

BERNHARD ZWISSLER

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Room G

INTRODUCTION

Patients with pre-existing cardiac disease are at an increased perioperative risk. This is due to the fact that 1) the cardiovascular system is at risk, 2) patients with cardiovascular disease often suffer from high risk non-cardiac diseases (e.g. renal insufficiency), and 3) these patients frequently undergo high-risk surgery (e.g. vascular surgery). Cardiac risk patients are often taking a wide variety of drugs when they present for surgery. Although most of these drugs are indicated and may improve outcome under normal circumstances, they also may cause complications in the perioperative setting. The specific benefit-risk ratio of most of these drugs in the perioperative setting has not been defined. Therefore, the anesthetist is often left with the dilemma that either the continuation or the withdrawal of medication may increase the incidence of perioperative complications. This review explores our present knowledge regarding the specific risk-benefit ratio of continuing or withdrawing the co-medication in cardiac risk patients.

DIFFERENT TYPES OF CO-MEDICATION**CARDIOVASCULAR DRUGS**

In the cardiac risk patient anti-ischemic, anti-hypertensive or anti-arrhythmic therapy is normally continued until the morning of surgery. This is particularly important for *β-blockers*, since acute withdrawal is known to increase the risk of myocardial ischemia and infarction. There is good data to suggest that *β*-blockade should be initiated prior to high risk surgery in patients with ischemic heart disease [1]. Preoperative withdrawal of therapy is much less common. For example, there is no evidence that continuing *diuretics* throughout the perioperative period results in better outcome. Continuing diuretics may result in perioperative hypovolemia and hypocalcemia. Patients taking *ACE-inhibitors* (angiotensin converting enzyme inhibitors) or *angiotensin II antagonists* (which inhibit the effects of angiotensin II at its AT1-receptor), are at an increased risk of perioperative hypotension. This may be difficult to treat with conventional vasoconstrictors and may require vasopressin or its analogues (2), (3). On the other hand, acute preoperative withdrawal may result in intraoperative hypertension. In clinical practice, many anesthesiologists discontinue AT-II antagonists or ACE inhibitors in patients who are undergoing operations with a potentially high blood loss or in those who have sympathetic blockade either by *β*-blockers or spinal/epidural anesthesia. It is worth remembering that many of these drugs have a half-life of 12-24 h and so stopping the drug the evening before surgery may be ineffective.

Cardiac glycosides given for heart failure are often withdrawn 1 to 2 days prior to surgery, because they have a small therapeutic range, a long half-life and can produce arrhythmias. However, when given for atrial fibrillation they should be continued as withdrawal may result in perioperative tachyarrhythmias. If overdose is suspected, serum levels should be measured preoperatively (therapeutic ranges for digoxin 0.8-2.0 ng/ml and digitoxin 10-25 ng/ml).

In general, *anti-arrhythmic drugs* should be continued perioperatively. The situation is not clear with amiodarone, since this drug has been associated with atropine-resistant bradycardias, AV-dissociation, vasodilation, reduction of cardiac output and perioperative fatalities (4). On the other hand, amiodarone maintains cardiac rhythm in many patients and is characterized by a long half-life time, and so acute preoperative withdrawal does not seem warranted.

The perioperative management of patients taking *calcium antagonists* is controversial. Calcium-blockers do not seem to maintain hemodynamic stability or prevent myocardial ischemia in cardiac risk patients. An increase in ischemic events has been described with nifedipine. Higham et al. found that the chronic intake of calcium blockers (not differentiating between the different classes) represents an independent risk factor for cardiac complications in the first postoperative year (5). On the other hand, preoperative withdrawal may result in postoperative hypertension (6). The benefit-risk ratio of continuing calcium-blockers perioperatively (especially those of the nifedipine type) has not yet been determined.

ANTIDIABETIC AGENTS

Oral antidiabetics from the *sulfonylurea* class (e.g. glibenclamide) block the ATP-dependent potassium channel in mitochondria of myocytes and thereby prevent both ischemia- and anesthetic-induced preconditioning, both of which have been shown to reduce myocardial damage in acute myocardial ischemia. After temporary coronary artery occlusion in animals taking glibenclamide, myocardial recovery is dramatically reduced and area of infarction increased compared to controls. The timely preoperative withdrawal of this class of drug may also be reasonable in humans (7), although this has not been clearly demonstrated in patients. If the drug is withdrawn, careful control of perioperative blood glucose is required.

The *biguanides* (e.g. metformin) have become increasingly popular in the last few years. They inhibit hepatic gluconeogenesis and intestinal glucose resorption, increase glucose uptake in muscle and, at high concentrations, modulate mitochondrial function, thereby impairing aerobic metabolism. As a result, anaerobic glycolysis may occur resulting in increased production of lactic acid. Lactic acidosis is more likely with renal insufficiency, hypoxia and tissue ischemia. Mortality rates of 1 in 50.000 patient-years have been described. Perioperative use of biguanides during major surgery is therefore discouraged. The manufacturer recommends stopping treatment at least 48 h before surgery.

ANTILIPID DRUGS

Antilipid drugs as *HMG-Co-A reductase inhibitors (statins)* are known to stabilize vascular plaques, have anti-inflammatory effects and inhibit platelet aggregation and thrombus formation. In several studies, statins have been shown to reduce the incidence of ischemia, myocardial (re-) infarction and death in patients with acute coronary syndrome (8,9). This effect is, in part, independent from their effects on cholesterol level. A recent case-controlled study in 2816 patients undergoing major vascular surgery showed that statins significantly reduced perioperative mortality (10). Postoperative rhabdomyolysis has been reported in one patient in whom statins were continued throughout the perioperative period. In conclusion, available data suggest that statins should be continued for the perioperative period. Multiple reports of the protective effects of statins in cardiac risk patients strongly suggest that in the near future we may recommend preoperative *initiation* of a statin (similar to β -blockers) in patients with increased cardiac risk undergoing high risk surgery.

INHIBITORS OF PLATELET AGGREGATION

Patients with coronary artery disease regularly take *acetylsalicylic acid (ASS, aspirin)* and increasingly *ADP-antagonists (e.g. clopidogrel)*. The benefit of prophylactic treatment has been clearly demonstrated in patients undergoing coronary revascularisation (either surgical or angiographic), and also in patients with acute coronary syndrome without ST-segment elevation. (11) (12) (13). Yet the *perioperative* risk-benefit ratio of platelet inhibitors is not clear at all. While continuing ASS did not increase blood loss (14) but did decrease cardiovascular mortality in patients undergoing coronary artery bypass grafting (15), there is little doubt that ADP-antagonists increase bleeding in this setting (13). In contrast, there is no prospective data on the benefits of continuing antiplatelet therapy in patients at increased cardiac risk undergoing *non-cardiac* surgery. Retrospective analyses have shown that maintaining ASS therapy throughout peripheral vascular surgery will increase the tendency to bleed and will reduce mortality (16).

While platelet aggregation is only partially blocked by ADP-antagonists or ASS, this effect is complete when *GIIB/IIIa antagonists* are used. Abciximab und tirofiban are most commonly used at present. The primary indication is prophylaxis against in-stent thrombosis and stent occlusion after percutaneous coronary interventions (PCI). In general, elective surgery should be postponed until GIIB/IIIa antagonists (and ideally ADP-antagonists) can be safely withdrawn (17). In urgent cases the anesthetist should be aware that abciximab will inhibit platelet aggregation for 24-48 h and tirofiban for about 8 hours after last administration.

In summary, if there is a significant risk of bleeding, current data suggest that ADP-antagonists should be withdrawn at least 7 to 10 days preoperatively. As a rule, ADP-antagonists must be withdrawn prior to epidural or spinal anesthesia due to the risk of haematoma formation within the spinal canal. The perioperative management of ASS has to be individualized. In patients with high coronary risk (recurring angina pectoris, previous myocardial infarction, and ulcerated plaques) it may be beneficial to continue 'low-dose' ASS therapy (e.g. 100 mg/day) throughout the perioperative period. Please note that the insertion of an epidural catheter may be justified in patients taking aspirin as the *only* anticoagulant drug (i.e. no heparin on board).

Patients with mechanical heart valves will take warfarin-like drugs for life and those with biological valves for at least 3 months after surgery. Depending on the type of artificial valve implanted, an INR (international normalised ratio) of 2.0–3.5 should be achieved. Additional low dose ASS can further reduce the risk of thromboembolic complications (18). The risk of thromboembolic events when therapy is interrupted will be between 0.02 and 0.05 % per day and has to be weighed against the risk of perioperative bleeding in each individual patient (18).

PSYCHOPHARMACOLOGICAL DRUGS

In general, medication for patients with psychiatric or neurological disease should not be interrupted perioperatively. There are specific side-effects and interactions of some of these drugs with anesthetic agents in the perioperative setting which, if not taken into account may result in severe hemodynamic compromise. A specific discussion of this topic is outside of the scope of this review.

SUMMARY

Patients at cardiac risk are often taking drugs which may interact with anesthetics or give rise to specific complications in the perioperative period (e.g. bleeding, hypotension). Withdrawal of these drugs, however, may also be detrimental (e.g. result in hypertension, myocardial ischemia). An evidence based risk-benefit ratio assessing the consequences of maintaining or withdrawing most of these drugs perioperatively is not available. For β -blockers withdrawal for surgery definitely increases cardiac risk. The anesthesiologist therefore must know the specific benefits and risks of continuing medications in the perioperative period and has to decide on the optimal procedure in each individual patient.

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