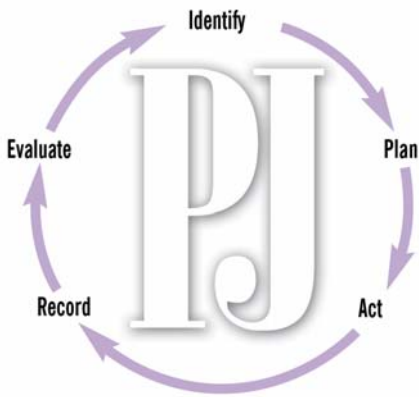


Peri-operative medication in patients with cardiovascular disease

In this article, **Mohamed H. Rahman** and **Jane Beattie** look at care of patients with cardiovascular disease who are to undergo a surgical procedure



Identify knowledge gaps

1. Which cardiovascular drugs can you consider stopping in patients having surgery?
2. Why are patients on warfarin switched to unfractionated or low molecular weight heparin in the peri-operative period?
3. If aspirin therapy is to be stopped, how far in advance of an operation should this be?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "clinical pharmacy" (see appendix 4 of "Plan and record").

When a patient with cardiovascular disease (CVD) is to undergo surgery, we need to consider whether or not any of the drugs used to treat his or her cardiovascular problems need to be stopped. The general principles of peri-operative medication were discussed in the first article in this series (*PJ*, 6 March, pp287–9). Most cardiovascular drugs should usually be continued in the peri-operative period. This article gives an overview of some special considerations.

Some drugs have clear evidence for continuation. For example, pre-operative alpha-adrenergic blockade (using phenoxybenzamine) to prevent hypertensive episodes in patients with a pheochromocytoma (catecholamine secreting tumour) must be continued until the tumour has been removed and there is full resolution of adrenergic symptoms.

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Conversely, sublingual nifedipine capsules should be used with caution for treating peri-operative hypertension because they have been associated with an increased risk of stroke. Similarly, potassium-sparing diuretics are usually omitted on the morning of surgery because tissue damage and reduced kidney perfusion in the peri-operative period may lead to hyperkalaemia. Alternatively, they may be substituted with a non potassium-sparing diuretic during the peri-operative period.

Many other drugs, such as angiotensin-II receptor antagonists, have no clear evidence for discontinuation so they are usually continued with caution. Caution is also needed if new drug treatments are initiated, or patients become hypovolaemic in the peri-operative period.

Patients with CVD need their established drug treatments, pulse and blood pressure closely monitored peri-operatively. They are at increased risk of peri-operative myocardial infarction (MI), with an in-hospital mortality of about 30 per cent.

Digoxin

Omission of digoxin for a prolonged period can cause a recurrence of atrial fibrillation (AF), which is associated with a significant risk of thromboembolism, hypotension, tachycardia and myocardial ischaemia. Although therapy with digoxin must, therefore, be continued peri-operatively, a change to an intravenous (iv) or oral liquid preparation may be required if the patient is nil by mouth or tube fed post-operatively. There are differences in bioavailability (liquids being better absorbed than tablets), but dose alteration is not normally recommended due to the large variation in absorption between individuals. However, if treatment is given intravenously, later conversion to the oral route (eg, as the patient recovers gastrointestinal function) may require a 25 per cent dose increase.

It is advisable to measure serum digoxin levels at least 6–8 hours post dosage to ensure therapeutic levels are achieved. Peri-operative electrolyte changes, such as hypokalaemia, hypomagnesaemia or marked hypercalcaemia increase myocardial sensitivity to cardiac glycosides. Both surgical sequelae (eg, ileostomies and fistulae) and medicines (eg, diuretics, lithium and corticosteroids) can cause hypokalaemia.

Symptoms of digoxin toxicity can occur at the upper end of the normal therapeutic range. It should be noted that nausea and

vomiting can be symptoms of digoxin toxicity but may be mistaken for nausea and vomiting relating to surgery.

In patients taking digoxin, the anaesthetist should use suxamethonium with caution because it can precipitate cardiac arrhythmias.

Diuretics

Thiazide and loop diuretics are usually continued peri-operatively. Chronic electrolyte imbalances, however, should be looked for and corrected before an operation, to reduce the risk of arrhythmias, particularly relating to hypokalaemia.

Hypovolaemia increases the risk of hypotension during anaesthesia, and is even more likely when pre-operative fluid intake has been restricted, or a patient has received purgative solutions (eg, before bowel surgery). It may be reasonable to withhold diuretics on the day of surgery to avoid patient discomfort (need to urinate) and volume depletion. It may also be unnecessary to continue diuretics during the nil-by-mouth period when iv fluids are being administered, but this decision should only be taken by a senior doctor. Inappropriate withdrawal may result in worsening symptoms of cardiac failure or advanced renal impairment, for which the diuretic was being taken.

The antihypertensive and diuretic effects of diuretics (especially loop) may be reduced by the concurrent administration of some non-steroidal anti-inflammatory drugs used peri-operatively. This combination need not be avoided, but the effects should be monitored closely and the diuretic dose adjusted if necessary.

Anti-arrhythmic drugs

Amiodarone has been associated with reports of peri-operative atropine-resistant bradycardia, profound vasodilatation, low cardiac output and death. Even so, it is usually continued peri-operatively because discontinuation can result in the recurrence of rhythm abnormalities despite the drug's long half-life (an average of 50 days according to the manufacturer).

Other anti-arrhythmic drugs should also be continued throughout the peri-operative period but not all are available as parenteral formulations and they may need to be substituted with an anti-arrhythmic from a different class. Parenteral anti-arrhythmics, especially substitutes, should be initiated under the advice of a cardiologist. Patients requiring parenteral anti-arrhythmics need close cardiac and fluid balance monitoring

blockers are withdrawn because an upregulated beta-adrenoceptor system is unmasked.

Beta-blockade has also been shown to reduce peri-operative cardiovascular morbidity and mortality beyond avoiding withdrawal symptoms. Beta-blockers directly or indirectly reduce peri-operative cardiac complications such as hypertension, AF, transient ischaemic attacks and stroke. They are especially useful in patients with pre-existing coronary heart disease, who are likely to suffer from peri-operative myocardial ischaemia or MI due to increased myocardial oxygen demand, complicated by coronary obstruction.

Mike Wyndham

Warfarin is usually replaced with heparin before surgery

(eg, electrocardiogram and central venous pressure monitoring) and are often admitted to a high dependency ward.

It should be noted that some anti-arrhythmics (eg, disopyramide, procainamide, and quinidine) can prolong the muscle relaxant effect of non-depolarising neuromuscular blockers.

Beta-adrenoceptor blocking drugs

There is good evidence to support peri-operative continuation of beta-blockade. Within 12–72 hours of stopping beta-blockade, withdrawal effects can develop. These include nervousness, tachycardia, headache and nausea, exacerbation of myocardial ischaemia, myocardial infarction (MI), arrhythmias and sudden death. Symptoms depend on the nature and severity of the underlying CVD, the level of stress (due to increased sympathetic activity in the peri-operative period following withdrawal) and type of surgery. In addition, patients who normally take beta-blockers are more sensitive to sympathetic stimuli if their beta-

Increased catecholamine levels in the peri-operative period play a major role in such cardiac complications.

There are two theories explaining the protective effect conferred by beta-blockers:

- Beta-blockers antagonise the sympathetic effect of stress hormones (eg, catecholamines), which are secreted in large amounts during the peri-operative period, by reducing heart rate and blood pressure
- Beta-blockers control the ventricular rate if post-operative arrhythmias develop (fast AF is a risk factor for cardiovascular complications following surgery)

Some hospitals have clinical guidelines for administration of peri-operative beta-blockers, but this practice is not yet routine in the UK.

If a parenteral beta-blocker is required, care should be taken not to change to a parenteral non-selective agent (eg, propranolol) in patients who have been taking oral cardioselective beta-blockers (eg, metoprolol and bisoprolol) or beta-blockers with some intrinsic sympathomimetic effects (eg, celiprolol). This is particularly important for patients with asthma or ventricular failure, where a change of beta-blockade could result in bronchospasm and marked bradycardia.

Post-operatively, beta-blockers are usually continued at the pre-operative dose.

ACEIs

Evidence for withholding angiotensin-converting enzyme inhibitors (ACEIs) peri-operatively is limited, so they are usually continued with caution. Clinical studies and case reports have described profound hypotension on induction of anaesthesia and reduced tolerance of hypovolaemia in patients taking ACEIs. There have also been reports that patients undergoing cardiopulmonary bypass

surgery and receiving ACEIs show a significant reduction in vasopressor response to conventional vasoconstrictors. Therefore, in such patients and in those with uncomplicated cases of hypertension, some anaesthetists may require ACEIs to be withheld for 12 hours in the case of captopril or quinapril or 24 hours for longer-acting ACEIs (eg, enalapril, lisinopril and ramipril).

If the ACEI is withheld, fluid intake may need to be restricted and patients should be monitored for development of congestive cardiac failure, especially if ventricular function is impaired. Renal function should also be monitored closely. ACEIs are usually restarted immediately post-operatively and patients who are unable to tolerate oral drugs may be offered unlicensed enalapril injection.

Conversely, in a small study of patients with chronic heart failure, continuing ACEIs pre-operatively did not cause an increase in severity of hypotension at induction,¹ and such evidence points towards continuation of ACEIs with caution.

Anticoagulant therapy

Although anaesthesia and surgery are not contraindicated in patients taking anticoagulants, major surgery poses an increased risk of haemorrhagic complications. There is good evidence that surgery increases the risk of venous thromboembolisms (VTE) and so, for most patients (especially those at high-risk of thromboembolism), some form of anticoagulant therapy should continue for most of the peri-operative period.

Pre-operative management The key principles of peri-operative anticoagulant management are summarised in Panel 1. Warfarin is usually discontinued three to four days before surgery to allow the international normalised ratio (INR) to fall below 1.5 — a level considered safe for most types of surgery to be performed. The British Committee for Standards in Haematology suggests that minor surface surgery can be carried out with INR of up to 2.5. Neurological or ocular procedures or surgery performed under epidural anaesthesia will require reversal of anticoagulation, to an INR of less than 1.3.

Vitamin K can be used to reverse the anticoagulant effect if there is insufficient time to allow the INR to fall to a desired level, but it should be noted that this can interfere with the effect of warfarin for many days. In an emergency, administration of clotting factors or fresh frozen plasma (under haematologist advice) may be warranted.

As the INR falls, intravenous unfractionated heparin (UH), or low molecular weight heparin (LMWH) is started. The dose used depends on the risk of thromboembolism. All patients considered as high-risk for VTE must be considered for a “treatment” dose of UH (eg, 15,000 units injected subcutaneously, twice daily) or a LMWH (eg, dalteparin 200units/kg sc once daily) as temporary replacement for oral anticoagulant therapy. High-risk patients are those with:

Panel 1: Principles of peri-operative anticoagulant therapy management

- Discontinue oral anticoagulant
- Start unfractionated heparin or low molecular weight heparin (LMWH)
- Ensure that the international normalised ratio (INR) falls to the desired level before surgery
- Discontinue unfractionated heparin or LMWH just before surgery
- Restart unfractionated heparin or LMWH after surgery
- Restart oral anticoagulant
- Discontinue heparin when INR returns to within the desired range

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Revise your knowledge of haemostasis, including the coagulation pathway and the various haematological blood tests used, in a standard medical or pharmacology textbook
2. Evaluate the evidence for the protective function of beta-blockers in patients undergoing surgery.
3. A patient comes into your pharmacy with a sore throat and asks for some soluble aspirin. She mentions that she is having an operation next week. Consider how you might advise her with respect to her purchase and discuss this with a colleague.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

- Prosthetic heart valves
- A history of acute VTE within the past three months (particularly within the four weeks before surgery)
- AF with history of stroke or systemic embolism
- Recurrent thrombosis
- A known hypercoagulable state (eg, antiphospholipid-antibody syndrome)

Patients considered as having a moderate-risk of VTE (eg, VTE over three to six months ago or AF without history of embolism but with multiple risk factors, such as diabetes and hypertension) should be considered for "treatment" doses on an individual basis. These patients may or may not be taking long-term oral anticoagulant therapy. If treatment doses are not prescribed, "prophylactic" doses of UH (eg, 5,000 units sc eight- to 12-hourly) or LMWH (eg, dalteparin 2,500 or 5,000 units sc once daily) should be considered. Low-risk patients (eg, remote episode of VTE over six months ago or AF without multiple risk factors), are unlikely to be taking oral anticoagulant therapy for life. They would not usually receive "treatment" doses of UH or LMWH and a "prophylactic" dose should suffice.

UH or LMWH are discontinued for a few hours pre-operatively to provide the surgical team with a short period when the patient has little systemic anticoagulation and it is safest to operate. The short half-life of heparin allows surgery to proceed within four to six hours of its discontinuation, hence minimising the period of "non-anticoagulation". Due to their longer duration of action, LMWHs must be stopped at least 12 hours before sur-

gery. A longer delay is advisable in patients with renal insufficiency, in whom excretion of LMWH is reduced.

In an emergency, the effect of UH may be cautiously reversed using protamine sulphate, but excessive doses of protamine sulphate have an anticoagulant effect. Haematologist consultation is advised. The disadvantage of using an LMWH is that it is not possible to reverse anticoagulation rapidly if bleeding occurs.

It should be noted that intramuscular injections administered to patients receiving full anticoagulant doses of heparin or warfarin, may cause painful haematoma and abscess formation.

Post-operative management If full anticoagulation is required post-operatively, UH can be restarted about 12 hours after surgery (when haemorrhage risk is reduced) with close monitoring of activated partial prothrombin time, usually six-hourly. Some vascular surgical patients may require uninterrupted heparinisation to optimise blood flow through — and prevent clot formation — within vessels that have been operated on.

Warfarin can be restarted as soon the patient is able to tolerate oral medication and the risk of bleeding has passed (eg, when all drains have been removed). Heparin treatment is continued until the desired INR is reached once more (usually two or three days after recommencing warfarin). Different hospitals adopt different warfarin loading dose regimens depending on for how long the warfarin has been discontinued.

Regional anaesthesia and anticoagulation Although it is not absolutely contraindicated, extreme caution is needed when patients receiving anticoagulants are being considered for regional anaesthesia. Spinal or epidural neural blockade is controversial, because of the risk of causing an epidural or subarachnoid haematoma which can lead to permanent neurological damage. The risk of bleeding is increased at the time of needle or epidural catheter insertion or removal. In general, regional anaesthesia is, therefore, contraindicated in patients concurrently receiving treatment doses of anticoagulants.

However, in patients receiving prophylactic doses, regional anaesthesia can be established provided sufficient time has elapsed between drug administration and establishing the neural blockade. This is six hours for UH and 12 hours for LMWHs. By this time the anti-Xa effect should have decreased to a level safe for surgery and anaesthesia to proceed. LMWHs indirectly inhibit factor Xa to prevent clotting. If treatment doses of LMWH have been used, 24 hours must elapse before regional anaesthesia.

Similarly, post-operatively, sufficient time must be allowed to elapse after catheter removal before the first dose of UH or LMWH is restarted. Using a regimen that allows a brief, but controlled, interruption to

anticoagulation should protect from the risks of thromboembolic incidents with no major increase in haemorrhage or hospital stay.

Low-dose aspirin Aspirin induces an irreversible inactivation of platelet cyclooxygenase, which lasts the lifetime of the platelet (seven to 10 days on average). There is no absolute consensus about whether or not low dose aspirin should be continued peri-operatively. The risk of haemorrhage versus the risk of predisposing the patient to a thromboembolic complication, such as a coronary event, transient ischaemic attack or stroke must be considered. Reports of MI following cessation of aspirin before coronary artery bypass graft surgery, prompt the suggestion that aspirin should not be stopped.

It is uncommon for serious complications to occur in patients taking aspirin in the peri-operative period, although surgical blood loss is increased. It is sensible to withdraw aspirin in patients whose risks of post-operative bleeding are high. Patients undergoing transurethral prostatectomy have been found to have significantly increased peri-operative bleeding if aspirin is continued and so, for these patients, aspirin is usually discontinued seven to 10 days pre-operatively. Other examples include patients for retinal, major orthopaedic or intracranial surgery. Patients undergoing minor surgery do not need to stop aspirin.

Patients taking aspirin may also be at an increased risk of haematoma formation with spinal or epidural anaesthesia. The clinical significance of this is of considerable debate and there are reports showing the safety of regional anaesthesia in patients receiving aspirin or non-steroidal anti-inflammatory drugs, although some anaesthetics consultants may wish to avoid this practice.

If stopped, aspirin is usually restarted when diet returns to normal. Following transurethral prostatectomy aspirin is sometimes withheld for one week.

Dipyridamole The manufacturer recommends that discontinuation of dipyridamole 24 hours pre-operatively is sufficient to reverse its effect. Dipyridamole is generally restarted in the immediate post-operative period.

References and further reading

1. Drugs in the peri-operative period: cardiovascular drugs. *Drug and Therapeutics Bulletin* 1999;37:89-92.
- Stafforth Smith M, Muir H, Hall R. Peri-operative management of drug treatment — clinical considerations. *Drugs* 1996;51:238-59.

Topics in this series

Further articles in this series on peri-operative drug therapy will look at:

- Peri-operative venous thromboembolism
- Peri-operative anti-bacterial prophylaxis
- Post-operative pain, nausea and vomiting