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Effect of famotidine on theophylline pharmacokinetics in the rat

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Summary

The effect of famotidine (4 mg/kg, p.o.) on the pharmacokinetic profile of coadministered theophylline was studied in the rat. Plasma theophylline concentration was measured serially for 12 h by HPLC. Peak plasma levels (Cp_{max}) and the time at which these were attained (T_{max}) were not significantly altered during coadministration. There were, however, reductions in both the elimination half-life ($t_{1/2}$) and the area under the curve (AUC) but only the changes in the latter parameter reached the level of significance. These data suggest that the kinetic interaction between famotidine and theophylline is very limited and that it may feature hepatic enzyme induction as opposed to the inhibitory effect documented for cimetidine.

Introduction

Famotidine, a guanylthiazole derivative, is a new member of the histamine H_2-receptor antagonist drugs that are currently used in the treatment of duodenal and benign gastric ulcers (Carpenter and Fisher, 1985). It is now firmly established from both animal and clinical studies that cimetidine, the commercial prototype H_2-antagonist, inhibits phase I hepatic metabolic reactions by binding with the cytochrome P-450 system (Knödell et al., 1982; Rendic et al., 1983). This pharmacological property is largely responsible for the bulk of drug interactions documented with cimetidine. By impairing hepatic microsomal drug oxidizing capacity, cimetidine and to a lesser extent ranitidine, reduce total body clearance of a number of coadministered drugs (Somogyi and Gugler, 1982). Famotidine, with its marked potency over its predecessors in inhibiting gastric acid secretion and its apparent lack of drug interaction (Humphries 1987; Somerville et al., 1986) would seem to offer an improved treatment for gastroduodenal ulcers and other hypersecretory conditions such as Zollinger-Ellison syndrome.

The drug interaction potential of famotidine has largely been evaluated with the use of model drugs that are dependent on either hepatic oxidative metabolism or tubular secretion for their total body clearance (Humphries, 1987; Klotz et al., 1985). A potential candidate for drug interaction study with famotidine is theophylline, a potent bronchodilator, which is extensively metabolized by liver microsomal enzymes. The occurrence of gastrointestinal ulcers in patients with asthma or chronic obstructive lung disease is not uncommon. It is likely, therefore, that famotidine may constitute the anti-ulcer therapy component in the

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clinical management of such conditions. In this study, we attempt to determine whether famotidine alters the pharmacokinetic profile of orally coadministered theophylline in the rat.

Materials and Methods

Animal preparation and sample collection

Male albino rats of Wistar origin weighing 300–350 g were randomly assigned to either test or control group ($n = 8$) and treated daily with famotidine (4 mg/kg p.o.) or vehicle (normal saline with 0.5% Tween 80) for 5 days. After the last dose, the animals were fasted overnight (water given ad-libitum) and cannulation of the right femoral artery was performed under light ether anaesthesia using a segment of heparinized polyethylene tubing (PE-50, Jenkons Sci. Ltd, U.K.). Following recovery from the anaesthesia, the test-group was orally dosed with famotidine (4 mg/kg) and theophylline (25 mg/kg) while the control group received theophylline and vehicle only. The animals were then placed in especially adapted rat restraining cages to facilitate subsequent blood sampling. Blood samples (ca. 0.3 ml) were collected via the indwelling cannula into small heparinized Eppendorff tubes before and then serially at 15, 30, 60 min and 2, 3, 4, 6 up to 12 h after theophylline administration. The cannula was flushed with an equal volume of normal saline after each sample withdrawal. The blood samples were immediately centrifuged and 100 μl aliquots of plasma were stored at $-20\,^{\circ}C$ for subsequent drug level assay.

Drug analysis

To each plasma sample was added 100 μl of acetonitrile (containing the internal standard caffeine) and the contents of the tube were vortex-mixed for 2 min to allow effective precipitation of plasma proteins. The mixture was then centrifuged at 4000 *g* for 15 min and the resulting supernatant used in the chromatographic assay which involved a reversed-phase HPLC technique. This comprised a Waters Associate chromatograph (M.A., U.S.A.) equipped with a sample processor (WISP-710B), a system controller (M-720), a data module (M-730) and a variable Wavelength UV detector (M-481). The samples were run on a μ-Bondapack C18 cartridge column (10 μ, 10 cm × 8 mm i.d.) using acetonitrile-phosphate (K_2HPO_4, 0.01 M) buffer mixture (8 : 92 v/v) adjusted to pH 6, at a flow rate of 4 ml/min, as the mobile phase. The effluent was monitored at 280 nm. Plasma theophylline level was quantified with the use of calibration curves prepared on the day of sample assay.

Data analysis

Peak plasma levels (Cp_{max}) and the times at which these values were attained (t_{max}) were determined by graphical inspection. The elimination half-life ($t_{1/2}$) was calculated from the elimination rate constant (K_{el}) derived from the slope of the terminal log-linear portion of the plasma concentration–time curve by using least square regression analysis. The area under the plasma concentration-time curve (AUC) was computed by means of the trapezoidal rule. Differences in the values of pharmacokinetic parameters between the treatment groups were statistically evaluated using a two-tailed Student's *t*-test with a probability (P) value of 0.05 or less taken as significant. All values are reported as the mean ± S.E.M.

Results

The mean plasma concentration–time profiles of theophylline (25 mg/kg, p.o.) under the single and drug combination regimens are shown in Fig. 1. The data fitted a single-compartment open model with first order kinetics and the pharmacokinetic parameters derived from this data are listed in Table I.

Theophylline absorption was fairly rapid in both study phases. Peak plasma levels of 21.39 ± 0.85 and 19.11 ± 1.4 were observed at 1.45 ± 0.28 and 1.59 ± 0.27 h in the single and drug combination group, respectively. Theophylline levels were generally lower at all time points in the famotidine–theophylline treated group than in the control. This was reflected in a significant difference between the values of the respective AUCs. Comparison of the Cp_{max} and T_{max} values in the two groups, however, failed to show a similar level of

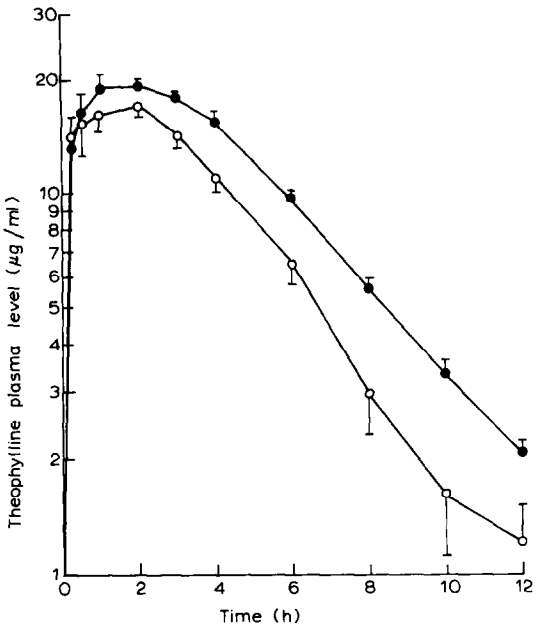

Fig. 1. Mean (±S.E.M.) plasma concentration–time profile of the theophylline (25 mg/kg, p.o) administered to rats alone (●) or in combination (○) with 4 mg/kg famotidine. ($n = 8$).

significance. The mean elimination half-life of theophylline in the control group (2.68 ± 0.18 h) was higher than that observed in the drug combination group (2.27 ± 0.24 h) but here too, the difference was not statistically significant.

TABLE 1

Mean (± S.E.M.) computed pharmacokinetic parameters for theophylline (25 mg/kg) administered alone or in combination with famotidine (4 mg/kg)

Pharmacokinetic parameters	Mean ± S.E.M. ($n = 8$)		Statistics (t-test)
	Alone	With famotidine	
Cp_{max} (μg/ml)	21.39 ± 0.85	19.11 ± 1.4	NS
T_{max} (h)	1.45 ± 0.28	1.59 ± 0.27	NS
$t_{1/2}$ (h)	2.68 ± 0.18	2.27 ± 0.24	NS
AUC up to 12 h (μg·h·ml^{-1})	123.31 ± 5.18	90.24 ± 4.49	S
AUC up to infinity (μg·h·ml^{-1})	131.68 ± 6.26	94.86 ± 5.60	S

Values are means ± S.E.M. S = significant; NS = non-significant.

Discussion

Histamine H_2-receptor antagonists have the potential to alter the disposition characteristics of other drugs through their effect on gastric pH and hepatic haemodynamics (Garg et al., 1982; Powell and Donn, 1984). Thus the absorption profile of weakly acidic or basic drugs may be particularly sensitive to changes in intragastric pH. Reduced hepatic blood flow induced by H_2-antagonists may also influence the disposition characteristics of drugs with high hepatic extraction ratio. The prominent feature of drug interaction seen with the histamine H_2-receptor antagonists, however, relates to their ability to inhibit hepatic oxidative metabolism of a number of drugs. This pharmacological property has been fully documented for cimetidine and to a lesser extent for ranitidine (Somogyi and Muirhead, 1987; Lee and McDowall, 1986).

The findings of the present study involving theophylline and famotidine do not seem to be like the type of interaction seen with cimetidine. The relatively small reductions in both the rate and extent of theophylline absorption seen during famotidine coadministration could have resulted from a combination of pH changes in the gastric milieu and reduced hepatic blood flow. The contribution of the latter may, however, be minimal since theophylline with its low hepatic extraction ratio is least affected by such haemodynamic changes (Powell and Donn, 1984).

The result also suggests that there may be a different form of drug interaction between famotidine and theophylline as evidenced by the apparent (but not significant) shifts in $t_{1/2}$ and the significantly reduced AUC values. Unlike the interaction seen with cimetidine, theophylline total body clearance appears to be enhanced by concurrently administered famotidine. This may imply a milder form of enzyme-inducing activity for famotidine in contrast to the inhibitory influence observed with cimetidine. Famotidine is structurally different from both cimetidine and ranitidine. Its guanylthiazole structural variation appears to be responsible for the marked H_2-antagonist activity while conferring on the molecule a much lower binding capacity for the hepatic cytochrome P450

system which is involved in the oxidative metabolism of many drugs (Klotz et al., 1985). Previous studies have noted low level enzyme-inducing activity with famotidine but this effect was not sufficiently highlighted (Humphries, 1987; Locniskar et al., 1986). The present study confirms the mild enzyme-inducing activity of famotidine and relates favourably with an earlier report comparing famotidine with cimetidine in human volunteers (Chermos et al., 1986). A much longer pretreatment period (our study used 5 days), and perhaps a higher dose of famotidine are required in further studies to characterise the significance of a famotidine–theophylline interaction.

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