Why warfarin was an important step forward in anticoagulation therapy

Jenny Bryan looks at how, despite promising data for the new generation of anticoagulants, it will take a lot to knock warfarin off its perch

It has taken over half a century for landmark drug warfarin to face serious competition at the forefront of anticoagulation therapy and, even now, with a new generation of drugs snapping at its heels, rumours of its demise are, as Mark Twain would say, “an exaggeration”.

Nothing will happen very quickly as the new drugs will be expensive, and physicians won’t want to switch patients who are stable on warfarin or to dismantle their anticoagulation clinics prematurely,” predicts John Camm, British Heart Foundation professor of clinical cardiology at St George’s, University of London.

So, how has a drug that everyone agrees is difficult to use lasted so long?

From rat poison to clot preventer
Warfarin was one of over 100 coumarin derivatives investigated by researchers at the Wisconsin Alumni Research Foundation (WARF), which gave the product the first half of its name, warfarin.

In 1951, a suicide attempt by a US army recruit using warfarin drew attention to its effects in humans, and subsequent studies led Endo Laboratories to produce it for clinical use. In 1955, warfarin was given to President Eisenhower after a heart attack, and the product gradually moved into general usage.

“Before the introduction of warfarin, people were aware that thromboembolic complications were a problem, but there was only aspirin or intravenous heparin to treat them, and it wasn’t practical to give daily heparin injections on a long-term basis. So the arrival of warfarin was a very important step forward,” Professor Camm points out.

A role in vitamin K recycling
Warfarin inhibits the synthesis of the vitamin K–dependent clotting proteins, factors II, VII, IX, and X, and anticoagulation proteins C and S, all of which are required in the coagulation cascade for the formation of thrombin and, ultimately, fibrin, the fibrous protein that combines with platelets to form blood clots and plug wound sites.

Specifically, warfarin blocks the vitamin K recycling mechanism that converts oxidised vitamin K back into the natural, reduced form needed to catalyse the carboxylation of vitamin K-dependent clotting proteins. Since some of these clotting factors have long half-lives, it can take several days for them to be cleared from the blood before the full effects of warfarin are seen.

Huge potential but big drawbacks
Today, warfarin has a wide range of indications related to treatment and prevention of venous thrombosis and pulmonary embolism, including post-operative prophylaxis in patients undergoing joint surgery or insertion of artificial heart valves, and following larger myocardial infarctions, especially of the anterior wall or with left ventricular aneurysm.

Potentially, the greatest use for warfarin is stroke prevention in people with atrial fibrillation

Potentially, the greatest use for warfarin is stroke prevention in people with atrial fibrillation (AF). But, as Professor Camm explains, patient selection and adherence problems related to the need for careful dose titration and regular monitoring mean that only a small proportion of AF patients who could benefit from warfarin actually do so:

“Of the 1 per cent of the population who have AF and significant risk of blood clotting, about 50 per cent are initially given warfarin but only about 50 per cent continue to take it and only 50 per cent of these have coagulation levels in the desired range. It takes a lot of effort, a lot of monitoring and a disciplined patient group to get warfarin dosing right. The UK is better than some countries, such as those in southern and eastern Europe, but the best results are achieved in Scandinavia and northern Europe.”

Haemorrhage is an ever-present risk of warfarin treatment, especially in the over-65s and those with a history of gastrointestinal bleeding, with uncontrolled hypertension, cerebrovascular disease or at risk of falls. Of the 297 warfarin fatalities reported to the Medicines and Healthcare products Regulatory Agency between 1963 and 2008, 208 were due to haemorrhage.

Another drawback of warfarin is that it interacts with drugs in almost every other class and with some foods. A racemic mixture of R- and S-entantiomers, warfarin is metabolised by a variety of cytochrome p450 enzymes. For example, azole antifungals, omeprazole, tamoxifen, paracetamol, fibrates and some statins are among the commonly used concomitants that prolong the anticoagulant effects of warfarin, while barbiturates, rifampicin, azathioprine, carbamazepine and oral contraceptives are among those that antagonise warfarin’s effects. A number of drugs should be avoided in patients using warfarin, including other anticoagulant drugs, such as aspirin, heparin and clopidogrel, as well as selective serotonin reuptake inhibitor and selective noradrenaline reuptake inhibitor antidepressants.

Acute ingestion of a large amount of alcohol can potentiate the effects of warfarin, while chronic heavy intake may induce its metabolism and hence reduce its anticoagulant effects. The anticoagulant effects may also be reduced by foods containing vitamin K, such as spinach, broccoli, Brussels sprouts and liver.

Thrombin inhibitors first to compete
With so many disadvantages of warfarin therapy, it comes as little surprise that the development of an effective, well tolerated oral alternative has been a major goal for pharmaceutical companies for many years.

Ximelagatran, the first orally active thrombin inhibitor, was briefly marketed by AstraZeneca in some countries for the prevention of thromboembolic events after hip or knee surgery, but its development was halted in 2006 owing to liver toxicity.

A second thrombin inhibitor, dabigatran, was launched by Boehringer Ingelheim in 2008 for thromboembolic prophylaxis after hip or knee surgery, and there have been no signs of liver problems. Recently published
results from two large studies have supported the advantages of dabigatran over warfarin. In the RE-LY trial of over 18,000 AF patients, those treated with dabigatran 150mg twice daily had a 4 per cent lower risk of stroke and systemic embolism than patients well controlled on warfarin (P<0.001), with a comparable risk of haemorrhage. Those treated with the lower dose dabigatran 110mg twice daily had a similar risk of stroke and systemic embolism to warfarin treated patients but with a 20 per cent reduction in major bleeding rate (P=0.003).4

**Factor Xa inhibitors wait in the wings**

Two other rivals — both of them factor Xa inhibitors — are also going head-to-head with warfarin. Rivaroxaban, like dabigatran, is already licensed for thromboembolic prophylaxis after hip or knee surgery, while a licence application for apixaban is expected to be submitted to European authorities for a similar indication in the first half of this year. At earlier stages of development are several more factor Xa inhibitors, such as edoxaban and betrixaban.

“Factor Xa inhibitors work higher in the coagulation cascade than thrombin inhibitors so have broader effects. Rivaroxaban and apixaban can be given once daily compared with twice daily for dabigatran, and they may have other advantages, such as being able to be used for patients with advanced renal failure,” Professor Camm explains.

**The end in sight?**

Despite the promising data for the new generation of anticoagulants, it will take a lot to knock warfarin off its perch. Given the cost of the new drugs and the number of patients needing long-term anticoagulation, Professor Camm predicts that the National Institute for health and Clinical Excellence will try to identify which high-risk patients are most in need of the newer drugs and which will do just as well on warfarin.

“There will still be groups, such as those with prosthetic heart valves, who will need warfarin, and most doctors won’t want to move away from warfarin completely, especially where they have good anticoagulation clinics which they have taken time and trouble to set up,” he says. “On the other hand, INR management takes a lot of hard work, and attracts a lot of phone calls, so some people won’t be sorry to see it go. It’ll be interesting to see what happens, but I can’t see the new drugs stealing the show just yet.”

**References**


