Investigation of patients with abnormal response to warfarin

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1 In 55 patients in whom warfarin control had been satisfactory for at least 4 months, warfarin dose, plasma warfarin concentration and plasma clearance were measured.

2 The mean dose to maintain the BCR (INR) between 2.3 and 3.3 was $5.1 \pm 2 \text{ mg day}^{-1}$ (range 1.5–10 mg). Plasma warfarin concentrations and warfarin clearance were log-normally distributed with 95% confidence limits between 0.8 and 2.4 mg l^{-1} and 2.5 and 8.7 l day^{-1} respectively. These confidence limits were used to construct algorithms which correctly predicted the cause of abnormal warfarin sensitivity in two patients and resistance in two further patients.

3 These algorithms should help to identify the cause of abnormal warfarin responsiveness in the clinical setting.

Keywords warfarin algorithms

Introduction

Warfarin is the most widely used oral anti-coagulant in Europe and is a potent and potentially dangerous drug. Patients differ widely in the dose of warfarin they require to maintain them within the therapeutic range of anticoagulation and variability up to 20-fold or more in dose has been reported (Routledge *et al.*, 1979). Some subjects, even when given fairly large or small doses of the drug may be difficult to maintain within the therapeutic range. Investigation of the mechanism of abnormal responsiveness is often useful in managing individual patients but guidelines for when and how to investigate these patients are sparse. We therefore investigated a population of well controlled patients receiving the drug in an attempt to construct a subsequent algorithm for investigation of patients with abnormal response to warfarin.

Methods

Fifty-five patients requiring long-term warfarin therapy were studied. All had the last four or

more consecutive one-stage prothrombin time ratios within the therapeutic range over a period of at least 4 months. Warfarin tablets were taken at approximately 18.00 h and venous blood was collected between 09.00 and 11.00 h. None was taking any drugs known to interact with warfarin.

One stage prothrombin time (BCR or INR) was measured on plasma after collection of venous blood into sodium citrate solution 3.13% (ratio 1:9 solution: blood) using Manchester Comparative Thromboplastin. Plasma warfarin concentration was measured on plasma from each sample used to measure the BCR and an estimate of plasma clearance of warfarin at steady-state was made by dividing the daily dose at each sampling time by the corresponding plasma warfarin concentration, measured by a modification of the method of Bjornsson *et al.* (1977). This involved the use of a 26 cm ODS, 5 μ Apex column, a mobile phase of acetonitrile: water 50:50 v/v solution containing 0.1% acetic acid (flow rate 2 ml min^{-1}) and the use of phenprocoumon (Roche) as an internal standard. The

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concentrations were corrected for dilution by the citrate anticoagulant.

The mean of each dose, plasma warfarin concentration and plasma clearance in each patient was used to determine the means and standard deviations of each of these variables in the whole group. Normality of distribution of each variable was tested using D'Agostino's D_x test (D'Agostino, 1971). When required, logarithmic transformation was performed in order to produce a distribution consistent with normality.

From the data algorithms were constructed (Figures 1 and 2) and this was used to identify the possible cause of abnormal warfarin responsiveness in four patients (of whom two have been previously reported in the literature) with markedly abnormal warfarin responsiveness.

Results

Fifty-five subjects aged between 17 and 83 years (mean 62.4) were studied. The mean $\pm$ s.d. BCR of the group was 2.7 ± 0.3 (range 2.2–3.3). Daily dose, the logarithm of warfarin concentration and logarithm of plasma warfarin clearance were consistent with a normal distribution ($D = 0.277, 0.272$ and 0.278 , respectively, $P < 0.05$ in all cases) and were therefore used to determine the 95% confidence limits for these variables. The mean ($\pm$ s.d.) warfarin dose was 5.1 ± 2 mg day⁻¹ (range 1.5–10 mg) and the 95% confidence limits for the population were 1.2–8.9 mg.

The plasma warfarin concentration varied between 0.6 and 2.9 mg l⁻¹ (mean 1.3 ± 0.4 mg l⁻¹) and the 95% confidence limits of the log transformed data lay between 0.8 and 2.4 mg l⁻¹.

The plasma warfarin clearance varied between 2.4 and 10.7 l day⁻¹ (mean 4.8 ± 1.4 l day⁻¹) and the 95% confidence limits of the log transformed data lay between 2.5 and 8.7 l day⁻¹.

Case 1

A 55-year-old woman reported by Breckenridge & Orme (1973) required 180–200 mg warfarin day⁻¹ to achieve anticoagulant control. Her plasma warfarin concentration was approximately 2.2 mg l⁻¹ while taking 180 mg warfarin daily. This is within the 95% confidence limits for plasma warfarin concentrations associated with anticoagulant control which suggests that pharmacodynamic resistance was not present (Figure 2). The clearance, however, was calculated to be 81.8 l day⁻¹ which indicated that this was a 'kinetic' resistance. Further questioning revealed that she had been taking nightly Tuinal (quinallbarbitone and amylobarbitone) for many

Figure 1 Distribution of daily warfarin dose requirements.

months. When this was withdrawn her warfarin requirements fell markedly whilst her plasma warfarin concentration remained at around 2 mg l⁻¹. Barbiturates are enzyme inducing agents and the increased plasma warfarin clearance was in keeping with a marked degree of enzyme induction. The algorithm thus correctly predicted that the warfarin resistance was due to an increase in warfarin metabolism (or reduced compliance).

Case 2

A man described by O'Reilly *et al.* (1964) was found to require 145 mg of warfarin day⁻¹ to achieve anticoagulant control whilst the plasma warfarin concentration was extremely high (55 mg l⁻¹). The calculated plasma warfarin clearance, however, was within our normal limits at 2.64 l day⁻¹. The algorithm thus indicated that the warfarin resistance was not due to altered warfarin metabolism, but to pharmacodynamic resistance (Figure 2). This man was, in fact, the first identified subject who had hereditary warfarin resistance, a rare autosomal dominant trait.

Case 3

A 35-year-old woman in our care could not be adequately anticoagulated despite a daily warfarin dose which had been increased to 30 mg daily. Her plasma warfarin concentration was 1.8 mg l⁻¹ and her apparent clearance was thus approximately 22 l day⁻¹. The algorithm thus in-

Figure 2 Algorithm to determine cause of warfarin resistance.

indicated either 'kinetic' resistance or poor compliance (Figure 2). When her tablet administration was supervised, she rapidly became over-anticoagulated (BCR 8) on the same dose and her plasma warfarin concentration rose to 6.4 mg l^{-1} . This indicates that poor compliance was the cause for the apparent warfarin resistance.

Case 4

A 56-year-old man attending the out-patient clinic required only 1 mg warfarin to maintain a BCR within the therapeutic range. His plasma warfarin concentration was 2.2 mg l^{-1} indicating from the algorithm that there was no evidence of tissue sensitivity (Figure 3). The plasma warfarin clearance, however, was abnormally low at 0.45 l day^{-1} . The patient was also receiving amiodarone for treatment of cardiac arrhythmias. This prompted a subsequent study of patients on warfarin and amiodarone which showed that the latter drug inhibited plasma warfarin clearance (Watt *et al.*, 1984). This inhibition is in large part responsible for the reduction in warfarin requirement associated with amiodarone therapy (Rees *et al.*, 1981).

Discussion

Although several studies have documented the wide variability in warfarin requirements, to our

knowledge, these have involved the use of thromboplastins other than British Comparative Thromboplastin. The latter is becoming the most widely used reagent to monitor oral anticoagulant therapy and we felt it would be useful to define a 'normal range' of warfarin doses necessary to maintain patients within that range. We do not advocate that all patients whose daily warfarin requirement falls outside the range should have plasma warfarin concentrations measured. Those subjects whose requirements change markedly, or in whom it is difficult to maintain an adequate degree of anticoagulation even with a very large or very small dose, are those in whom further investigation might lead to better anticoagulant control.

The plasma warfarin concentration range associated with the therapeutic range for the BCR has not been previously reported in detail, although the values we have seen are similar to those described with other thromboplastins.

Plasma warfarin clearance estimates will of course be independent of the method used to monitor anticoagulant therapy. They do assume that steady-state has been achieved, however, and for warfarin, this requires that the same dose be administered for at least a week and preferably longer. The clearances we have observed ($4.8 \pm 1.4 \text{ l day}^{-1}$) are quantitatively similar to those reported by Yacobi *et al.* (1976) ($4.3 \pm 1.6 \text{ l day}^{-1}$) and Hotraphinyo *et al.* (1978) ($4.3 \pm 2.4 \text{ l day}^{-1}$).

Figure 3 Algorithm to determine cause of warfarin sensitivity.

although both authors assumed the distribution of plasma warfarin clearances to be normal, despite the fact that the data of Hotraphinyo *et al.* (1978) are skewed to the right. Our values were clearly skewed to the right, although logarithmic transformation provided a distribution consistent with normality.

From these three variables, an algorithm has been constructed which correctly identified the course of abnormal warfarin responsiveness in four patients with different mechanisms for the abnormality. Two of the subjects showed marked resistance to warfarin, one because of abnormal pharmacokinetics of the drug and the other because of 'pharmacodynamic' or 'tissue' resistance. The changes described were marked and therefore relatively easy to identify, but one is more often faced with lesser degrees of abnormal responsiveness and the algorithm may then be of much greater help in indicating the mechanism. It is possible of course, that kinetic and tissue resistance or sensitivity may co-exist and the algorithm should also help to identify this situation.

The validity of the plasma warfarin clearance value is dependent on three other assumptions being true. The first is that the oral warfarin dose is completely absorbed (i.e. that bioavailability is 100%). In virtually all circumstances, this assumption is valid (Andreasen & Vessell, 1974).

Only when the ion-exchange resin cholestyramine is administered at the same time as warfarin is absorption likely to be incomplete (Robinson *et al.*, 1971). The second is that the patient is actually taking the prescribed dose (i.e. that compliance is also 100%). Poor compliance is a relatively common cause of apparent warfarin resistance. Case 3 illustrates this problem and only in circumstances of supervised drug administration can one distinguish with certainty those with poor compliance from those with 'kinetic' resistance. The third assumption is that the ratio of the two enantiomers of warfarin are not significantly altered in patients with abnormal warfarin responsiveness. This may not always be true but until a method to measure the enantiomers in plasma is widely available, measurement of the racemic drug (which is technically simpler) will often help to identify the cause.

Finally, Case 4 illustrates that use of the algorithm can provide insights into the probable mechanisms of abnormal responsiveness to warfarin. The algorithm indicated that the patients sensitivity had a kinetic explanation and this was confirmed by a definitive study in a larger group of subjects (Watt *et al.*, 1985).

We believe that use of the algorithm will help to distinguish the causes of abnormal responsiveness to warfarin in many cases and will therefore

aid the physician in modifying those variables which are correctable in any particular circumstance. A knowledge of the mechanisms involved will also enable the physician to anticipate the

effects of factors over which he has little control but on which by adjusting dosage accordingly, he can reduce the risks associated with poor anti-coagulant control.

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