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Factors affecting the response to inhibition of drug metabolism by cimetidine—dose response and sensitivity of elderly and induced subjects

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1 The effect of cimetidine on oxidative drug metabolism was characterised using antipyrine clearance in a group of healthy volunteers.

2 In six subjects cimetidine produced a dose dependent reduction of antipyrine clearance: 400 mg/day (16.8 ± 2.2%, mean ± s.e. mean), 800 mg/day (26.3 ± 1.5%) and 1600 mg/day (33.5 ± 2.4%).

3 The effect of cimetidine (800 mg/day) was of similar magnitude (approximately 25%) in two groups of six young (21–26 years) and six elderly (65–78 years) subjects.

4 The effect of pretreatment begun just 1 h before administration of antipyrine was similar to that of 24 h pretreatment and that reported for chronic cimetidine pretreatment.

5 The percentage reduction in antipyrine clearance produced by cimetidine 800 mg/day was greater (44 ± 5 *vs* 24 ± 3%; $P < 0.05$) in six subjects who had been pretreated with the hepatic enzyme inducer rifampicin (600 mg/day for 21 days) than in the control uninduced state.

6 Although cimetidine was capable of rapidly reversing the effect of rifampicin on antipyrine clearance, following withdrawal of both rifampicin and cimetidine there was still evidence of enzyme induction.

7 These results suggest that the effect of cimetidine on oxidative metabolism is dose dependent, is more marked in enzyme induced subjects, is independent of the duration of pretreatment and is of similar magnitude in young and elderly subjects.

Keywords cimetidine elderly subjects induced subjects drug metabolism

Introduction

Cimetidine has been shown in man to impair the oxidative metabolism of a wide range of drugs including antipyrine (Serlin *et al.*, 1979; Klotz & Reimann, 1980), chlordiazepoxide (Patwardhan *et al.*, 1981) diazepam (Klotz & Reimann, 1980), propranolol (Feely *et al.*, 1981) and warfarin (Serlin *et al.*, 1979). As a substitutued imidazole compound it was anticipated and confirmed that cimetidine inhibits oxidative metabolism in liver-microsomes (Rendic *et al.*, 1979). Preliminary observations (Feely *et al.*, 1981) in man suggested that the inhibition of propranolol metabolism by cimetidine is related to the circulating steady-state concentrations of cimetidine. As this histamine H_2-antagonist is relatively non-toxic (Feely & Wormsley, 1983) and widely used in patients of all ages it provides a useful tool for the further study of factors affecting the response to inhibition of drug metabolism in man. We used antipyrine clearance as the *in vivo* index of oxidative metabolism because it is highly reproducible and sensitive to drug induced alteration in metabolism (Vesell, 1979).

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Methods

The clearance of antipyrine was measured in healthy volunteers with normal renal and hepatic function in three separate studies which had the approval of the Local Ethics Committee.

Cimetidine dose-response

Six young subjects (aged 20–28 years) (three female) were studied in random order during treatment with:

(i) placebo (control);
(ii) cimetidine 100 mg;
(iii) cimetidine 200 mg;
(iv) cimetidine 400 mg;

All doses were given orally four times daily for 24 h before and throughout the sampling period (30 h) following administration of antipyrine. Each study was separated from each other by at least 5 days.

Comparison of young with elderly subjects

Two groups of six male subjects one young (21–26 years) and the other elderly (65–78 years) were studied during treatment in random order with either placebo (control) or cimetidine 200 mg given four times daily for 24 h before and throughout the sampling period.

Non-induced vs *induced state*

Six young (20–30 years) subjects (three female) were studied in random order (i) as control and (ii) during treatment with cimetidine 200 mg given four times daily but commencing only 1 h before antipyrine administration and continuing throughout the sampling period. One week later subjects were again studied (iii) as control and then commenced on rifampicin 600 mg daily. Antipyrine clearance was determined (iv) on day 15 of treatment with rifampicin and (v) on day 21 when cimetidine 200 mg four times daily, commencing 1 h before antipyrine administration, was given and continued throughout the sampling period. Rifampicin therapy was stopped after 21 days and 3 days later in three subjects antipyrine clearance (vi) was determined once more.

One additional subject (J.D.) was studied as above except that in (ii) cimetidine 400 mg was administered and during (v) cimetidine 400 mg was given 12 h following antipyrine administration and the sampling period was extended to 36 h.

Antipyrine (8 mg/kg) was administered orally, diluted in orange juice (200 ml), in the morning to fasting subjects. Salivary samples were collected before and 3, 6, 9, 12, 24 and 30 h following administration of antipyrine. Samples were frozen at −20°C until assayed in duplicate by gas-liquid chromatography as previously described (Prescott *et al.*, 1973). Samples from each individual were assayed at the same time and the coefficient of variation of the assay was 6%. Clearance values were estimated from the elimination rate constant of the logarithm of the salivary concentration-time curve and the extrapolated zero time sample. Statistical analysis was performed using ANOVA, a paired Student's *t*-test and correlation by least squares regression analysis.

Results

Cimetidine dose-response

The effect of increasing doses of cimetidine on the oral clearance of antipyrine is shown in Table 1 with the data from one subject shown in Figure 1. The percentage reduction in antipyrine clearance (400 mg/day–16.8 ± 2.2%; 800 mg/day–26.3 ± 1.5%; 1600 mg/day–33.5 ± 2.4%) appeared less marked with increasing doses of cimetidine.

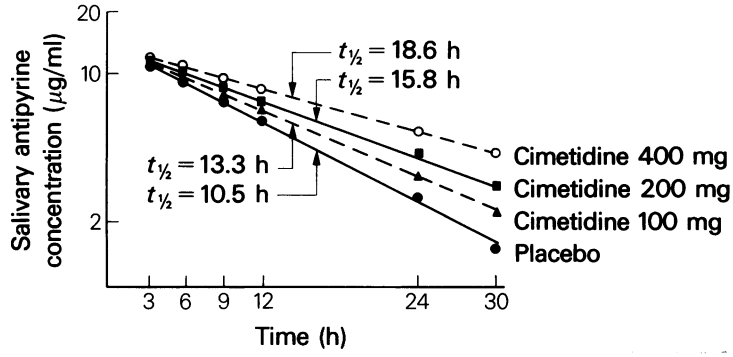

Figure 1 Antipyrine concentrations and elimination half-life ($t_{½}$) during treatment with either placebo, cimetidine 100 mg, 200 mg or 400 mg four times daily.

Table 1 Effect of increasing doses of cimetidine on antipyrine clearance in six subjects (mean ± s.e. mean)

	Elimination $t_{1/2}$ *(h)*	*Clearance (ml/min)*
Control (placebo)	9.9 ± 0.8	49.4 ± 2.5
Cimetidine 400 mg	11.3 ± 1.0	41.0 ± 1.9*
Cimetidine 800 mg	13.0 ± 1.3	36.3 ± 1.6*
Cimetidine 1600 mg	14.1 ± 1.1	32.9 ± 2.1*

*$P < 0.05$; 1600 > 800 > 400 > Control

Comparison of young with elderly subjects

The magnitude of effect of cimetidine 800 mg/day was similar in young and elderly subjects (Figure 2).

Non-induced vs *induced state*

The percentage reduction in antipyrine clearance following cimetidine was significantly greater (44 ± 5% *vs* 24 ± 3%; $P < 0.05$) in the induced than in the non-induced state (Table 2). In the three subjects who had antipyrine clearance determined 3 days following cessation of rifampicin there still was evidence of enzyme induction (placebo 46 ± 3.1 ml/min, rifampicin (day 15) 91.8 ± 11.5 ml/min, rifampicin and cimetidine 62.0 ± 9.1 ml/min and off rifampicin 68.2 ± 2.7 ml/min). Figure 3 summarises the results from subject J.D. where cimetidine (1600 mg/day) was commenced 12 h following administration of antipyrine.

In the five subjects who participated in both the first and third studies the effect of cimetidine commenced 24 h (25%) prior to antipyrine was similar to that (24%) seen when cimetidine was commenced 1 h before antipyrine.

Discussion

Cimetidine produced a dose dependent reduction in antipyrine clearance (Table 1) in keeping with preliminary observations of its concentration related effect on propranolol metabolism in man (Feely *et al.*, 1981). There is evidence that inhibition of aminopyrine demethylation *in vivo* in the rat (Desmond *et al.*, 1980) and of benzo (a) pyrene hydroxylation *in vitro* in human liver microsomes by cimetidine is concentration dependent (Puurunen *et al.*, 1980). Recent studies (Rendic *et al.*, 1983; Reilly *et al.*, 1983) suggest that cimetidine interacts with the hemin iron of cytochrome P-450 both with its imidazole and cyano co-ordinating groups and that there are two distinct and independent classes of microsomal site, one with a high affinity, which may explain the effect of cimetidine in concentration ranges that are encountered in patients (Reilly *et al.*, 1983).

As antipyrine clearance is highly reproducible in individual subjects (Vessel, 1979) and is completely oxidised in the liver it is ideally suited for this type of study. There is also a suggestion that with increasing doses of cimetidine the incremental decrease in antipyrine clearance becomes less marked. It should, however, be noted that the effect of cimetidine on antipyrine clearance does not always quantitatively predict the magnitude of effect on the metabolism of other drugs such as diazepam (Klotz & Reiman, 1980) and

Table 2 Comparison of effect of cimetidine on antipyrine clearance in induced and non-induced state ($n = 6$; Mean ± s.e. mean, *$P < 0.05$ significantly different from control)

	Elimination $t_{1/2}$ *(h)*	*Clearance (ml/min)*
Control (placebo)	9.7 ± 0.7	49.0 ± 3.0
Cimetidine 800 mg	12.9 ± 1.2	37.0 ± 2.4*
Control (placebo)	9.4 ± 0.6	48.8 ± 2.9
Rifampicin (14 days)	5.5 ± 0.7	99.5 ± 7.6*
Rifampicin + cimetidine 800 mg	8.5 ± 1.6	56.6 ± 8.0

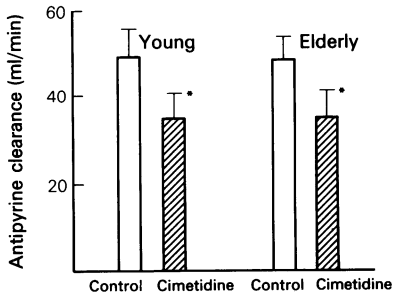

Figure 2 Comparison of the reduction in antipyrine clearance produced by cimetidine (800 mg/day) in young and elderly subjects (mean ± s.e. mean, $n = 6$, *$P < 0.05$).

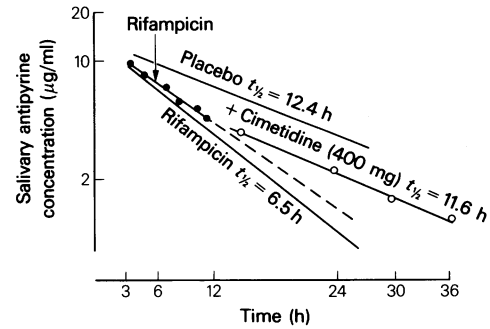

Figure 3 Elimination half-life of antipyrine as control (placebo) during treatment with rifampicin (day 15; $t_{1/2}$ = 6.5 h) and day 21 when cimetidine (400 mg four times daily) was commenced 12 h following antipyrine.

theophylline (Roberts *et al.*, 1981). Nevertheless, low dose cimetidine (300 mg at bedtime) has been reported (DeAngelis *et al.*, 1983) to decrease the clearance of theophylline.

It is recognised that the responsiveness of hepatic enzymes to inducing agents may be reduced in the elderly (Salem *et al.*, 1978; Wood *et al.*, 1979) but their responsiveness to enzyme inhibition was not known. These results (Figure 2) suggest that elderly subjects are as sensitive to the inhibitory effects of cimetidine on oxidative metabolism as young subjects. This may be due to the fact that the former process requires protein synthesis while binding to cytochrome P-450 does not. It should be remembered, however, that because of a reduced glomerular filtration rate cimetidine levels may be elevated in some elderly patients (Somogyi *et al.*, 1980; Drayer *et al.*, 1982). Furthermore, this age group, in which the clearance of a number of drugs is already reduced, shows a marked propensity to adverse drug reactions (O'Malley *et al.*, 1980) thus caution should be exercised when commencing cimetidine in elderly patients receiving concomitant medication.

The degree of inhibition of oxidative metabolism was more marked in subjects who had been pretreated with the hepatic enzyme inducing drug rifampicin (Table 2). A previous study (Daneshmend *et al.*, 1981) noted that the degree of inhibition of antipyrine metabolism by cimetidine was in part related to the initial oxidising capacity. Furthermore, another study (Miners *et al.*, 1981) reported that the effect of cimetidine on the clearance of theophylline was more marked in smokers who had higher initial clearance values, presumably due to enzyme induction. In support of this finding the same group (Grygiel *et al.*, 1981) showed a more marked effect of cimetidine on theophylline clearance in rats who had been pretreated with enzyme inducing drugs. May *et al.* (1982), however, did not find evidence of an enhanced effect of cimetidine in smokers. There are also contradictory reports with regard to the sensitivity of patients with liver disease (who may have reduced oxidising capacity) to the inhibitory effects of cimetidine. Rollinghoff *et al.* (1981) reported an enhanced effect of cimetidine on the inhibition of demethylation of aminopyrine while Staiger *et al.* (1981) noted little or no effect on antipyrine clearance. A third study (Nelson *et al.*, 1981) found that the absolute fall in clearance of chlordiazepoxide was somewhat less than in normal subjects.

It is of interest that the effect of cimetidine on antipyrine is similar irrespective of the duration of pretreatment (1 h or 24 h) and the magnitude of the effect in this study is in agreement with others (Somogyi & Gugler, 1982) where 1 to 4 weeks of pretreatment was given. From Figure 3 it is clear that cimetidine given 12 h following antipyrine may influence its subsequent elimination. Thus while cimetidine can rapidly reverse the effects of rifampicin (Table 2) on antipyrine clearance it should be noted that the enzyme induction is still in evidence after cessation of cimetidine therapy in these subjects. It has also previously been shown both in animals (Speeg *et al.*, 1982) and in man (Patwardhan *et al.*, 1981; Vestal *et al.*, 1983) that the effects of cimetidine on oxidative metabolism dissipate rapidly (within 24 to 48 h) following cessation of therapy and that tolerance does not occur during chronic therapy (Patwardhan *et al.*, 1981). Klotz & Reimann (1980) reported that cimetidine, last dose given 30 min before diazepam, impaired the elimination of diazepam throughout the sampling period (96 h). This suggests that the elimination of a drug, given while cimetidine is in the body, may be impaired for considerably longer than it takes to clear cimetidine from the circulation (10–12 h) possibly due to binding of cimetidine within the liver.

The results of this study are consistent with competitive and reversible binding to cytochrome P-450 by cimetidine in man.

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