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The new oral anticoagulants

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Anticoagulants have been used for over 70 years for prevention and treatment of potentially fatal thromboembolic events. Heparins and vitamin K antagonists have been the mainstay of treatment and, although effective if managed properly, also have significant drawbacks. Unfractionated heparins (UFH) were developed in the 1930s and potentiate the action of the physiological anticoagulant antithrombin. UFH requires injection and because of a short t $^1/_2$ and unpredictable plasma levels, requires monitoring making it inconvenient for use out of the hospital setting. Further risks include allergy, heparin-induced thrombocytopenia (HIT), and osteopaenia with long-term use.

The low molecular weight heparins (LMWHs) were developed in the 1980s and, like UFH, bind to antithrombin but, unlike UFH, have a greater inhibitory effect on Factor Xa than on thrombin. LMWHs have predictable pharmacokinetics, and only require monitoring in renal failure or for high body mass index. They have a longer t $^1/_2$, are suitable for outpatient use and have lower risk of HIT and osteoporosis than UFH.

Fondaparinux is a more recently developed synthetic form of the heparin pentasaccharide molecule responsible for binding and activating antithrombin, resulting in only an anti-Xa effect. It has a license in Europe for similar indications as LMWH, but has not been widely used due to its cost, except in the management of acute coronary syndrome as OASIS-5 showed it was superior to LMWH.[1]

Vitamin K antagonists (VKAs), such as warfarin and acenocoumarol, were the first oral anticoagulants. They ensure an anticoagulant effect by preventing gamma carboxylation of the vitamin K-dependent factors II, VII, IX and X, Protein C and S. Regular monitoring with the international normalised ratio (INR) is required because their metabolism is by enzymes of varied activity in the population, they have many drug interactions and dietary intake of Vitamin K alters the degree of anticoagulation. Bleeding is the main side effect with a 1% risk per annum of major haemorrhage for those on long-term anticoagulation. Reversal of anticoagulant effect requires cessation of the drug but this alone takes 72 hours, however the use of oral or intravenous vitamin K reverses the effect within six hours. Urgent reversal is preferably with prothrombin complex concentrate to replace the missing active coagulation factors. The use of fresh frozen plasma is not recommended due to the high volume required. Approximately one million people in the UK are prescribed VKA and overdose is a major cause of iatrogenic admission. An industry has developed around the monitoring of vitamin K antagonists – most patients attend anticoagulant clinics, although a growing number use home monitoring which has been shown to be as reliable.[2]

Although there was a clear need for development of new oral anticoagulants with predictable pharmacokinetics, little progress had been made until recent years. Ximelagatran, an oral direct thrombin inhibitor, was widely trialled in around 2005. It obtained a license for thromboprophylaxis, after elective orthopaedic surgery in mainland Europe, but was withdrawn because of associated liver dysfunction.

The new oral anticoagulants in 2010

There are currently four new oral anticoagulants in advanced stages of development with more to come. Two are already licensed in Europe as thromboprophylactic agents for elective hip and knee replacement. These agents have been developed to antagonise a single target in the clotting cascade, have predictable pharmacokinetics, and few food, but some drug, interactions. There are currently no safety sweets for these agents in pregnancy or breast feeding.

Their predictable pharmacokinetics will reduce the need for patients to require contact with health professionals and may lead to both reductions in hospital stay and administration costs, although compliance may become an issue. Further new similar compounds and novel vitamin K antagonists are currently at various stages of development.

Dabigatran etexilate

Dabigatran etexilate is a prodrug, rapidly absorbed and converted (after hepatic processing) to the active form, dabigatran, which acts as a direct thrombin inhibitor, binding both free and clot-bound thrombin.

The t $^1/_2$ is 14–17 hours and up to 80% of the drug is excreted unchanged renally. Dose reductions are advised in renal impairment, notably patients with signifcant renal impairment have been excluded from most clinical trials involving dabigatran. The main reported side effects are gastrointestinal disturbances possibly due to the use of tartaric acid as a drug carrier. Important drug interactions include amiodarone and verapamil which may increase the plasma concentration of dabigatran. As with the other anticoagulants, use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the bleeding risk.

In the phase III non-inferiority trials, RE-NOVATE and RE-MODEL, dabigatran was compared to enoxaparin (LMWH) in patients undergoing elective hip and knee surgery.[4,5] Non-inferiority and similar bleeding rates were demonstrated in both

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trials. The RE-MOBILIZE study, however, failed to show equivalence of dabigatran compared to the US-licensed thromboprophylactic dose of enoxaparin (30 mg) bd and so this is not used in North America.[6]

Over 18,000 patients with atrial fibrillation (AF) were randomised to receive either dabigatran or warfarin in the RELY trial.[7,8] When compared to warfarin, dabigatran was shown to have similar rates of cerebrovascular accident and embolic complications at daily doses of 110 mg and 150 mg, less bleeding complications with the 110-mg dose and similar bleeding rates at the 150-mg dose. Most recently, when dabigatran was compared to warfarin for treament of acute venous thromboembolism (VTE), results demonstrated similar efficacy and safety profiles of both drugs – but it is important to note that patients randomised to dabigatran were stabilised at an INR of 2 or above before commencing dabigatran.[9]

Rivaroxaban

Rivaroxaban is an oral agent which directly inhibits factor Xa. It has predictable, dose-dependent pharmacokinetics with a t $^1/_2$ of four to nine hours. It is mainly excreted renally so should be used with caution in patients with impaired renal function and is contraindicated in patients with a creatinine clearance of less than 30 mls per minute. The main reported side effects are gastrointestinal disturbances. Important interactions occur with use of potent CYP3A4 (eg ketoconazole) and P-glycoprotein inhibitors (eg protease inhibitors – ritonavir, atazanavir), potentially enhancing plasma concentration of rivaroxaban.

Four large phase III trials have compared rivaroxaban to enoxaparin for prevention of VTE in patients undergoing hip or knee surgery – the RECORD 1–4 trials.[10–13] Rivaroxiban proved superior to enoxaparin in all four studies, no difference in bleeding rates was seen between the two groups, and RECORD-1 also demonstrated its non inferiority for use in extended thromboprophylaxis.[10] More phase III studies of rivaroxaban are currently being perfomed in prevention of hospital-acquired VTE (MAGELLAN), management of acute coronary syndrome (ATLAS), stroke prevention in AF (ROCKET AF) and in management of acute VTE (EINSTEIN). Results of the EINSTEIN-DVT study were recently presented and are awaiting publication.

Apixaban

Apixaban is an oral agent directly targeting Factor Xa. It is partially metabolised by CYP3A4 and CYP-independent mechanisms in the liver. The t $^1/_2$ is approximately 12 hours and it is partially renally excreted. Safety data are unclear on its use in renal failure. Side effects appear to include gastrointestinal disturbance and drug interactions are likely to occur with CYP3A4 inhibitors.

Apixaban is now in advanced stages of clinical development. The ADVANCE-1 trial (phase III study) comparing apixaban to enoxaparin in surgery, failed to demonstrate non-inferiority of apixaban to enoxaparin.[14] However, the ADVANCE-2 trial which randomised patients to apixaban versus enoxaparin following knee surgery showed apixaban to be more effective with similar bleeding rates.[15] Trials of apixaban for primary thromboprophylaxis in AF, and use in treatment of acute venous thromboembolism, are in progress.

Edoxaban

Edoxaban is an oral direct factor Xa inhibitor and is in earlier stages of development. It is renally excreted with a t $^1/_2$ between five and 10 hours. Reported side effects include gastrointestinal disturbance. There is currently no available advice regarding drug interactions.

Phase II trials have now been performed assessing edoxaban compared to dalteparin in patients undergoing elective hip replacement. Edoxaban appeared to be a safe and effective agent.[16] Similar results were found when comparing edoxaban to fondaparinux in patients undergoing elective knee replacement.[17] The use of edoxaban compared to warfarin for stroke prevention AF has been assessed in a recent phase II trial and again, found it to be safe and efficacious when used at a once daily dose. Increased rates of bleeding were reported at higher doses of edoxaban when compared to warfarin.

Phase III trials are underway further assessing the use of edoxaban in patients with AF (ENGAGE AF) and recurrent VTE (HOKUSAI VTE).

Conclusion

There has been major investment from pharmaceutical companies in the development of an exciting batch of new oral anticoagulants. Two have already entered short-term use. However, unanswered questions remain regarding long-term safety and post-marketing surveillance will be required for many years. Appropriate dosing and efficacy of these new agents for smaller groups of patients with conditions such as prosthetic valves or recurrent VTE on anticoagulation, is not known as there have been no trials in these areas. Furthermore, there are currently no agents available to reverse the anticoagulant effect of these drugs due to haemorrhagic complications, but fortunately these drugs have a relatively short half life and appear to have a relatively low bleeding risk.

These promising agents are likely to significantly change the current practice of anticoagulation in the very near future and, in the long term, will move the management of thrombotic disease into the community.

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