LACK OF EFFECT OF RANITIDINE ON WARFARIN ACTION

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- 1 In five volunteers taking daily subtherapeutic doses of warfarin the addition of ranitidine 200 mg twice daily for 14 days did not affect prothrombin time or plasma warfarin concentration.
- 2 Ranitidine had no effect on the single dose pharmacodynamics and pharmacokinetics of warfarin in the rat.
- 3 Ranitidine had no effect on pentobarbitone sleeping time in the rat whereas cimetidine significantly prolonged the sleeping time.
- 4 The interaction between cimetidine and oral anticoagulants is unrelated to histamine H₂-receptor antagonism.

Introduction

Ranitidine is a new histamine H₂-receptor antagonist which is approximately five times more potent on a weight basis than cimetidine in inhibiting gastric acid secretion (Peden, Saunders & Wormsley, 1979). Cimetidine potentiates the action of warfarin by inhibiting its hepatic metabolism (Serlin *et al.*, 1979, 1980) and it has been shown to have similar effects on the metabolic elimination of other drugs e.g. antipyrine (Serlin *et al.*, 1979; Puurunen, Sotaniemi & Pelkonen, 1980) and diazepam (Klotz & Reimann, 1980). The chemical structures of cimetidine and ranitidine are quite different; the imidazole ring structure of the former has been substituted by a furan ring in the latter and the side chain has been modified. To determine whether potentiation of anticoagulant action is a common attribute of histamine H₂-receptor antagonists we have investigated the effect of ranitidine on the steady state pharmacodynamics and pharmacokinetics of warfarin in man using a protocol previously described (Serlin *et al.*, 1979) and the effect of ranitidine on the single dose pharmacodynamics and pharmacokinetics of warfarin in the rat.

Methods

1. Effect of ranitidine on the steady state pharmacodynamics and pharmacokinetics of warfarin in volunteers

Five healthy male volunteers (aged 28–42 years) took part in this study which had the approval of the ethical

committee of the Mersey Regional Health Authority. A daily dose of racemic warfarin was determined for each volunteer that would just prolong the prothrombin time by a few seconds and this dose was then maintained throughout the study. After 2 weeks of this dose of warfarin, ranitidine 200 mg twice daily was taken in addition to warfarin for 2 weeks followed by a final 2 week period of warfarin alone. Blood samples were taken at intervals throughout the study for measurement of prothrombin times and plasma warfarin concentrations. Venesections were performed at the same time of day (mid-morning), before daily warfarin therapy.

Prothrombin times were measured using the Manchester Comparative Thromboplastin (National [U.K.] Reference Laboratory for Anticoagulant Reagents and Control) using an automated coagulometer. Plasma warfarin concentrations were determined by gas-liquid chromatography with an electron-capture detector (Kaiser & Martin, 1974).

The results at the end of each treatment period were compared by analysis of variance.

2. Rat studies

(a) *Effect of ranitidine on the single dose pharmacodynamics and pharmacokinetics of warfarin in the rat*
Twelve male inbred Wistar rats (200 g) were given a single intraperitoneal injection of racemic warfarin 0.22 mg/kg containing 43 μ Ci [¹⁴C]-warfarin/mg (Radiochemical Centre, Amersham, UK, specific activity 51 mCi/mmol). They then received i.p. injections of either ranitidine 166 mg/kg or 0.9% saline at

12 hourly intervals commencing 1 h after warfarin and continuing until completion of the study (55 h). Three further rats were given ranitidine (166 mg/kg) as above but did not receive warfarin. Blood samples were taken from the tail artery, under light ether anaesthesia and added to 3.8% trisodium citrate (0.1 ml).

Prothrombin times were measured as in man and converted to prothrombin complex activity by reference to a standard dilution curve (Park *et al.*, 1979). Plasma [^{14}C]-warfarin concentrations were measured by liquid scintillation spectrometry after extraction and thin layer chromatography (Yacobi, Wingard & Levy, 1974). The recovery of warfarin from plasma was $83.2 \pm 3.0\%$ (mean $\pm$ s.d. $n = 9$).

The pharmacokinetics of warfarin were determined assuming a single compartment model (Yacobi *et al.*, 1974).

- (b) *Pentobarbitone sleeping times* (i) Sleeping times were determined in randomized groups of five male Wistar rats after intraperitoneal injection of pentobarbitone 40 mg/kg, 30 min after intraperitoneal injection of either ranitidine 83 mg/kg (238 μM /kg), ranitidine 166 mg/kg (476 μM /kg), cimetidine 120 mg/kg (476 μM /kg) or 0.9% saline. (ii) The effect of chronic drug administration was determined by dosing rats with either ranitidine 166 mg/kg or 0.9% saline 12 hourly for 4 days. A 24 h period was then allowed between final drug administration and measurement of pentobarbitone sleeping time.

Results

1. Effect of ranitidine on the steady state pharmacodynamics and pharmacokinetics of warfarin in volunteers

A mean daily warfarin dose of 3.4 mg (range 2.5–4.5 mg) prolonged the mean prothrombin time by 3.3 s. The addition of ranitidine did not significantly alter the prothrombin time nor was there a significant change in plasma warfarin concentration (Figure 1,

Figure 1 Effect of ranitidine on steady state warfarin concentrations and prothrombin times (mean $\pm$ s.e. mean) in five volunteers.

Table 1). There was not a significant change in prothrombin time or plasma warfarin concentration when ranitidine was discontinued.

2. Rat studies

(a) *Effect of ranitidine on the single dose pharmacodynamics and pharmacokinetics of warfarin in the rat* There was no difference in the anticoagulant effect of the single dose of warfarin in rats treated with either ranitidine or saline (Figure 2). There was no difference in the pharmacokinetics of warfarin (half-life, apparent volume of distribution or clearance) in rats treated with either ranitidine or saline (Table 2). Ranitidine alone had no anticoagulant effect.

- (b) *Pentobarbitone sleeping times in rats* (i) When ranitidine was given 30 min before pentobarbitone sleeping times were not affected (Table 3) but an equivalent dose of cimetidine produced a highly significant ($P < 0.001$) prolongation of sleeping time. (ii) Chronic pretreatment with ranitidine did not

Table 1 Effect of ranitidine on steady state warfarin dynamics and kinetics. Mean results at the end of each treatment period $\pm$ s.e. mean.

	Control	Warfarin (Days 12–14)	Warfarin + ranitidine (Days 26–28)	Warfarin (Days 40–42)
Prothrombin time (s)	14.9 ± 0.4	18.2 ± 0.5	17.1 ± 0.4	16.3 ± 0.3
Plasma warfarin concentration ($\mu\text{g/ml}$)		0.61 ± 0.13	0.62 ± 0.13	0.70 ± 0.14

Differences between treatment periods not significantly different.

Figure 2 Prothrombin complex activity in the rat after a single dose of warfarin (mean $\pm$ s.e. mean). $\blacktriangle$ ranitidine treated rats ($n = 6$), $\blacktriangledown$ saline treated rats ($n = 6$) and $\square$ ranitidine treated rats which did not receive warfarin.

affect the sleeping times. Ranitidine treated animals slept for 63 ± 9 min; saline treated animals 69 ± 6 min (mean $\pm$ s.e. mean).

Discussion

We have previously shown that the addition of cimetidine significantly increased the anticoagulant effect of warfarin and produced a rise in steady state warfarin concentration in volunteers (Serlin *et al.*, 1979). Using a similar protocol, we have been unable to show that ranitidine caused a significant change in either the prothrombin times or in plasma warfarin concentration in five volunteers. Since the doses of cimetidine and ranitidine were therapeutically equivalent in terms of inhibition of gastric acid secretion (Domschke, Lux & Domschke, 1979) it appears unlikely that the potentiation of warfarin action by cimetidine could be due to histamine H_2 -receptor antagonism.

Table 3 Pentobarbitone sleeping times 30 min after pretreatment (mean $\pm$ s.e. mean).

Pretreatment	Sleeping time (min)
0.9% saline (control)	79 $\pm$ 8
Ranitidine 83 mg/kg	73 $\pm$ 1
Ranitidine 166 mg/kg	84 $\pm$ 7
Cimetidine 120 mg/kg	318 $\pm$ 52***
Significance of difference from control *** $P < 0.001$.	

The lack of effect of therapeutic doses of ranitidine on plasma warfarin concentrations suggests that, unlike cimetidine, it does not inhibit warfarin metabolism. A similar lack of effect by ranitidine on antipyrine and aminopyrine metabolism has been shown by Henry *et al.* (1980). Because of its greater potency the therapeutic dose of ranitidine is only one third that of cimetidine. We therefore conducted studies in the rat using equivalent doses of ranitidine and cimetidine (a dose of cimetidine being chosen which had previously been shown to inhibit drug metabolism and potentiate warfarin action in the rat (Serlin *et al.*, 1980)). Ranitidine did not affect the anticoagulant action of a single dose of warfarin nor did it have any effect on warfarin distribution or elimination, whereas the same molar dose of cimetidine potentiated warfarin action and slowed its elimination (Serlin *et al.*, 1980). Similarly ranitidine pretreatment did not prolong pentobarbitone sleeping times whereas cimetidine produced a highly significant increase in sleeping time. The lack of effect on sleeping times of repeated ranitidine administration suggests that it is not acting as an inducer of liver microsomal enzymes.

Substituted imidazoles (of which cimetidine is an example) are potent inhibitors of hepatic microsomal enzyme oxidase activity (Wilkinson, Hetnarski & Hicks, 1974). The results of these studies suggests that ranitidine, lacking an imidazole ring also lacks the property of inhibiting drug metabolism possessed by cimetidine and that the difference between the two drugs is not merely due to their different potencies as H_2 -receptor antagonists. Since ranitidine does not interact with warfarin in volunteers it may be more suitable for anticoagulated patients who require treatment with a histamine H_2 -receptor antagonist.

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Table 2 Single dose warfarin kinetics in male Wistar rats (mean $\pm$ s.e. mean)

	Half-life (h)	V_d (ml/kg)	Clearance (ml kg^{-1} h^{-1})
Ranitidine treated animals ($n = 6$)	12.1 $\pm$ 0.4	308 $\pm$ 21	17.5 $\pm$ 0.8
Saline treated animals ($n = 6$)	12.5 $\pm$ 0.4	359 $\pm$ 23	19.8 $\pm$ 0.8

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