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Since the serendipitous discovery of heparin in 1916 and dicoumarol (the precursor to warfarin) in 1939, anticoagulation has changed very little – until now.¹ Warfarin remains the most widely prescribed anticoagulant worldwide but continues to pose many challenges. Nurses spend hours dispensing and administering these cumbersome drugs with their many food and drug interactions; patients have frequent blood tests and healthcare professionals spend endless hours chasing laboratories for international normalised ratio and activated partial thromboplastin time values, with their narrow therapeutic windows; even more time is spent adjusting drug doses and endless elective procedures are cancelled as results are out of the safe range.

In an era of frequent handovers, we may forget to hand over looking up results or even acting on them. The consequences for our patients can be disastrous, leading to death from thrombosis or haemorrhage.

Great effort has gone into the production of newer agents that are administered orally, have fixed doses and do not require monitoring. Of course, these bring new challenges to anaesthetists and surgeons about how to manage them practically.

Although many and conflicting guidelines exist, the decision to stop anticoagulants hinges on a balance of the risk of thrombosis and bleeding associated with the various alternatives available. This article provides a practical guide to managing anticoagulation for both elective and emergency surgical patients.

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Peri-operative antithrombotic therapy: bridging the gap

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Scenario

A 76-year-old man requires an elective anterior resection for rectal adenocarcinoma. He has a drug eluting coronary stent that was implanted six months previously following a myocardial infarction with new onset atrial fibrillation and subsequent transient ischaemic attack. He takes aspirin 75mg, clopidogrel 75mg and warfarin. How should his peri-operative antithrombotic therapy be managed?

General considerations

The peri-operative management of surgical patients who are taking vitamin K antagonists or antiplatelet medication is complicated. It requires individual assessment of the risk of thromboembolism versus the risk of bleeding, in conjunction with local guidelines and advice from a consultant

haematologist. In this article we discuss general principles for elective and emergency surgery.

Risk assessment

1. Risk of haemorrhage

It is a common assumption that warfarin must be stopped prior to any surgery. However, some procedures can be undertaken safely without interrupting anticoagulation, eg removal of skin lesions.¹ For procedures with a higher risk of haemorrhage, eg neurosurgery, it is desirable to fully reverse anticoagulation, aiming for an international normalised ratio (INR) of <1.3.

Antiplatelet therapy is continued for most arterial procedures due to the risk of thromboembolism (eg aspirin during carotid endarterectomy). A few herbal supplements

Table 1 High and moderate risk thromboembolic categories (adapted from the 2008 guidelines of the American College of Chest Physicians). Reproduced with permission from the American College of Chest Physicians).⁶

Risk factor	High risk	Moderate risk	Low risk	Predisposes to
Atrial fibrillation	Prior stroke CHADS ₂ score of 5–6 Rheumatic valve disease	CHADS ₂ score of 3–4 or past cerebrovascular event	CHADS ₂ score of ≤2 with no prior cerebrovascular event	Arterial embolism including stroke
Mechanical heart valve	Ball and cage valve Tilting disc valve Mitral valve Stroke within 6 mths	Bileaflet aortic valve Prior stroke Hypertension Heart failure Diabetes Age >75 yrs	Bileaflet aortic valve without additional risk factors	Valve thrombosis Arterial embolism
Venous thromboembolic event (VTE)	VTE <3 mths Antiphospholipid syndrome Protein C or S deficiency	Active cancer Recurrent VTE VTE 3–12 mths	Single VTE >12 mths without ongoing risk factors	VTE
Ischaemic heart disease	Drug eluting stent <12 mths Bare metal stent <6 wks Myocardial infarction <3 mths	Ischaemic heart disease without prior revascularisation		Myocardial infarction

(garlic, ginseng, ginkgo and ginger) inhibit platelet aggregation and there are case reports of severe haemorrhage in patients taking them. However, there is no firm evidence on which to base recommendations during the peri-operative period.

2. Risk of thromboembolism

It is useful to stratify patients into risk categories (Table 1). In atrial fibrillation, validated risk scores such as CHADS₂ give an indication of the risk of thromboembolism:²

- > congestive cardiac failure – 1 point
- > hypertension – 1 point
- > age >75 years – 1 point
- > diabetes mellitus – 1 point
- > previous stroke or transient ischaemic attack – 2 points

Those at low risk (eg CHADS₂ scores of 0–1) may not require bridging therapy. For those at high (>10% annual arterial or >10% monthly venous) risk, antithrombotic therapy is either continued or bridging therapy substituted.

Interrupting antithrombotic therapy

If it is necessary to interrupt antithrombotic therapy, the following can be used as a guide:

- > Aspirin irreversibly inhibits platelet function and the platelet pool is replaced every 7–10 days. Aspirin should therefore be stopped 7–10 days pre-operatively to allow this pool to replenish. It should be resumed at the normal pre-operative dose 24 hours after surgery or the next morning providing haemostasis is adequate.
- > Clopidogrel irreversibly affects platelet activation and aggregation, and although it has a plasma half-life of ap-

proximately eight hours, it must be stopped seven days prior to surgery. Like aspirin, it can be restarted 24 hours after surgery or the next morning, once haemostasis is adequate.

- > Dipyridamole reversibly affects platelet function and has a half-life of approximately ten hours. It should be stopped 48 hours prior to surgery and can be restarted when haemostasis is adequate.
- > Combinations of the above antiplatelet agents are suspended 7–10 days before surgery.
- > Warfarin has a half-life of three days and is discontinued approximately five days pre-procedure, aiming for an INR of <1.5. The INR should be measured on the day before surgery, if possible, but can be measured on the morning of surgery for patients admitted on the same day. If the INR is >1.5 the day before surgery, 1mg of oral vitamin K can reduce the INR to a safe level in the vast majority of patients although it may slightly prolong re-warfarinisation.⁵ For many patients, warfarin can be restarted at the pre-operative dose the day after surgery, with serial INR tests until the INR is within the required therapeutic range.
- > Phenindione is a synthetic anticoagulant and should be managed in a similar manner to warfarin.

Bridging therapy

Bridging therapy is the substitution of long acting anticoagulants with short acting agents such as unfractionated heparin (UFH) or low molecular weight heparin (LMWH). When using bridging therapy, patients should be monitored for a sudden drop in platelet count and paradoxical thrombosis, which is indicative of heparin induced thrombocytopenia. This necessitates switching to a direct thrombin inhibitor (eg lepirudin).

When does warfarin need to be stopped?

Warfarin is stopped five days pre-operatively to achieve an INR of <1.3 for safe surgery. Always check the INR.

Is bridging therapy necessary?

This requires a balance between the risk of thromboembolism off anticoagulation versus the risk of bleeding and type of surgery.

When should bridging therapy start?

Bridging therapy commences when INR falls below the therapeutic range (usually 24 hours after the last dose of warfarin).

Which agent should one use?

LMWH can be self-administered by patients at home and do not require intravenous cannulation or routine monitoring. Available agents are:

- > enoxaparin 1.5mg/kg subcutaneous once daily
- > dalteparin 200u/kg subcutaneous once daily

They are contraindicated in morbid obesity and in patients whose creatinine clearance is <30ml/min. UFH is used if LMWH is contraindicated, and requires monitoring and dose titration. A loading bolus followed by an infusion is prescribed. Example bridging regimens are available although local protocols are preferred for consistency and medicolegal reasons.⁴

When is bridging therapy stopped pre-operatively?

LMWH has a half-life of approximately 4 hours (depending on renal function) and the last dose should be administered 24 hours before surgery whereas UFH has a half-life of 45 minutes and is stopped approximately 4 hours before surgery. Because of this short half-life, UFH allows more precise control of anticoagulation on the day of surgery.

Are any precautions required for spinal or epidural anaesthesia?

Spinal and epidural anaesthesia carry an increased risk of developing an epidural haematoma when performed in patients who have received anticoagulant medications. Removing an epidural catheter may also increase the risk of epidural bleeding. A 24-hour time interval from the last dose of therapeutic LMWH or 4 hours from UFH is therefore recommended for patients receiving spinal or epidural anaesthesia.

If an epidural catheter is sited, then these intervals should also be observed for catheter removal. An interval of 1–2 hours after removal is recommended before restarting bridging therapy.

Resuming anticoagulation

Bridging therapy is resumed once haemostasis is secure. Instructions should be documented and communicated in the operation note, eg UFH to restart after 1–2 hours for a patient with a mechanical aortic valve (Table 1). Warfarin takes ap-

proximately five days to exert its full effect and dosing can be guided using the Fennerty nomogram. Warfarin loading should only be prescribed in patients receiving bridging anticoagulation as it initially creates a prothrombotic state. For low risk patients (eg atrial fibrillation with a CHADS₂ score of 0–1), warfarin can be restarted at the usual dose while the patient receives normal thromboprophylaxis. Antiplatelet agents are resumed at the normal dose the following day if haemostasis is adequate.

New oral agents

Fondaparinux is licensed for the treatment of venous thromboembolism and in the peri-operative setting it should be managed in the same way as LMWH.

Dabigatran (Pradaxa® [Boehringer Ingelheim], an oral direct thrombin inhibitor) and *rivaroxaban* (Xarelto® [Bayer], an oral factor Xa inhibitor) are currently under review by the National Institute for Health and Clinical Excellence for prevention of thromboembolism in atrial fibrillation. Both should be stopped 24–48 hours before an elective invasive procedure. Dabigatran is most reliably monitored using thrombin time, and consideration of dose and renal function is required before deciding on when to stop therapy pre-operatively (between 1 and 5 days). Unlike warfarin, there is no specific reversal agent.

Emergency surgery

Patients admitted for emergency surgery on antithrombotic therapy should be discussed with the on-call haematologist. There is no drug to reverse the effects of aspirin and clopidogrel. For that reason, platelets should be made available but only transfused if there is significant haemorrhage.

For urgent but not emergency surgery (eg hip fracture), an alternative is to wait 24 hours to allow circulating antiplatelet drug levels to fall. These can inactivate any platelets transfused during surgery, negating their effect.

For urgent reversal of warfarin, a dose of 25–50 units/kg of prothrombin complex containing factors II, VII, IX and X normalises the INR within 10 minutes. However, because these factors have a short half-life, 5mg of intravenous vitamin K is recommended concurrently. If less urgent, vitamin K at a dose of 1–3mg alone is sufficient.

In trauma, use of the antifibrinolytic agent tranexamic acid within three hours of injury can be considered.⁵

Management strategy for scenario

This patient is at high risk for stent thrombosis. The patient's cardiologist therefore advises continuation of dual antiplatelet therapy. The patient is also at high risk for embolic stroke and hence commences bridging therapy 24 hours after warfarin is discontinued. After liaison with a haematologist, two pools of platelets are made available for the day of operation and the anaesthetist avoids epidural anaesthesia. The following day, bridging therapy is restarted after the surgical ward round with LMWH and the patient is restarted on warfarin.

SUMMARY

In patients receiving antithrombotic therapy prior to a procedure consider:

1. Does the procedure require antithrombotic therapy to be suspended?
2. Is bridging therapy required?
3. Is neurosurgery, spinal or epidural anaesthesia planned?
4. Are platelets required for the day of operation?
5. Has a plan for restarting bridging therapy post-operatively been documented in the patient's medical notes?

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