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# Perioperative medication management

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The management of a patient's usual medications in the preoperative period is often a difficult and perplexing problem. Among the challenges faced by the physician when managing medication issues for surgical patients are the patient's response to the stresses of surgery, the patient's underlying diseases and the degree of control afforded by ongoing treatment, and the likelihood of some period where oral treatment is not an option. In addition, there are few controlled trials regarding perioperative medication discontinuation and resumption, so decisions regarding management are often made based on manufacturer's recommendations, consensus, or anecdotes. This article will attempt to provide data, when available, for adjusting medications in the perioperative setting and will provide advice when data are lacking.

Because some medications are known to influence surgical risk or surgical decisions (eg, antiplatelet agents, anticoagulants, some hormonal therapies, and herbal remedies), it is important to obtain a complete medication list from the patient, including over-the-counter medications and dietary supplements. Adjusting doses or discontinuing certain potentially complicating medications in advance of surgery is one obvious reason that elective procedures are less prone to complications than emergent procedures.

Most medications are tolerated well through surgery and do not interfere with anesthetic administration. Therefore, most drugs should be continued through the morning of surgery unless totally unnecessary (eg, vitamins) or contraindicated (eg, herbal products). In particular, antihypertensive, anticonvulsant, and antipsychiatric medications should be given unless specifically contraindicated.

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For medications where therapeutic monitoring may provide important information regarding subtherapeutic or supratherapeutic doses, serum levels should be checked perioperatively (eg, digoxin, theophylline, phenytoin, and carbamazepine). Necessary medications can be given with a sip of water a few hours before surgery. Medications that are known to cause a withdrawal or rebound syndrome when held (eg, clonidine) should be continued throughout the perioperative period with as little interruption as possible.

## Cardiac drugs

Drugs with long durations of action, such as digoxin and amiodarone, can be discontinued before surgery and restarted when the patient is able to eat. If necessary, intravenous doses of either digoxin or amiodarone could be used if the duration of inability to eat is extended or if their parenteral use is clinically indicated.

Beta blockers used for patients with cardiovascular disease (as opposed to use in patients with migraine syndrome, for example) should not be discontinued abruptly before surgery. Observational data have shown an increased risk of perioperative infarction and death in patients with vascular disease whose beta blockers were discontinued [1]. If patients are not able to resume oral intake of beta-blockers soon after surgery, parenteral preparations such as esmolol or propranolol could be used.

For patients who usually take oral nitrates, preoperative substitution of nitroglycerin ointment or patches is not reliable because of the likelihood of poor intraoperative absorption. The severity and stability of the patients' angina, plus their usual dose of oral nitrates, will influence the assessment of whether intravenous nitroglycerin may be needed. Perioperative and intraoperative events (eg, ST depressions on ECG monitor) may influence the anesthesiologist to start intravenous nitroglycerin, and postoperative titration and switch to outpatient agents will require ongoing assessment of response. In the postoperative period, transdermal nitroglycerin via ointment or patch is an alternative to either intravenous or oral nitrates.

Patients who regularly take antiarrhythmic drugs should continue them as long as possible before surgery, but they can usually be discontinued for a few days and resumed when the patient is eating again. Class IA agents, such as quinidine, procainamide, and disopyramide, are used with much less frequency than in years past. Parenteral procainamide is available for the patient whose continued treatment with this agent would be considered essential during the perioperative period. More recent antiarrhythmics, such as flecainide or sotalol, do not have an alternative, nonoral dosing route. For patients who take these agents for atrial arrhythmias (eg, atrial fibrillation or atrial flutter) and develop problems with these rhythms perioperatively, ventricular rate control could be attempted using intravenous diltiazem, beta blockers, or digoxin. For patients who take chronic outpatient medication for a history of monomorphic ventricular tachycardia and

who then develop a recurrence while nil per os (NOS) perioperatively, procainamide or amiodarone can be used parenterally. For polymorphic ventricular tachycardia, lidocaine or amiodarone are options. Especially important in these patients is the need to assure normal serum magnesium, potassium, and calcium, because deficiences of these cations can contribute to ventricular irritability.

## Antihypertensives

Overall, the large variety of nonoral agents available to control perioperative and intraoperative hypertension provides sufficient options to handle blood pressure elevations when patients cannot take their usual antihypertensives after the morning-of-procedure dose. Nevertheless, there may be hazards in introducing new agents preoperatively with unpredictable response in the individual patient in order to achieve "normal" blood pressure. In the perioperative period, mild degrees of elevated blood pressure may be acceptable and would be preferable to causing autonomic instability or volume depletion in the effort to maximize blood pressure control.

Sudden cessation of treatment with clonidine has been associated with worrisome, even dangerous, rebound hypertension. Using alternative parenteral agents or the clonidine patch may avoid acute hypertension. Such parenteral agents include esmolol, propranolol, hydralazine, diltiazem, and nitrates. Rebound hypertension also may occur after stopping guanfacine (Tenex®, AH Robins Co., Richmond, VA), another alpha 2-adrenergic agonist, but it occurs with less frequency and later (after 2–4 days) with guanfacine, presumably because of its longer half-life.

## Pulmonary drugs

This group of drugs consists primarily of those used to treat asthma and/or chronic obstructive lung disease. Patients using inhalers can use them up to immediately before surgery and can resume them soon after surgery. This applies to inhaled steroids, beta agonists, and anticholinergic agents. If patients develop bronchospasm before they can resume their inhalers, then nebulized or parenteral beta agonists can be used. Because thoracic or abdominal surgery reduces lung function even in patients with normal lungs, some authorities favor nebulizers over metered-dose inhalers in the immediate postoperative period for asthmatic patients undergoing such surgeries. Another parenteral alternative is aminophylline, but both parenteral beta agonists and theophylline may cause tachycardia, hypertension, or ventricular arrhythmias. Intravenous steroids may be necessary if the bronchospasm does not respond to bronchodilators.

Little is known about the implications of stopping leukotriene inhibitors, such as zafirlukast (Accolate®, AstraZeneca Pharmaceuticals, Wilmington, DE) or montelukast (Singulair®, Merck and Co., West Point, PA), or

lipoxygenase inhibitors, such as zileuton (Zyflo Filmtab®, Abbott Laboratories, Abbott Park, IL), before surgery. There are no parenteral formulations of these drugs. Because there are no known interactions between these agents and anesthetics, consider continuing them through the morning of surgery.

The treatment of exacerbations of chronic obstructive pulmonary disease (COPD), which may be associated with surgery involving intubation, can follow the same principles employed for treating spontaneous acute exacerbations [2].

## Diabetes

Patients requiring insulin for usual management of their diabetes can generally be managed with perioperative glucometer testing and sliding-scale regular insulin. Whether to use a morning dose of longer-acting insulin or to continue use of bedtime glargine insulin the night before surgery depends on how long the patients will be fasted before surgery, the severity of their diabetes, the timing of administration of intravenous solutions containing dextrose, and how soon the patients are likely to resume eating after surgery. For example, with outpatient surgery or diagnostic procedures performed under conscious or deep sedation, a common practice is to reduce the morning-of-procedure dose of long-acting insulin to 50% of the usual dose, and then use glucometer readings and sliding-scale insulin as needed to control periprocedure serum glucose.

For diabetic patients adequately treated with oral agents, the drugs should be held on the morning of surgery, with sliding-scale insulin supplementation as needed. One important exception is metformin, which has been associated with the development of lactic acidosis, although rare. Metformin should be discontinued for at least 1 day before surgery and restarted after 2–3 days when it is certain that no acute renal dysfunction has developed perioperatively. In general, oral agents should be held postoperatively until patients are eating again.

## Antiplatelet agents and anticoagulants

Aspirin inhibits platelet cyclooxygenase with subsequent irreversible platelet dysfunction. Because it takes 7–10 days to renew the circulating pool of platelets, traditional recommendations are to stop aspirin 7–10 days preoperatively. Although aspirin has been known to increase intraoperative bleeding, there is little evidence for any significant increased morbidity or mortality [3,4]. One study showed increased use of transfusions in patients undergoing coronary artery bypass grafting (CABG) but no increase in length of stay [4]. It is prudent to stop aspirin at least 7 days before surgery where possible, especially for surgeries in which excess bleeding would cause significant complications, such as vascular procedures, neurosurgery, and

certain ophthalmologic procedures. It is especially important to stop aspirin in alcoholic patients, as they often have underlying platelet dysfunction secondary to alcohol. Aggrenox, which is composed of aspirin and dipyridamole, should be stopped 7–10 days in advance of surgery because of its aspirin component. The dipyridamole has a half-life of about 10 hours and has a reversible effect on platelets [5].

The nonsteroidal anti-inflammatory COX-1 agents cause reversible inhibition of platelet cyclooxygenase. When possible, they should be stopped 1–3 days preoperatively depending on their individual half-lives. Drugs like ibuprofen and indomethacin have shorter half-lives (2–5 hours) and can be stopped 1 day before surgery, whereas naproxen and sulindac have longer half-lives (12–17 hours) and should be stopped 3 days before. The newer nonsteroidal anti-inflammatory drugs (NSAIDs), the COX-2 inhibitors, have little or no effect on platelets. All NSAIDs can have adverse effects on renal function; this effect may be accentuated in the perioperative period, which is another reason for holding these drugs perioperatively. The COX-2 inhibitors should be held at least 2–3 days before surgery because of the potential renal issues [5].

Clopidogrel (Plavix®, Sanofi-Synthelabo Inc., New York, NY) and ticlopidine (Ticlid®, Parcor) are structurally similar agents that irreversibly inhibit platelet aggregation, probably by blockade of adenodiphosphate (ADP) binding to its receptor on the surface of platelets [6]. Because of the increased frequency of drug interactions, thrombotic thrombocytopenic purpura, and severe neutropenia with ticlopidine, its use has decreased in favor of clopidogrel. For elective procedures, both agents should be stopped 7 days preoperatively because of their irreversible effect on platelets.

Cilostazol (Pletal®, Otsuka America Pharmaceutical, Inc., Rockville, MD) is a phosphodiesterase inhibitor that has both antiplatelet and vasodilatory actions. Because its action on platelets is reversible, and because it has a fairly short half-life (11–13 hours) [5], it can be stopped 3 days before surgery.

One would think intuitively that it is always best to discontinue oral anticoagulants before any surgical procedure, or to at least reduce the dose to allow nearly normal coagulation. Though this is generally true, data show that cataract surgery, using current techniques, can be performed safely with the International Normalized Ratio (INR) in the therapeutic range. In fact, the studies suggest that, with cataract surgery, the risk of systemic complications from discontinuing warfarin is greater than the risk of perioperative bleeding. Antiplatelet agents, on the other hand, can increase perioperative complications of cataract surgery and should be discontinued preoperatively as described above.

The use of unfractionated heparin and low-molecular-weight heparins for prophylaxis of perioperative thromboembolic complications is covered in another section. But one issue regarding stopping and restarting these perioperative medications deserves comment here. A worrisome and serious complication of deep venous thrombosis (DVT) prophylaxis with

low-molecular-weight heparins is spinal hematoma with epidural anesthesia or analgesia [7]. This problem is most likely to occur when inserting or removing the epidural catheter. Interestingly, patients who undergo epidural anesthesia in the presence of antiplatelet agents are not at increased risk for epidural hematoma compared with patients not taking these agents. Patients receiving warfarin appear to be at intermediate risk. Recommendations regarding the time of epidural catheter manipulation in relation to doses of anticoagulants and antiplatelet agents are provided in Table 1 [8–12].

## Osteoporosis agents

As the population ages, and as osteoporosis awareness increases, an increasing number of patients will present for surgery while taking medications for this condition.

Raloxifene (Evista®, Eli Lilly and Co., Indianapolis, IN) is a selective estrogen receptor modulator (SERM) that mediates decreased resorption of bone and decreased bone turnover via binding to estrogen receptors [13]. Because it has been shown to increase 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 [5]. 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.

Estrogen is used by millions of women both to alleviate premenopausal symptoms and to prevent and treat osteoporosis. The use of hormone replacement therapy is associated with an increase in thromboembolic events by threefold [14]. This phenomenon is even more dramatic in the perioperative setting. The Heart and Estrogen/progestin Replacement Study (HERS) in 2763 postmenopausal women found that the risk for deep venous thrombosis increased approximately 6-fold for patients admitted for hip fracture, 18-fold for other types of lower extremity fracture, and 5-fold for nonfracture surgeries within 90 days of surgery [15]. For elective surgery, it is unclear how far in advance of surgery estrogen should be held to decrease this risk; some have suggested stopping 4 weeks preoperatively [16]. After surgery, the risk for DVT decreases when the patient is fully ambulatory, although the HER study showed an increased risk for 90 days postoperatively [15].

Alendronate (Fosamax®, Merck and Co., Inc., West Point, PA) is a bisphosphonate that inhibits osteoclast-mediated bone resorption. Because of its possible upper gastrointestinal (GI) side effects (esophagitis, esophageal erosions, and ulcers), there are specific guidelines regarding its administration. Patients must take it with 6–8 oz of water at least 30 minutes before ingesting the first beverage, food, or medication of the day, and then remain upright for 30 minutes. Given the difficulty for hospitalized patients to comply with the requirement to remain upright, it is best held in the perioperative period. Calcitonin (Miacalcin®, Novartis, East Hanover, NJ) is

Table 1
Epidural anesthesia or analgesia: special considerations for patients receiving antiplatelet or anticoagulant therapy

| Medication | Risk of epidural hematoma with medication | Suggested time interval before removal of epidural catheter | Lab tests necessary prior to discontinuation of epidural catheter | Time interval before therapy may be re-instituted after catheter removed |
|---|---|---|---|---|
| Heparin (standard) (IV or Sub-Q routes) (Therapeutic aPTT 1.5 × control) | High | 4–6 hours after stopping heparin aPTT should be within normal limits prior to catheter removal | aPTT | At least 2 hours after epidural catheter removal, providing clinical monitoring checks are within normal limits, including no apparent bleeding |
| Heparin (minidose-prophylaxis) | Low | 12 hours after the last dose | None | Immediately |
| Low molecular-weight Heparins | High | 12–24 hours after last dose | None | 12–24 hours |
| Fibrinolytic and thrombolytic drugs | High | At least 12 hours after the last dose of the thrombolytic drug | None | At least 24 hours after catheter removal |
| Warfarin (Coumadin®, Dupont, Wilmington, DE, End) (Therapeutic INR > 2.0) | Moderate-high | Prothrombin time (PT) INR <1.5 prior to removal of the epidural catheter | PT | Immediately |
| Warfarin (Coumadin®, Dupont, Wilmington, DE, End) (Low dose-Prophylaxis) | Low-moderate | Prothrombin time (PT) INR <1.5 prior to removal of the epidural catheter | PT | Immediately |
| Aspirin | Low | No Restriction | None | Immediately |
| Dipyridamole | Low | No Restriction | None | Immediately |
| Ticlopidine | Low | No Restriction | None | Immediately |
| Clopidogrel | Low | No Restriction | None | Immediately |
| NSAIDs | Low | No Restriction | None | Immediately |

*Abbreviations:* aPTT, partial thromboplastin time; INR, International Normalized Ratio; NSAIDS, nonsteroidal anti-inflammatory drugs; PT, prothrombin time.

given intranasally; there are no specific medication interactions or contraindications to using this drug in the perioperative period.

## HIV agents

Both because HIV-infected patients are living longer, and because the virus continues to spread, more and more HIV-positive patients are presenting for various types of surgery. There are a wide variety of antiretroviral medications; patients who use these medications generally are on two or more at a time. Because resistance to these drugs develops so easily, patients should not miss doses and should maintain an "all or none" approach to taking them. Thus, in the perioperative period, these drugs should be continued up to the time of surgery, stopped together, and then restarted together when the patient can tolerate oral medications. There are no known significant interactions between antiretrovirals and anesthetic agents [17].

## Herbal remedies

The use of herbal medications has become increasingly popular over the past several years [18,19]. Many studies have found that patients often do not report use of such agents to their physicians, even in the preoperative setting, unless specifically asked [18,19]. Of concern is the fact that some of the more commonly used herbal remedies have been found to cause a variety of perioperative complications [20,21]. Many patients erroneously believe that herbal remedies are safe because they are "natural." On the contrary, because they are not regulated by the U.S. Food and Drug Administration (FDA), their purity and concentrations may differ significantly between batches, and there are few well-controlled human trials to document safety [22].

Echinacea is commonly used to enhance immune function, possibly by stimulating the production of phagocytes. The enhancement of immune function, however, is thought to be a short-term effect; the long-term effect may actually be immunosuppression. Thus, there is a theoretical risk of problems with postoperative healing [18].

Garlic is used to lower lipid levels, but, because it inhibits platelet aggregation, patients who use large amounts of garlic could have problems with postoperative bleeding [18,23].

Ginkgo biloba has become very popular because of its purported beneficial effects on cognitive function. It has also been used to treat peripheral vascular disease and macular degeneration. Ginkgo has been found to inhibit platelet aggregation via inhibition of platelet-activation factor [18]. There have been rare reported cases of spontaneous bleeds, as well as one known episode of postoperative bleeding linked to the use of this herb [24].

Ginseng is used both as a hypoglycemic agent and to protect one's health in the face of stress. It inhibits platelet aggregation, possibly irreversibly, and has been known to cause headache, tremulousness, and mania [18].

Ma huang, or ephedra, has potent sympathomimetic effects and can increase both blood pressure and pulse [18]. It should be stopped whenever possible and not restarted because of the serious potential complications associated with its use [25]. Kava is used as a sedative and can accentuate the sedative effects of anesthetics. It has been associated, however, with severe liver injury, and the FDA suggests caution in using kava-containing products [26]. St. John's wort, because it induces cytochrome P450 enzymes, has the potential to affect the metabolism of multiple drugs [23]. Valerian is used as a sedative and can affect anesthetic requirements. Reports vary as to whether or not it can cause acute withdrawal upon cessation [22].

Multiple herbal preparations have been found to interfere with the action of warfarin. These include Danshen, garlic, dong quai, ginseng, ginger, and fever few [27,28].

Because there are likely drug interactions and perioperative effects of herbal remedies that are yet unknown, it is safest to have patients refrain from use of these agents for 1–2 weeks preoperatively.

## Neurologic medications

### *Antiparkinsonian agents*

Antiparkinsonian medications should be given the morning of surgery and restarted as soon as possible postoperatively. The main problem in using these agents in the perioperative period is that very few of them have an intravenous form available for patients who are unable to take oral medications for a prolonged period. Patients who have their carbidopa/levodopa held for several hours may develop a swift return of their parkinsonian symptoms, and with prolonged cessation they can develop a levodopa withdrawal syndrome characterized by symptoms similar to neuroleptic malignant syndrome [29]. Although carbidopa/levodopa can interact with anesthetic agents leading to possible arrhythmias [16], the benefits of continued treatment outweigh the risks.

Selegiline (Eldepryl®, Somerset, Tampa, FL) is a selective monoamine oxidase inhibitor used as an adjunctive treatment to carbidopa/levodopa. It has been reported to have a potentially life-threatening reaction with meperidine consisting of rigidity, hallucinations, fever, confusion, and (when severe) coma and death. It is possible for this reaction to occur with other narcotics as well [5], but it is best known for the reaction with meperidine. Meperidine should be avoided perioperatively, and the patient should be monitored carefully while on narcotics. The relatively new

catechol-o-methyltransferase (COMT) inhibitors (entacapone and tolcapone) work by extending the duration of action of levodopa [5,30]; there are no specific contraindications regarding their use perioperatively. Like carbidopa (Sinemet®, Merck & Co.), abrupt withdrawal can cause hyperpyrexia, rigidity, confusion, and elevated serum creatine kinase, so they should be continued as much as possible in the perioperative period. Because they can cause abnormalities of liver function tests, it is prudent to check liver enzymes before surgery [30], as abnormalities may influence anesthetic management. For patients who are NPO, there are a few effective alternatives. The only antiparkinsonian agents that are available intravenously or intramuscularly are medications with anticholinergic actions that can help limit rigidity and bradykinesia. The available agents are trihexyphenidyl (Artane®, Lederle), benztropine (Cogentin®, Merck & Co.), and diphenhydramine (Benadryl®, Parke, Davis) [31]. Trihexyphenidyl may be especially helpful for tremor [32]. All of these agents can cause postoperative confusion and should be used in the lowest doses possible.

For patients who are NPO, but have a feeding tube, a levodopa/carbidopa solution can be delivered to the duodenum via a weighted feeding tube. The solution is prepared by pulverizing and dissolving 4 tablets of 25/250-strength carbidopa in 1 L of water with 1 g of ascorbic acid (to prevent oxidation) to produce a 1 mg carbidopa/mL solution. The hourly rate of the infusion depends on what the patient's oral dose is; a suggested starting dose is 25 mL/hr [32].

If patients can take oral medications within several hours after surgery, their usual doses of agents such as carbidopa, bromocriptine, amantadine, and pergolide can be used; there are no specific interactions known between these medications and commonly used perioperative medications.

### *Antiseizure medications*

Antiseizure agents should be continued in the perioperative period whenever possible. The major antiseizure medications are central nervous system (CNS) depressants; these agents include phenytoin, carbamazepine, valproic acid, clonazepam, phenobarbital, and primidone. Their depressant effects can decrease the required doses of anesthetic agents [3]. Although there is no published information regarding the use of newer agents (ie, gabapentin, topiramate) in the perioperative period, they should be continued to avoid perioperative seizure.

## Psychiatric medications

### *Antidepressants*

Tricyclic antidepressants act by making nonadrenergic neurotransmitters more available via presynaptic blockade of reuptake. Drugs in this class that

are commonly used include amitriptyline, nortriptyline, imipramine, and desipramine. They have several side effects, most notably anticholinergic effects, as well as a variety of cardiac effects, most notably a quinidine-like action such as a widened QRS and QT intervals and potential slowing of AV conduction [33]. Although there have been reports of arrhythmias in patients on tricyclic antidepressants who receive halothane, and animal studies show a proarrhythmic effect in the presence of pancuronium [34], these events are rare. Because the anticholinergic effects of these medications are likely to be additive with other anticholinergics, care should be taken regarding drug choices perioperatively.

Monoamine oxidase (MAO) inhibitors are not commonly used at the present time, but they still may be used in cases of depression resistant to other agents. MAO inhibitors, such as pargyline and phenelzine, have been associated with life-threatening hypertensive reactions to indirect-acting sympathomimetics that are sometimes used intraoperatively. Theses agents are also known to interact with meperidine to cause a syndrome with some similarities to neuroleptic malignant syndrome (including symptoms of hyperpyrexia, hypertension, rigidity, hallucinations, coma, and death). It has been conventional practice to stop MAO inhibitors 2 weeks preoperatively to avoid perioperative medication interactions. There have been reports of patients undergoing general anesthesia while on MAO inhibitors without complication, however [35,36]. Thus, for patients undergoing elective surgery without major psychiatric risk to stopping therapy, it would be prudent to withhold MAO inhibitors; but, for patients undergoing urgent surgery or who are psychiatrically unstable without them, it appears that MAO inhibitors can cautiously be continued, along with care to avoid or minimize sympathomimetics, anticholinergics and meperidine. These patients may be particularly susceptible to complications from sympathetic responses to anesthesia.

### *Selective serotonin reuptake inhibitors*

The selective serotonin reuptake inhibitors (SSRIs) have become the first-line agents for treatment of depression. This class includes fluoxetine (Prozac®, Eli Lilly, Indianapolis, IN), sertraline (Zoloft®, Pfizer Inc., New York, NY), paroxetine (Paxil®, SmithKline Beecham, Philadelphia, PA), citalopram (Celexa®, Forest Pharmaceuticals, St. Louis, MO), and fluvoxamine (Luvox®, Solvay Pharmaceuticals, Marietta, GA). The most common side effects are nausea, vomiting, diarrhea, agitation, anxiety, and insomnia. These agents act by inhibiting the reuptake of serotonin in the brain.

There are no specific interactions between the SSRI's and anesthetics. There are reports of development of the "serotonin syndrome" after concurrent use of tramadol (Ultram®, Ortho-McNeil Pharmaceutical, Raritan, NJ) and SSRIs. The SSRIs can also increase the INR in patients who are on warfarin [37].

Stopping SSRIs can result in a withdrawal syndrome that can start as soon as 1 day after discontinuing the agent. A wide range of symptoms is associated with this syndrome, including dizziness, agitation, lethargy, nausea, chills, myalgias, gait instability, shortness of breath, and decreased short-term memory [37]. Therefore, it is prudent to continue SSRIs in the perioperative period for patients who can tolerate oral medications.

Other commonly used antidepressants (venlafaxine [Effexor®, Wyeth-Ayerst Pharmaceuticals, PA], bupropion [Wellbutrin®, Glaxo Wellcome Inc., Research Triangle Park, NC], mirtazapine [Remeron®, Organon Inc., West Orange, NJ], and nefazodone [Serzone®, Bristol-Myers Squibb Co., Princeton, NJ]) have not been associated with withdrawal syndromes and do not have any known interactions with anesthetic agents [37].

*Antipsychotics*

Phenothiazines and butyrophenones are commonly used as antipsychotics; these agents can cause a wide variety of side effects, including sedation, depression, dystonia, and orthostatic hypotension. These drugs include haloperidol (Haldol®, McNeil Consumer Healthcare, Fort Washington, PA), fluphenazine (Prolixin®, Apothecon, Princeton, NJ), droperidol (Inapsine®, McNeil Consumer Healthcare, Fort Washington, PA), chlorpromazine (Thorazine®, SmithKline Beecham, Philadelphia, PA), and risperidone (Risperdal®, Janssen Pharmaceutical Products, Titusville, NJ).

Usually, these agents do not cause any significant perioperative problems. But they can enhance CNS depression caused by narcotics and barbiturates. The phenothiazines can also decrease the seizure threshold in susceptible patients. They can cause a variety of ECG abnormalities such as flattened T waves, ST segment depression, and prolonged QT and PR intervals. Rarely, these drugs cause ventricular irritability with resultant premature ventricular complexes (PVCs) and even torsades de pointes, recently resulting in a blackbox warning for droperidol, with recommendations for an ECG before potential treatment with droperidol, avoidance of droperidol in patients with long QT intervals, and cardiac monitoring after its use. Rarely, patients on antipsychotics can develop neuroleptic malignant syndrome, characterized by muscle rigidity, profound hyperthermia, autonomic instability, and at times ventricular irritability. Neuroleptic malignant syndrome shares many symptoms with malignant hyperthermia, which is seen intraoperatively and postoperatively in susceptible individuals.

Abruptly stopping antipsychotics can cause withdrawal dyskinesia or rebound agitation [38], so these drugs should be continued perioperatively if possible.

*Mood stabilizers*

The most commonly used mood-stabilizing medication is lithium. It acts by decreasing the release of neurotransmitters mimicking the action of

sodium [3]. It has a wide variety of side effects, most commonly hypothyroidism. It can also cause ECG changes such as T-wave inversion or flattening. Sinus node dysfunction and ventricular irritability are uncommonly seen [39]. Lithium can prolong the action of depolarizing and nondepolarizing muscle relaxants [3], but this has rarely been of any clinical significance. Current practice is to continue lithium perioperatively, although it may be wise to check serum levels perioperatively to ensure that they are not in the toxic range. Other common mood stabilizers, valproic acid and gabapentin, have no contraindications for use in the perioperative period.

### *Anxiolytics*

Patients who take significant amounts of benzodiazepines require less medication for anesthesia induction and maintenance. Because abrupt cessation of benzodiazepines after chronic use can cause a significant withdrawal syndrome, they should be continued in a modest dose perioperatively. At times, chronic benzodiazepine use can lead to higher requirements for postoperative opiates.

## Endocrine agents

### *Thyroid*

Patients taking levothyroxine for hypothyroidism can stay on their usual dose throughout the perioperative period. Because of the long half-life of the medication (7 days), it can be withheld for a few days if necessary without any untoward effect [40]. For patients who are NPO for a prolonged period, intravenous L-thyroxine can be given. Patients who are mildly hypothyroid can undergo surgery without significant clinical problems, but severely hypothyroid patients are at risk for major complications. For emergency surgery in such patients, they should receive a bolus of 200–500 mcg by slow infusion, then receive 50–100 mcg per day of L-thyroxine as well as hydrocortisone to treat for possible adrenal insufficiency [41].

Patients who are significantly hyperthyroid who must undergo urgent or emergency surgery may develop thyroid storm perioperatively. The treatment should include intravenous beta blockers, such as propranolol or esmolol, which can decrease adrenergic activity as well as decrease the peripheral conversion of T4 to T3. Beta blockers should be given with the goal of lowering the pulse to less than 90. Propranolol can be given in doses of 2–5 mg IV every 4 hours, and then orally every 6 hours in doses as high as 320–480 mg per day to maintain heart rate control. Propylthiouracil (PTU) and methimazole inhibit synthesis of new thyroid hormone, and PTU can also prevent conversion of T4 to T3. One gram of propylthiouracil should be given as a loading dose by nasogastric tube, followed by 200 mg every 6 hours. To prevent the release of T4 and T3 from the thyroid gland, inorganic iodide should be used. Iodide can

be given in a variety of methods but should be delayed by 1–2 hours after the antithyroid therapy with PTU or methimazole, as iodide alone will increase thyroid hormone stores and worsen the hyperthyroidism. Because adrenal gland function may be inadequate, patients should receive 100 mg of hydrocortisone every 8 hours [41]. Glucocorticoids also help to decrease the peripheral conversion of T4 to T3 [42].

Hyperthyroid patients should not receive medications such as pancuronium, ephedrine, norepinephrine, epinephrine, or atropine, which are vagolytic or sympathomimetic. Nitrous oxide, isoflurane,and the opioids have been found to be safe.

### *Adrenal gland*

Patients who have taken steroid medications for more than 1 week in the several months prior to major surgery may be at risk for secondary adrenal insufficiency, and they should be considered for perioperative "stress dose" steroids. Study results differ on what dose and duration of steroid therapy puts patients at risk. Much of the available data do suggest, however, that the hypothalamic-pituitary-adrenal (HPA) axis can be suppressed for up to 1 year after use of steroid medication of greater than 10 mg per day of hydrocortisone or equivalent doses of other steroids for 5 days or more. Evidence suggests that use of low-dose steroids (ie, 5–7.5 mg prednisone every other day or less than 5 mg per day) does not produce HPA axis suppression.

In choosing doses of hydrocortisone for patients undergoing surgery, consider the degree of stress of the procedure itself. For example, major surgery is much more stressful than minor procedures and therefore requires more hydrocortisone. General anesthesia for procedures is more stressful and requires more hydrocortisone than local anesthesia, even for similar degrees of surgery. The normal adrenal gland, under nonstress conditions, produces approximately 25–30 mg of cortisol per day. Under major stress, it produces approximately 200–500 mg per day [42]. If the adrenal gland has been suppressed because of exogenous steroid use, the patient requires exogenous replacement of this amount as hydrocortisone. (Hydrocortisone is equipotent to cortisol.) After surgery, the endogenous production of cortisol remains increased for approximately 3 days, then returns to normal. A variety of closing and tapering schedules have been put forth, but none have been formally studied.

It is common practice to give 100 mg hydrocortisone IV every 8 hours, starting immediately preceding the surgery. After the operative day, some practitioners continue the same dose of hydrocortisone unchanged, and then discontinue it abruptly after the third day. But this total course of hydrocortisone may be excessive, and, if the patient is not under substantial physical stress (eg, sepsis, fever, or significant pain), the dose can usually be tapered by 50% per day, then discontinued by the fourth day. For minor procedures,

one dose of 50–100 mg of hydrocortisone immediately before surgery may suffice, with another dose given 6–8 hours postoperatively [40,42,43].

*Hormones*

It has long been known that the estrogen in oral contraceptives can cause thromboembolism in women. Given that major surgery increases the risk of thromboembolism, there is concern that patients taking either oral contraceptives or estrogen for hormone replacement therapy will have a further increase in thromboembolic risk. And, although the biologic potency of postmenopausal hormone replacement therapy is only 1/4–1/5 of the estrogen in oral contraceptives, recent evidence has shown that even this amount of hormone therapy increases the risk of postoperative venous thromboembolic events, especially for lower extremity repair of fractures [14]. Grady et al attempted to determine how long after cessation of hormone therapy the risk for thromboembolism is increased. Results showed that the relative risk was increased for at least 1 month after cessation, but the power of the study was too small to produce definite conclusions. There are no other such studies available to validate these findings, but it seems prudent to stop estrogen therapy when possible for 4 weeks preoperatively, especially for procedures with high thromboembolic risk, such as lower extremity orthopedic procedures and cancer-related procedures. Estrogen can be restarted postoperatively when patients are mobile and when the operative-related risk of venous thromboembolism is decreased (for example, 4–5 weeks after joint replacement or hip fracture repair). For patients using oral contraception, the risks and benefits of perioperative thromboembolism versus perioperative pregnancy should be discussed with the patient.

## Rheumatologic drugs

Using methotrexate for the treatment of rheumatoid arthritis has become a more common approach, and may be considered usual treatment for patients whose disease is not adequately controlled with NSAIDs. There has been particular concern about the effect of this medication on wound healing and infectious complications postoperatively. In 2001, Grennan et al published a study suggesting that methotrexate did not cause problems with healing or early postoperative complications, and that it did not need to be discontinued days or weeks before surgery [44]. Caution should be taken, however, in patients with renal failure or sepsis [45].

The new immune modulator leflunomide (Arava®, Aventis Pharmaceuticals, Parsippany, NJ) is used as an antiproliferative agent in rheumatoid arthritis. There are no known adverse effects of this drug in the perioperative period, although no controlled trials have been done. Because it can rarely cause pancytopenia and hepatic dysfunction, it would be wise to check routine laboratory studies preoperatively.

## Summary

One of the consultant's roles is to make recommendations regarding the use of medications in the perioperative period. Unfortunately, the data in this area are often insufficient to provide evidence-based recommendations. In this article, we have provided advice considering the pharmacokinetics of the drug, the effect on the primary disease of stopping medications, and the effect of the medication on perioperative risk, including potential drug interactions with anesthetic agents.

## References

[1] Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. Am Heart J 2001;141:148–53.
[2] Stoller JK. Acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 2002;346:988–94.
[3] Smith MS, Muir H, Hall R. Perioperative management of drug therapy. Drugs 1996;51: 238–59.
[4] Taggart DP, Siddiqui A, Whaeatley DJ. Low-dose preoperative aspirin therapy, postoperative blood loss, and transfusion requirements. Ann Thorac Surg 1990;50:425–8.
[5] Physicians Desk Reference. Montvale, NJ: Medical Economics Company; 2002.
[6] Abu-Hajir M, Masseo AJ. The pharmacology of anti-thrombotic and antiplatelet agents. Anesth Clin North Am 1999;17:749–86.
[7] Horlocker TT, Wedel DJ. Neurological complications of spinal and epidural anesthesia. Reg Anesth Pain Med 2000;25:83–98.
[8] Enneking FK, Benzon H. Oral anticoagulants and regional anesthesia: a perspective. Reg Anesth Pain Med 1998;23(Suppl 2):140–5.
[9] Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing perioperative analgesia and thromboprophylaxis. Reg Anesth Pain Med 1998;23(Suppl 2): 164–77.
[10] Liu SS, Mulroy MF. Neuraxial anesthesia in the presence of standard heparin. Reg Anesth Pain Med 1998;23(Suppl 2):157–63.
[11] Rosenquist RW, Brown DL. Neuraxial bleeding: fibrinolytics/thrombolytics. Reg Anesth Pain Med 1998;23(Suppl 2):152–6.
[12] Urmey WF, Rowlingson J. Do antiplatelet agents contribute to the development of perioperative spinal hematoma? Reg Anesth Pain Med 1998;23(Suppl 2):146–51.
[13] Haynes B, Dowsett M. Clinical pharmacology of selective estrogen receptor modulators. Drugs Aging 1999;14:323–36.
[14] Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992;117:1016–37.
[15] Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increase risk for venous thromboembolic disease. Ann Intern Med 2000;132:689–96.
[16] Spell NO. Stopping and restarting medications in the perioperative period. Med Clin North Am 2001;85:1117–28.
[17] Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. U.S. Dept. of Health and Human Services, 2002, 21.
[18] Ang-Lee MK, Moss J, Yuan C-S. Herbal medicines and perioperative care. JAMA 2001;286:208–16.
[19] Tsen LC, Segal S, Pothier M, et al. Alternative medicine use in presurgical patients. Anesthesiology 2000;93:148–51.

[20] Crove S, Fitzpatrick G, Jamaluddin MF. Use of herbal medicines in ambulatory surgical patients. Anaesthesia 2002;57:203–4.
[21] Kaye AD, Heavner JE, Sabar R. Nutraceuticals and risk of neuraxial bleeding. Reg Anesth Pain Med 2001;26:92–3.
[22] O'Hara MA, Kiefer D, Farrell K, et al. A review of 12 commonly used medicinal herbs. Arch Fam Med 1998;7:523–36.
[23] Ernst E, Pittler MH. Herbal medicine. Med Clin North Am 2002;86:149–61.
[24] Fessenden JM, Wittenborn W, Clarke L. Ginkgo biloba: a case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. Am Surg 2001;67:33.
[25] Haller CA, Banowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000; 343:1833–8.
[26] Taylor CL. FDA letter to health care professionalsAvailable at: http://www.cfscan.fda.gov/~dms/ds-ltr29Accessed March 25, 2002.
[27] Cheng TO. Herbal interactions with cardiac drugs. Arch Int Med 2000;160:870.
[28] Vickers A, Zollman C. Herbal medicine. Brit J Med 1999;319:1050–1053.
[29] Friedman JH, Feinberg SS, Feldman RG. A neuroleptic malignant like syndrome due to levodopa therapy withdrawal. JAMA 1985;254:2792–5.
[30] Waters C. Catechol-O-methyltransferase inhibitors in Parkinson's disease. J Am Geriat Soc 2002;48:692–8.
[31] Bell RD, Merli GJ. Perioperative assessment and management of the surgical patient with neurologic problems. In: Merli GJ, Weitz HH, editors. Medical management of the surgical patient. 2nd edition. Philadelphia, PA: W.B. Saunders Co.; 1998. p. 2183–312.
[32] Arar MG, Dairi Y, Corman LC. Perioperative management of neurologic conditions and complications. In: Gross RJ, Caputo GM, editors. Kammerer and Gross' medical consultation. 3rd edition. Maryland: Williams and Wilkins, Maryland; 1998. p. 553–6.
[33] Drugs for psychiatric disorders. The Medical Letter 1986;28(725):99–105.
[34] Edwards RP, Miller RD, Roizen MF, et al. Cardiac responses to imipramine and pancuronium during anesthesia with halothane and enflurane. Anesth 1979;50:421–5.
[35] Michaels I, Serrins M, Shier NQ, et al. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. Anesth Analg 1984;63:1041–4.
[36] El-Ganzouri AR, Ivankovich AD, Braverman B, et al. Monoamine oxidase inhibitors: should they be discontinued preopertively? Anesth Analg 1985;64:592–6.
[37] Sarko J. Antidepressants, old and new. Emerg Med Clin North Am 2000;18:637–54.
[38] Goldberg JF. New drugs in psychiatry. Emerg Med Clin North Am 2000;18:211–32.
[39] Stoudemire A, Fogel BS, Gulley LR, et al. Psychopharmacology in the medically ill. In: Psychopharmacology in the medically ill. In: Stoudemire A, Fogel BS, editors. Psychiatric care of the medical patient. New York: Oxford University Press; 1993. p. 155–206.
[40] Cygan R, Waitzkin H. Stopping and restarting medications in the perioperative period. J of Gen Int Med 1987;2:270–83.
[41] McGlynn TJ, Simons RJ. Endocrine Disorders. In: Kammerer WS, Gross RJ, editors. Medical consultation. 1st edition. Baltimore, MD: Williams and Wilkins; 1990. p. 275–309.
[42] Wall RT. Unusual endocrine problems. Anesth Clin North Am 1996;14:471–93.
[43] McGlynn TJ, Simons RJ. Endocrine disorders. In: Gross RJ, Caputo GM, editors. Kammerer and Gross' medical consultation. 3rd edition. Maryland: Williams and Wilkins; 1998. p. 334–40.
[44] Grennan DM, Gray J, Loudon J, et al. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Ann Rheum Dis 2001;60:214–7.
[45] Wluka A, Buchbinder R, Hall S, et al. Methotrexate and postoperative complications. Ann Rheum Dis 2002;61:86–7.