Anticoagulation treatment

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Abstract

Anticoagulant therapy using heparins and vitamin K antagonists has been used effectively for prevention and treatment of thromboembolic events for many years. However, therapy is associated with a significant risk of haemorrhagic complications, warranting careful consideration of the need for anticoagulation. Recognized drawbacks of current anticoagulants are their unpredictable pharmacokinetics and the need for laboratory monitoring, which have led in recent years to the development of direct oral anticoagulant agents.

Keywords Anticoagulant monitoring; heparin; reversal of anticoagulation; warfarin

Key points

- Anticoagulants are used for prevention and treatment of arterial and venous thrombosis
- Current anticoagulants such as unfractionated heparin and warfarin require monitoring owing to their unpredictable pharmacokinetics
- Anticoagulation is associated with a significant risk of bleeding
- Direct oral anticoagulants have more predictable pharmacokinetics and do not require monitoring

Introduction

Anticoagulation is used for the prevention and treatment of arterial and venous thromboembolism.[1] The choice of anticoagulant is influenced by the indication for anticoagulation, mode of administration and duration for which it is required. Anticoagulants currently in use comprise:

- heparinoids – unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and fondaparinux
- vitamin K antagonists (VKAs) – warfarin, phenindione and acenocoumarol
- new oral agents – dabigatran, rivaroxaban, apixaban and edoxaban.

Indications and contraindications to anticoagulants

There are multiple indications for anticoagulation, including prevention and treatment of venous thromboembolism[1] and stroke prevention in atrial fibrillation. Each agent has a recommended dose according to the indication for which it is required. Contraindications to full anticoagulant therapy include severe uncontrolled hypertension, a recent cerebrovascular accident, a history of inherited or acquired bleeding disorder, thrombocytopenia ($<50 \times 10^9$/litre) or a history of active bleeding. Concomitant use of antiplatelet agents and non-steroidal anti-inflammatory agents is not advised because of the increased bleeding risk. UFH is currently the only anticoagulant licensed for use in pregnancy; LMWHs are widely used and accepted to be safe and efficacious although none is licensed for use in pregnancy. Heparin and warfarin are safe for use in breastfeeding mothers.

Reversal of anticoagulation

Anticoagulants are one of the most commonly reported drug groups associated with medication errors. Overtreatment with anticoagulants leads to increased haemorrhagic risk, which in some cases can be fatal. Specific antidotes or agents to reverse anticoagulant effect are available for heparin and VKA but dabigatran is currently the only direct anticoagulant agent with a licensed antidote. Antidotes for the anti-Xa agents are currently undergoing Phase III trials.

Current anticoagulants

Unfractionated heparin

Heparin's anticoagulant effect was first discovered in 1916. UFH, the first anticoagulant to be developed in the 1930s, consists of a series of glycosaminoglycan chains and is processed from animal intestinal mucosa, usually of porcine origin, in Europe.

Mode of action, indications, dosing, drug interactions and monitoring: UFH is administered by intravenous infusion or subcutaneous injection. It causes an anticoagulant effect by potentiating the action of the physiological anticoagulant antithrombin ten thousand-fold. UFH has unpredictable pharmacokinetics and a short elimination half-life, and therefore requires monitoring. There are no specific drug interactions. Indications for its use include prevention of thrombosis of peripheral catheters, haemodialysis, prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), treatment of cardiac ischaemia and critical ischaemia of the lower limb, coronary or peripheral artery angioplasty, and bypass surgery. Adverse effects include allergy, heparin-induced thrombocytopenia, and osteopenia with long-term use.

Laboratory monitoring of heparin is performed using the activated partial thromboplastin time (APTT). The APTT ratio (APTTR) provides a measure of anticoagulant effect of UFH; the usual target ratio is two to three times higher than a normal APTT. Dosing of UFH requires a bolus dose for initiation of an UFH infusion, followed by a continuous infusion. APTTR monitoring allows subsequent adjustment of dosage. The dosage of UFH for administration by subcutaneous injection is fixed.

Low-molecular-weight heparins

LMWHs, first developed in the 1980s, are produced by depolymerization of UFH chains to produce a shorter glycosaminoglycan chain. They have more predictable pharmacokinetics, a

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longer half-life and an easier mode of administration (subcutaneous injection) than UFH.

Mode of action, indications, dosing, drug interactions and monitoring: like UFH, LMWH binds to antithrombin, but it has a greater inhibitory effect on factor Xa. Because of their longer half-lives, LMWHs are suitable for outpatient use and have a lower risk of heparin-induced thrombocytopenia and osteoporosis than UFH. Dosing depends on the LMWH subtype and indication for use, which includes prevention and treatment of DVT and PE, and treatment of severe unstable angina. There are no specific drug interactions. Monitoring is required only in patients with renal failure and those at extremes of body weight, and is performed using anti-Xa concentration. Measurement of peak anti-Xa concentration is suggested (samples taken 4 hours after administration); target reference ranges depend on heparin type and indication.

Fondaparinux

Fondaparinux is a synthetic form of the heparin pentasaccharide molecule.

Mode of action, indications, dosing, drug interactions and monitoring: fondaparinux binds and activates antithrombin, resulting in only an anti-Xa effect, and has a half-life of 17–21 hours. It has a marketing authorization in Europe for indications similar to LMWH, but has not been widely used for thromboprophylaxis because of its cost. However, in the management of acute coronary syndrome, it has proved superior to LMWH in many patient groups. The dosage of fondaparinux depends on the indication for use, and as its pharmacokinetics are predictable there is no requirement for monitoring.

Vitamin K antagonists

VKAs were the first oral anticoagulants in use and currently include acenocoumarol, phenindione and warfarin. Only warfarin is discussed in this article.

Mode of action, indications, dosing, drug interactions and monitoring: warfarin prevents γ-carboxylation of vitamin K-dependent clotting factors (II, VII, IX, X), producing an anticoagulant effect by reducing their concentrations. Factor VII has the shortest half-life, whereas factors II, VII, IX and X have half-lives of 8–72 hours, so warfarin takes several days to have full anticoagulant effect.

The pharmacokinetics of warfarin are unpredictable, mainly because of its metabolism by enzymes of varied activity in the population. Numerous drug and food interactions contribute to its variable anticoagulant effect. Warfarin requires laboratory monitoring, which is based on the prothrombin time (PT). Variability in reagents used to determine PT has led to international standardization of the assay, now known as the international normalized ratio (INR), a PT-based measure of anticoagulant effect. Warfarin is teratogenic in the first trimester of pregnancy and should be stopped as soon as possible on confirmation of pregnancy. LMWH is a suitable alternative anticoagulant in pregnancy (although none is licensed for use in this setting).

The recommended INR varies according to the indication for anticoagulation with warfarin.[2] It is difficult to target a specific INR, and the usual aim is to maintain INR within 0.5 of a target INR. Recommended target INRs in relation to different indications for warfarin are shown in Table 1.

Dosing regimens for initiation of warfarin therapy vary according to age and indication for anticoagulation. Patients with

Indications for VKAs and recommended target INR

Indication	Target INR	Duration
PE	2.5	At least 3 months — consider extending beyond 3 months if risk of recurrent thrombosis high[a]
Proximal DVT	2.5	At least 3 months — consider extending beyond 3 months if risk of recurrent thrombosis high[a]
Calf vein thrombosis	2.5	3 months
Recurrent venous thrombosis on warfarin therapy (with therapeutic INR)	3.5	Consider indefinite anticoagulation depending on risk of recurrent thrombosis[a]
Recurrent venous thrombosis in patient taking warfarin therapy with subtherapeutic INR or off anticoagulation	2.5	Consider indefinite anticoagulation depending on risk of recurrent thrombosis[a]
Non-rheumatic atrial fibrillation ($CHADS_2$ score >1)	2.5	Indefinite
Cardioversion	2.5	Indefinite
Mural thrombus	2.5	Indefinite
Cardiomyopathy	2.5	Indefinite
Mechanical prosthetic aortic heart valve	2.5	Indefinite
Mechanical prosthetic mitral heart valve	3.5	Indefinite
Bioprosthetic valve	2.5	Indefinite

'$CHADS_2$' is a mnemonic for a clinical risk prediction tool to estimate risk of stroke associated with atrial fibrillation: C — congestive heart failure, H — hypertension, A — age, D — diabetes mellitus, S_2 — previous stroke, transient ischaemic attack or thromboembolism.
DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary embolism; VKA, vitamin K antagonist.
[a] Patients with unprovoked DVT or PE should be considered for lifelong anticoagulation, taking into account risk of recurrence balanced against risk of bleeding on anticoagulant therapy. Patients with provoked DVT or PE have lower risk of recurrence and do not warrant lifelong anticoagulation. Provoking factors include recent surgery, immobilization, long-haul flight and oestrogen therapy.

Table 1

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