Perioperative medication management:

A case-based review of general principles

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Understanding and applying general principles of perioperative medication management can greatly improve the outcomes of patients undergoing surgery. Although published clinical trial data in this area are limited, the medical consultant can follow a conceptual framework based on case reports, expert consensus, in vitro studies, and pharmaceutical manufacturer recommendations. Other important considerations include pharmacokinetics, the effects of various medications on the primary disease, the impact on perioperative risk, and potential drug interactions with anesthetic agents.

This review uses a series of case studies to illustrate general principles that are the essence of effective perioperative medication management. These principles are helpful in formulating recommendations for the use of medications in this setting, which has been the focus of very few controlled trials. Because discussion of every possible medication is beyond the scope of this article, I will focus on medications known to have perioperative effects and those in common use.

ROLE OF THE MEDICAL CONSULTANT

The primary role of the medical consultant in perioperative medication management is to understand the patient and his or her diseases. A detailed medical history should be taken prior to surgery, including the use of prescribed medications, over-the-counter medications, vitamins, and herbal products.

Medications associated with known morbidity when withdrawn abruptly should be continued during the perioperative period whenever possible; the classic example is clonidine. Medications thought to increase the risk of surgical complications that are not essential for short-term improvement in quality of life should be held through the perioperative period.[1]

Medications not meeting either of these criteria can be discontinued or continued at the managing physician's discretion. If continued, the physician should keep in mind that many other medications are administered perioperatively during a short period and that these may interact with chronic medications. Moreover, the metabolism and elimination of chronic medications and their metabolites may be altered during the perioperative period.

CASE 1: CHRONIC ASPIRIN USE IN A PATIENT UNDERGOING WISDOM-TOOTH EXTRACTION

A 28-year-old woman is scheduled for a wisdom-tooth extraction. She has a history of migraines and uses the combination analgesic product Fiorinal (aspirin, caffeine, and the nonnarcotic barbiturate butalbital) almost daily. What perioperative recommendations should be made regarding this aspirin use?

The decision to continue or discontinue aspirin use preoperatively should balance the consequences of perioperative hemorrhage against the risk of perioperative vascular complications. Aspirin is an irreversible inhibitor of platelet cyclo-oxygenase. This effect leads to increased intraoperative blood loss and transfusion requirements.[2] Nonetheless, in selected patient populations, especially those who are undergoing coronary artery bypass graft surgery, observational studies suggest that withdrawal of aspirin preoperatively is associated with increased in-hospital mortality.[3,4] A similar risk has been observed in patients undergoing surgery for peripheral vascular disease.[5] On the other hand, with cataract surgery, the risk of ocular hemorrhage in patients taking aspirin is extremely low and similar to that in patients not taking aspirin. Aspirin should be withheld before surger-

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ies in which perioperative hemorrhage could be catastrophic (eg, central nervous system surgery).

Remember that the circulating platelet pool is replaced every 7 to 10 days.[6] Since aspirin is an irreversible inhibitor of platelet cyclo-oxygenase, aspirin use should be stopped 7 to 10 days prior to surgery, when applicable.

CASE 2: NSAID USE AND HORMONE REPLACEMENT THERAPY IN A HIP REPLACEMENT CANDIDATE

A 68-year-old woman with severe osteoarthritis is scheduled for a total hip replacement. She takes acetaminophen and ibuprofen for her arthritis, and she is also receiving postmenopausal hormone replacement therapy (HRT). What recommendations should be provided regarding this patient's medications?

Acetaminophen is relatively safe, has few side effects, and does not affect bleeding and therefore can be continued safely in patients undergoing major surgery.

NSAIDs. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID), and NSAIDs are reversible inhibitors of platelet cyclo-oxygenase. They can induce renal failure in combination with other drugs, specifically angiotensin-converting enzyme (ACE) inhibitors, particularly in the presence of hypotension and dehydration. Cyclo-oxygenase-2 (COX-2) inhibitors (ie, celecoxib) have much less effect on platelet function, although the potential for nephrotoxicity remains.

In general, because they are reversible inhibitors of platelet cyclo-oxygenase, NSAIDs should be held approximately 3 days before surgery. However, this recommendation is not evidence-based, as illustrated by a recent study by Goldenberg et al,[7] who prospectively examined the duration of platelet dysfunction after a 7-day course of ibuprofen in 11 healthy subjects. They were able to show that platelet function normalized by 24 hours after the last dose. This was a small study, however, and the generalizability of its findings is limited because only healthy subjects were included. We clearly need more studies to answer this question fully.

HRT. In 2000, the large randomized Heart and Estrogen/progestin Replacement Study (HERS) revealed that postmenopausal HRT increased the risk of deep vein thrombosis and pulmonary embolism in women with coronary heart disease (Table 1).[8] This risk increased after patients sustained a lower extremity fracture. After surgery, the risk was magnified and stayed magnified for about 3 months postoperatively. For this reason, many experts recommend stopping HRT for approximately 4 weeks before major surgery.

TABLE 1
Key findings of HERS trial of hormone replacement therapy and venous thromboembolic risk*

- HRT increased risk of VTE 2.7-fold overall
- HRT increased risk of VTE 18-fold in patients with lower extremity fractures
- HRT increased risk of VTE approximately 5-fold in the 90 days following inpatient surgery
- HRT increased risk of VTE 5.7-fold in the 90 days following hospitalization

* In postmenopausal women with coronary heart disease. Data are from reference 8.

HERS = Heart and Estrogen/progestin Replacement Study; HRT = hormone replacement therapy; VTE = venous thromboembolism

The HERS trial included only women with coronary heart disease, however, and routine discontinuation of HRT for major noncardiac surgery is controversial. A recent case-control study with 108 cases and 210 controls found no association between perioperative HRT use and postoperative venous thromboembolism.[9]

At The Cleveland Clinic's IMPACT (Internal Medicine Preoperative Assessment, Consultation, and Treatment) Center and at many other institutions across the country, patients are typically seen 1 to 2 weeks before surgery. In that situation, the prothrombotic state that HRT produces is not going to dissipate if the patient stops the drug 1 week prior to surgery; this prothrombotic state actually takes a few weeks to dissipate. Several experts feel that routine HRT discontinuation may be unnecessary in patients receiving appropriate pharmacologic antithrombotic prophylaxis.[9]

CASE 3: CARDIOVASCULAR AND PULMONARY DRUGS IN THE SETTING OF ABDOMINAL SURGERY

A 64-year-old man with a history of stable angina, congestive heart failure (CHF), ventricular tachycardia, and chronic obstructive pulmonary disease (COPD) is scheduled for inguinal hernia repair. His medications include digoxin, atenolol, atorvastatin, amiodarone, furosemide, clopidogrel, lisinopril, and inhalers for his COPD. How should these cardiovascular and pulmonary medications be managed perioperatively?

Cardiovascular medications

The most commonly prescribed cardiovascular drugs or drug categories include clopidogrel, nitrates, digoxin, beta-blockers, calcium channel blockers, antiarrhythmics, ACE inhibitors, angiotensin II receptor

TABLE 2
Perioperative recommendations for common cardiovascular drugs

Drug/drug category	Recommendations
Clopidogrel	Discontinue 7–10 days before major surgery (due to irreversible antiplatelet effect)
Nitrates Digoxin Clonidine Beta-blockers Calcium channel blockers Antiarrhythmics	Continue up to and including day of surgery, particularly clonidine and beta-blockers. If therapy cannot be interrupted and patient is on parenteral feeding, consider transdermal or intravenous administration.
Diuretics ACE inhibitors Angiotensin II receptor blockers	Hold on morning of surgery, especially if the indication is congestive heart failure[10,11]
Niacin Fibric acid derivatives Cholestyramine Colestipol	Hold at least 1 day before surgery
Statins	Continue in the perioperative period[12–14]

blockers, diuretics, and cholesterol-lowering medications, including statins.

The decision about whether and when to withhold various cardiovascular drugs prior to surgery varies by the type of medication, as detailed in Table 2.[10–14]

Clopidogrel is an irreversible platelet inhibitor: it blocks the adenosine diphosphate receptor, which prevents fibrinogen binding at that site and thereby reduces the possibility of platelet adhesion and aggregation. For this reason, clopidogrel should be stopped 7 to 10 days before surgery.

Nitrates, digoxin, clonidine, beta-blockers, calcium channel blockers, and antiarrhythmic drugs are essentially safe to continue perioperatively. If therapy cannot be interrupted and the patient is being fed parenterally, consider transdermal or intravenous administration as needed.

At our institution, we generally hold diuretics, ACE inhibitors, and angiotensin II receptor blockers the morning of surgery, especially if CHF is the indication for their use.[10,11] If the indication is hypertension and the systolic blood pressure is, for example, 160 mm Hg, the physician may make an informed decision to continue the medication on the day of surgery. However, if the medications are being taken for CHF and the systolic blood pressure is 110 mm Hg or lower, it is typically advisable to hold the drug on the day of surgery. This approach is based on two studies from the 1990s that demonstrated an increased risk of hypotension after induction of anesthesia if patients received ACE inhibitors on the day of surgery.[10,11] It is generally advisable to hold diuretics in light of their associated risk of hypokalemia.

Several cholesterol-lowering medications, including niacin, fibric acid derivatives, cholestyramine, and colestipol, carry a theoretical risk of rhabdomyolysis and myositis, and the literature does not demonstrate that these medications have an impact on short-term cardiovascular outcomes. Hence, patients should be advised to stop these medications 1 day before surgery.

Statins are a different issue, however. Evidence is emerging that statins may prevent vascular events through mechanisms other than cholesterol reduction (ie, plaque stabilization, reduction in inflammation, decreased thrombogenesis). These benefits may be lost if statins are discontinued, and some data from animal models suggest that discontinuation of statins in patients who have been taking them chronically can produce a rebound prothrombotic state. For these reasons, statins should be continued in the perioperative period.[12–14]

Pulmonary medications

Commonly prescribed pulmonary medications include theophylline, inhaled beta-agonists, inhaled ipratropium, inhaled corticosteroids, and leukotriene inhibitors.

Theophylline can be a difficult drug to manage. It has a very narrow therapeutic window and is associated with several drug-drug interactions that can lead to toxicity. We typically ask our patients to discontinue theophylline the evening before surgery. The individual managing physician may decide to continue the drug, however, in which case monitoring for symptoms and signs of theophylline toxicity, including taking a blood level, is important.

Other pulmonary medications, including inhaled beta-agonists, inhaled ipratropium, inhaled corticosteroids, and leukotriene inhibitors, are typically continued up to and including the day of surgery. These medications are essential for reducing postoperative pulmonary complications, especially in patients who have COPD or asthma.

CASE 4: ELECTIVE SURGERY AFTER RECENT DRUG-ELUTING STENT PLACEMENT

A 55-year-old man is referred for medical evaluation. He is scheduled to undergo elective total right-sided

knee replacement in the coming week. His medical history includes known coronary artery disease, and he underwent coronary revascularization with placement of a paclitaxel-coated stent 8 weeks ago. His medications include aspirin (81 mg/d), clopidogrel (75 mg/d), atenolol (50 mg/d), and atorvastatin (40 mg/d). How should these medications be managed in the perioperative period?

Stent placement calls for full course of antiplatelet therapy

The patient's atenolol and atorvastatin could be continued safely (see previous case); the question here centers on the antiplatelet agents. There is significant controversy over the optimal management of patients undergoing noncardiac surgery who have not completed their course of antiplatelet therapy for a recently implanted drug-eluting coronary stent. Mounting evidence suggests that premature discontinuation of antiplatelet therapy is associated with a very high rate of stent thrombosis and may be associated with a high case fatality rate.[15,16]

With a paclitaxel-eluting coronary stent system, current recommendations call for a minimum of 6 months of uninterrupted dual-antiplatelet therapy. With a sirolimus-eluting coronary stent, a minimum of 3 months of uninterrupted antiplatelet therapy is recommended. The reason that aggressive antiplatelet therapy is recommended with the use of drug-eluting stents is because the sirolimus and paclitaxel coatings may retard the endothelialization process, thereby markedly raising the risk of thrombogenesis.

A case like this is further confounded by the following factors:

- Surgery is a prothrombotic state.
- The true incidence of stent thrombosis and postoperative myocardial infarction (MI) in patients undergoing noncardiac surgery is not known.
- Most surgeons will not operate on patients receiving antiplatelet therapy, which can pose a real dilemma.

Further studies needed—and under way

Because this patient's scheduled surgery is an elective one, the prudent course would be to delay it until his full recommended course of post-stenting antiplatelet therapy is completed, after which the antiplatelet agents can be more safely stopped for the surgery.

Cases in which surgery is not elective, however, demand better answers to the questions raised by this case. To help further clarify such questions, we recently initiated a study at our IMPACT Center to examine the incidence and the predictors of postoperative MI, stent thrombosis, and bleeding outcomes in patients with implanted drug-eluting coronary stents undergoing noncardiac surgery (elective and emergent) who had premature cessation of antiplatelet therapy. These results will be available in the next few months.

CASE 5: TOE AMPUTATION IN A PATIENT WITH TYPE 2 DIABETES

A 72-year-old man who has a history of type 2 diabetes mellitus treated with insulin for the past 20 years develops a diabetic foot infection. Despite 6 weeks of intravenous antibiotics, the foot does not heal and it is determined that his toe needs to be amputated. He is receiving neutral protamine Hagedorn (NPH) insulin (20 U in the morning and 10 U in the evening) and 8 U of fast-acting insulin lispro with each meal. How should his diabetes therapy be managed in the perioperative period?

While there are no clear evidence-based recommendations for perioperative management of insulin or other medications for type 2 diabetes, a few general principles can be set forth:

Insulin. Current consensus among clinicians generally supports giving long-acting insulin at half the normal dose and holding short-acting insulin. At our institution, however, we hold all insulin on the morning of surgery and we generally resume the home insulin regimen when the patient resumes taking medication orally postoperatively. Patients with type 2 diabetes are triaged to be the first surgical cases of the day so that the anesthesiologists can assume the diabetes management early on.

Metformin is held for 2 days before surgery because of the risk of lactic acidosis if a patient were to develop a renal problem perioperatively.

Other oral antidiabetic agents. Sulfonylureas, thiazolidinediones, and alpha glucosidase inhibitors are held the morning of surgery.

CASE 6: PSYCHOTROPIC DRUGS IN A MASTECTOMY CANDIDATE WITH SEVERE DEPRESSION

A 38-year-old woman with a history of severe depression is scheduled for a mastectomy for breast cancer. Her medications include fluoxetine, olanzapine, and lorazepam, all taken for many years. How should these agents be managed?

Antidepressants. Selective serotonin reuptake inhibitors such as fluoxetine are very safe in the perioperative setting and may be continued without concern. Tricyclic antidepressants inhibit the uptake of norepinephrine and serotonin and may enhance the action of sympathomimetics. Little evidence is available to guide decisions about their perioperative use,

but our institution typically continues tricyclic antidepressants throughout the perioperative period, especially for patients on high doses.

Monoamine oxidase inhibitors (MAOIs) carry a potential risk for hypertensive crises and a large number of drug-drug interactions. MAOIs are usually taken by patients with more refractory depression. A MAOI-safe anesthetic technique has been described and used in patients requiring emergency procedures. The decision to continue or withhold MAOIs before surgery requires close collaboration with the patient's anesthesiologist and psychiatrist.

Benzodiazepines such as lorazepam are very safe perioperatively. For this reason and because their abrupt withdrawal can lead to an excitatory state (with hypertension, agitation, delirium, and seizures), they should be continued.

Antipsychotics such as olanzapine are also continued perioperatively.

CASE 7: HERBAL PRODUCTS AND PRESCRIPTION DRUGS IN A HIP REPLACEMENT CANDIDATE

A 68-year-old woman with a history of hypertension, osteoarthritis, and osteoporosis is scheduled for total hip replacement and presents for a consult. Her medications include atenolol, hydrochlorothiazide, and alendronate. She also reports taking the herbal supplements ginkgo biloba and echinacea. How should these herbal products be managed?

Herbal use widespread, perioperative risks real

A comprehensive literature review published in JAMA in 2001 documented widespread use of herbal supplements among the presurgical population: approximately one third of patients from the included studies were taking herbal products.[17] The review identified eight common herbal supplements that may pose a safety concern during the perioperative period: ginkgo biloba, echinacea, ephedra, garlic, ginseng, kava, St. John's wort, and valerian. The potential complications identified were serious, including MI, stroke, bleeding, and prolongation of the action of anesthetic drugs, which can cause inadequate anesthesia and interference with other drugs.

In light of these findings, patients should generally be asked to stop all herbal supplements at least 5 to 7 days before surgery. Risks specific to individual herbal preparations are detailed below.

The "three Gs" and bleeding risk. Ginkgo biloba, garlic, and ginseng—sometimes referred to as the "three Gs"—may all increase the risk of bleeding.

- Ginkgo biloba can cause bleeding through inhibition of platelet-activating factor, so patients should be asked to stop this supplement 36 hours before surgery.
- Garlic inhibits platelet aggregation (potentially as an irreversible inhibitor), may increase fibrinolysis, and has equivocal antihypertensive activity. Its use should be discontinued at least 7 days before surgery.
- Ginseng also inhibits platelet aggregation (potentially as an irreversible inhibitor). There is also some suggestion of an increased risk of hypoglycemia in chronic users of ginseng. This product may also reduce the anticoagulant activity of warfarin. It should be stopped at least 7 days before surgery.

Echinacea. The pharmacologic effect of echinacea is activation of cell-mediated immunity. Allergic reactions and immune system dysfunction also may occur. Data on perioperative discontinuation of echinacea are extremely limited, but patients at our institution are typically asked to discontinue it before surgery as a safeguard.

Ephedra. Perioperative concerns include tachycardia and hypertension, MI, stroke, hemodynamic instability, and drug-drug interactions with some psychiatric medications. Patients should be asked to stop ephedra 24 hours before surgery.

Kava causes sedation and potentiation of anesthetic medications, and its use is associated with concerns about withdrawal, tolerance, and addiction. Patients should be asked to stop kava 24 hours before surgery.

St. John's wort is associated with many potential drug-drug interactions through its induction of cytochrome P-450 enzymes. This supplement should be discontinued at least 5 days before surgery.

Valerian has a sedative pharmacologic effect, so it can increase the sedative effect of anesthesia, whereas its withdrawal may raise anesthetic requirements. No data are available on its perioperative discontinuation or use.

What about vitamins?

Many surgical patients are likely to also be taking vitamins. Multivitamins are highly safe perioperatively. Because vitamin E supplements carry a risk of bleeding, patients should be asked to stop their use 10 days before surgery.

CASE 8: RHEUMATOID ARTHRITIS DRUGS IN A PATIENT UNDERGOING CHOLECYSTECTOMY

A 55-year-old woman is scheduled to undergo laparoscopic cholecystectomy in 2 weeks. She has a history of stable rheumatoid arthritis, and her medications include weekly methotrexate and hydroxychloroquine. What medication recommendations are in order?

Hydroxychloroquine is believed to be safe in the perioperative period.

Methotrexate and other DMARDs. Data on the perioperative use of methotrexate are limited. One prospective randomized trial published in 2001 focused on rheumatoid arthritis patients taking methotrexate who underwent elective orthopedic surgery, and it found no increase in infection rate or surgical complications when methotrexate was continued.[18]

There are no published data on the perioperative use of other disease-modifying antirheumatic drugs (DMARDs). Because many DMARDs are renally excreted, impaired kidney function can lead to an accumulation of these drugs or their metabolites, which may lead to bone marrow suppression. Methotrexate should be held for 2 weeks before surgery in patients with renal insufficiency.

TNF-alpha inhibitors. Only one study has been published on the perioperative use of tumor necrosis factor (TNF)-alpha inhibitors in patients with rheumatoid arthritis.[19] This single-center, nonrandomized, prospective cohort trial involved 31 patients with rheumatoid arthritis who underwent elective foot and ankle surgery. Half of the patients were receiving TNF-alpha inhibitors and half were not; all patients continued their antirheumatic drug regimens unaltered in the perioperative period. Postoperative outcomes were similar between the patients who received TNF-alpha inhibitors and those who did not in terms of surgical healing and infection rates. The authors concluded that TNF-alpha inhibitors may be safe in the perioperative period, but further studies are needed.

SUMMARY

Medical consultants need to recommend the safest and the most effective ways to manage chronic medications in the perioperative period. Outcomes data from clinical trials are limited in regard to perioperative medication management, so specific clinical trials are not available to guide decision-making in most circumstances. More studies in this field are needed. Communication and collaboration with anesthesiologists and surgeons as well as with primary care physicians are key to achieving optimal outcomes.

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