Case study 2: Warfarin

The anticoagulant Warfarin is one of the world's most widely used oral treatments for a range of thrombotic conditions, including deep vein thrombosis (DVT), pulmonary embolus and atrial fibrillation/stroke. The aim of treatment with Warfarin is to prevent arterial and venous thromboembolism by thinning the blood to a safe and effective level. This is referred to as achieving anticoagulation: a state that is measured by the International Normalized Ratio (INR) for prothrombin time. Ideally patients receiving Warfarin treatment should have stable INR's within a specified and disease specific range: for example, in order to prevent recurrent myocardial infarction patients should have INR's of between 2.5 to 3.5 (this article from the website www.anticoagulation.org provides a patient-oriented, introductory-level guide to Warfarin and its use). However a stable and acceptable patient INR is notoriously difficult to achieve, hence Warfarin is said to have a 'narrow therapeutic index' (see diagram below).

Despite the longstanding and widespread use of Warfarin, both loading and maintenance dose, for any particular patient, displays wide variability. While the majority of such variation is thought to be due to lifestyle and environmental factors¹, Warfarin action and metabolism also has a pharmacogenetic component.

Above, in CASE STUDY 1: CODINE/MORPHINE the role of enzymes belonging to the cytochrome P450 family was noted. Here again, in the case of Warfarin, CYP P450 genes are again important in drug response. However, in this case, it is variation in the CYP2C9 gene that is important as well Single Nucleotide Polymorphism (SNP, or 'snip') variation in the VKORC1 gene.

As in the case of thiopurine metabolism, mutations of the CYP2C9 gene can create phenotypes that are extremely sensitive to Warfarin and, hence, are at an increased risk of ADR (even given a standard loading and/or maintenance dose). Thus, in a similar way to thiopurine treatment, Warfarin pharmacogenetics can be used to improve safety in drug prescription. However, in this case, another gene is also implicated in drug metabolism at the other end of the spectrum: here SNP variation in the VKORC1 gene appears to mediate the efficacy of Warfarin treatment.

As noted above Warfarin has a narrow therapeutic index. This means that, even for patients that are 'normal' - in this context, homozygous for the wild-type variants of both CYP2C9 and VKORC1 - the difference between being under-anticoagulated (i.e. deriving minimal therapeutic benefit from Warfarin treatment) and being over-anticoagulated (i.e. being at increased bleeding risk - the primary ADR associated with Warfarin therapy) is small.

Schematic diagram illustrating the relationship between safety and efficacy in Warfarin treatment for patients who are homozygous for the wild-type variants of both CYP2C9 and VKORC1.
However, when pharmacogenetic effects are taken into account, this ‘window’ can shift significantly up or down the dosage scale.

Schematic diagram illustrating the relationship between safety and efficacy in Warfarin treatment for patients who are either heterozygous or homozygous for mutant variants of CYP2C9 (most commonly CYP2C9*2 and/or CYP2C9*3) and homozygous for wild-type VKORC1

Schematic diagram illustrating the relationship between safety and efficacy in Warfarin treatment for patients who are homozygous for wild-type CYP2C9 and either heterozygous or homozygous for mutant variants of VKORC1

That CYP2C9 variants mediate the safety of Warfarin treatment, and VKORC1 - independently - mediate its efficacy, are not the only complications for clinicians in making both, initial, and long-term, prescribing decisions. The effect of Warfarin is heavily influenced by a number of lifestyle and environmental factors, including: age, weight, alcohol consumption, drug regime compliance, and diet. These account for around 80% of variation in Warfarin patient INR and, given the serious consequences of both over- and under-anticoagulation, require that this drug therapy is accompanied by intensive and costly pharmacovigilance regimes. While many hope that pharmacogenetics may help to reduce the need for - and cost of - weekly, or even daily, INR monitoring (which, in the UK, is conducted within the time and budget of NHS hospital or GP surgeries), others believe that scaling back this service may be the ultimate ‘false hope’ and greatest danger of placing too much certainty in pharmacogenetic information in the future.

Selected references & sources:


1 GCSE SCIENCE/BIOLOGY CURRICULUM LINK. Click here for specification detail from the BioethicsBytes "Bioethics in the UK Curriculum" website