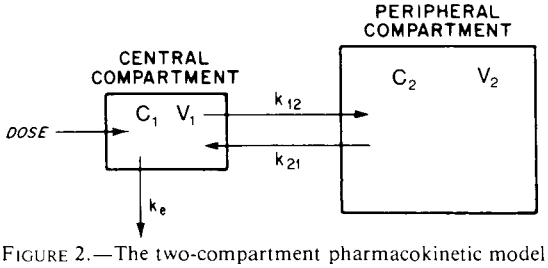

FIGURE 2.—The two-compartment pharmacokinetic model derived from the bi-exponential plasma decay curve shown in Figure 1. C_1 and C_2 represent drug concentrations in the two compartments, while V_1 and V_2 represent the calculated volumes of the two compartments. K_{12} and K_{21} are first-order rate constants that characterise intercompartmental drug transfer, while k_e is a first-order rate constant for overall drug elimination from the body.

By relating the drug dose to the plasma concentration, one can calculate the volume of the central compartment and the overall volume of distribution at steady state (sum of the central and peripheral compartment volumes in Figure 2). The volume of the central compartment and overall steady-state distribution volume represents a theoretical mathematical approximation of the extent of drug distribution in the body. The volume of the central compartment will govern the peak plasma concentrations achieved immediately after a bolus intravenous administration. The steady-state distribution volume will govern the plasma concentrations after distribution has been completed. The volume of distribution at steady state (Vd_{ss}) of some drugs can be extremely large, frequently exceeding the mass of the body. Since the drug concentration is measured only in plasma and not in tissues, the Vd_{ss} calculation assumes that the steady state partitioning between plasma and all tissues is one. A Vd_{ss} larger than anatomic volumes can be explained by drug-tissue concentrations that exceed the plasma concentration.

The removal of drug from the body, generally by the liver or kidney, constitutes the pharmacokinetic parameter of clearance. Drug clearance is the volume of blood or plasma from which the drug is completely removed per unit of time. Just as creatinine clearance is used to assess the efficiency of renal function, so drug clearance may be used to measure the ability of the body or an individual organ to eliminate a drug. To assess the clearance of a drug by the liver, a measure of that organ's efficiency in removing the drug is obtained by calculating the hepatic extraction ratio:

$$\text{Hepatic extraction ratio} = \frac{C_a - C_v}{C_a} \qquad \text{(Eq. 2)}$$

where C_a is the mean drug concentration in the portal vein and hepatic artery (drug concentration entering the liver), and C_v is the drug concentration in the hepatic vein (drug concentration leaving the liver).

The hepatic clearance of a drug is the product of hepatic blood flow and hepatic extraction ratio. If the hepatic extraction ratio is large (0.7 to 1.0), the clearance of the drug will be very dependent on hepatic blood flow. Changes in hepatic perfusion will change drug clearance; changes in hepatic enzyme activity (e.g. enzyme

induction) will have only minimal effect on the hepatic drug clearance. This high hepatic extraction ratio results in 'perfusion-dependent' elimination.[7] If the hepatic extraction ratio is low (0.0 to 0.3), only a small fraction of the drug delivered to the liver is removed per unit of time. Therefore, an excess of drug is available for the hepatic elimination mechanisms, and changes in hepatic perfusion will not markedly affect hepatic clearance. For a low hepatic extraction ratio drug, an increase in the hepatic extraction ratio through enzyme induction or an increase in the fraction of free drug (i.e. not bound to protein) can markedly affect hepatic clearance. This type of hepatic elimination is termed 'capacity-dependent'.[7]

The clearance and distribution volume of a drug determine the elimination half-life in the following manner:

$$\text{Elimination half-life} = \frac{0.693 \times Vd_{ss}}{Cl} \qquad \text{(Eq. 3)}$$

where 0.693 is the natural log of 2, Vd_{ss} is the steady-state volume of distribution, and Cl is clearance. The above equation assumes that the body behaves like a one-compartment model; for two- or three-compartment behaviour, the mathematical expressions become more complex. In general, a large steady-state volume of distribution will increase the elimination half-life while a high clearance will decrease it. The elimination half-life is determined by clearance and steady-state volume of distribution.

The concepts of compartment analysis, drug distribution, elimination half-life, volume of distribution, and drug clearance can be used to discuss the pharmacokinetic fate of two intravenous anaesthetics, thiopentone and methohexitone.

THIOPENTONE AND METHOHEXITONE PHARMACOKINETICS

There is a distinct difference in the pharmacokinetic profile of these intravenous barbiturates (Figure 3 and Table 1).[8-9] Thiopentone and methohexitone exhibit either tri-exponential or bi-exponential behaviour after an intravenous bolus injection. Methohexitone has a short elimination half-life of 3.9 hours *vs* 11.6 hours for thiopentone. The volume of distribution at steady state is similar for thiopentone and methohexitone. The clearance of methohexitone is approximately four times greater than thiopentone's clearance.

TABLE 1

Pharmacokinetic data for methohexitone and thiopentone

	Methohexitone	Thiopentone
Age (yrs)	30.1 (5.4)	30.0 (4.4)
Weight (kg)	76.6 (10.6)	68.9 (11.3)
Dose (mg/kg)	2.4 (0.4)*	6.7 (0.7)
Distribution half-life (min)		
Rapid	5.6 (2.7)	8.5 (6.1)
Slow	58.3 (24.6)	62.7 (30.4)
Elimination half-life (hr)	3.9 (2.1)+	11.6 (6.0)
Clearance (ml/kg/min)	10.9 (3.0)	3.4 (0.5)
Central compartment volume of distribution (l/kg)	0.35 (0.1)	0.38 (0.09)
Steady-state volume of distribution (l/kg)	2.2 (0.7)	2.5 (1.0)

Values are mean with SD in brackets (data from reference 9).
*$P<0.001$
+$P<0.005$

What are the implications of such pharmacokinetic data on the clinical use of these drugs? After a single-bolus intravenous injection, distribution of drug from brain to muscle and fat terminates the anaesthetic effect of each drug. Hepatic metabolism will have a

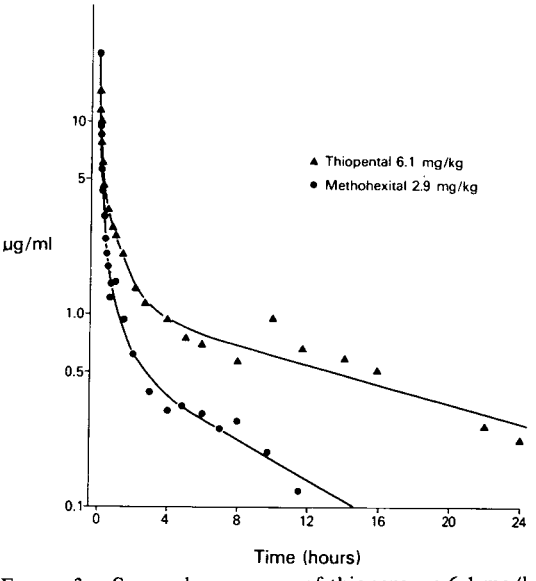

FIGURE 3.—Serum decay curves of thiopentone 6.1 mg/kg (▲) and methohexitone 2.9 mg/kg (●) given as an intravenous bolus. Reproduced with permission from reference 9.

greater role in terminating the effects of methohexitone than those of thiopentone. The high clearance of methohexitone results from high hepatic extraction, reflecting a greater intrinsic ability of the liver to metabolise methohexitone than thiopentone. Clearance of methohexitone would be influenced by changes in cardiac output that alter hepatic perfusion. The clearance of thiopentone, which has a low extraction ratio, would indicate capacity-dependent elimination that is not influenced by hepatic perfusion but is affected by enzyme induction and the degree of plasma protein binding. When multiple doses are given throughout an anaesthetic procedure, the higher clearance of methohexitone will result in more drug having been eliminated by the end of anaethesia than would occur with thiopentone. The degree of residual post-anaesthetic effects should be less with methohexitone than with thiopentone.

RATIONALE FOR CONSTANT DRUG-PLASMA CONCENTRATIONS

The drug concentration at the site of action (biophase) generally governs the degree of pharmacologic effect.[10]. For an intravenously administered drug, the plasma concentration will govern the degree of drug concentration at the biophase. The factors that govern the relationship between the plasma concentration of a drug and the pharmacologic effect has been termed pharmacodynamics. Immediately after a bolus intravenous injection, there is a finite delay in the onset of the drug effect as the drug distributes into the biophase. When the peak biophase concentration is achieved, peak drug effect generally occurs. As the drug continues to distribute throughout the body, plasma concentration, biophase concentration, and the drug effect decline. If there is rapid plasma concentration and biophase equilibration along with rapid drug distribution/redistribution, the drug effect can change from therapeutic to subtherapeutic in a short period of time. This is the pharmacological basis for the short duration (10 to 15 minutes) of drug effect for thiopentone and methohexitone after clinical anaesthetic doses in spite of having long terminal elimination half-lives (see Table 1).

If a constant, stable drug effect is desired, it is logical to achieve a constant biophase concentration. This becomes the rationale for using a continuous infusion to achieve constant plasma concentrations that result in a constant degree of drug effect. Repeated, frequent intravenous bolus injections of a drug, as commonly practised in anaesthesia, will cause fluctuating plasma concentrations and therefore variable drug effects. The most common anaesthetic example of continuous infusion occurs with the inhalational anaesthetics. The infusion process occurs with a gaseous phase through the lungs to achieve constant alveolar, blood, and brain concentrations.

ACHIEVING CONSTANT DRUG PLASMA CONCENTRATIONS

Pharmacokinetic concepts can be used to develop the rationale basis of intravenous drug infusion. If a constant infusion of a drug is started in a patient, eventually a steady state will be achieved. This steady state indicates that the rate of drug administration exactly equals the rate of drug elimination from the body and therefore the plasma concentrations of the drug are constant — the plasma concentration is in complete equilibrium with all of the tissue concentrations (no distribution is occurring). As shown in Figure 4, four to five drug elimination half-lives are required to achieve constant plasma concentrations. Since the elimination half-life is determined by both the clearance and steady-state distribution volume (see Equation 3), a large volume of distribution will result in a long elimination half-life and therefore a long period of time to achieve steady state from a single, fixed-infusion rate. With a large distribution volume, more drug, and therefore more time, is required to achieve an equilibrium between the plasma concentration and tissue concentrations. Increasing the infusion rate does not increase the time to achieve a given steady state. The time to steady state is independent of the rate of infusion; however, the rate of infusion will govern the ultimate steady-state drug concentrations that are achieved (Figure 4). The infusion rate needed to achieve a given steady-state plasma concentration is determined by the following equation:

$$\text{Infusion rate} = Cp_{ss} \times Cl \qquad \text{(Eq. 4)}$$

where Cp_{ss} is the desired steady-state plasma concentration and Cl is the drug clearance.

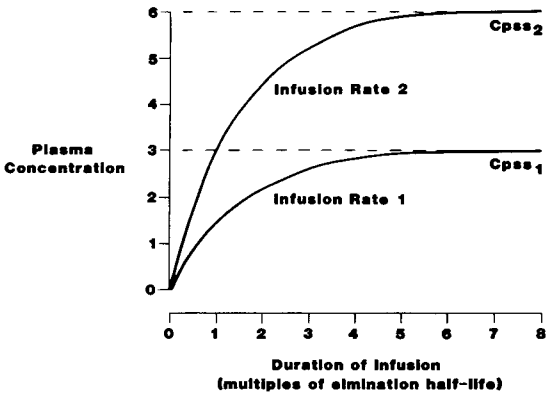

FIGURE 4.—Plasma concentration *vs* time after starting a fixed-rate infusion. Three to four elimination half-lives are needed to reach steady state (Cp_{ss_1}). Doubling the infusion rate doubles the steady state achieved (Cp_{ss_2}); however, the amount of time required to achieve the higher steady state is unchanged.

Given that most drugs have a relatively long elimination half-life relative to the short time one is willing to wait for a drug effect, how can the process of achieving constant plasma concentrations be enhanced? The most practical approach is to give a loading dose of drug immediately prior to starting the fixed-rate infusion. The loading dose delivers a relatively large amount of drug to the tissues in a very short period of time to rapidly attain a tissue concentration of the drug. This will decrease the amount of time needed for the plasma concentration to equilibrate with the various tissue concentrations. The loading dose can be determined from the steady-state distribution volume (Vd_{ss}) of the drug and desired steady-state plasma concentration (Cp_{ss}), as indicated by the following equation:

$$\text{Loading dose} = Vd_{ss} \times Cp_{ss} \qquad \text{(Eq. 5)}$$

The resulting plasma concentrations *vs* time curve is shown in Figure 5. By giving a loading dose based on the steady-state distribution volume, one achieves plasma concentrations higher than desired for a finite period of time. As the loading dose distributes into the tissues, the desired steady-state plasma concentration is approached. Drug toxicity or excessive drug effect may occur during this early time of supratherapeutic drug concentrations. An alternative approach is to scale the loading dose relative to the initial distribution volume (V_1) as shown below:

$$\text{Loading dose} = V_1 \times Cp_{ss} \qquad \text{(Eq. 6)}$$

The resulting plasma concentration *vs* time profile is shown in Figure 5. The desired plasma concentration is achieved immediately; however, because of drug distribution, the concentrations will fall to a subtherapeutic level for a period of time (i.e. the valley of no drug effect).

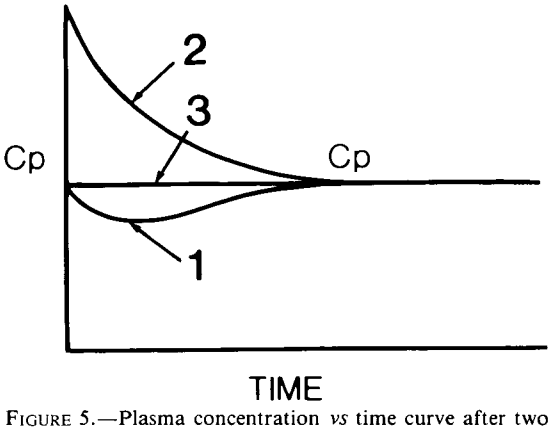

FIGURE 5.—Plasma concentration *vs* time curve after two different loading doses. For curve 1, the loading dose was calculated from the initial distribution volume (Eq. 6). For curve 2, the loading dose was calculated from the steady-state volume of distribution (Eq. 5). Curve 3 represents the desired steady-state plasma concentration.

Wagner[11] proposed another approach that involves giving a rapid then slow infusion that will initially underachieve then overachieve the desired steady-state plasma concentration. The rapid infusion rate is determined by the desired infusion time and distribution/elimination pharmacokinetics of the drug.

The ideal approach to drug infusion would involve achieving the desired concentration immediately, then maintaining it. Using pharmacokinetic concepts, Kruger-Theimer[12] first described the following approach with subsequent expansion by Vaughan and Tucker,[13] Rigg and Wong,[14] and Schwilden:[15,16] A bolus (B) is first given to achieve the desired plasma concentration in the central compartment as defined by Equation 6. A maintenance infusion rate is initiated to replace the drug that is being eliminated (E) as in Equation 4. Finally, an exponentially declining infusion rate is also started to compensate for the drug transfer (T) to the peripheral compartment or tissues. The exponential infusion rate or transfer function is a constantly decreasing rate of infusion that adjusts for

decreasing tissue uptake over time. As the tissues reach an equilibrium with the plasma concentration, the exponential infusion rate approaches zero. Equation 7 indicates how the exponential infusion rate is determined from the pharmacokinetic parameters of a two-compartment model:

$$\text{Transfer infusion rate at time } t = V_1 \times Cp_{ss} \times k_{12} e^{-k_{21}t} \quad \text{(Eq. 7)}$$

where k_{12} and k_{21} are the micro-rate constants of the pharmacokinetic model (Figure 2), and e is the base of the natural log. Figure 6 is a sample calculation of the infusion rates needed to achieve a constant plasma concentration of etomidate.

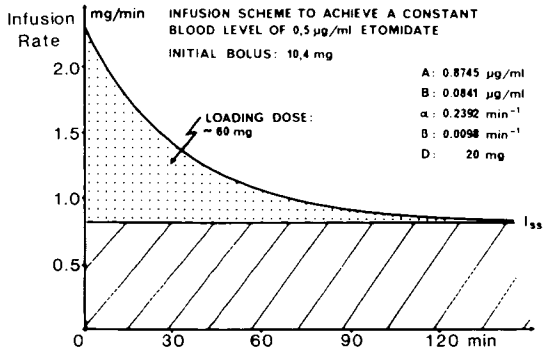

FIGURE 6.—The BET infusion scheme for etomidate, aiming at a constant plasma concentration of 0.5 µg/ml. The following pharmacokinetic data were used to derive the infusion rates: rapid distribution half-life, 2.9 min; elimination half-life, 70.7 min; central volume of distribution, 20.9 litres steady-state volume of distribution, 118.9 litres clearance, 1634 ml/min. The initial bolus dose was 10.4 mg. Reproduced with permission from reference 16.

To achieve the above approach, the transfer infusion rate must be calculated at frequent intervals, i.e. 5 to 10 times/minute), and the infusion rate varied accordingly. This can best be achieved by a computer-driven infusion pump. The computer hardware and software (TIAC) to implement exponential infusion schemes for a two-compartment pharmacokinetic model has been implemented by Janssen Scientific Instruments (Beerse, Belgium). Schuttler *et al.*[17] and Ausems *et al.*[18] have examined the accuracy of average alfentanil pharmacokinetic data in a group of patients. Alvis *et al.*[19,20] have also implemented the above concept for a three-compartment pharmacokinetic model to administer fentanyl to patients having cardiac surgery. The algorithm used by Alvis *et al.* to calculate the transfer infusion rate differs from that proposed by Schwilden.[15] Sebaldt *et al.*[21] and Riddell *et al.*[22] have also implemented an exponential infusion scheme for lidocaine using a simple infusion pump and two different drug concentrations. The latter approach is limited to achieving only one drug concentration in a patient, whereas the computer-driven devices allow the anaesthesiologist to achieve multiple, different steady-state concentrations. Figure 7 is an example of using the computer-driven infusion pump to administer alfentanil. The predicted alfentanil plasma concentration was varied to the patient's clinical needs in an interactive manner. The actual measured plasma concentrations are also indicated.

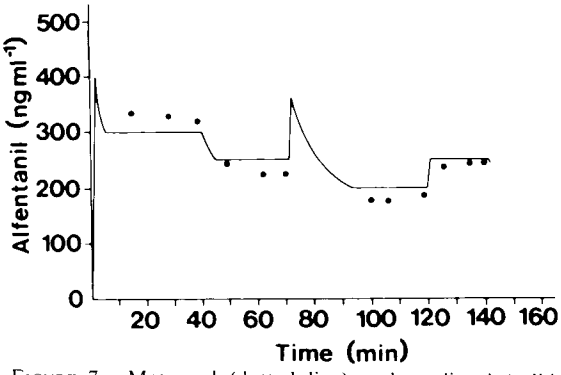

FIGURE 7.—Measured (dotted line) and predicted (solid line) alfentanil plasma concentrations in a patient receiving a computer-driven infusion regimen for an abdominal surgical procedure. Reproduce with permission from reference 18.

The application of computer-driven infusions that achieve instantaneous steady-state plasma concentrations is relatively limited to date. The two published studies with alfentanil[17,18] and fentanyl[20] have shown an acceptable relationship between the predicted plasma concentrations and the actually achieved concentrations. It remains to be determined how well computer-driven infusion pumps and population pharmacokinetic data, which adjusts for relevant factors (age, weight, sex, disease, concurrent drugs), can provide accurate and predictable steady-state drug plasma concentrations. Also the clinical advantage of using steady-state plasma concentrations that minimise fluctuations of drug effect will require rigorous scientific evaluation.

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