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EFFECTS OF EQUIMOLAR DOSES OF CIMETIDINE AND RANITIDINE ON THEOPHYLLINE ELIMINATION

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ABSTRACT

The disposition of theophylline was studied on four occasions in eight healthy adult males. The control mean theophylline half-life and clearance were 7·32 h and 0·86 ml $min^{-1}kg^{-1}$, respectively. After 5 days pretreatment with placebo the corresponding values of 7·01 and 0·88 were not significantly different, as were those of 7·43 and 0·85 after 5 days pretreatment with ranitidine (1·2 g daily). Five days pretreatment with cimetidine (1·0 g daily) resulted in a significant 44·4 per cent rise in the mean theophylline half-life and a 36·1 per cent fall in clearance. The fall in clearance correlated positively (r=0·9407) with the initial value. The volume of distribution did not change significantly throughout the study period. The fact that, at as large a dose as 1·2 g daily, ranitidine did not impair theophylline metabolism suggests that similar results reported earlier with therapeutic doses of 300 mg daily cannot be ascribed to the lower dose of ranitidine employed. It is also suggested that the risk of theophylline toxicity consequent on cimetidine coadministration will be more likely in individuals with initial high theophylline clearance.

KEY WORDS Cimetidine Placebo Ranitidine Theophylline clearance

INTRODUCTION

The histamine H_2-receptor antagonist, cimetidine, has become one of the most widely prescribed drugs.[1] Used in the management of peptic ulcer its action cannot, however, be considered specific. It has antiandrogenic activity and also inhibits hepatic microsomal mixed function oxygenases.[2] Because of this, cimetidine impairs the biotransformation of other drugs catalysed by the same enzyme system.[3] With the introduction of a substituted aminoalkylfuran ranitidine as another histamine H_2-receptor blocker for the management of peptic ulcer, its comparison with cimetidine was inevitable. While it is agreed that ranitidine is more potent than cimetidine,[4,5] it cannot be absolved of endocrine side-effects similar to those of cimetidine.[6] As regards its effect on the

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hepatic cytochrome P-450 enzyme system most studies indicate that ranitidine does not inhibit metabolism of other drugs catalysed by this enzyme system.[7]

In an earlier report[8] we observed that the usual therapeutic doses of cimetidine (1000 mg daily) and ranitidine (300 mg daily) employed in assessing their interaction or otherwise with mixed function oxygenases in liver microsomes are in a molar ratio of about 4·2 to 1 and went further to suggest the need to evaluate ranitidine at a molar dose comparable to that of cimetidine with the view to finding out if this high dose will significantly impair metabolism of other drugs. The need for such assessment is supported by the fact that microsomal enzyme inhibition is dose-dependent in both animals[9] and man[10] and that ranitidine at high doses does indeed impair aminopyrine and acetaminophen metabolism.[9,11]

Although the usual therapeutic dose of ranitidine is 0·3 g daily higher doses cannot be ruled out in therapeutics. Daily maintenance doses of 0·45 – 3·6 g (mean ± SD, 2·16 ± 1·71) were reported by Collen *et al.*[12] in thirteen patients (twelve with Zollinger–Ellison syndrome and one with idiopathic gastric hypersecretion). The median daily maintenance dose for these patients was 1·2 g and this, incidentally, is equimolar to 1 g cimetidine used for peptic ulcer management.

Thus the assessment of the potential of ranitidine, as a hepatic microsomal inhibitor, at as high a dose as 1·2 g was of clinical relevance. This realization, as well as reports that ranitidine, at a dose of 0·3 g daily, impaired metabolism of metoprolol[13] and warfarin,[14] prompted the undertaking of this study.

MATERIALS AND METHODS

Eight healthy non-smoking males participated after informed consent. Non drink alcohol. They were 22 to 32 years of age (mean ± SEM; 26·13 ± 1·29) and weighed 52·5 to 72 kg (mean ± SEM 63·38 ± 2·37). They were adjudged healthy on the basis of clinical examination and laboratory investigations: Hb, WBC (total and differential), PCV, MCHC, plasma urea and electrolytes (Na^+, K^+, CL^-, HCO_3-), bilirubin, alkaline phosphatase, SGOT, SGPT, and plasma proteins. Drugs known to either inhibit or induce hepatic microsomal enzymes had not been taken by any of the subjects within 3 months prior to participation.

Theophylline disposition was studied on four occasions in each subject:

1. without any drug pretreatment (control);
2. after pretreatment with purchased cimetidine (200 mg thrice daily and 400 mg at night);
3. after pretreatment with purchased ranitidine (300 mg four times daily);
4. after pretreatment with cimetidine placebo (equivalent to cimetidine 200 mg thrice daily and 400 mg at night).

The placebo was indistinguishable from the 200 mg tablets of active drug. All medications were coded and given to each volunteer at the beginning of the

study and the order of the four phases was left to his discretion. The order of treatments is shown in Table 1. Throughout the study, the investigator was not aware of who was taking what at any time. Medication was for 5 days and the same duration was allowed as "washout" period between treatments. Each study of theophylline disposition was preceded by a 48 h abstention from dietary methylxanthines and an overnight fast.

Table 1. Order of treatments in eight healthy subjects (Co: control, PL: placebo, CM: cimetidine, RN: ranitidine)

Subject	Treatment		Sequence	
	1	2	3	4
1	CO	PL	RN	CM
2	CO	RN	CM	PL
3	PL	CO	RN	CM
4	RN	PL	CO	CM
5	PL	CO	CM	RN
6	CM	RN	PL	CO
7	PL	CM	CO	RN
8	CO	RN	CM	PL

On the morning of the fifth day of each treatment theophylline (5·0 mg kg^{-1}) was given as aminophylline (6·25 mg kg^{-1}) intravenously over 30 min. Using the midpoint of this period as the time zero, venepuncture was made at 1, 2, 4, 6, 8, 10, 12, 15, and 24 h post dosing, dietary methylxanthine restriction being maintained till the last blood sampling time. Blood taken immediately before theophylline dosing served as 'blank'. All blood samples were immediately centrifuged and the plasma kept frozen for theophylline assay within 2 weeks by the method of Schwertner *et al.* as previously reported.[15] For this study recovery at 2·5, 5, 10, and 20 $\mu g\,ml^{-1}$ (n=4 at each concentration) were (mean ± S. D.) 88·17 per cent ± 1·23, 86·84 per cent ± 2·02, 89·96 per cent ± 2·55 and 91·39 per cent 2·25, respectively. At these concentrations, coefficients of variation were <4·0 per cent.

Regression analysis of the curve relating plasma theophylline concentration to time was conducted with a model HP – IIC Hewlett-Packard programmable calculator (Figure 1). The overall elimination rate constant, k, was obtained from the slope of the curve and the theophylline half-life, $t_{1/2}$(h), was calculated from the relationship $t_{1/2}=0{\cdot}693/k$.

The area under the plasma concentration–time curve from zero to 24 h was calculated by the trapezoidal rule. Extrapolation to infinity was effected by

adding this to the quotient C_{24}/k (C_{24}=plasma theophylline concentration at 24 h). Total clearance, CL (ml $min^{-1}kg^{-1}$), and volume of distribution, V_d ($l\,kg^{-1}$), were calculated as follows:

$$CL = \frac{D \times 10^3}{(AUC) \times 60 \times BW}$$

$$V_d = \frac{D}{(AUC) \times k \times BW}$$

where BW = body weight (kg), D = dose of theophylline (mg) given and (AUC) = area under plasma concentration–time curve from zero to infinity ($mg\,h\,l^{-1}$).

Data analysis was by means of analysis of variance and, when indicated, a paired Student's t-test was used for comparison between means. In all cases $p<0{\cdot}05$ was taken as the minimum level of significance. Results are presented as means ± S.D.

RESULTS

Clinical examination and laboratory investigations were normal in all the volunteers after the study period. None admitted, upon inquiry, to non-

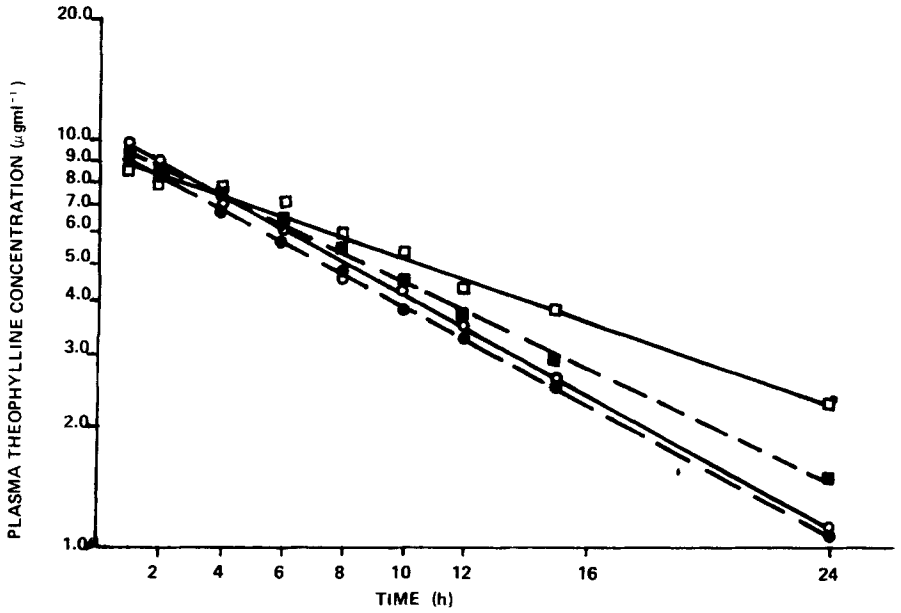

Figure 1. Theophylline plasma concentration–time profiles in subject 3 before (●———●) and after pretreatment with placebo (○———○), ranitidine (■———■), and cimetidine (□———□)

compliance to medication throughout the study period. Aside of pretreatment with cimetidine which was associated with reduction in theophylline clearance in all cases irrespective of the preceding treatment no consistent pattern of changes in relation to treatment sequence was discernible in other phases of the study.

Plots of plasma theophylline concentration against time on a semilogarithmic scale for subject 3 are shown in Figure 1. Data for this subject were chosen because they gave the most distinct curves. However, although curves for others were less distinct, on no occasion was the correlation coefficient (r) from regression analysis inferior to –0·9633.

Table 2. Pharmacokinetic parameters of theophylline in eight healthy subjects before (control) and after pretreatment with placebo, ranitidine and cimetidine (mean ± S.D.)

Treatment	$t_{1/2}$ (h)	V_d ($l\,kg^{-1}$)	CL ($ml\,min^{-1}\,kg^{-1}$)
Control	7·32 ± 1·16	0·534 ±0·108	0·86 ±0·24
Placebo	7·01 ± 1·24	0·524 ±0·114	0·88 ±0·20
Ranitidine	7·43 ± 1·66	0·526 ±0·133	0·85 ±0·28
Cimetidine	10·57* ± 1·52	0·495 ±0·095	0·55* ±0·10

*Significant compared with the control value ($p<0·001$).

Neither placebo nor ranitidine pretreatment significantly altered the control theophylline $t_{1/2}$ or CL (Table 2). However, the change in theophylline $t_{1/2}$ from a mean control value of 7·32 h ± 1·16 to 10·57 h ± 1·52 (representing 44·4 per cent increase) after cimetidine pretreatment was significant (t=6·845, $p<0·001$). There was a consistent fall in theophylline CL (Figure 2) and the mean 36·1 per cent fall from 0·86 $ml\,min^{-1}kg^{-1}$ ± 0·24 to 0·55 $nl\,min^{-1}kg^{-1}$ ± 0·10 was also significant (t=5·471, $p<0·001$) (Table 2). Compared with placebo, cimetidine induced similar changes ($p<0·001$) in both $t_{1/2}$ and CL, and the same could be said of its comparison with ranitidine ($p<0·001$ for $t_{1/2}$ and $p<0·005$ for CL).

When analysed, the data showed that the absolute fall in CL was very much dependent on the initial CL value. With the former on the ordinate, the equation $y = 0·6451\,x - 0·2393$ relates the two variables and the correlation coefficient, r, was 0·9407 (Figure 3).

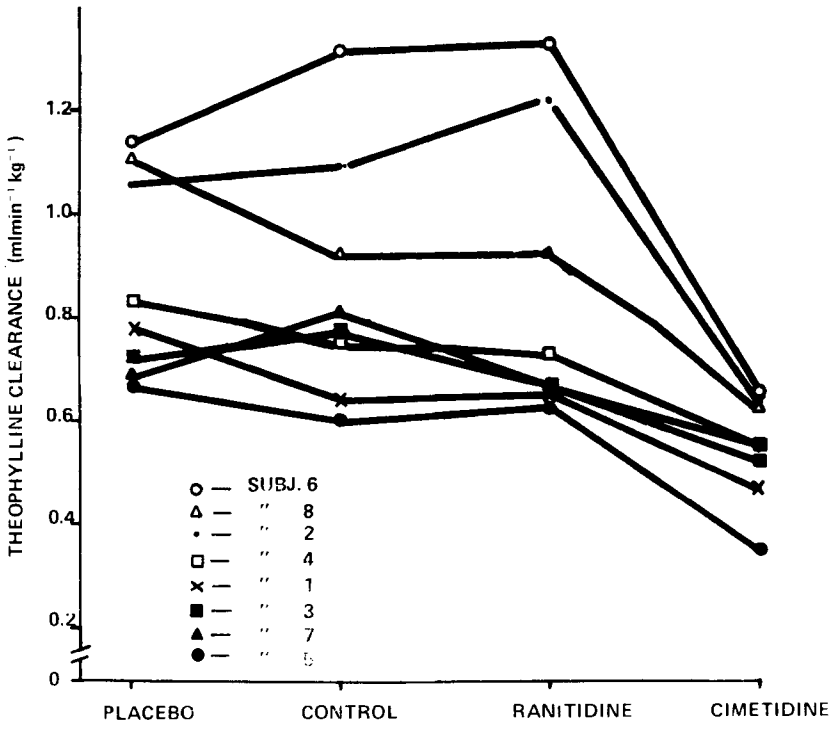

Figure 2. Theophylline clearance in volunteers before and after pretreatment with placebo, ranitidine, and cimetidine

The volume of distribution did not change significantly throughout the study period ($F = 0{\cdot}1802$) (Table 2).

DISCUSSION

The relationship between the absolute fall in CL and its initial value obtained in this study is similar to that from the data by Reitberg *et al.*[16] ($y = 0{\cdot}8052x - 0{\cdot}2871$; $r = 0{\cdot}9206$). For individuals on theophylline therapy, the steady state plasma concentration, C_{ss}, is related to CL as follows (assuming complete absorption): $C_{ss} = \frac{D}{\tau\,CL}$ (where D = the maintenance dose of theophylline and τ □ dosing interval). Consequently, with a particular maintenance dose and a fixed dosing interval (as is usually the case) CL becomes the sole determinant of C_{ss}. On the basis of the above relationship, it would appear that cimetidine coadministration, in the absence of a reduction in theophylline maintenance

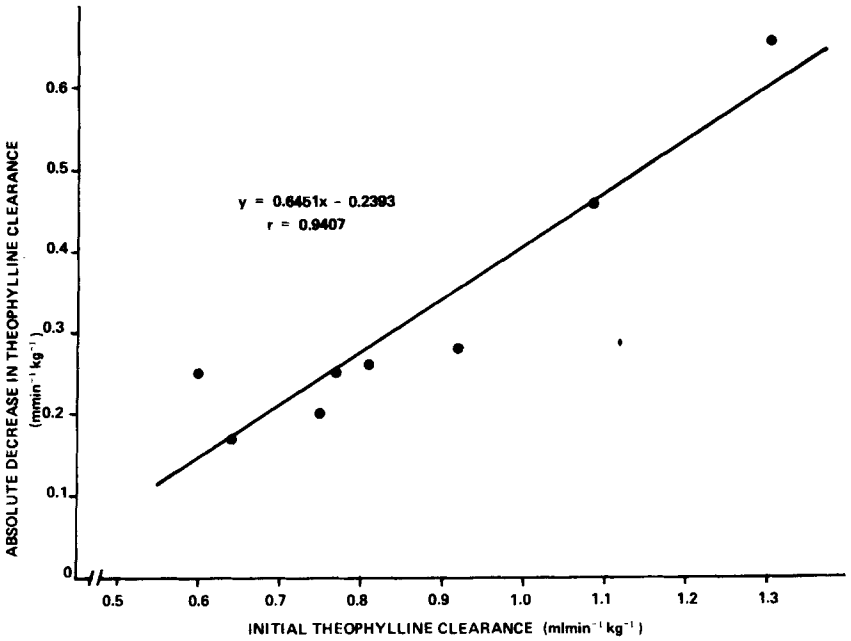

Figure 3. Relationship between initial theophylline clearance and its absolute fall after pretreatment with cimetidine (1·0 g daily for 5 days) in eight healthy volunteers

dose or/and prolongation of dosing interval, would be more likely to lead to theophylline toxicity in individuals with high initial CL values.

Table 2 shows that after pretreatment with placebo and ranitidine, the mean theophylline CL did not change significantly from its control value. A look at Figure 2, however, shows considerable changes in this parameter in each volunteer during these three phases of the study. This, perhaps, is to be expected given the large intraindividual variation in theophylline kinetics reported in both children[17] and adults.[18]

The observation that ranitidine, at an equimolar dose to that of cimetidine, did not impair theophylline clearance suggests that similar results reported earlier[8,19,20] were not due to the lower but therapeutic dose (300 mg) employed in such studies.

On the basis of the fact that ranitidine is more potent than cimetidine,[4,5] it also suggests that histamine H_2-receptor antagonism and hepatic microsomal enzyme inhibition could be unrelated and dissociated attributes of histamine H_2-receptor antagonists. That this could be true is attested to by the fact that a substituted thiazole, famotidine, though even more potent that ranitidine,[21] failed to alter antipyrine disposition in healthy subects despite the fact that cimetidine did impair the metabolism of the pyrazolone derivative in the same individuals.[22]

Theophylline toxicity occasioning ranitidine coadministration has been reported in two elderly patients on maintenance dose with a sustained-release formulation.[23,24] While inhibition of theophylline metabolism by ranitidine may be suggested as one of the possible factors responsible for this adverse reaction, the reported unpredictable inconsistency in absorption from this formulation[25,26] is a strong point contesting the validity and acceptability of such suggestion.

A non-randomized, non-placebo controlled study by Spahn *et al.*[13] indicated that a 300 mg daily dose of ranitidine for 7 days impaired metoprolol elimination. Interference with the metabolism of the drug was suggested as the cause. It is, however, noteworthy that the fact that metoprolol has a high extraction ratio[27] implies that reduction in liver blood flow could significantly impair its clearance.[28] For the inhibition of microsomal enzymes by ranitidine to be considered responsible for the impaired metoprolol elimination, therefore, this possibility need be excluded because ranitidine is known to be capable of reducing liver blood flow by about 20 to 40 per cent.[6] However, it may well be that impairment of liver blood flow was of no importance as Arditi *et al.*,[29] using a sorbitol clearance technique, have questioned its significance.

If the need to exclude the effect of ranitidine on hepatic blood flow is considered critical to ascribing its impairment of metoprolol elimination to inhibition of hepatic microsomal enzymes, the same cannot be said for its impairment of warfarin clearance as reported by Desmond *et al.*[14] This drug has a low extraction ratio[27] and a perfusion limited model of hepatic drug elimination suggests that its clearance could be very sensitive to alteration in enzyme activity but independent of liver blood flow.[28] However, although the report by Desmond *et al.*[14] will be inconsonance with the theoretical expectation if it is true that ranitidine does indeed inhibit hepatic mixed-function oxygenases, it need be noted that reports on the ranitidine/warfarin interaction are discrepant, Serlin *et al.*[30] having reported a lack of inhibitory effect of ranitidine on warfarin metabolism.

Results from this study show that impairment of theophylline metabolism by ranitidine is unlikely even when the histamine H_2-receptor antagonist is given at a large daily dose (1·2 g) equimolar to that of cimetidine (1·0 g daily). The earlier reported lack of interaction of ranitidine, at the therapeutic dose of 300 mg daily, with the bronchodilator could not, therefore, have been due to the lower dose of the antihistamine employed in such studies.

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