determination of leachable chromium VI in sutures provides reproducible results with acceptable linearity. The American Public Health Association procedure has the advantage of determining precisely the total amount of leachable chromium present in the sutures and it is recommended this procedure be adopted together with the BP limit in the official requirements for these products.

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J. Pharm. Pharmacol. 1984, 36: 689–690
Communicated February 10, 1984

Warfarin—sulfinpyrazone interaction on binding to human serum albumin

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Sulfinpyrazone displacement of warfarin from human serum albumin was studied in-vitro. At low sulfinpyrazone concentrations one molecule of warfarin is displaced on binding by one molecule of sulfinpyrazone. Clinical plasma concentrations of sulfinpyrazone are, however, too low to cause significant displacement.

Haemorrhage during combined treatment with warfarin and sulfinpyrazone has repeatedly been reported (Weiss 1979; Bailey & Reddy 1980; Gallus & Birkett 1980). The mechanism involved is probably reduced metabolic clearance of *S*-warfarin (O'Reilly 1982). A possible role of competition of the two drugs for binding to plasma albumin has been suggested by Bailey & Reddy (1980) but this effect has not been studied in-vitro although Seiler & Duckert (1968) have demonstrated that sulfinpyrazone displaces another coumarin anticoagulant, phenprocoumon, from binding to albumin.

Materials and methods

Human serum albumin was obtained from AB Kabi, Stockholm, Sweden (Lot Nr. 75953) and was defatted with charcoal in acid solution, lyophilized and stored at 4 °C (Chen 1967). [^{14}C]Warfarin (3-α-acetonyl[α-^{14}C]-benzyl-4-hydroxycoumarin) was obtained from The Radiochemical Centre (Amersham, UK) and purified by tlc using toluene–dioxane 9:1 and tested. The specific activity was 177 μCi mg^{-1}. Sulfinpyrazone was a gift from Ciba-Geigy A/S (Copenhagen). The interaction between warfarin and sulfinpyrazone was investigated by utilizing a recently developed technique for dialysis rate determination (Brodersen et al 1982). Twenty μl of a solution of [^{14}C]warfarin and albumin in buffer was placed on one side of a cellophane membrane with 20 μl of an identical buffered albumin solution on the other side. Dialysis was for 20 min at 37 ± 0·3 °C. Sulfinpyrazone was added in varying amounts, equally on both sides of the membrane. An increased dialysis rate is observed if warfarin is displaced by the second drug. [^{14}C]Warfarin concentration on either side of the membrane was measured by liquid scintillation counting.

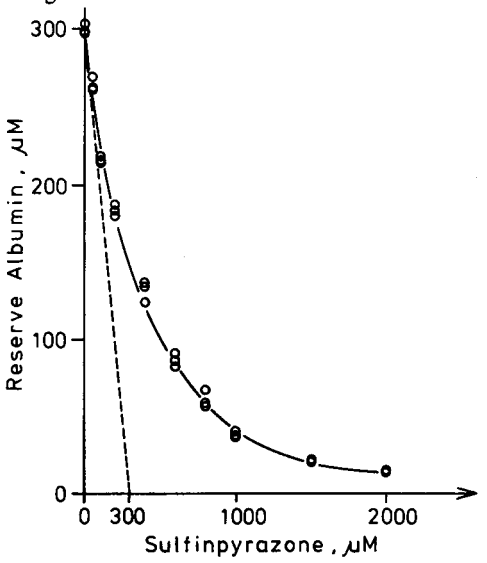

FIG. 1. Reserve albumin-equivalent for binding of warfarin as a function of sulfinpyrazone concentration, measured by rate of dialysis in a 300 μM solution of defatted human serum albumin in 66 μM sodium phosphate buffer, pH 7·4, 37 °C.

Results and discussion

The reserve albumin-equivalent for binding of warfarin in a sample containing sulfinpyrazone is defined as the concentration of albumin in pure solution which will bind warfarin equally tight as in the sample (Brodersen et al 1982). Results are seen in Fig. 1 where the reserve albumin-equivalent for binding of warfarin in a 300 μM (20 g litre^{-1}) human serum albumin solution containing 10 μM of racemic warfarin is plotted on the ordinate with varying concentrations of sulfinpyrazone on the

* Correspondence.

abscissa. At low sulfinpyrazone levels the slope of the curve is −1; the decrease is equal to the molar displacer concentration, indicating that sulfinpyrazone is tightly bound and that each molecule of it occupies the same binding area as one molecule of warfarin. Sulfinpyrazone thus shows a maximal warfarin displacing effect.

The significance of this finding for the possible displacing effect in the clinical setting can be evaluated as follows. The ratio of free/bound warfarin is inversely proportional to the albumin reserve (Brodersen et al 1982). The maximal plasma level of sulfinpyrazone obtained at an oral dosage of 800 mg daily to adult females was 50 μM, in a study by Rosenkranz et al (1983). From Fig. 1 we read that at this sulfinpyrazone level the albumin reserve is decreased from 300 to 260 μM. The free warfarin fraction is therefore increased by a factor 300/260 = 1·15. This result depends upon the albumin concentration used in the test; a higher albumin would give a lower increase of free warfarin fraction. We have chosen a low concentration, 300 μM, as in hypoalbuminaemic patient in order to be on the safe side. In a healthy individual the increase of free warfarin would rather be by a factor about 1·05 to 1·1.

Sulfinpyrazone, in spite of its maximal warfarin displacing potential, should thus produce displacement to a moderate or insignificant degree at clinically relevant plasma levels. This is in agreement with the findings of O'Reilly & Goulart (1981). At lower sulfinpyrazone dosage, 400 mg daily, these authors could not demonstrate an increase of free warfarin in healthy volunteers.

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J. Pharm. Pharmacol. 1984, 36: 690–693
Communicated February 20, 1984

o- and *m*-Iodohippurate binding to plasma proteins as a model drug transport mechanism

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The pharmacokinetics of two isomers, *o*- and *m*-iodohippurate, were determined in rabbits and rats and the effect of protein binding on their elimination is demonstrated. Both isomers are rapidly eliminated by transport systems in the kidney and their clearance by the kidney approaches the renal plasma flow regardless of protein binding, *m*-Iodohippurate is more highly bound to plasma proteins than *o*-iodohippurate and its rate of elimination is enhanced in comparison with *o*-iodohippurate. In the case of these two isomers, the binding to plasma proteins should be considered as a transport mechanism and not as a storage depot.

The assumption that drug-plasma protein binding can serve as a transport system is generally accepted and the effect on drug elimination calculated (Gillette 1973), but evidence of how the mechanism of drug-plasma protein binding affects the pharmacokinetics of a drug is scanty.

This communication is concerned with a comparison of pharmacokinetic parameters of *o*- and *m*-iodohippurate, two isomers with similar biodistribution (Lázníček et al 1984) but different binding to plasma proteins, in rats and rabbits. For analysis of the mechanism of elimination of both isomers, their clearances are compared with that of inulin, which is generally accepted as a standard for glomerular filtration rate measurement (Blaufox et al 1975). The effect of plasma protein binding on pharmacokinetic parameters of the isomers is discussed.

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Material and methods

Substances used. [^{125}I]*o*-Iodohippurate and [^{125}I]*m*-iodohippurate (Nuclear Research Centre, Řež near Prague) specific activity of 2 GBq g^{-1}, dissolved in 0.9% NaCl (saline), radiochemical purity over 97.5%.

[Methoxy-^{14}C]methoxyinulin (ÚVVVR Prague) specific activity 1.5 GBq g^{-1}, radiochemical purity over 98%.

Rate studies. Wistar strain male rats (170–220 g) were fasted for 18–24 h before the experiment, water was freely available. The rats were dosed intravenously