AANA Journal Course

Update for Nurse Anesthetists

6

6 CE Credits*

Should I Continue or Discontinue That Medication?

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Patients are admitted for surgery while taking a wide array of medications, and nurse anesthetists must evaluate their effectiveness and compatibility with anesthesia. Anesthetists must be familiar with the basic pharmacology of each drug and the potential adverse effects and possible drug interactions that may occur when anesthetic drugs are administered. If a medication requires discontinuation, we must ensure that the patient's disease remains controlled throughout the perioperative period. It is estimated that up to 50% of patients admitted for surgery will be taking some of type of medication preoperatively.

The most common types are the drugs used to treat cardiovascular, central nervous system, and gastrointestinal disorders. There are few clinical or evidence-based guidelines regarding the preoperative management of many of these drugs. Most medications taken for minor disorders that do not have systemic effects can be safely continued without incident. Some medications may require discontinuation or temporary alteration of the dosing schedule to avoid problems in the perioperative period. This course reviews the current literature regarding the anesthetic management of several commonly encountered drug classes.

Keywords: *Anticoagulants, antidiabetic medication, cardiovascular drugs, preoperative medications, thyroid medications.*

Objectives

At the completion of this course, the reader should be able to:

1. Describe the current practice guidelines regarding the perioperative use of beta-blocking medications.
2. Appropriately apply pharmacokinetic and pharmacodynamic principles of antidiabetic agents to the preoperative care of patients.
3. Plan proper management of anticoagulant and antiplatelet agents during the perioperative period.
4. Summarize the physiologic effects of corticosteroids.
5. Discuss the anesthetic concerns associated when patients are prescribed medications used to treat psychological disorders.

Introduction

One of the challenges of current anesthesia practice is managing patients with increasingly complex preoperative medication profiles. Although most clinicians must remain current with therapies within their specialties, anesthetists must keep up-to-date with a wide spectrum of diverse medications. Anesthesia providers must direct the administration of these medications through the perioperative period and address a number of important issues. These issues require a thorough understanding of patients' prescriptions and over-the-counter medications. The pharmacokinetics and pharmacodynamics of many drugs are affected by significant surgery-related and anesthesia-related neurohumoral changes due to the stress response and altered gastric function. Typical concerns revolve around the indications, dosing schedule, and efficacy. Practical questions arise such as the following: Are there relevant side effects? What are the consequences of withdrawal? How will these medications interact with the anesthetics? If I decide to discontinue a medication, when do I recommend that it be restarted in the postoperative period? When will the patient be able to resume the preopera-

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tive oral medication schedule? Is substitution of an alternative medication appropriate?

More than 52 million inpatient and outpatient surgeries and diagnostic procedures are performed in the United States each year, and a significant number of the surgical patients are taking prescription or over-the-counter medications.[1,2] A report noted that nearly 50% of patients admitted for surgery were taking medications unrelated to their surgical condition.[3] The number of medications taken by people increases with age and in patients undergoing major surgical procedures.

The most common reasons for administration of preoperative medications are to treat a cardiovascular disease followed by central nervous system and gastrointestinal disorders. The safety of withdrawing or continuing drug therapy before surgery has not been comprehensively studied despite the millions of patients affected each year.[4] Furthermore, patient care may be fragmented among medical, surgical, and anesthesia providers.[5]

Medications prescribed for minor medical problems and without significant systemic actions in patients undergoing routine procedures may be continued throughout the surgical period without difficulty. Others may require special consideration with regard to chronic disease management, type of surgery and anesthesia, and the expected postoperative course. This article reviews the current literature and recommendations regarding management of some common preoperative medications.

Cardiovascular Drugs

Cardiovascular drugs are the most common type of long-term medication therapy. Included are drugs such as diuretics, beta-receptor blockers, calcium channel blockers, angiotensin converting-enzyme (ACE) inhibitors, angiotensin receptor blockers, statins, and clonidine and related centrally acting agents.

• *Diuretics.* Some clinicians have expressed concerns regarding continuing diuretic therapy due to the common side effects of hypokalemia and hypovolemia associated with long-term use.[5] It has been suggested that diuretics other than the potassium-sparing agents, triamterene and amiloride, as well as hydrochlorothiazide prescribed for hypertension, should be withheld the morning of surgery.[6,7] Others believe that the volume-depleting and hypokalemic effects are generally mild and intervention with fluids and electrolyte measurement with potassium supplementation is relatively easy.[8] In addition, withholding 1 dose probably has little clinical effect. Recent recommendations favor continuation up to and including the day of surgery.[9]

• *Beta-Receptor Blockers.* Beta-receptor blocking drugs are mainstays in the treatment of most major cardiac diseases, including angina, arrhythmias, congestive heart failure, and hypertension. Rebound side effects caused by abrupt withdrawal are well documented and must be avoided.[10] Therapy-induced up-regulation of beta receptors coupled with abrupt withdrawal may produce a rebound in the symptoms of the underlying disease. Additional adverse withdrawal effects include increased platelet aggregation, shifts in the oxygen-hemoglobin dissociation curve, rebound elevation of plasma renin activity, changes in thyroid hormone metabolism, and increased sympathetic nervous system activity leading to increased morbidity and mortality.[11]

There has been substantial research addressing varied protocols for the use of perioperative beta blockade. Evidence suggests that instituting beta-blocker therapy reduces perioperative myocardial infarction and cardiac death and improves long-term outcome in patients with cardiac disease, particularly after vascular surgery.[12-16] There is disagreement, however, regarding which patient groups may benefit and specific clinical management regimens.[13-21] Clarification may come from the results of a current large-scale clinical trial, the Peri-Operative Ischemic Evaluation trial.[22] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines have recently been revised to reflect recent research.[23] The guidelines recommend that patients receiving beta-blockers should continue taking beta-blockers, and patients with a positive stress test or at high risk for cardiac problems undergoing vascular surgery should be prescribed beta-blockers. Accumulating evidence suggests that effective heart rate control with beta-blockers should be targeted at less than 65 beats per minute.[23]

• *Calcium Channel Blockers.* Calcium channel blockers are widely used to treat certain types of angina, hypertension, and atrial tachyarrhythmias. Their primary actions include vasodilation and decreased inotropic, chronotropic, and dromotropic effects. Despite some early concerns about additive myocardial depression when given in conjunction with anesthetics,[24] their beneficial effects in treating cardiac disease far outweigh these concerns.[25] Current practice is to continue therapy throughout the perioperative period unless severe left ventricular dysfunction is evident.[26]

• *ACE Inhibitors and Angiotensin Receptor Blockers.* The ACE-inhibiting drugs are considered drugs of choice for the treatment of congestive heart failure and hypertension, especially in certain patient groups, such as patients with diabetes.[27] Data on their safe use when combined with anesthetics have been conflicting.[28-30] Reports of refractory hypotension and bradycardia during anesthesia induction led many clinicians to recommend discontinuation before surgery.[31-33] Others have reported safe use during anesthesia.[28,29] Similar findings resulting in hypotensive episodes have been noted with the angiotensin receptor blockers.[34,35] When hypotension occurred, the administration of fluids and vasopressors and, occasionally, in severe cases, the vasopressin analogue terlipressin have been successfully used.[36] A clear con-

sensus is still lacking; however, many clinicians report that withholding ACE inhibitors and angiotensin receptor blocking drugs for 1 dosing interval (ie, the evening before or morning of surgery depending on the duration of action of the drug) is a safe approach.[31]

• *Clonidine.* The current ACA/AHA guidelines suggest that the use of alpha-2 agonists such as clonidine for perioperative control of hypertension may be considered for patients with known coronary artery disease or at least 1 clinical risk factor who are undergoing surgery.[23] Clonidine is associated with severe withdrawal reactions and should be continued in the perioperative period in patients currently taking this medication. When patients cannot take oral medications, a topical patch formulation can be substituted. The patch reaches steady state concentrations in 48 to 72 hours and lasts approximately 7 days.[37]

Amiodarone. Several reports of bradycardia, hypotension, and a proarrhythmic effect raised concerns regarding the administration of anesthesia to patients taking amiodarone.[38,39] In addition, long-term amiodarone use is associated with numerous serious respiratory, ocular, and hepatic toxic effects.[40-42] Recent data suggest that anesthesia can be safely given to patients taking amiodarone.[43,44] In fact, the ACC/AHA/European Society of Cardiology guidelines for the treatment of atrial fibrillation recommend that prophylactic amiodarone be considered for patients with a contraindication for beta-blocker therapy.[45,46] Amiodarone has a long elimination half-life, 94 days (when the active metabolites are considered); therefore, discontinuation is impractical. Amiodarone should be continued during the perioperative period.

• *Digoxin.* Digoxin is used primarily for 2 cardiac indications: congestive heart failure and atrial tachyarrhythmias. It has been safely used for many years during anesthesia, and, because of the long half-life (36-48 hours), missing a dose will not significantly change the clinical effects. Digoxin should be continued throughout the perioperative period as it is safe for controlling cardiac disease.[47]

• *Statins.* Statin therapy has shown some usefulness for reducing mortality following noncardiac surgery when used perioperatively, although the evidence is inadequate to recommend routine administration.[48,49] Withdrawal of statin therapy may be potentially hazardous following acute coronary syndromes but not necessarily in patients with stable coronary artery disease.[49,50] Three potential mechanisms of perioperative cardioprotection have been postulated: (1) The statins decrease the level of low-density lipoprotein cholesterol, which decreases inflammation. (2) They stabilize vulnerable plaque secondary to pleiotropic effects. (3) They reduce the inflammatory response to surgery, resulting in less plaque disruption. Withdrawal for more than 4 days postoperatively is an independent predictor of cardiac myonecrosis.[49] Statins have no significant interactions with anesthetic agents; therefore, they should be continued throughout the perioperative period.

• *Intraoperative Use of Volatile Anesthetics.* The recent ACC/AHA guidelines note that it can be beneficial to use volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in patients in hemodynamically stable condition who are at risk for myocardial ischemia.[23] This benefit is likely due to a protective effect on the myocardium associated with preconditioning.

Psychotropic Drugs

Evidence-based guidelines for the management of patients taking psychotropic agents have not been published, although many small studies and case reports are available.

• *Tricyclic Antidepressants.* Tricyclic antidepressants (TCAs) are used for their mood-elevating properties and the treatment of neuropathic pain. Their actions are due in part to blockade of the reuptake of norepinephrine and serotonin in presynaptic nerve terminals. The TCAs may lead to receptor down-regulation and depletion of catecholamine stores, and the effects on the autonomic nervous system of short-term vs long-term therapy can differ. There are a few case reports of adverse reactions in patients taking TCAs who underwent anesthesia.[51] The most common adverse effects included hypotension and increased or decreased responsiveness to administered sympathomimetics. The TCAs have a long half-life; therefore, discontinuation shortly before surgery is unlikely to have a significant effect. Withdrawal symptoms usually occur in the first 2 days following discontinuation.[52] The TCAs are generally considered safe to continue preoperatively; however, if hypotension is encountered and a vasopressor is needed, the response to direct-acting and indirect-acting agents may be difficult to predict.[53] Direct-acting sympathomimetics such as phenylephrine remain the pressors of choice, although careful titration of norepinephrine or dopamine has been suggested as well.[11,52]

• *Monoamine Oxidase Inhibitors.* Clinicians are aware of the numerous drug and food interactions, such as the "cheese effect," with long-term use of monoamine oxidase inhibitors (MAOIs). A significant untoward interaction has long been known to exist between MAOIs and meperidine. There have been numerous reports of hemodynamic instability, including severe hypertensive episodes during anesthesia in patients taking MAOIs.[54-56] The MAOIs are used for the treatment of anxiety and depressive disorders and Parkinson and Alzheimer diseases.[57,58] There are 2 forms of the enzyme, MAO-A and MAO-B. The MAO-A form is found in the highest amounts in the intestinal mucosa and intraneuronally in the brain. The MAO-B form is found in platelets and extraneuronally in the brain. The older MAOIs, isocar-

boxacid (Marplan), tranylcypromine (Parnate), and phenelzine (Nardil), are nonspecific irreversible inhibitors of both isoforms, and recovery occurs slowly after discontinuation because of the interval required for new enzyme synthesis. Moclobemide (Aurorix) is a new reversible inhibitor of MAO-A designed to minimize food interactions.[59] Selegiline (Deprenyl, Eldepryl, and Emsam patch) is an MAO-B–specific irreversible inhibitor with fewer interactions than older drugs. Severe hypertensive episodes have been reported during anesthesia when certain catecholamines and indirect-acting vasopressors such as ephedrine were used. Fatal drug reactions result from an excess of serotonin and catecholamines. Drug reactions can also occur because of inhibition of opiate metabolism, resulting in excess depression. Direct-acting vasopressors such as phenylephrine are metabolized by the enzyme catechol *O*-methyltransferase and are considered safer. In the past, recommendations were to discontinue MAOIs for at least 2 weeks before surgery. Because treatment with an MAOI is an indication of the presence of a complicated behavioral disorder, a psychiatric consultation is in order if discontinuation is desired. Although there is not a consensus, many clinicians do not believe it is necessary to discontinue MAOIs before surgery.[52,60-62] The use of either meperidine and indirect-acting sympathomimetics in patients who are taking MAOIs should be avoided.

• *Select Serotonin Reuptake Inhibitors.* These agents are the most widely used antidepressants and include drugs such as sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), citalopram (Celexa), and fluvoxamine (Luvox). Their action is to selectively block the reuptake of serotonin into presynaptic nerve terminals. Some minor pharmacokinetic drug interactions of little clinical significance have been noted.[52] Selective serotonin reuptake inhibitors are generally considered safe when continued perioperatively.[11,37]

• *Antipsychotic, Antiseizure, Parkinson Drugs, Lithium and Other Psychotropics.* First-generation antipsychotics such as chlorpromazine (Thorazine) and haloperidol (Haldol) frequently produce dopamine receptor blockade, which may lead to extrapyramidal actions. Fluid boluses and vasopressors may be necessary to address hypotension when these agents are present during anesthesia.[8,63]

Antiseizure agents should be continued throughout the perioperative period because their withdrawal may result in significant disease reccurence.[64] Discontinuation of clozapine (Clozaril) may result in severe withdrawal phenomena and disease relapse; therefore, a psychiatric consultation may be necessary if major surgery is planned.[52] Hypotension has been reported in a patient taking clozapine after pulmonary bypass.[65] Medications for treating Parkinson disease should be maintained perioperatively because symptoms can reoccur within hours of a missed dose and there are no specific contraindications for use with anesthetic drugs. Lithium has been reported to cause prolongation of the action of neuromuscular blocking agents and can lead to renal and cardiac toxic effects; however, these effects have rarely been of any clinical significance, and lithium treatment should be maintained perioperatively.

Other commonly used antidepressants, including venlafaxine (Effexor), bupropion (Wellbutrin), mirtazapine (Remeron), and nefazodone (Serzone), have not been associated with withdrawal syndromes and do not have known interactions with anesthetic agents.[66]

Antidiabetic Medications

Proper preoperative management of antidiabetic agents is important to patient safety during the perioperative period. Diabetes mellitus (DM) is a disruption of normal carbohydrate, fat, and protein metabolism due to an absolute deficit of endogenous insulin (type 1 DM) or insulin resistance (type 2 DM). Due to a lack of evidence-based clinical guidelines, judgments made regarding preoperative management of antidiabetic medications must be based on a clear understanding of the factors bearing on glycemic control. Alterations of consciousness, impaired subcutaneous tissue absorption, preoperative fasting, and medication side effects and interactions are important considerations.[67]

Current pharmacologic therapy in DM attempts to mimic normal carbohydrate metabolism and is described as basal-prandial-correction therapy. Basal-prandial therapy involves administration of intermediate-acting or long-acting insulin (eg, glargine) or an oral antidiabetic agent (eg, metformin) to provide a basal component of therapy. The prandial component of therapy is supplemented by a short-acting or rapid-acting insulin (eg, lispro) or oral antidiabetic agent (eg, α–glucosidase inhibitors) to moderate the postprandial increase in the blood glucose level.[68] In certain circumstances (eg, preprandial hyperglycemia), additional insulin (the "correction" component) may be added.[69] Some commercial antidiabetic agents combine basal and prandial components into a single preparation (eg, NovoLog Mix 70/30 and a glyburide-metformin mix).[68]

Several insulin formulations are available to facilitate basal-prandial therapy[70-73] (Table 1). For example, NPH insulin combines regular insulin and protamine, resulting in insulin that has a slower onset and longer duration of action than regular insulin. Newer formulations of insulin, known as insulin analogs (eg, glargine and lispro insulins), are genetically engineered to produce a drug with clinically desirable pharmacokinetic properties. Since people with type I DM do not produce appreciable amounts of insulin and become ketotic and catabolic in its absence, therapy of type I DM is based on the administration of insulin.[70]

Insulin type	Onset	Peak, h	Duration, h
Rapid-acting analogues			
Insulin lispro	10 - 15 min	1 - 2	3-5
Insulin aspart	10 - 15 min	1 - 2	3-5
Insulin glulisine	10 - 15 min	1 - 2	3-5
Short-acting insulin			
Regular	30 - 60 min	2 - 4	4-8
Intermediate-acting insulin			
NPH	1-3 h	4-10	10-18
Lente	2-4 h	4-12	12-20
Long-acting analogues			
Insulin glargine	2-3 h	None	>24
Insulin detemir	1 h	None	Up to 24
Premixed insulins			
70/30 (70% NPH and 30% regular)	30 - 60 min	2 - 10	10 - 18
50/50 (50% NPH and 50% regular)	30 - 60 min	2 - 10	2 - 10
Humalog mix 75/50 (75% lispro protamine and 25% lispro)	10 - 15 min	1 - 3	10 - 16
Humalog mix 50/50 (50% lispro protamine and 50% lispro)	10 - 15 min	1 - 3	10 - 16
NovoLog mix 70/30 (70% aspart protamine and 30% aspart)	10 - 20 min	1 - 4	10 - 16

Table 1. Classification and Pharmacokinetics of Insulins
(Adapted from Tamai et al,[67] Conill et al,[70] Jacober and Sowers,[74] and Glister and Vigersky.[77]

Type 2 DM is characterized by a state in which the body produces insulin, but, because of tissue resistance to insulin, the level of blood glucose is not adequately controlled. Because a person with type 2 DM produces endogenous insulin, glycemic control can be managed by the injection of additional insulin from an exogenous source or administration of oral antidiabetic agents that work by a variety of mechanisms to decrease blood glucose (Table 2).

Preoperative management of antidiabetic medications is based on the principle that therapies aimed at providing basal insulin can, with careful management, be continued in a fasting patient. Therapy includes adjustment of routine dosing regimens and provision and careful monitoring of the blood glucose level. Correction therapy (ie, sliding-scale insulin) may be needed but should not be relied on as the sole therapy for long periods.[69] Prandial therapies should be held in a fasting patient.[68]

Patients undergoing short, simple procedures early in the morning can be managed by delaying the usual diabetes treatments until food is ingested in the early postoperative period.[74,75] It should be noted that procedures requiring a person with DM to fast are customarily scheduled early in the morning to minimize disruption of routine treatments for DM.[67]

Specific recommendations for preoperative management generally call for a reduction in the dose of insulin the evening before surgery and the omission of insulin or administration of a decreased dose the morning of surgery.[67,70,74-77] A sample preoperative insulin regimen is provided in Table 3.

The insulin analog glargine warrants special attention. Glargine has a prolonged duration of 20 to 24 hours but is unique in that its activity is without a significant peak. Because of an absence of peak activity, some experts believe that glargine is well suited for the perioperative period, although a reduction in dose may be warranted.[67,76]

Recommendations for management of patients using insulin pumps include decreasing the insulin dose delivered the evening before and the morning of surgery and the use of an intravenous insulin drip for glycemic control during the procedure.[76,77] If the patient is undergoing a short, simple case under local anesthesia, continuation of use of the insulin pump is safe.[70,76]

In addition to managing medications in the preoperative period, monitoring of the blood glucose level and administration of carbohydrates are important to proper patient management. Provision of glucose is requisite in patients with type 1 DM to prevent hypoglycemia and

Oral agent	Peak	$t_{1/2}$, h	Duration
Sulfonylureas			
Glyburide	4 h	10	12-24 h
Micronized glyburide	2 h	4	12-24 h
Glipizide	1-3 h	2-4	12-24 h
Glipizide-GITS	6-12 h	NA	24 h
Glimepiride	2-3 h	9	24 h
Nonsulfonylurea secretagogues			
Repaglinide	1 h	1	4-6 h
Nateglinide	18 min	1	4 h
Thiazolidinediones			
Rosiglitazone	NA	3-4	Days-weeks
Pioglitazone	NA	16-24	Days-weeks
Biguanides			
Metformin	2-3 h	6	12-18 h
Metformin extended release	4-8 h	NA	24 h
α-Glucosidase inhibitors			
Acarbose	NA	NA	2-3 h
Miglitol	NA	NA	2-3 h

Table 2. Classifications and Pharmacokinetics of Oral Antidiabetic Agents
GITS indicates gastrointestinal therapeutic system; NA, not applicable.
(Adapted from Tamai et al,[67] Poortmans,[72] Jacober and Sowers,[74] and Glister and Vigersky.[77])

Outpatient regimen	Evening before surgery	Morning of surgery
Subcutaneous NPH and regular insulin	Give two-thirds of evening or bedtime NPH and two-thirds of evening regular insulin.	Give half of morning NPH; hold all regular insulin.
Subcutaneous glargine and lispro or aspart insulin	Give two-thirds of bedtime glargine and 100% of evening lispro or aspart.	Hold all insulin.
Insulin pump	Give 70% of basal insulin rate and two-thirds of evening bolus rate.	Give 70% of basal insulin rate; hold all boluses.

Table 3. Sample Preoperative Insulin Management Regimen
Patients who are NPO and receiving basal insulin require blood glucose monitoring every 1-2 h, glucose infusion (unless patient very hyperglycemic) to prevent hypoglycemia, and correction insulin titrated to maintain adequate glycemic control.
(Adapted from Marks[76] and Glister and Vigersky.[77])

ketosis.[77] People with DM require approximately 5 g/h of glucose to meet basal energy requirements. An infusion of a 5% dextrose solution at 100 mL/h will provide 5 g of glucose each hour.[75-77] The blood glucose level should be monitored every 1 to 2 hours during the preoperative transitional period.[67,69,75]

Oral antidiabetic agents should be discontinued before surgery, although the reason for and precise timing of discontinuation vary depending on the agent (see Table 2). One rationale for holding sulfonylureas preoperatively is that they interfere with ischemic preconditioning and may increase the risk of perioperative myocardial injury.[72] The most common justification for holding sulfonylureas and nonsulfonylurea secretagogues is that these agents may precipitate perioperative hypoglycemia. Short-acting secretagogues should be discontinued the evening before or morning of surgery.[67,70,72,76] If long-acting agents are discontinued for a prolonged period before surgery, the patient may require insulin therapy.[70,72,76] If long-acting sulfonylureas are not halted

well before surgery, glucose supplementation in the perioperative period may be required.[70]

The biguanide metformin is associated with increased risk of lactic acidosis, especially in settings in which the glomerular filtration rate is decreased (as in surgery or radiological procedures involving the injection of iodinated dyes). Published recommendations for the discontinuation of metformin vary. Some experts advise holding the medication for as long as 48 hours before surgery,[67] whereas others suggest holding metformin only on the day of surgery.[75]

Thiazolidinediones have a prolonged duration of action and little risk of precipitating hypoglycemia, so whether they are discontinued for a short period before or during the perioperative period will have little impact on glycemic control.[67,76]

The need for emergency surgery may preclude proper preoperative preparation. Patients taking oral antidiabetic agents who require emergency surgery should have oral agents discontinued and receive insulin and/or glucose for glycemic management.[68] Patients undergoing emergency surgery who have recently received long-acting insulin should be monitored frequently and administered adequate glucose to prevent hypoglycemia.[74]

Anticoagulants and Antiplatelet Drugs

The management of perioperative anticoagulant medications presents several challenges. The most compelling challenge is balancing an increased risk of bleeding with invasive procedures against the risk of thromboembolism or disease exacerbation if the agents are withdrawn. Although there are guidelines for management in many situations, recommendations regarding crucial aspects of management are still evolving.

Periprocedural thromboprophylaxis, or *bridging*, refers to the conversion of long-term oral anticoagulation therapy (warfarin) to an injectable alternative for surgery or invasive procedures. The patients affected include patients with prosthetic heart valves, atrial fibrillation, or hypercoagulable states. In addition, perioperative administration of anticoagulants for prevention of thromboembolism is an essential component of modern clinical practice.[78,79]

There are several classes of drugs that effect coagulation, and their indications are varied. They include heparin, warfarin, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), low-molecular-weight heparins, the purinergic or adenosine diphosphate receptor blockers clopidogrel (Plavix) and ticlopidine (Ticlid), and the platelet glycoprotein (GP)11b/111a receptor antagonists abciximab (Reopro), eptifibatide (Integrilin), and tirofiban (Aggrastat).

The primary considerations when deciding to continue, discontinue, or change a patient's therapy involve the type of procedure, type of anesthesia such as general vs region-

Bleeding risk category/invasive procedures	Recommendations
High/Cardiac surgery, abdominal aortic aneurysm repair, neurosurgery, most cancer surgery, bilateral knee replacement, TURP, kidney biopsy	**Low-risk thromboembolism** Stop warfarin (Coumadin) 4-5 d before surgery, and allow INR to return to near normal. Restart warfarin after surgery. Use prophylactic LMWH or unfractionated heparin if procedure predisposes to thrombosis. **Intermediate-risk thromboembolism** Stop warfarin 4-5 d before surgery. Consider no bridge therapy vs starting prophylactic LMWH or unfractionated heparin 2-3 d before surgery. After surgery, start warfarin and prophylactic LMWH or unfractionated heparin. Alternatively, follow bridge therapy protocol using prophylactic LMWH or unfractionated heparin after surgery. **High-risk thromboembolism** Follow bridge therapy protocol. After surgery, await hemostasis before restarting LMWH, or consider prophylactic doses of LMWH or unfractionated heparin.
Intermediate (surgical)/Abdominal surgery, hemorrhoidal surgery, axillary node dissection, dilatation and curettage, hydrocele repair, orthopedic surgery, pacemaker insertion, internal cardiac defibrillator	**Low-risk thromboembolism**

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Bleeding risk category/invasive procedures	Recommendations
insertion, endarterectomy or carotid bypass surgery, noncataract eye surgery (complex lid, lacrimal, orbital), extensive dental surgery (multiple tooth extractions)	Stop warfarin 4-5 d before surgery, and allow INR to return to near normal. Restart warfarin after surgery. Use prophylactic LMWH or unfractionated heparin if procedure predisposes to thrombosis. **Intermediate-risk thromboembolism** Stop warfarin 4-5 d before surgery. Consider no bridging vs starting prophylactic LMWH or unfractionated heparin 2-3 d before surgery. After surgery, restart warfarin and prophylactic LMWH or unfractionated heparin. Alternatively, follow bridge therapy protocol. **High-risk thromboembolism** Follow bridge therapy protocol Await hemostasis before restarting LMWH, and consider using therapeutic dosages of LMWH or unfractionated heparin
Intermediate to low (nonsurgical)/Coronary angiography with or without percutaneous coronary intervention, noncoronary angiography, upper endoscopy with endosphincterotomy, colonoscopy with polypectomy, bronchoscopy with or without biopsy, biopsy (prostate, bladder, thyroid, breast, lymph node, pancreas)	**Low-risk thromboembolism** Stop warfarin 4-5 d before procedure and allow INR to return to near normal. Restart warfarin after procedure. Use prophylactic doses of LMWH or unfractionated heparin if procedure predisposes to thrombosis. **Intermediate-risk thromboembolism** Stop warfarin therapy 4-5 d before procedure. Consider no bridging vs starting prophylactic LMWH or unfractionated heparin 2-3 d before procedure. After the procedure, restart warfarin and prophylactic LMWH or unfractionated heparin. Alternatively, follow bridge protocol. **High-risk thromboembolism** Follow bridge therapy protocol. Await hemostasis before restarting LMWH, and consider using therapeutic doses of LMWH or unfractionated heparin.
Low to minimal/Arthrocentesis, general dental treatment (hygiene, restorations, endodontics, prosthetics, minor periodontal therapy, and uncomplicated extractions), ophthalmic procedures (cataract, trabeculectomy, vitreoretinal), TURP with laser surgery, upper and lower gastrointestinal endoscopy with or without mucosal biopsy	**All risks of thromboembolism** Continue warfarin therapy. Check INR the day of or the day before surgery to be sure the ratio is not supratherapeutic.

Table 4. Bleeding Risk Associated with Invasive Procedures and Recommendations for Perioperative Management

TURP indicates transurethral resection of the prostate; INR, international normalized ratio; LMWH, low-molecular-weight heparin. (Adapted from Geerts et al,[84] Jafri and Mehta,[85] and du Breuil and Umland.[86])

12 mo of dual antiplatelet therapy after DES and postponement of all elective operations for 1 year
No perioperative modification of antiplatelet regimen
No discontinuation of low-dose aspirin (≤300 mg/d) for secondary prevention
Maintenance of clopidogrel in unstable coronary syndromes and during the reendothelialization phase of stents (6-24 wk)
Reduction of combined aspirin-clopidogrel treatment to aspirin alone and heparin if hemorrhage in a closed space is a risk
Performance of only lifesaving operations during the first 6-12 wk after PCI and stent
During PCI, adaptation of the type of stent, if any, to the presumed subsequent noncardiac surgery

Table 5. Recommendations for Management of Patients with DESs

DES indicates drug-eluting stent; PCI, percutaneous coronary intervention.
(Adapted from Grines et al[96] and Hodgson JM, Stone GW, Lincoff AM, et al. Late stent thrombosis: considerations and practical advice for use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. *Catheter Cardiovasc Interv.* 2007;69(3):327-333.)

al, patient-specific risk factors and anticoagulant agent being used.[11] Recommendations are given in Table 4. Most patients can undergo dental, cataract, diagnostic, low-risk gastrointestinal procedures, and minor, minimally invasive procedures without discontinuing or changing anticoagulants.[78]

In the absence of a bleeding disorder, endoscopic procedures with a low risk of bleeding such as upper endoscopy or colonoscopy (with or without) biopsy and retrograde cholangiopancreatography with stent insertion may be performed in patients taking anticoagulants.[80,81] Gastrointestinal procedures associated with a high risk of bleeding such as polypectomy, sphincterotomy, gastric tube placement, laser therapy or mucosal ablation and treatment of varices require discontinuation of warfarin therapy with or without bridging as appropriate. It is not necessary to discontinue aspirin or NSAIDs, when used in standard doses, for endoscopic procedures.

Anticoagulants are a concern in neurosurgical, reconstructive, and major plastic surgeries; retinal, cardiac, vascular, and emergency procedures; and when major nerve blocks are planned. Careful planning and consultation are required among the medical, surgical, and anesthesia providers to optimize patient care and minimize risk.[82,83] The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy provides guidelines for outpatient management of anticoagulation therapy and thromboembolism.[84] They are summarized in Table 4.[85,86]

• *Aspirin and the Nonsteroidal Anti-inflammatory Agents.* It has been common practice to recommend that patients taking aspirin or NSAIDs discontinue taking them up to a week before routine surgery. Recent data noting an increase in coronary events and stroke when patients discontinue these medications for even short periods during long-term use are making practitioners rethink these recommendations and continue these mild platelet inhibitors.[87,88] It has been noted that more than 125 compounds that contain aspirin, many of them over the counter, are on the market. The numbers are similar for NSAIDs. The likelihood that a patient admitted for surgery has taken one of these platelet-inhibiting drugs is high.[89] Specific reports of bleeding problems associated with these agents are rare. Discontinuation of monotherapy with aspirin or NSAIDs before surgery is rarely indicated.

• *Antiplatelet Drugs.* The antiplatelet drugs clopidogrel and ticlopidine are used for secondary prevention of vascular events in patients with established atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina, peripheral vascular disease, acute coronary syndrome, or the need for vascular bypass or angioplasty. They are commonly used in combination with aspirin to reduce stent-related complications. These agents have been shown to increase the risk of postoperative bleeding, reoperation, and mortality in patients requiring coronary artery bypass grafting.[90,91] In patients without a coronary stent, when possible, clopidogrel should be discontinued 5 to 7 days and ticlopidine up to 14 days before surgery. Decisions to discontinue these drugs must be made in consultation with the surgeon and weighed against the risk of recurrent cardiac or cerebrovascular events. In emergency situations, administration of platelets, corticosteroids, and/or fresh frozen plasma has been helpful in reducing bleeding.[92,93]

• *Antiplatelet Drugs and Noncardiac Surgery: Patients With Coronary Stents.* The number of patients admitted for surgery with coronary artery disease who have had coronary stents placed has grown exponentially.[94] They commonly are receiving dual antiplatelet therapy with aspirin and clopidogrel.[95] Patients with coronary stents require special attention preoperatively. Important information to assess includes the date of stent implantation, the type of stent deployed, antiplatelet therapy, and type of operation planned and the associated risk of bleeding. The current medication regimen must be assessed because many patients have discontinued their antiplatelet medications depending on the type (bare metal vs drug-eluting) of stent and when the stent was inserted. Surgery in which the risk of bleeding is low may not require discontinuation of antiplatelet therapy. Patients who require emergency surgery should be evaluated on a

Unfractionated heparin

Subcutaneous
No contraindications, delay heparin administration until after block

Intravenous
Heparinize 1 h after neuraxial technique; remove catheter 2-4 h after last heparin dose

Antiplatelet medications
NSAIDs no contraindications, discontinue ticlopidine 14 d, clopidogrel 7 d, and GP 11b/11a inhibitors 8-48 h in advance

Warfarin
Document normal INR after discontinuation (before neuraxial technique); remove catheter when INR ≤ 1.5

LMWH
Twice daily dosing; LMWH 24 h after surgery, regardless of technique; remove neuraxial catheter 2 h before first LMWH dose

Thrombolytics
No data on safety interval for performance of neuraxial technique or catheter removal; follow fibrinogen level

Herbal therapy
No evidence for mandatory discontinuation before neuraxial technique

Table 6. American Society of Regional Anesthesia Pain Management Guidelines Neuraxial Anesthesia in Patient Receiving Thromboprophylaxis

NSAIDs indicate nonsteroidal anti-inflammatory drugs; GP IIb/IIa, platelet glycoprotein receptor IIb/IIa inhibitors; INR, international normalized ratio; LMWH, low-molecular-weight heparin.
(Adapted from Horlocker et al.[101])

case-by-case basis and the risks of bleeding vs the risks of thrombosis weighed.

The ACC/AHA Science Advisory and the Society of Cardiovascular Angiography drug-eluting stent task forces have recently updated their guidelines for management of patients with drug-eluting stents.[96-98] The guidelines are noted in Table 5. Their additional recommendations include the following: Aspirin is a lifelong therapy; it should not be stopped before surgery when it is prescribed as a preventive measure after stroke, angina, myocardial infarction, or revascularization. If clopidogrel is prescribed for unstable angina or during the reendothelialization period of a stent, it should not be stopped before a noncardiac procedure. The reendothelialization period lasts 2 to 4 weeks after simple dilatation, 6 weeks after a bare metal stent, and up to 12 months after a drug-eluting stent and may be prolonged more in unstable situations.

In tonsillectomy or surgery in closed spaces, minor postoperative hemorrhage might have disastrous consequences, particularly in neurosurgery. Aspirin should be continued but clopidogrel withdrawn for 1 week before intracranial open-skull surgery. It would be safer to give low-molecular-weight heparin, although the degree of protection is inferior. In the case of stereotactic intracranial procedures, aspirin therapy should also be interrupted, but if possible, the operation should be postponed until the patient can safely stop taking all antiplatelet medications. If it is essential to continue antiplatelet therapy for as long as possible, intravenous infusion of GP IIb/IIIa receptor inhibitors may be used.

The monoclonal antibody fragments abciximab, eptifibatide, and tirofiban are platelet GP IIb/IIIa antagonists

Thioamides
Methimazole
Propylthiouracil

Anion inhibitors
Perchlorate
Pertechnetate
Thiocyanate

Iodides
Ipodate sodium (Oragrafin)
Sodium iodide
Potassium iodide (Lugol solution)

Radioactive iodine
Iodine 131

Adrenergic blocking agents
Propranolol
Metoprolol

Table 7. Antithyroid Medications

used to reduce ischemia in high-risk patients undergoing percutaneous coronary interventions. Occasionally, patients will require urgent cardiac surgery after a failed intervention. The time required for reversal of these drugs varies, with abciximab requiring the longest. Expect an increased risk of bleeding if fewer than 4 to 8 hours have passed since the administration of eptifibatide and tirofiban. Clinical recovery from abciximab requires 12 to 24 hours.[92,99]

The use of regional anesthesia in the presence of anticoagulants was recently reviewed in an *AANA Journal* course.[100] The American Society of Regional Anesthesia has issued guidelines (Table 6).[101] A recent study by Moen

Hypotension that does not respond to vasopressor therapy
Hyperdynamic circulation
Hypoglycemia
Hyperkalemia
Hyponatremia
Hypovolemia
Metabolic acidosis
Decreased level of consciousness

Table 8. Signs and Symptoms of Acute Adrenal Crises

Impaired responsiveness to a test of adrenocortical reserve, such as a short adrenocorticotropic hormone stimulation test
Urgent surgery needed in the presence of:
1. Clinical findings of Addison disease
2. Otherwise unexplained findings consistent with adrenocortical insufficiency, such as hypotension, hyponatremia, hyperkalemia, and eosinophilia
3. Risk for hypothalamic pituitary adrenal axis suppression and adrenal insufficiency based on the course of therapy

Table 9. Conditions Requiring Consideration of Perioperative Steroid Coverage
(Adapted from Axelrod[106] and Roizen and Fleisher.[9])

et al[102] on the incidence of severe neurological complications following central neural blockade during a 10-year period in Sweden led to the possibility that a revision to more conservative guidelines may be necessary.[79]

Thyroid Medications

• *Thyroid Hormone Supplementation.* Hypothyroidism develops for a variety of reasons that include thyroid gland, hypothalamic, or pituitary dysfunction and thyroid hormone deficiency. Thyroid hormone regulates the metabolic rate of cells within the body. Levothyroxine, also known as Synthroid, is the synthetic equivalent of thyroxine. Thyroid replacement hormones should be continued throughout the perioperative period. One omitted dose of levothyroxine is unlikely to have a clinical effect because this medication has a half-life of several days.

Antithyroid Medications

Antithyroid medications are administered to patients to decrease the thyroid gland's output of thyroid hormone, to decrease the peripheral conversion of thyroxine to triiodothyronine, and to decrease sympathetic nervous system activity. Antithyroid medications are grouped into various categories (Table 7).

Various antithyroid medication regimens have been suggested and are best regulated by an endocrinologist. All antithyroid medications should be administered as directed until surgery. Methimazole is 10 times as potent as propylthiouracil, and 1 dose exerts an antithyroid effect lasting 24 hours. Beta-blockers may be added to control hyperthyroid-induced symptoms such as tachycardia.[103] Beta-blockers inhibit the peripheral conversion of thyroxine to triiodothyronine. In patients with low-output cardiac failure who exhibit thyroid storm, propranolol must be administered with caution because of the possibility of cardiovascular collapse.[104]

Corticosteroids

The primary glucocorticoid that is produced and secreted by the adrenal cortex is cortisol. Cortisol is necessary for the maintenance of homeostasis of many physiologic functions, but it is also a powerful stress hormone released to augment sustained sympathetic nervous system activity. The normal secretory rate of cortisol is 10 to 20 mg/d; however, during periods of physiologic stress such as surgery, cortisol output can increase to approximately 50 to 150 mg/d.[105] Maximal cortisol secretion rarely exceeds 200 mg/d. The amount of cortisol release is a function of the magnitude of the procedure and the duration of anesthesia.[106-108]

Adrenocortical atrophy can occur when patients take corticosteroid medications on a routine basis. The exogenous corticosteroid inhibits corticotropin releasing hormone from the hypothalamus and adrenocorticotropic hormone from the pituitary gland. This phenomenon is known as hypothalamic-pituitary-adrenal (HPA) axis suppression. Regaining normal HPA axis function after exposure to high doses of corticosteroids is dependent on the dose and duration of therapy. Thus, patients with HPA axis suppression are at risk for acute adrenal crises during periods of physiologic stress. Signs and symptoms of acute adrenal crises are listed in Table 8.

It was thought that patients who received corticosteroids in doses equivalent to at least 20 mg/d of prednisone for more than 5 days within a month before surgery were at risk for HPA axis suppression.[106] However, researchers have recently determined that as little as 5 mg/d of prednisone or its equivalent for more than 5 days can cause HPA axis suppression.[109,110] If doses are given late in the day, HPA axis suppression may occur as a consequence of inhibiting the diurnal surge of adrenocorticotropic hormone (ACTH) release. If the patient has received supraphysiologic doses, a prolonged course, or frequent intermittent doses, HPA axis suppression may be evident for up to a year after the cessation of therapy.[106] Conditions for which preoperative steroid replacement should be considered are listed in Table 9. An example of a steroid replacement regimen is given in Table 10. A comparison of various steroids is included in Table 11.

Oral Contraceptives, Hormone Replacement Therapy and Osteoporosis Agents

Oral contraceptives increase the risk of deep venous thrombosis (DVT) via actions on the activity of clotting

Degree of surgical stress	Recommended dose
Minor (inguinal hernia repair)	Preoperative corticosteroid dose plus hydrocortisone, 25 mg, or equivalent
Moderate (lower extremity revascularization, total joint replacement)	Preoperative corticosteroid dose plus hydrocortisone, 50-75 mg, or equivalent
Major (cardiac surgery, aortic aneurysm repair)	Preoperative corticosteroid dose plus hydrocortisone, 100-150 mg, or equivalent every 8 h for 48-72 h

Table 10. Recommendations for Perioperative Glucocorticoid Coverage

Hydrocortisone has mineralocorticoid activity at doses above approximately 100 mg/d. The mineralocorticoid activity of hydrocortisone may produce undesirable side effects, including fluid retention, edema, and hypokalemia. It is preferable to use a glucocorticoid without mineralocorticoid activity such as methylprednisolone when the total dose of hydrocortisone exceeds 100 mg/d. Methylprednisolone, 4 mg, is equivalent to hydrocortisone, 20 mg.
(Adapted from Axelrod[106] and Salem et al.[107])

Compound	Anti-inflammatory potency	Sodium-retaining potency	Duration of action (h)	Equivalent dose[a]
Cortisol	1	1	8-12	20
Cortisone	0.8	0.8	8-36	25
Dexamethasone	25	0	36-54	0.75
Prednisone	4	0.8	18-36	5
Methylprednisolone	5	0.5	12-36	4
Betamethasone	25	0	36-54	0.75

Table 11. Comparative Properties of Steroids

[a] Equivalent dose based on 20 mg/d of cortisol secretion.
(Adapted from Grover VK, Babu R, Bedi SPS. Steroid therapy: current indications in practice. *Indian J Anaesth.* 2007;51(5):389-393.)

factors.[111] The surgical risk is highest in orthopedic procedures and following major oncological surgery requiring prolonged immobility. In women having low-risk surgery, with rapid postoperative ambulation, continuation of these medications is appropriate. With major surgery requiring prolonged immobility, discontinuation 4 weeks before surgery is recommended.[36]

Millions of postmenopausal women take estrogen hormone replacement therapy. In elective surgery, it is unclear how far in advance estrogen should be discontinued to decrease the thromboembolic risk, although stopping 4 weeks preoperatively is widely suggested. After surgery, the risk of DVT decreases when the patient is fully ambulatory, although research has indicated an increased risk for 90 days postoperatively.[66]

Raloxifene (Evista) is a selective estrogen receptor modulator used to treat osteoporosis that mediates decreased resorption of bone and decreased bone turnover via binding to estrogen receptors. Because of the risk of thromboembolic events, it should be stopped at least 1 week preoperatively for surgeries associated with a moderate to high risk of DVT and not restarted until the patient is fully mobile postoperatively.[66] Tamoxifen, which is structurally similar, has a similar risk of DVT, but, before discontinuing it perioperatively, the patient's oncologist should be consulted to discuss the risk-benefit ratio.

Therapy for Human Immunodeficiency Virus Infection

Long-term therapy and management of human immunodeficiency virus infection requires multiple drugs with complex scheduling. An interruption of drug therapy promotes resistance in the virus; therefore, adherence to dosing regimens is essential. These drugs should be continued throughout the perioperative period.[36,112]

A significant drug interaction occurs between midazolam and the protease inhibitors. Midazolam metabolism is significantly decreased, leading to prolonged sedation and respiratory depression, and it should not be used in patients taking protease inhibitors.[113]

Asthma Therapy

Routine medications for therapy in asthma include beta-2 receptor agonists, bronchodilating anticholinergics such as ipratropium (Atrovent) and tiotropium (Spiriva), inhaled corticosteroids, leukotriene modifiers, mast cell stabilizers, and, occasionally, theophylline. All of these medications should be continued throughout the perioperative period with careful monitoring. Routine preoperative medications may be given to relieve anxiety. Histamine-releasing opiates such as morphine, codeine, and hydrocodone should be avoided. The use of histamine-2 receptor blocking agents such as ranitidine for a "gastric prep" before induction should be avoided.

Bronchospasm has been associated with their use due to histamine release resulting from loss of inhibitory feedback control on presynaptic autoreceptors.[114]

Summary

Important decisions as to the management of patients' preoperative medications are dealt with on a daily basis during clinical practice. Effective communication with the surgeon and other medical specialists is vital for formulating approaches to care. Careful history taking and physical examination will provide essential information needed to evaluate each individual patient situation. Choices will vary depending on the medication and disease indication, type and duration of the surgery and anesthesia, and expected postoperative course. Informed anesthesia management can make a positive contribution to the continuum of care of the patients we treat.

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