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Editors' view

Warfarin: almost 60 years old and still causing problems

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If you have ever doubted that pharmacologically potent compounds can be derived from plants, consider the history of warfarin. In the 1920s cattle in the Northern USA and Canada were afflicted by an outbreak of an unusual disease, characterised by fatal bleeding, either spontaneously or from minor injuries. Mouldy silage made from sweet clover (*Melilotus alba* and *M. officinalis*) was implicated, and L M Roderick in North Dakota showed that it contained a haemorrhagic factor that reduced the activity of prothrombin. However, it was not until 1940 that Karl Link and his student Harold Campbell in Wisconsin discovered that the anticoagulant in sweet clover was 3,3′-methylenebis(4-hydroxy coumarin) [1]. Further work by Link led in 1948 to the synthesis of warfarin, which was initially approved as a rodenticide in the USA in 1952, and then for human use in 1954. The name warfarin is derived from *WARF* (Wisconsin Alumni Research Foundation) and *–arin* from coumarin.

Warfarin is now the most widely used anticoagulant in the world. Given the recent demise of ximelagatran, the first oral thrombin inhibitor, it is likely to maintain its place for many years to come. In the UK it has been estimated that at least 1% of the whole population and 8% of those aged over 80 years are taking warfarin [2, 3]. The increase in its use over the last decade can undoubtedly be traced to overwhelming evidence of its effectiveness in preventing embolic strokes in patients with atrial fibrillation [4].

The main adverse effect associated with warfarin is bleeding. Major and fatal bleeding events occur respectively at rates of 7.2 and 1.3 per 100 patient-years, according to a meta-analysis of 33 studies [5]. Warfarin is also number three on the list of drugs implicated in causing hospital admission through adverse effects [6]. Warfarin's narrow therapeutic index makes it difficult to maintain patients within a defined anticoagulation range. A recent analysis of 6454 patients with atrial fibrillation taking warfarin showed that for almost 50% of the time, the INR was outside the target range of 2–3 [7]. An INR over 3 increases the risk of bleeding, while an INR less than 2 increases the risk of thrombotic events [8]. The problem is further compounded by the fact that individual dosage requirements vary widely between and within individuals (more about this later).

Intuitively, one would expect that the more closely you monitor patients, the more likely you will be to hit the desired target range. Indeed, this seems to be the case [8], but there are no good guidelines on how often patients should be monitored. Herein also lies a problem of resources: the more closely you monitor patients, the more expensive the direct costs to your service [9]. Of course, this does not take into account the savings that may be made through preventing hospital admissions from either under- or over-anticoagulation, but it nevertheless informs monitoring practice. Consequently, the frequency of monitoring varies widely in different places [8].

The usual model of care of patients taking anticoagulants involves attendance at a physician-run hospital-based clinic. However, over the last decade there has been increasing interest in developing other models of care. These have included anticoagulation clinics based in primary care [10] and self-monitoring [11], both of which are as effective as hospital-based monitoring, or more so. In this issue, Chan *et al.* [12] show that phar-

macists were more effective, and less costly, than physicians at achieving target INRs in Chinese patients. This finding is consistent with US and UK comparisons of pharmacist- and physician-managed anticoagulant clinics [13–15]. Nurses are also safe and effective in managing anticoagulant clinics [16], which is reflected by the increased number of anticoagulant specialist nurses in the UK. These findings do not indicate that physicians have inadequate knowledge or expertise (in the trials many were experienced haematologists), but rather reflect the fact that there was often increased frequency of monitoring, contact time, and advice between clinic visits in clinics run by other health-care professionals, a luxury not afforded to physicians. There can be no doubt that managing patients taking warfarin requires a multi-disciplinary and multi-functional approach. Patient education should be an important component, although surprisingly little attention has been paid to this [17].

Warfarin is associated with other adverse effects, including skin necrosis and hair loss. A population-based case-control study in 2000 suggested that warfarin treatment was associated with an increased risk of at-fault car crashes [18]. Since warfarin does not affect psychomotor performance, the finding was thought to be due to the diseases for which warfarin was being used, rather than a direct effect of warfarin itself. However, the association between warfarin and road traffic accidents was not replicated in a recent study published in the *Journal* [19], and this is again emphasized in this issue [20]. Nevertheless, as Alvarez points out [21], assessment of whether drugs cause road traffic accidents is highly complex, and confounding by indication, concomitant medications, alcohol intake, and driving experience can all influence the findings. It is therefore not surprising that replication of initial findings is often difficult.

So where are we heading with warfarin prescribing? Warfarin will continue to be the oral anticoagulant of choice, possibly for the next decade, while we await an oral thrombin inhibitor that is both effective and safe. In the meantime, there is increasing interest in improving warfarin dosage regimens by elucidating the environmental and genetic factors that determine dosage requirements. Individual warfarin dosages are highly variable and range from 0.5 mg/day to over 20 mg/day [3]. Environmental factors that determine dosage requirements include concomitant medications, diet, and alcohol intake. More recently, genetic polymorphisms in the genes encoding CYP2C9, the main enzyme responsible for the metabolism of S-warfarin, the more potent of warfarin's two stereoisomers, and VKORC1, vitamin K [ep]oxide reductase, the enzyme that warfarin inhibits, have been shown to act as major determinants of warfarin dosage requirements [3]. Combining age and body surface area together with genetic polymorphisms in CYP2C9 and VKORC1 accounts for 55% of the variance in dosage requirements [22]. It has been suggested that this may serve to improve the benefit to harm balance of warfarin therapy, but the clinical value of this approach needs to be proven. Further studies are currently being carried out in the UK and elsewhere to identify other genetic and non-genetic factors that better predict warfarin dosage requirements. These studies, if successful, may herald a new era of personalized medicine, in which the dosage of warfarin, and hence INR control, can be better predicted through the development of algorithms that use environmental and genetic factors as co-variates. The importance of this lies not only in improving the use and safety of warfarin, but because it also serves as a paradigm for introducing pharmacogenetics into other therapeutic areas.

Competing interests: Munir Pirmohamed is Principal Investigator for a study, funded by the UK Department of Health, evaluating environmental and genetic factors that determine warfarin dosage requirements.

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