Peri-procedural management of patients taking oral anticoagulants

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Introduction
Oral anticoagulants are used for the treatment and prevention of thromboembolism in many patients, including those with atrial fibrillation, venous thromboembolism, and mechanical heart valves. Although vitamin K antagonists (VKAs) have been the primary class of oral anticoagulants for decades, new ones—such as dabigatran, rivaroxaban, apixaban, and edoxaban—are now approved for use.

This review summarizes the pharmacology of oral anticoagulants relevant to the peri-procedural period, reported outcomes of peri-procedural management of oral anticoagulants used for therapeutic purposes, and selected guidelines. It also reviews the management of oral anticoagulation in emergency situations.

Vitamin K antagonists
VKAs act by depleting the active (reduced) form of vitamin K, which is needed for normal coagulation. The anticoagulant effect of VKAs is the result of a decrease in the carboxylated forms of factors II, VII, IX, and X.4 Management of patients taking these drugs is complicated by variable dietary vitamin K content and drug-drug interactions.45 Monitoring of the international normalized ratio (INR) allows VKAs to be titrated to the target level of effect.46 47 All of the VKAs reviewed have been used in patients with atrial fibrillation, venous thromboembolism, and mechanical heart valves.

Warfarin is a highly bioavailable VKA that is readily absorbed from the gastrointestinal tract. Warfarin has a half life of 36–42 hours, so it usually takes several days for its anticoagulant effect to develop when it is started and to abate when it is stopped.

Phenprocoumon is another VKA that is highly bioavailable. Phenprocoumon differs from other VKAs in that its elimination half life is long—estimated to be 100–150 hours.”4 21 22 As a result, this drug regimen needs to be interrupted for longer when patients undergo invasive procedures.

The bioavailability and metabolism of acenocoumarol is similar to that of other VKAs.44 However, acenocoumarol has the shortest estimated half life of the VKAs considered in this review—eight to 12 hours.21 23

Target specific oral anticoagulants
The limitations of VKAs have led to the development of alternative oral anticoagulants. Currently, four such drugs—dabigatran, rivaroxaban, apixaban, and edoxaban—which as a group are referred to as target specific oral anticoagulants, have been approved by the Food and Drug Administration. Importantly these drugs are given at fixed doses and coagulation does not routinely need to be monitored. They are categorized on the basis of where in the coagulation cascade they exert their inhibitory effect.

Oral direct thrombin inhibitors
Dabigatran
Dabigatran is a direct thrombin inhibitor administered as the prodrug dabigatran etexilate. Once absorbed it is converted to its active form and promotes anticoagulation by directly binding to the active site of thrombin, competitively inhibiting the conversion of fibrinogen to fibrin.4 Peak plasma concentrations are reached in about 1.5 hours and the half life ranges from about eight to 14 hours, with about 80% of the drug being eliminated through the kidneys.4 18 36 Of the target specific oral anticoagulants, dabigatran has the highest degree of renal elimination. Dabigatran has been approved by the FDA for use in patients with atrial fibrillation and venous thromboembolism on the basis of clinical trials.49 51 Dabigatran is the only target specific oral anticoagulant to be studied for use in patients with mechanical heart valves and was shown to increase thromboembolic and bleeding complications compared with warfarin.11

Oral factor Xa inhibitors
Rivaroxaban
Rivaroxaban and other oral factor Xa inhibitors target the prothrombin binding site on factor Xa, which converts prothrombin to thrombin.11 Rivaroxaban reaches peak plasma concentrations in two to four hours; its half life is seven to 11 hours, and about 33% of the active drug is renally excreted.26 27 The bioavailability of the 20 mg dose in the fasting state is about 66% and absorption is enhanced if it is taken with food.26 Clinical trials have
shown the safety and efficacy of rivaroxaban to be non-inferior to warfarin in patients with atrial fibrillation and venous thromboembolism.15-17

**Apixaban**

Apixaban is a direct inhibitor of factor Xa with a short time to peak plasma concentration (~3 h) and a half life of eight to 15 hours.17 18 19 Only about 25% of the drug is eliminated renally, with most being eliminated through hepatic metabolism and the feces. Apixaban has been approved for use in atrial fibrillation and acute and extended treatment of VTE.18-20

**Edoxaban**

This direct factor Xa inhibitor has been compared with warfarin for the management of atrial fibrillation and VTE and is now approved for these indications.12 18 19 Edoxaban reaches peak plasma concentration rapidly after administration (1-2 h) and its half life is similar to that of other direct Xa inhibitors (9-10 h); about 35% of the drug is renally excreted.20 21 22

**Selected guidelines for management of VKA during elective procedures**

The most detailed guideline for the peri-procedural management of patients taking a VKA who have atrial fibrillation, VTE, or a mechanical heart valve comes from the American College of Chest Physicians (ACCP) and is based on expert review of the literature.21

ACCP recommendations are based on assessments of the patient’s thromboembolic and bleeding risks and are designed to guide individualized decisions. The ACCP provides a scheme for thrombosis risk in which low, moderate, and high risk correspond to an estimated annual risk of thrombosis without anticoagulation of less than 5%, 5-10%, and more than 10%, respectively (fig 5 on the bmj.com). For bleeding risk assessment, the ACCP identifies the following as high risk procedures:

- Urologic surgery (transurethral resection of the prostate, bladder resection, tumor ablation, nephrectomy, kidney biopsy)
- Cardiac device procedures (implantation of a pacemaker or internal cardiac defibrillator)
- Colon polypectomy (particularly >1-2 cm in length)
- Surgery on highly vascular organs
- Bowel resection in which bleeding may occur at the anastomotic site
- Major surgery with extensive tissue injury
- Cardio, intracranial, or spinal surgery.

The guideline suggests stopping warfarin five days before the procedure and restarting it 12-24 hours afterwards, assuming that adequate hemostasis is maintained. It does not specify the timing of such pre-procedure discontinuation for phenprocoumon or acenocoumarol. Figure 6 summarizes a suggested approach to elective preprocedure management of VKAs.

Figure 7 summarizes suggested post-procedure strategies for patients taking VKAs. The ACCP endorses bridging therapy for patients with a high risk of thrombosis while recognizing the potential for post-procedure bleeding when anticoagulation is used too aggressively in low or moderate risk patients.

To allow assessment and communication of competing risks, the ACCP recommends evaluating patients seven days before an intended procedure.

The American College of Cardiology and American Heart Association (ACC/AHA) guideline statements for peri-procedural management of patients taking VKA are in general agreement with those from the ACCP.16 17 The ACCP guideline for patients with mechanical heart valves suggests that bridging therapy is not needed in those with one bileaflet aortic mechanical valve only who have none of the following risk factors: atrial fibrillation, previous thromboembolism, “hypercoagulable condition,” older generation-type prosthesis, or left ventricular ejection fraction 30% or less. Bridging therapy is recommended in patients with a mitral, tricuspid, or aortic mechanical heart valve who have any of the risk factors listed above.
The European Society of Cardiology (ESC) and the British Committee for Standards in Haematology (BCSH) have both published recommendations on peri-procedure management of VKAs. For patients who have had a VTE more than three months earlier the BCSH recommends prophylactic doses of LMWH rather than therapeutic dose bridging therapy. It also states that bridging therapy is not needed for patients with atrial fibrillation and no history of stroke or a transient ischemic attack or for patients with a bileaflet aortic mechanical valve and “no other risk factors.” It does recommend bridging therapy for patients with atrial fibrillation with any of the following risk factors: previous stroke or transient ischemic attack, a mitral mechanical valve, or VTE in the preceding three months.

Recommendations and guidelines for elective interruption of target specific oral anticoagulants

Figure 9 summarizes manufacturers’ recommendations and the schedule used in the RE-LY trial for the timing of pre-procedure discontinuation of target specific oral anticoagulants. The recommendations state that pre-procedure bridging therapy is generally not needed. The manufacturers of rivaroxaban, apixaban, and edoxaban suggest restarting the drug when adequate hemostasis has been established. There is no explicit instruction for dabigatran but the principle should be the same. Because the time to peak concentration with all target specific oral anticoagulants is rapid, adequate hemostasis is vital to prevent bleeding complications.

The European Heart Rhythm Association (EHRA) has published guidelines for the management of target specific oral anticoagulants during elective procedures. EHRA recommendations incorporate procedure related bleeding risk and patient’s renal function. The association recommends discontinuing rivaroxaban and apixaban at least 24 hours and 48 hours before low and high bleeding risk procedures, respectively. The same recommendations apply to dabigatran if creatinine clearance is greater than 80 mL/min. For patients taking dabigatran who have creatinine clearance 50-80 mL/min, the association recommends interrupting anticoagulation at least 36 hours and 72 hours before low and high bleeding risk procedures, respectively. Finally, for creatinine clearance 30-50 mL/min, discontinuation is recommended at least 48 hours and 96 hours before low and high risk procedures. For patients taking rivaroxaban or apixaban with creatinine clearance 15-30 mL/min, the association recommends that the drug be stopped at least 36 hours before low bleeding risk procedures.

Urgent and emergent peri-procedural management of oral anticoagulants

When a patient taking a VKA or a target specific oral anticoagulant needs an urgent or emergent procedure or has developed bleeding after resumption of anticoagulation, the approach differs from that in the elective setting.

Discontinuation of the anticoagulant and supportive care for those who are actively bleeding is the first management step. With VKAs, INR testing will indicate the degree of anticoagulation and provide information on how to proceed. It is also important to know when the last dose of a target specific oral anticoagulant was taken because this could identify patients for whom the current level of anticoagulation is minimal. The degree of urgency for a necessary procedure should also be assessed. If a procedure can be safely delayed for 24-48 hours to allow normalization of coagulation, no further intervention for reversal is needed in patients taking a target specific oral anticoagulant. For patients taking these drugs, it is also important to know about current kidney function because drug clearance may be partially or substantially renal, which will have an effect on the drug’s half life. For instance, if a patient has acute kidney injury, drug clearance may be prolonged and the anticoagulant effect may persist longer than otherwise anticipated.

Prothrombin complex concentrates

For patients taking a VKA who need emergency surgery or who have serious bleeding complications, phytomenadione is administered to provide reduced form vitamin K, which is necessary for factor activation, and coagulation factors are supplemented with prothrombin complex concentrates.

These concentrates were developed to treat patients with hemophilia B and contain either three (factors II, IX, and X) or four (factors II, VII, IX, and X) inactive-form coagulation factors. They provide higher than normal concentrations of these factors and can be associated with a risk of thromboembolism. To mitigate the risk of thrombosis, most concentrates also contain protein C, protein S, antithrombin, or heparin. Concentrates are stored in a lyophilized form and can be prepared and administered more rapidly than fresh frozen plasma, which must be thawed before administration. Compared with fresh frozen plasma, concentrates do not require...
results depending on animal bleeding model, dose of factor concentrate, and laboratory assays used. In addition, the applicability of animal models and in vitro data to clinical situations involving target specific oral anticoagulants is unclear. However, on the basis of preclinical data, some experts have suggested that prothrombin complex concentrates may be considered for severe or life threatening bleeding in patients taking a target specific oral anticoagulant. These would be off-label uses for these factor concentrates but not unreasonable in dire circumstances. For less than severe bleeding and for patients who are not bleeding but who need surgery, the thrombotic risk of administering these products must be considered. For patients taking dabigatran, hemodialysis is another possibility—four hours of hemodialysis removes about 50% of the dabigatran present.

Antidotes to target specific oral anticoagulants for use in emergency situations are in development. ABO matching, carry a lower risk of infection risk and transfusion related acute lung injury, and are administered in smaller volumes.

Currently, the only prothrombin complex concentrate approved by the FDA for patients on warfarin who have serious bleeding or are in need of urgent surgery is Kcentra—a four factor concentrate. The ACCP 2012 guideline for management of serious bleeding in patients taking a VKA recommends co-administration of a four factor concentrate and slow infusion of 5-10 mg of intravenous vitamin K.

Reversal of target specific oral anticoagulants
Recombinant factor VIIa and activated prothrombin complex concentrates were developed for use in hemophilia related bleeding in patients with factor inhibitors. Activated prothrombin complex concentrate contains factors II, VII, IX, and X in activated forms, produced during the manufacturing process. Studies of these agents have shown mixed

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CASE REVIEW
Knee injury in a 12 year old girl
1. The most likely diagnosis is acute anterior cruciate ligament (ACL) injury. Differential diagnoses include meniscal tear, osteochondral injury, tibial spine injury, patella dislocation, and collateral ligament injury.
2. Popping and immediate swelling during a pivoting activity are highly suggestive of an acute ACL tear. Lachman’s test, the anterior drawer test, and, depending on the child’s compliance and age, the pivot shift test are all useful.
3. Plain anteroposterior and lateral radiographs are useful to exclude concurrent fractures. Magnetic resonance imaging is the gold standard radiological investigation.
4. The initial approach is non-operative, comprising analgesia, knee immobilisation, and urgent referral to a specialist paediatric knee clinic. Operative management comprises surgical reconstruction of the ACL. Early surgery carries a risk of physeal injury but delayed surgery increases the risk of secondary injuries.

SPOT DIAGNOSIS
Anatomy of a swallow
The imaging modality used is a barium swallow investigation and it shows a pharyngeal pouch. An incidental note was made of fusion of the C5-C7 vertebrae.

STATISTICAL QUESTION
Bias in experimental study designs: randomised controlled trials with parallel groups
Answers c, d, e, and f are true, whereas a and b are false.