Interaction between warfarin and sulphamethoxazole

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Summary

A patient is described in whom there was strong circumstantial evidence of an interaction between warfarin and co-trimoxazole. To test the validity of this hypothesis a series of *in vitro* and *in vivo* human studies were undertaken. The results indicate that interaction may occur in which the sulphamethoxazole moiety of co-trimoxazole displaces warfarin from its binding sites on plasma albumin. Nevertheless, this interaction occurs only at high plasma levels of warfarin and is most likely to be clinically significant only in patients receiving high doses of warfarin who have low plasma albumin concentrations. These studies indicate that the use of co-trimoxazole is not contra-indicated in patients receiving warfarin therapy, but care should be exercised, especially in patients with high plasma warfarin : albumin ratios.

Introduction

With increasing use of powerful therapeutic agents, patients are now likely to be exposed to the effects of drug interactions in increasing numbers (Boston Collaborative Drug Surveillance Program, 1972). Although interactions between many different drugs have been described (Hansten, 1973) perhaps the patients most likely to experience trouble are those receiving oral anticoagulants. These drugs are potent, highly protein-bound, competitive inhibitors of the vitamin K-induced production of coagulation factors. Koch-Weser and Sellers (1971) have reviewed the extensive literature on drugs interacting with the coumarin anticoagulants. Their review includes data on the effect of anti-bacterial drugs on coumarin-induced anticoagulation and emphasizes the hypothetical nature of some of the reported interactions.

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Recently, several workers have reported a possible interaction between the new sulphonamide-trimethoprim mixture, co-trimoxazole and the oral anticoagulant warfarin (Barnett and Hancock, 1975; Hassall *et al.*, 1975). The present study describes a further patient with severe warfarin-induced gastrointestinal haemorrhage possibly related to recent co-trimoxazole therapy. The mechanism whereby these two drugs interact was then investigated and those patients at greatest risk were identified.

Case report

A 39-year-old female patient with rheumatic heart disease, atrial fibrillation and a past history of pulmonary embolism, presented to Glasgow Royal Infirmary with a massive haematemesis. She had been well controlled on warfarin therapy (daily dose 6 mg: thrombotest readings 9-15%) for 4 years. Four weeks before her admission she developed an upper respiratory tract infection associated with general malaise, myalgia and dyspnoea. Her practitioner diagnosed influenza and prescribed a 7-day course of ampicillin therapy. Thereafter her condition improved for 1 week before recurring. On this occasion she complained of right-sided pleuritic chest pain and was found to have signs of consolidation. Pneumonia was diagnosed and she was given co-trimoxazole, two tablets twice daily. Her admission with haematemesis occurred after 2 weeks of co-trimoxazole therapy. During her illness warfarin therapy was continued at normal dosage without repeat thrombotest readings.

On admission to hospital she was found to have spontaneous bleeding from her gums, haematuria and haematemesis. Investigations showed a one-stage prothrombin time of over 90 sec (control 14 sec), a cephalin-kaolin clotting time of over 180 sec (control 46 sec) together with normal thrombin time and platelet count. Her haemoglobin was 11 g/dl and

her total plasma albumin 35 g/l. Her coagulation defect was corrected by infusion of prothrombin concentrate and an injection of 10 mg vitamin K₁. She was transfused 3 u. of whole blood to maintain her circulation and she rapidly settled. Barium meal and intravenous pyelography were within normal limits and the patient was discharged 2 weeks after admission.

Methods

Warfarin binding to human albumin was studied by equilibrium dialysis and by ultrafiltration (Sellers and Koch-Weser, 1970; Solomon and Thomas, 1971), the experiments being conducted at pH 7.4 and temperatures of 4°C or 25°C. Warfarin levels were measured as described by Corn and Berberich (1967).

Studies were also made on volunteer patients. Four subjects who were to be given co-trimoxazole for therapeutic reasons agreed to donate blood before and on the third and tenth days of treatment with two tablets of co-trimoxazole twice daily. The blood samples were withdrawn before the morning dose. Plasma was separated and pooled. Warfarin, containing tracer ¹⁴C-warfarin, was added to give a final concentration of 112 µmol/l and binding measured by ultrafiltration. The albumin concentration of the pooled plasma was 36 g/l.

A further four volunteers who had been consuming warfarin regularly for periods exceeding 6 months were given co-trimoxazole, two tablets twice daily for 3 days and their one-stage prothrombin times measured throughout the period of interest.

Results

A slight but significant displacement of warfarin from its binding sites was observed in the *in vitro* studies when co-trimoxazole was present. The displacement was about 10% of that produced by phenylbutazone and was attributable to the sulphamethoxazole and not the trimethoprim. The magnitude of the effect was such that a clinically significant response in terms of prolongation of prothrombin could be anticipated only at high warfarin : albumin ratios in the presence of high levels of sulphamethoxazole (Table 1). Both the affinity of warfarin for its binding protein and the number of sites available for warfarin binding were approximately halved in the presence of sulphamethoxazole at high concentrations (50 µg/ml); the affinity constant falling from 2.8×10^5 to 0.7×10^5 mol⁻¹ and the average number of binding sites per 100 mol of albumin from 300 to 130.

No displacement of warfarin from its binding sites was found after co-trimoxazole administration to volunteers, the proportion of free warfarin observed at 3 and 10 days being equal at 3.3% (s.d. 0.3) compared with an expected value from the *in vitro*

TABLE 1. Effect of co-trimoxazole and phenylbutazone on warfarin-binding to human albumin

Drugs tested*	Number of studies†	Proportion of free warfarin (%)	Warfarin: albumin (molar ratios)
W _{2.5}	4	13.5 ± 0.6	0.11
W _{2.5} + T ₅	3	15.5 ± 2.8	0.11
W _{2.5} + S ₂₅	3	16.0 ± 0.2	0.11
W _{2.5} + S ₂₅ + T ₅	3	16.0 ± 0.3	0.11
W _{2.5} + PB ₂₀	2	47.8 ± 3.8	0.11
W ₅	3	3.3 ± 0.1	0.03
W ₅ + S ₅₀	3	3.1 ± 0.1	0.03
W ₃₅	5	4.5 ± 0.2	0.20
W ₃₅ + S ₅₀	5	10.0 ± 2.0	0.20

*W, Warfarin; T, trimethoprim; S, sulphamethoxazole; PB, phenylbutazone. Subscripts indicate concentrations (µg/ml).

†Each study done in triplicate, results are the mean ± s.d.

studies of 4.5% (s.d. 0.2). Conversely no effect on prothrombin time was found in four patients on warfarin given co-trimoxazole, the mean prothrombin time being 1.9 (s.d. 0.1) times control value before and 2.0 (s.d. 0.4) times control value after commencing co-trimoxazole.

Discussion

This paper describes a patient receiving warfarin in whom co-trimoxazole may have been partly responsible for the development of a major gastrointestinal haemorrhage. Since there have been several other reports of possible interactions between these two drugs, and since these drugs may be administered together commonly, detailed studies were carried out in an attempt to define a possible cause for such an interaction.

Because both drugs are highly protein-bound, it seemed likely that this was the most promising area for a major co-trimoxazole-warfarin interaction, particularly since a sulphonamide, sulphaphenazole, has already been reported as displacing warfarin from its binding sites on serum albumin (Solomon and Schrogie, 1967) and as having a similar effect on phenindione (Varma *et al.*, 1975). From the known pharmacology of the sulphonamides, it is unlikely that these drugs would interfere with warfarin handling via increased absorption, decreased excretion, or altered receptor site affinity of this drug. Certain sulphonamides have been reported as altering coumarin biotransformation rates, notably sulphamethizole (Lumholtz *et al.*, 1975), but the evidence provided for this statement is scanty. It is theoretically possible that sulphonamides could reduce vitamin K bioavailability by reducing bacterial synthesis of this drug in the gut lumen. However, since there are no methods available for assaying this vitamin in biological fluids, such an

interaction cannot readily be provided, and in any case should occur with all antibacterial agents, not particularly sulphonamides. There is also no evidence to suggest that sulphonamides interfere with hepatic synthesis or degradation of coagulation factors or with the effect of these factors in the plasma.

The *in vitro* studies reported in this investigation demonstrate that the sulphonamide moiety of co-trimoxazole displaces warfarin from its binding site on plasma proteins. The observed effect was substantially smaller than that resulting from phenylbutazone displacement but nevertheless may be sufficient to cause a significantly increased hypoprothrombinaemic effect, particularly in patients with high plasma warfarin : albumin ratios. In none of the experiments was an effect of trimethoprim on warfarin binding observed. Despite the observed *in vitro* effects of sulphamethoxazole on warfarin, when co-trimoxazole was given for a short period to subjects receiving warfarin, no effect on prothrombin levels was detected. In addition, when warfarin was added *in vitro* to plasma from patients taking co-trimoxazole, no alteration in plasma binding was observed.

It is concluded that although sulphamethoxazole may rarely displace sufficient warfarin from its binding sites to cause serious hypoprothrombinaemia, this effect could occur particularly in the elderly in whom the binding of warfarin to plasma proteins is already reduced (Hayes, Langman and Short, 1975), in those receiving high daily doses of warfarin and co-trimoxazole, and in those with low plasma albumin concentrations. In these patients particular care is necessary to ensure regular measurement of prothrombin times during co-trimoxazole therapy.

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