

Anesthetic Pharmacology Update

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Increasingly we are learning that interventions made during the perioperative period, including, during anesthesia make significant differences in surgical outcomes. Anesthesiologists have taken a strong interest in examining these potential interventions with the idea that perioperative risk could be reduced and outcomes improved. Anesthesia providers have risen to this challenge by incorporating perioperative beta-blockers and timely administration of prophylactic antibiotics to their anesthetic regimens.

We will examine some of the pharmacologic interventions that are currently under discussion and investigation. Some of these may be among the drugs that we will all be getting from the OR pharmacy for our routine cases in the near future.

Beta Blockers

Significant risk exists for cardiac complications in patients having noncardiac surgery. The *Revised Cardiac Risk Index* by Lee and colleagues is that most widely used method for calculating this risk. They give one point each for the presence of high-risk procedure, history of ischemic heart disease, history of CHF, history of CVA, preoperative insulin or a serum creatinine of 2.0 or greater. The incidences of “major cardiac complications” (myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and/or complete heart block) with an index of 0, 1, 2, or 3 (or higher) were 0.4%, 0.9%, 7% and 11% respectively. In a study of 200 noncardiac surgical patients at the SF VA, Mangano et al. showed that IV atenolol given at the time of discharge and continued (IV and oral) until discharge from the hospital significantly lowered mortality among the atenolol-treated patients versus those who were given placebo over the six months following hospital discharge (0 vs. 8 percent, $P < 0.001$), over the first year (3 percent vs. 14 percent, $P = 0.005$), and over two years (10 percent vs. 21 percent, $P = 0.019$).

This set the stage for the ACC/AHA recommendations for perioperative beta blocker therapy. Most agree that Lee score of 2 or greater would merit initiation of perioperative beta blocker therapy (PBB). However, questions still remain: how long before surgery is PBB efficacious, is titration to a $HR = 60 \pm 5$ necessary, and does pre-induction titration of PBB to HR make a difference in outcome? In addition, there is a lack of definitive data on this subject, specifically:

- Most trials are inadequately powered.
- Few randomized trials of medical therapy to prevent perioperative major adverse cardiac events (MACE) have been performed.
- Few randomized trials have examined the role of perioperative beta-blocker therapy, and there is particularly a lack of trials that focus on high-risk patients.
- Studies to determine the role of beta blockers in intermediate- and low-risk populations are lacking.

- Studies to determine the optimal type of beta blockers are lacking.
- No studies have addressed care-delivery mechanisms in the perioperative setting, identifying how, when, and by whom perioperative beta-blocker therapy should be implemented and monitored.

Two new studies call into question the routine treatment of low and intermediate risk of perioperative myocardial ischemia from being treated with beta-blockers. The POISE Study Group reported the results of a large, multicenter RCT on the acute perioperative use of metoprolol.¹ They found that for every 1000 patients with a similar risk profile undergoing non-cardiac surgery, metoprolol will prevent 15 patients from suffering a myocardial infarction, three from undergoing coronary revascularization, and seven from developing new significant atrial fibrillation. However, their results also suggest that metoprolol will cause *an excess* of eight patients to die and five to suffer a stroke for every 1000 treated with a perioperative beta-blocker. The authors concluded that patients may not accept the risks to gain the benefits.

Another large meta-analysis published in December of 2008² of 33 studies involving over 12,000 patients found that beta blockers were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure. Their use was associated with a decrease in non-fatal myocardial infarction (number needed to treat [NNT] 63) and decrease in myocardial ischemia (NNT 16) at the expense of an increase in non-fatal strokes (number needed to harm [NNH] 293). Again, it appears careful patient selection is required for starting beta blockers in the perioperative period.

Statins

Statins inhibit the rate-limiting step in biosynthesis of cholesterol.³ There is compelling evidence that chronic statin use decreases cardiovascular events. Traditionally, a statin is accepted as successful lipid-lowering therapy that reduces cardiovascular events over years. Recently, statins have been promoted as perioperative risk reduction strategies because of their short-term effects on endothelium-dependent vasodilation, coagulation, platelet aggregation, vascular plaque stability, and inflammation. Because perioperative myocardial infarctions (MI) occur equally from coronary stenosis and plaque rupture, statins are postulated to decrease perioperative cardiovascular complications.

While increasing cholesterol levels correlate with increasing risk of cardiovascular events, there is no threshold cholesterol level below which there is no occurrence of cardiovascular events. Accordingly, populations with low cholesterol levels still benefit from lipid-lowering therapy. A trial of primary prevention reported a 37% reduction (95% confidence interval 0.50–0.79; $P < 0.001$) in the incidence of a first acute major coronary event in people taking a statin even with “normal” cholesterol levels.

Benefits from statins administered both immediately after acute coronary syndromes (ACS) and chronically in higher doses continue to be demonstrated. These benefits include reduced nonfatal MI at 2 years (hazard ratio 0.83, 95% CI 0.71–0.98).

Retrospective studies of ACS and MI databases identify reduced cardiovascular morbidity and mortality when statins are administered within hours of ACS. This same benefit requires years to achieve if statins are started in a delayed fashion. This implies that patients should be on a statin after any perioperative cardiac event, if not preoperatively. Analysis of patients who took statins before hospitalization indicates that they are less likely to have ST segment elevation or a “large” infarct perioperatively. These same patients, however, have higher troponin levels and are more likely to die if statins are discontinued after ACS. In light of evidence for a “rebound” phenomenon, it is not advisable to discontinue statin therapy perioperatively in patients at risk for acute cardiac stress.

Statins inhibit the rate-limiting step for cholesterol synthesis by preventing conversion of HMGCoA to mevalonate. Statins also cause hepatocytes to increase LDL-receptor expression, increasing cholesterol uptake thus decreasing circulating cholesterol and apolipoprotein B levels. Alternate lipid-lowering agents appear to confer less reduction in cardiovascular risk compared with statins, relative to the absolute reduction in cholesterol level. The hypothesis as to why statins reduce cardiovascular risk out of proportion to its lipid-lowering potential is that by blocking HMG-CoA reductase mevalonate is depleted as well as the subsequent isoprenoid intermediates. These isoprenoid intermediates are responsible for posttranslational modification of small intracellular signaling G-proteins that influence many intracellular signaling pathways (Ras, Rho, Rac).

Vasomotor Effects

LDL inhibits endothelium-dependent vasodilation through suppression of nitric oxide (NO). Statins prolong endothelial NO synthase activity via a non-cholesterol-lowering mechanism, likely related to the G-protein Rho pathway. Lovastatin decreases coronary vasoconstriction in response to acetylcholine and improves Holter monitor measured ST segment depression in patients with stable CAD. In hypercholesterolemic patients, enhanced myocardial perfusion is 6-fold greater in ischemic coronary segments than nonischemic coronary segments after 12 weeks of fluvastatin. Statins decrease expression of vasoconstrictors such as endothelin I and angiotensin II in animals. In animal models of MI a reduction in infarct size with as little as 3 days of pretreatment with atorvastatin was identified. Statin-treated animals exhibited better coronary relaxation, improved left ventricular wall motion scores, and required fewer therapeutic cardioversions. NO synthase inhibitors abolished these protective effect of statins.

Simvastatin improves peripheral vascular function. Patients with claudication treated with crivastatin had longer pain-free periods and prolonged walking distance in at 6 months. Vasomotor improvement even occurred in normocholesterolemic subjects.

Coagulation

Tissue factor is expressed by endothelial cells, smooth muscle cells, and macrophages. Statins reduce thrombin-induced and lipopolysaccharide (LPS)-induced expression of tissue factor in a time- and concentration-dependent manner in both animals and humans. Interestingly, these effects occur before an alteration in lipid profile.

Hypercholesterolemia increases platelet aggregation and statins normalize platelet function in familial hypercholesterolemia. No correlation was identified with LDL cholesterol or platelet cholesterol level changes, implicating a noncholesterol-mediated effect of statins.

Statins also affect the fibrinolytic side of the coagulation balance. Patients with CAD exhibit reduced levels of tissue plasminogen activator and elevated circulating plasminogen activator inhibitor (PAI)-1. Plasma PAI-1 is an independent risk factor for recurrent MI. In vitro data indicates that statins increase tissue plasminogen activator and decrease PAI-1 in endothelial cells (lovastatin), vascular smooth muscle cells (simvastatin), and macrophages (cervastatin).

Coronary Plaques and Inflammation

Pathologic studies indicate that deadly postoperative MI occur with equal frequency from arterial stenosis and plaque rupture and the myocardium at risk does not correlate with the degree of feeding artery stenosis. This supports the conclusion that risk of coronary occlusion is related to both plaque composition and plaque size. Since statins reduce the inflammatory atherosclerotic process that leads to plaque instability MI from plaque rupture is reduced.

Statins may even affect sepsis-induced inflammation. Healthy normocholesterolemic men administered simvastatin (80 mg/d for 3 days) (versus placebo), given an intravenous injection of endotoxin (LPS), had reduced LPS-induced increases in monocyte chemoattractant protein 1, as well as other inflammatory markers. In a mouse model of cecal ligation and puncture, 18-hour pretreatment with statins prolonged survival 4-fold and survival even increased by 50% when statins were administered 6 hours after sepsis induction.

Perioperative Studies

A large meta-analysis⁴ that included 19 studies and over 30,000 patients undergoing cardiac surgery showed a 43% reduction in risk of all-cause mortality, a 33% reduction in atrial fibrillation and a 26% reduction in stroke. Also of note was the report of the JUPITER Group⁵ where rosuvastatin was administered to over 17,000 apparently healthy patients over the age of 60 with normal cholesterol levels, reduced the rate of cardiovascular events by 33% (a greater risk reduction than found in patients with hypercholesterolemia). The door seems wide open for further studies in a wide variety of patient groups to test whether statins confer a beneficial effect in surgical outcomes.

Carbon Monoxide

In a recent editorial in *Anesthesiology*⁶ Kevin and Laffey point out that carbon monoxide is popularly held as a nasty atmospheric pollutant and poison. Most of us continuously inhale low concentrations; the cigarette smokers inhale much more. Carbon monoxide binds avidly to hemoglobin, forming carboxyhemoglobin and compromising oxygen-

carrying capacity, accounting for the poisonous effects that are seen at high doses. However, at low doses evidence points to a protective effect against tissue injury.

Like statins, CO has antiinflammatory, antioxidative, antiproliferative, and antiapoptotic effects have all been demonstrated, but the relative importance of these and the exact cellular mechanisms remain active areas of research. This editorial accompanied a fascinating article by Goebel et al.⁷ showing that pretreatment with carbon monoxide before CPB was effective in protecting the lung. This along with protection of other organs may make intraoperative use of CO something we see in our future.

Peripheral Opioid Antagonists

By adding a methyl group to naltrexone Leon Goldberg, M.D., at the University of Chicago developed a polar compound that would be excluded from the central nervous system, but would be able to antagonize peripheral opioid receptors. Another drug, alvimopan is a large polar compound with opioid receptor specificity that is also in the FDA testing pipeline. The first indication being worked on for the New Drug Applications for both drugs is as a GI motility agent in patients taking opioids for acute or chronic pain and methadone maintenance. I suppose it could also be used to reverse an Imodium overdose.

It is now clear that there are other peripheral opioid receptors that we will learn more about now that there is a specific antagonist. Two that could have an impact on perioperative outcomes are ones that stimulate angiogenesis and stimulate bacterial growth. Recent studies in mice show that morphine in clinically relevant doses stimulates angiogenesis and breast cancer progression. So far only one study in humans found a much increased breast cancer recurrence rate in patients receiving morphine PCA vs those who received thoracic epidurals. Opioids may play an important role in the enhancement of breast and other cancer progression. In fact this year another study from this Ireland-based group showed a similar association with prostate cancer recurrence rates when systemic opioids were used instead of regional analgesia for post-op pain following radical prostatectomy.⁸ Blocking or preventing these effects could be very important perioperatively.

Evidence exists that exogenous (as opposed to endogenous) opioids decrease the inflammatory and immune response to infection. In addition, bacteria express opioid receptors and exposure of bacteria to opiates induces increased bacterial virulence.

Sugammadex

Sugammadex, a modified [γ]-cyclodextrin, is a selective relaxant-binding agent. Sugammadex achieves rapid reversal of muscle relaxation by forming a tight complex with unbound steroidal NMBA molecules, thereby preventing their action at the neuromuscular junction. It has been shown that sugammadex rapidly and effectively reverses rocuronium-induced neuromuscular blockade, including profound

blockade.⁹ In a surprise, the FDA has rejected Schering-Plough's application to sell sugammadex. This will delay its clinical introduction in the US for 1-3 years.

Fospropofol

With its safety profile, speedy onset, and rapid recovery propofol has become a popular sedative-hypnotic widely used for producing sedation and inducing general anesthesia. A number of disadvantages stem from the formulation of propofol as a lipid emulsion. Chief among these disadvantages are pain on injection, risk of infection from decreased bacterial clearance, high lipid intake during long-term administration, and dose-related cardiac and respiratory depression. Fospropofol is a water-soluble prodrug of propofol designed to bypass the disadvantages inherent in the lipid formulation of propofol. Although the water-soluble preparation of fospropofol bypasses the disadvantages of lipid formulation, the prodrug preparation leads to a delayed time to peak concentration of propofol. This slow onset was touted as a 'safety factor' that would allow the safe administration of propofol by nonanesthesia-trained proceduralists. In 2008 the FDA rejected this argument when it approved fospropofol for marketing and retained the black box warning regarding the need for personnel trained in the administration of general anesthesia for its administration.

BIBLIOGRAPHY

1. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; 371: 1839-47
2. Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH: Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* 2008; 372: 1962-76
3. Le Manach Y, Coriat P, Collard CD, Riedel B: Statin therapy within the perioperative period. *Anesthesiology* 2008; 108: 1141-6
4. Liakopoulos OJ, Choi YH, Haldenwang PL, Strauch J, Wittwer T, Dorge H, Stamm C, Wassmer G, Wahlers T: Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. *Eur Heart J* 2008; 29: 1548-59
5. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359: 2195-207
6. Kevin LG, Laffey JG: Carbon monoxide: from poison to therapy for cardiopulmonary bypass-induced lung injury? *Anesthesiology* 2008; 108: 977-8

7. Goebel U, Siepe M, Mecklenburg A, Stein P, Roesslein M, Schwer CI, Schmidt R, Doenst T, Geiger KK, Pahl HL, Schlensak C, Loop T: Carbon monoxide inhalation reduces pulmonary inflammatory response during cardiopulmonary bypass in pigs. *Anesthesiology* 2008; 108: 1025-36
8. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ: Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* 2008; 109: 180-7
9. Jones RK, Caldwell JE, Brull SJ, Soto RG: Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology* 2008; 109: 816-24
10. Daumerie G, Fleisher LA: Perioperative beta-blocker and statin therapy. *Curr Opin Anaesthesiol* 2008; 21: 60-5
11. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI: Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006; 105: 660-4
12. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, Hebbel RP: Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Res* 2002; 62: 4491-8
13. Homburger JA, Meiler SE: Anesthesia drugs, immunity, and long-term outcome. *Curr Opin Anaesthesiol* 2006; 19: 423-8
14. Liroy DT, Sheridan PA, Hurley SD, Walton JR, Martin AM, Olschowka JA, Moynihan JA: Acute morphine exposure potentiates the development of HSV-1-induced encephalitis. *J Neuroimmunol* 2006; 172: 9-17
15. Yuan CS, Foss JF: Oral methylnaltrexone for opioid-induced constipation. *JAMA* 2000; 284: 1383-4
16. Yuan CS, Foss JF, O'Connor M, Karrison T, Osinski J, Roizen MF, Moss J: Effects of enteric-coated methylnaltrexone in preventing opioid-induced delay in oral-cecal transit time. *Clin Pharmacol Ther* 2000; 67: 398-404
17. Yuan CS, Foss JF, O'Connor M, Osinski J, Karrison T, Moss J, Roizen MF: Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA* 2000; 283: 367-72
18. Zaborina O, Lepine F, Xiao G, Valuckaite V, Chen Y, Li T, Ciancio M, Zaborin A, Petroff E, Turner JR, Rahme LG, Chang E, Alverdy JC: Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa*. *PLoS Pathog* 2007; 3: e35