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# DECREASED SYSTEMIC CLEARANCE OF CAFFEINE DUE TO CIMETIDINE

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**1** Five normal subjects received pre-treatment with cimetidine 200 mg three times daily and 400 mg at night for 6 days, or matching placebo.

**2** Caffeine (300 mg) was given orally before any treatment and at the beginning of the last day of each treatment course. Treatments were randomly allocated and separated by at least one week.

**3** A significant reduction occurred in the systemic clearance of caffeine and the half-life was prolonged as determined from measurement of caffeine in plasma and saliva. No change occurred in the apparent volume of distribution.

**4** The oral bioavailability of caffeine was found to be complete in the one subject studied.

**5** It is suggested that cimetidine inhibits the microsomal metabolism of caffeine. Although the steady state plasma caffeine would increase by approximately 70%, it is unlikely that this would produce adverse clinical effects.

## Introduction

Caffeine, due to its widespread consumption in beverages, is probably the most widely consumed drug today. The average adult consumer in the Western World has an intake of 186 mg/day (Graham, 1978). Its ubiquitous usage means that it will often be taken during chronic therapy with other drugs. One such drug is cimetidine, the histamine $H_2$-receptor antagonist, which is commonly used in the management of peptic ulceration and other gastric hyperacidity states. Cimetidine has been shown to impair microsomal drug metabolism in rats (Puurunen & Pelkonen, 1979) and impairs the elimination of warfarin (Serlin *et al.*, 1979) and diazepam from the blood in man (Klotz & Reimann, 1980). Caffeine also undergoes extensive microsomal metabolism and therefore evidence was sought for the existence of a possible interaction with cimetidine.

## Methods

Written, informed consent was obtained from all volunteers to undertake this study which had the approval of the appropriate ethical committee. Five normal non-smoking volunteers (two females, three males, aged 20–21 years, body weights 59.8–73.2 kg) were randomly allocated to one of the following regimes:-

i) cimetidine (Cimetex®, Smith, Kline & French) 200 mg three times daily and 400 mg at night for 6 days; or

ii) a similar course of matched placebo tablets.

Each subject received a total of 300 mg of anhydrous caffeine base in two gelatine capsules on the day before cimetidine or placebo treatment was initiated and on the final day of each treatment regime. The alternative treatment was administered following an interval of at least 7 days. Previous to any caffeine dose the subjects were rendered caffeine-free by abstention from all dietary sources of caffeine (tea, coffee, chocolate, cola and squash beverages) for a period of 3 days. Alcohol was not allowed during this period of caffeine abstention or on any treatment day. Each caffeine dose was taken after an overnight fast and food was allowed 2 h after administration. Caffeine (300 mg) is approximately equivalent to four cups of coffee (Graham, 1978).

Baseline samples of blood (5 ml) and mixed, unstimulated saliva (2 ml) were taken and following caffeine administration, blood and saliva samples were collected at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12 and 24 h. Plasma and saliva were stored at −20°C pending analysis by gas liquid chromatography (Bradbrook *et al.*, 1979).

The slope of the terminal part of the plasma or saliva concentration-time curve ($k_e$) was determined

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by linear regression of ln (plasma or saliva concentration) on time (t). Examination of the concentration, time profiles revealed that the fit was good enough to overcome any inaccuracies introduced by the non-normal distribution of the dependent variable. The area under the concentration-time curves was estimated from the trapezoidal approximation with the addition of a correction for the terminal portion of the curve (= last measured concentration/$k_e$). The half-life was calculated from $T_{\frac{1}{2}} = 0.693/k_e$, the clearance (Cl) from FX/AUC where F is the bioavailability fraction of dose X and AUC is the area under the plasma concentration, time curve. The apparent volume of distribution was found from $V_d = Cl/k_e$.

Previous studies have indicated that the bioavailability of orally administered caffeine is virtually complete in adults (Axelrod & Reichenthal, 1953) and neonates (Aranda, Cook, Gorman, Collinge, Loughnan, Outerbridge, Aldridge & Neims, 1979). This was confirmed for the caffeine preparation used in these experiments by administration of 300 mg caffeine orally and by intravenous infusion to a 36 year old male subject. Plasma and salivary caffeine concentrations were estimated as described above and the AUC's estimated from 10 and 15 observations respectively. F was calculated from

$$F = \frac{(AUC)_{oral}}{(AUC)_{i.v.}}.$$

Statistical analysis of the results was made by analysis of variance.

## Results

### *Caffeine bioavailability*

The apparent bioavailability of caffeine in a single subject using the gelatine capsules prepared in this laboratory and containing 300 mg caffeine base was 0.92 based on the plasma estimations and 1.01 based on the salivary data.

### *Reproducibility of estimates of pharmacokinetic parameters of caffeine*

The pharmacokinetic parameters of caffeine calculated from data when it was administered pre-placebo, post-placebo and pre-cimetidine are all estimates of these characteristics in the absence of cimetidine. Inspection of Table 1 shows that there is good reproducibility of this data and analysis of variance confirms that no statistically significant difference exists between these various estimates. The values found for the various parameters are broadly comparable with those determined in other studies (Axelrod & Reichenthal, 1953; Parsons & Neims, 1978; Brazier *et al.*, 1980; Patwardhan *et al.*, 1980).

**Table 1** Pharmacokinetic parameters of a single dose of caffeine in plasma and saliva and the effect of placebo and cimetidine treatment

| *Subject* | *Caffeine dose* | *Plasma elimination rate constant* ($k_e$) ($h^{-1}$) | *Plasma half-life* ($T_{\frac{1}{2}}$) (*h*) | *Clearance* (*Cl*) (*l/h*) | *Apparent volume of distribution* ($V_d$) (*l*) | *Salivary half-life (h)* |
|---|---|---|---|---|---|---|
| 1 | Pre-placebo | 0.155 | 4.5 | 5.42 | 34.9 | 5.1 |
| | Post-placebo | 0.165 | 4.2 | 5.74 | 34.8 | 3.8 |
| | Pre-cimetidine | 0.173 | 4.0 | 6.55 | 37.9 | 3.7 |
| | Post-cimetidine | 0.095 | 7.3 | 3.32 | 34.9 | 7.7 |
| 2 | Pre-placebo | 0.165 | 4.2 | 5.66 | 34.3 | 4.2 |
| | Post-placebo | 0.185 | 3.8 | 6.58 | 35.6 | 3.8 |
| | Pre-cimetidine | 0.163 | 4.3 | 6.30 | 38.7 | 4.6 |
| | Post-cimetidine | 0.089 | 7.8 | 3.60 | 40.5 | 7.1 |
| 3 | Pre-placebo | 0.182 | 3.8 | 7.04 | 38.7 | 3.8 |
| | Post-placebo | 0.162 | 4.3 | 6.93 | 42.8 | 3.9 |
| | Pre-cimetidine | 0.181 | 3.8 | 6.48 | 35.8 | 3.7 |
| | Post-cimetidine | 0.115 | 6.0 | 4.13 | 35.9 | 6.1 |
| 4 | Pre-placebo | 0.050 | 13.9 | 1.41 | 28.2 | 13.6 |
| | Post-placebo | 0.048 | 14.4 | 1.63 | 34.0 | 13.1 |
| | Pre-cimetidine | 0.072 | 9.6 | 1.88 | 26.1 | 13.1 |
| | Post-cimetidine | 0.034 | 20.4 | 1.15 | 33.8 | 17.3 |
| 5 | Pre-placebo | 0.285 | 2.4 | 12.99 | 45.6 | 2.4 |
| | Post-placebo | 0.273 | 2.5 | 12.21 | 44.7 | 2.1 |
| | Pre-cimetidine | 0.221 | 3.1 | 10.53 | 47.9 | 2.7 |
| | Post-cimetidine | 0.157 | 4.4 | 10.77 | 68.6 | 3.9 |

*Effect of cimetidine treatment on the pharmacokinetics of a single dose of caffeine*

Table 1 shows that cimetidine pre-treatment reduces the rate of elimination of caffeine. For all the pharmacokinetic parameters except the apparent volume of distribution, the effect produced by cimetidine was significant ($P<0.02$). A *t*-statistic was calculated by subtracting the post-treatment mean value from the pre-treatment mean value and dividing this difference by the standard error of the difference of means. The probability of the difference between the before and after means for each treatment being due to chance alone is shown in Table 2. It will be noted that there is no significant difference in any parameter following placebo administration. The increase in plasma AUC is reflected by an increase in the observed maximum plasma caffeine concentration ($C_{max}$) from the mean (±s.d.) pre-cimetidine $C_{max}$ of 7.2 (±1.4) μg/ml to 7.7 (±1.0) μg/ml post-treatment. This difference was not significant, however.

**Table 2** Significance table of changes in pharmacokinetic parameters of caffeine due to placebo and cimetidine treatments

| | *Parameter* | *Treatment* | *P for difference of before and after treatment means* |
|---|---|---|---|
| *Plasma* | $k_e$ | Placebo | 0.956 |
| | | Cimetidine | 0.007 |
| | Cl | Placebo | 0.812 |
| | | Cimetidine | 0.004 |
| | AUC | Placebo | 0.488 |
| | | Cimetidine | 0.002 |
| *Saliva* | $k_e$ | Placebo | 0.271 |
| | | Cimetidine | 0.003 |
| | AUC | Placebo | 0.323 |
| | | Cimetidine | 0.0003 |

*Relationship between plasma and salivary caffeine concentrations*

Salivary caffeine elimination has been used to determine caffeine pharmacokinetics in adults (Parsons & Neims, 1978) and neonates (Khanna, Bada & Somani, 1980). The mean saliva/plasma concentration ratio was 0.71 (s.d. 0.05). No significant difference was found between the elimination rate constant estimates from plasma and salivary data. The time of peak concentration was significantly ($P<0.003$) earlier in the plasma than in the saliva.

No adverse effects occurred during this study.

## Discussion

Cimetidine increases the hexobarbital sleeping time and half-life of antipyrine in rats. More significantly, in vitro, cimetidine inhibits microsomal aminopyrine *N*-demethylation activity and it has been suggested that cimetidine interacts with the microsomal cytochrome $P_{450}$ mono-oxygenase system (Puurunen & Pelkonen, 1979). It has been found that administration of cimetidine to patients taking warfarin results in significantly increased plasma warfarin concentrations and anticoagulation. Single dose studies performed in normal subjects produced somewhat confusing results in that warfarin clearance decreased in all four subjects but in two this was associated with a decreased elimination half-life and in the other two the apparent volume of distribution was increased (Serlin *et al.*, 1979). The elimination half-life of the model drug antipyrine is prolonged and the total plasma clearance is decreased by cimetidine although the apparent volume of distribution is unaltered (Serlin *et al.*, 1979; Klotz & Reimann, 1980). It has also been shown that five 200 mg doses of cimetidine are sufficient to impair elimination of both diazepam and desmethyldiazepam in normal volunteers (Klotz & Reimann, 1980).

The present study has found that the mean area under the plasma concentration, time curve, the half-life and first order elimination rate constant and the systemic clearance of caffeine are all significantly altered after five days' treatment with cimetidine in the usual therapeutic dosage. Similar changes were found in the area under the salivary caffeine concentration, time curve and the elimination rate constant determined from the salivary data. The increase in the plasma and salivary AUCs ($P<0.03$) and the decrease in plasma and salivary elimination rate constants ($P<0.01$) and systemic clearance ($P<0.005$) would all indicate that cimetidine inhibits caffeine metabolism. Unlike the interactions reported between cimetidine and warfarin (Serlin *et al.*, 1979) and diazepam (Klotz & Reimann, 1980), the apparent volume of distribution of caffeine was not obviously altered by cimetidine.

Like warfarin, diazepam and antipyrine, caffeine undergoes microsomal metabolism. It is a particularly good substrate for the form of cytochrome $P_{450}$ induced by polycyclic aromatic hydrocarbons in the rat (Welch, Hsu & Angelis, 1977) and it has been suggested that the markedly reduced rate of caffeine metabolism in the neonate is related to the deficiency of aryl hydrocarbon hydroxylase activity compared to the other functions of the mono-oxygenase complex in the human foetal liver (Pelkonen *et al.*, 1973). This hypothesis is supported by the increased caffeine clearance found in smokers which may reflect a greater state of hepatic enzyme induction in these

subjects (Parsons & Neims, 1978). Like diazepam (Schwartz & Postma, 1968), the metabolism of warfarin and caffeine is induced by phenobarbitone (Welch *et al.*, 1977; MacDonald *et al.*, 1969). Furthermore, caffeine itself has been shown to induce microsomal drug metabolising enzymes (Mitoma *et al.*, 1969). It is thus possible to infer that the locus of the interaction between caffeine and cimetidine may be at the microsomal level. This inhibitory effect of cimetidine is, however, rapidly reversible within at least a week of discontinuation of the drug. It remains to be shown whether it is cimetidine itself or one of its metabolites which is responsible for this interaction. This type of interaction with cimetidine is in contrast with the lack of clinically significant interaction found with tetracycline (Fisher *et al.*, 1980), ampicillin and cotrimoxazole (Rogers *et al.*, 1980), all of which drugs are not eliminated by microsomal metabolism.

The decreased clearance of caffeine will result in an increased mean steady state concentration with multiple ingestion of caffeine. On the basis of the data from these single dose experiments it would be anticipated that the average steady state concentration in the presence of cimetidine would be about 1.7 times that in its absence. There will also be a slower rate of elimination following caffeine ingestion: the mean increase in half-life was 68%. The inhibition of caffeine metabolism by cimetidine is relatively small in comparison with that occurring with idrocilamide (Brazier *et al.*, 1980) which produced severe neuropsychiatric disturbances associated with a seven-fold elevation of the steady state caffeine levels. The inhibition of caffeine clearance occurring with cimetidine is of a similar order to that found with the oral contraceptive (Patwardhan *et al.*, 1980). The possibility of insomnia, nervousness and anxiety or even tachycardia and arrhythmias remains, however, and as pointed out by Greden (1974), caffeinism is rarely considered in the differential diagnosis of anxiety state.

Although there has been controversy over heavy caffeine ingestion and the aetiology of cardiovascular disease, this association does not appear to have been proven (MacCornack, 1977). In a small group of non-coffee drinkers it was shown that oral administration of 250 mg caffeine elevated the blood pressure by 14/10 mm Hg, and suggested that caffeine might enlarge the population of hypertensives by increasing the pressure of those with borderline hypertension (Robertson *et al.*, 1978). Others, however, have found no relation between daily coffee consumption and blood pressure elevation (Bertrand *et al.*, 1978). There is presently therefore no firm basis for anticipating adverse effects on this score from concurrent consumption of caffeine with cimetidine. A more relevant consideration might be if this interaction extended to related methylxanthines such as theophylline. This is particularly likely perhaps since this compound demonstrates non-linear pharmacokinetics (Weinberger & Ginchansky, 1977) and would therefore accumulate disproportionately with a corresponding risk of toxicity.

LJB was an MRC research student and this work formed part of his submission for the BSc degree of London University.

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