INTERACTIONS WITH WARFARIN

Oral anticoagulants have been described as a taboo of therapeutics but a totem of pharmacology (O'Reilly & Aggeler, 1970). By this is meant that to the physician the role of these drugs remains largely undefined and when used, the constant risk of haemorrhage has to be balanced against the benefit their use might confer, while to the pharmacologist the fact that their therapeutic response can be documented with extreme precision has made them of considerable research potential. This interest has been heightened by certain recent advances. First, it is now possible to measure by specific chemical methods, the concentrations of both warfarin and its metabolites in plasma and other body fluids (Lewis, Ilnicki & Carlstrom, 1970). Second, using radio-labelled vitamin K₁, the relationship between concentrations of oral anticoagulants and vitamin K₁ and its metabolites can be examined in a variety of experimental situations (Shearer, McBurney & Barkhan, 1973). Third, the enantiomers of warfarin are proving useful tools in studying the mechanism of several hitherto ill understood drug interactions with warfarin (Lewis, Trager, Chan, Breckenridge, Orme, Rowland & Schary, 1974).

At normal therapeutic plasma concentrations, over 99% of warfarin is bound to plasma albumin. If one accepts that the free moiety of warfarin in plasma is in equilibrium with free (and therapeutically active) drug in the liver, a change from, say, 99.7% bound to 99.4% bound represents a doubling of the biologically active drug. Most studies of displacement of warfarin from protein binding have so far been carried out *in vitro*, that is, warfarin and the putative displacing agent have been added to plasma and the change in free drug concentration estimated by techniques such as ultrafiltration or equilibrium dialysis. The relevance of these types of study may indeed be questioned; measurements have rarely been made from plasma obtained from patients dosed with the appropriate drugs. Further, any discussion of displacement of oral anticoagulants from protein binding is of necessity limited to the proteins of the plasma, and the failure of such studies to explain changes in pharmacological responses seen clinically may well indicate that displacement from other sites, for example, within the liver, may be of considerably greater importance. The pharmacokinetics of displacement of oral anticoagulants are complex (Koch Weser & Sellers,

1971). Administration of repeated daily doses of a displacing drug to a patient on long term treatment with an oral anticoagulant will potentiate the hypoprothrombinaemic effect only temporarily. The time required for the potentiation of the anticoagulant effect and for the subsequent return to previous values depend on several factors—the time that the displacing drug takes to accumulate, the rate of elimination of the anticoagulant in the presence of the displacing drug, and on the kinetics of the vitamin K sensitive clotting factors themselves. Potentiation of the anticoagulant response may be seen within 24 h of drug administration, and by four to five days of continuous dosing, the response may have returned to control values. Thus unless an alteration of the prothrombin time is looked for within this period of time, it may be missed.

One of the most widely cited examples of warfarin displacement from protein binding is that shown by phenylbutazone (O'Reilly, 1970). Recent studies suggest that this may not be the only mechanism whereby the anticoagulant effect of warfarin is enhanced (Lewis *et al.*, 1974). Warfarin is a racemic mixture of two enantiomers, R and S warfarin, which, in several respects are quite different drugs. First, both in man and the rat (Breckenridge & Orme, 1972; Breckenridge, Orme, Wesseling, Gibbons & Lewis, 1974) S warfarin is a more potent anticoagulant than R warfarin and second, the enantiomers differ in their rates and routes of metabolic elimination (Lewis *et al.*, 1974). R warfarin is oxidized to 6-hydroxy warfarin and reduced to the (R, S) alcohol (its principal product) whereas S warfarin is largely oxidized to 7- and 6-hydroxy warfarin and reduced to the (S, S) alcohol (a minor pathway). While the oxidative metabolic products of warfarin are produced by liver microsomal enzymes, the site of production of the reductive metabolic products remains to be identified. The rate of elimination of S warfarin (the more potent isomer) is slowed in patients dosed with phenylbutazone but the rate of elimination of R warfarin is enhanced (Lewis *et al.*, 1974). These enantiomers may well prove potent tools in our understanding of other drug interactions with warfarin in man. Administration of liver microsomal enzyme inducing agents might be expected to produce a differential effect on the rate of elimination of these enantiomers. Preliminary

studies of this in man have proved interesting but inconclusive.

While interindividual variations in rates of drug oxidation are widely appreciated, variations in enzyme induction are less well known. Administration of the same dose of an inducing agent for a prolonged period to patients stabilized on warfarin may cause no significant change in either plasma drug concentration or prothrombin time in some patients but a profound decrease in drug concentration and a corresponding change in the therapeutic response in another. The reason for this variability is not clear. It is unrelated to the rate at which the patient eliminates warfarin; whether it is related to the rate at which he eliminates the inducing agent apparently differs with the agent under study (Breckenridge, Orme, Davies, Thorgeirsson & Davies, 1973; Vesell &

Page, 1969). The dose of inducing agent given to various patients may be of importance in considering the extent of induction produced. Moreover, studies in rats have shown that dose response relationships of different inducing agents vary widely. The same may be true in man.

Although interindividual differences in response to oral anticoagulant therapy will always exist, perhaps the taboo referred to above may finally be proscribed through veneration of the totem.

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