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Effects of cimetidine on the pharmacokinetics of proguanil in healthy subjects and in peptic ulcer patients

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Abstract

The pharmacokinetics of orally administered proguanil and its metabolites were determined in six healthy volunteers and in six peptic ulcer patients, before and after a 3-day course of cimetidine (400 mg given two times daily for 2 days and 400 mg on the third day 1 h before proguanil). Cimetidine significantly increased C_{max} ($P < 0.05$), AUCo-∞ ($P < 0.005$) and elimination half-life $t_{1/2b}$ of proquanil in plasma of healthy subjects. In ulcer patients, cimetidine significantly increased, AUCo-∞ ($P < 0.05$), elimination half life ($P < 0.005$) and C_{max}. Cimetidine significantly reduced ($P < 0.05$) Total body clearance in both healthy subjects and in peptic ulcer patients. The C_{max} and AUCo-∞ of the active metabolite cycloguanil was significantly decreased ($P < 0.05$) in both the healthy subjects and in the peptic ulcer patients. The C_{max} of the inactive metabolite, 4-CPB was significantly decreased in healthy subjects and AUCo-∞ significantly decreased in peptic ulcer patients.

Keywords: Proguanil; Cimetidine; Pharmacokinetics; Drug–drug interaction

1. Introduction

Malaria is endemic in Africa south of the Sahara while peptic ulcer and epigastric pain is prevalent in the adult population. Antimalarial prophylactics are widely recommended for adults including pregnant women and children alike, whether under going peptic ulcer treatment or not. The antimalarial arylbiguanide proguanil is considered to be safest of all drugs used for malaria prophylaxis. Proguanil, a pro-drug, is metabolised to an active dihydrotriazine metabolite, cycloguanil, and is eliminated with a terminal half-life of ~ 16 h [1–3]. This conversion is mediated by the mephenytoin hydroxylase isoenzyme, a member of the ^{11}C-subfamily of the cytochrome P450 dependent mixed function oxidases [4–6]. Cycloguanil is eliminated more rapidly than the

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parent compound. Antimalarial efficacy thus depends on absorption, distribution, disposition and extent of biotransformation as well as susceptibility of the malaria parasite. Pharmacokinetic drug interactions with cimetidine occur at the sites of gastrointestinal absorption and elimination including metabolism and excretion. Aspirin absorption was halved by cimetidine when gastric pH was raised above 3.5. Cimetidine did not affect the absorption of ampicillin, co-trimoxazole or prednisolone, but absorption of chlorpromazine ketoconazole and indomethacin are reduced [7]. Cimetidine has also been reported to affect hepatic blood flow and reduce renal blood clearance of drugs with organic cations, by competing for active tubular secretion in the proximal tubule of the kidney, thus reducing the renal clearance of procainamide, ranitidine, triamterene, metformin and flecainide [5,6]. Cimetidine has presently been found not to inhibit conjugation mechanisms including glucuronidation, sulphation and acetylation or deacetylation (or ethanol dehydrogenation). Caballeria et al. [8] and DiPadova et al. [9], however, reported an elevation in blood concentration of ethanol due to inhibition of gastric alcohol dehydrogenase (ADH). Cimetidine binds to the haem portion of cytochrome P-450 and is thus an inhibitor of phase-1 drug metabolism. However, to date cimetidine does not inhibit the metabolism of theophylline 8-oxidation, tolbutamide hydroxylation, ibuprofen hydroxylation, misonidazole demethylation and steroid hydroxylation [10]. Diazepam and chlordiazepoxide [11] were reported to be metabolised by different forms of cytochrome P-450.

Since proguanil is largely metabolised by hepatic microsomal oxidative biotransformation, a clinically important interaction between cimetidine and proguanil could occur. The present study, therefore investigates this possibility in healthy volunteers and peptic ulcer patients.

2. Materials and methods

Proguanil (Paludrine®) bought in Jos Nigeria, cycioguanii and 4chlorophenylbiguanide (4-CPB) were kindly donated by ICI (Zeneca, Macclesfield, UK) and tetrabutylammonium bromide were obtained from Aldrich (Gillingham, Dorset, UK). Cimetidine, cimetidine sulphoxide (SKF924521RS2) and cimetidine amide (SKF92422LRS2) were gifts from SmithKline-Beecham (west Sussex, England, UK) and Tagamet® was from SKF-Beecham (Lagos, Nigeria). Acetonitrile was obtained from Rathburn Chemicals (Walkerburn, UK), water was distilled and further purified by a Millipore Milli-Q system (Millipore-Waters, Mitford, MA, USA) and all other chemicals were of AnalaR or equivalent grade. The liquid chromatograph used was a modular system consisting of a Jasco 980 pump and Jasco 975 variable wavelength ultraviolet detector (Jasco, Tokyo, Japan) and incorporated and Rheodyne 7125 injection valve (Cotati, CA, USA) fitted with a 20-μl loop. The wavelength of detection used was 254 nm. The chromatographic column was 100 × 2 mm I.D., slurry packed in the laboratory with 3 μm particle size ODS Hypersil (HETP, Macclesfield, UK) at a pressure of 55 MPa in a solvent of propan-2-ol-hexanemethanol.

Samples to be analysed were plasma samples (0.1 ml) which had been applied to filter paper and allowed to dry.

2.1. Clinical procedure

2.1.1. Subject selection and treatment

Two groups of subjects were studied, consisting of a healthy male adult group and peptic ulcer patients with each group acting as its own control. Ethical approval was obtained from the Jos University Teaching Hospital. All subjects were confirmed fit to undertake the study and written consent was obtained. All subjects were non-smokers and none of the subjects took alcohol or any other medication 1 week before and during the study.

2.1.2. Healthy subjects

The subjects were six healthy young adults aged from 23 to 36 years (mean ± SD = 28.67 ± 5.75 years) and weighing from 68 to 72 kg (mean ± SD = 70.67 ± 1.51 kg). After an overnight fast, the subjects swallowed a single oral 200 mg dose

proguanil tablet (Paludrine ICI) with ~150 ml of water. Venous blood (3 ml) was then drawn through an indwelling catheter just before dosing and 0.5, 1, 1.5, 2, 2.5, 3, 6, 9, 12, 24, 48, and 60 h after dosing. Blood was collected in EDTA-pretreated blood sample bottles. Subjects were not allowed to eat or drink within the first 3 h of the study.

After a washout period of 2 weeks, subjects repeated the above process with cimetidine administered before the antimalarial. One cimetidine (400 mg) tablet was administered morning and night for 2 days and after an overnight fast on the third day, subjects received a single oral 400 mg cimetidine tablet (Tagamet) 1 h before the single oral doses of proguanil tablets. Samples were collected and treated as above.

2.1.3. Peptic ulcer patients

The subjects were six endoscopically (or by barium meal X-ray examination) certified peptic ulcer patients (male adults). All subjects were non-smokers and outpatients of the Jos University Teaching Hospital. Subjects were requested to abstain from other medications just before and during the course of the study, Subjects aged from 36 to 39 years (mean ± SD = 37.75 ± 1.26 years) weighing from 65 to 72 kg (mean ± SD = 68.5 ± 2.9 kg). Four of the patients completed the two phases of the study while two could not complete the study because of gastrointestinal irritation and severe dizziness.

2.1.4. Treatment of samples

The whole blood sample was centrifuged (at 5 g for 5 min) and 0.1 ml plasma was pipetted out with a micropipette and adsorbed on filter paper. The filter paper was then air dried at room temperature (30°C). All samples were stored in polyethylene bags which were not transparent to light. Samples were stored at −20°C until analysis (except during transportation to the UK).

2.1.5. Drug analysis

Proguanil and its metabolites were assayed in samples from plasma adsorbed and dried on filter papers, according to the methods of Kolawole et al. [12] This method involves liquid–liquid extraction of plasma from the filter papers and subsequent solid-phase extraction before reverse phase ion-pairing chromatography. The recoveries for proguanil, cycloguanil and 4-CPB in plasma were 75, 82.3 and 87%, respectively. A preliminary pharmacokinetics studies using whole blood gave a comparable C_{max} of 848 ± 70 ng ml^{-1} and elimination half life of 18.8 ± 7.0 h for proguanil.

2.1.6. Pharmacokinetics analysis

Preliminary pharmacokinetic values were obtained from concentration–time profiles. Data were then fitted to one and two compartmental models using the Dixon [13] non-linear regression curve fitting program, to obtain the best least squares fit to the individual concentration-time curves. Standard pharmacokinetic parameters were then calculated. Elimination and absorption half lives were calculated from the ratio 0.693/β and 0.693/ka, respectively. AUCo-∝, (ng ml^{-1} h^{-1}) was calculated by the trapezoidal rule from the beginning of the drug administration to the last data point and with extrapolation to infinity. The area from the last data point Ct to infinity was obtained as Ct/β. Total body clearance Cl_T, was calculated from the ratio of dose to area under the plasma drug concentration–time curve, assuming bioavailability was equal to one ($F = 1$). Apparent volume of distribution V_D/F (l or l kg^{-1}) was calculated from the ratio of the plasma clearance to rate of elimination.

Student's two tailed *t*-test was used to assess differences between paired data. Minitab software package for two group analysis was employed. Group data are presented as mean ± SD.

3. Result and discussion

3.1. Effect of cimetidine on the pharmacokinetics of proguanil in healthy subjects

The pharmacokinetics of proguanil obtained for healthy subjects compared well with the reported pharmacokinetics of proguanil after oral administration of 200 mg dose [2,3,6]. The plasma concentration–time profiles for the six healthy subjects are shown in Fig. 1. The mean proguanil

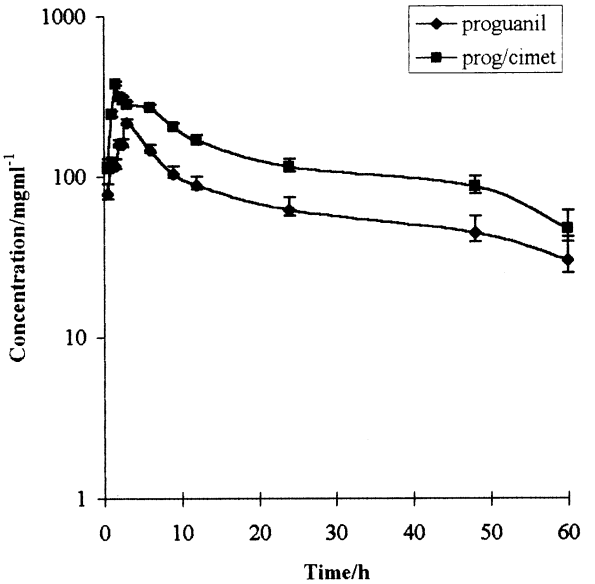

Fig. 1. Mean plasma concentration-time profile of proguanil in six healthy subjects before and after cimetidine.

absorption and elimination kinetics before and after cimetidine treatment are listed in Table 1(a). Proguanil absorption was significantly enhanced ($P < 0.05$) by the shortening of absorption half-life $t_{1/2a}$, and a significant increase ($P < 0.05$) in C_{max} at a shorter T_{max} in plasma. There was $\sim 92.5\%$ significant increase ($P < 0.05$) in plasma

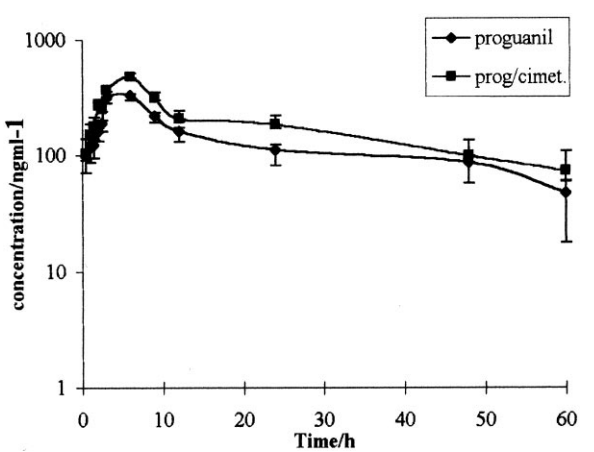

Fig. 2. Mean plasma proguanil concentration-time profile after 200 mg oral proguanil in four ulcer patient subjects before and after 400 mg cimetidine.

AUCo-∞ while V_d/f was marginally reduced and total body clearance $Cl_{T/f}$ was significantly reduced ($P < 0.05$). Elimination half-life was significantly increased ($P < 0.05$).

Cimetidine was found to affect the absorption of proguanil by probably hastening dissolution and increasing the gastric pH thereby making it favourable for rapid absorption. The $t_{1/2a}$ and T_{max} were significantly ($P < 0.05$) reduced with a corresponding increase in C_{max}. Cimetidine has been reported to affect the absorption of other drugs such as ketoconazole, penicillin, indomethacin and aspirin by increasing the pH of the stomach and the proximal small bowel [7]. The significant increase in plasma C_{max} and AUCo-∞ and the right shift of $t_{1/2a}$ and T_{max} might be due to the effect of cimetidine on the gastrointestinal pH and possibly its effect on gastrointestinal tract motility. Also since proguanil is a drug with a high first pass metabolism the effect of cimetidine on portal blood flow might have contributed to the increased bioavailability of proguanil after the cimetidine treatment. The total clearance and elimination half-life were significantly ($P < 0.05$) increased. Proguanil undergoes high first pass mechanism and it is metabolised to cycloguanil through CP450 enzyme systems. It is therefore possible for cimetidine to influence the clearance and elimination (including metabolism) of proguanil. This agreed with the reports on cimetidine interaction through its effect on hepatic blood flow and CP450 inhibition associated with drugs having high first pass metabolism [14–16]. The increase in $t_{1/2b}$ elimination of proguanil and the increase in AUCo-∞ suggest that cimetidine inhibits the biotransformation process thereby keeping proguanil concentration high in the blood for a longer period of time. This effect might be clinically significant since the active species is cycloguanil. The plasma concentration of cycloguanil was significantly reduced ($P < 0.05$) after the cimetidine treatment. There was also significant decrease in AUCo-∞ ($P < 0.05$) of cycloguanil after the cimetidine in plasma (Table 1(b)).The changes reflected in the significant reduction in the inactive metabolite 4-CPB in plasma (Table 1(c)).

Table 1
Pharmacokinetic parameters and profiles of proguanil, cycloguanil and 4-CPB in six healthy subjects following oral 200 mg proguanil before and after oral cimetidine (plasma data)

(a) Pharmacokinetic parameters of proguanil in six healthy subjects following oral 200 mg proguanil before and after oral cimetidine (plasma data)

Parameter	Proguanil alone ($n=6$)		Proguanil and cimetidine	
	Mean ± SD		Mean ± SD	
$t_{1/2ab}$ (h)	1.00	0.35	0.86	0.42
T_{max} (h)	3.3	1.4	3.0	1.6
C_{max} (ng ml^{-1})	208.3	30.3	393.4	104*
AUCo-$\propto$ (ng ml^{-1} h^{-1})	4670	1049	8991	2101**
V_D (l kg^{-1})	14.00	5.04	10.74	3.37
$t_{1/2b}$ (h)	15.27	3.73	22.55	4.19*
$Cl_{T/f}$ (ml min^{-1} kg^{-1})	10.51	2.17	5.47	1.14

(b) Pharmacokinetic profile of cycloguanil following 200 mg oral proguanil before and after cimetidine in healthy subjects

	Plasma	
	Before	After
T_{max} (h)	5.0 ± 2.5	8.0 ± 1.7
C_{max} (ng ml^{-1})	43.7 ± 16	17.8* ± 13.2
AUCo-$\propto$ (ng ml^{-1} h^{-1})	399.7 ± 186	250.0* ± 104

(c) Pharmacokinetic profile of 4-chlorophenyibiguanide (4-CPB) in six healthy subjects following 200 mg oral proguanil before and after cimetidine

	Plasma	
	Before	After
	Mean ± SD	Mean ± SD
T_{max} (h)	7.8 ± 1.6	9.0 ± 2.9
C_{max}(ng ml^{-1})	11.25 ± 7.7	5.73* ± 3.3
AUCo-$\propto$ (ng ml^{-1} h^{-1})	145.2 ± 85	114.2 ± 51

* $P<0.05$, Significant.
** $P<0.005$.

3.2. Effect of cimetidine on proguanil in peptic ulcer subjects

Table 2(a) show the pharmacokinetic parameters of proguanil in the ulcer patients before and after administration of cimetidine. The concentration-time profiles for four ulcer patients is shown in Fig. 2. Proguanil absorption, distribution and elimination in the ulcer patients are not identical, though similar to those of the healthy subjects. Absorption half-life and T_{max} were not significantly altered by cimetidine administration while cimetidine significantly ($P<0.05$) increase the C_{max} and AUCo-$\propto$ in plasma. Cimetidine prolonged the elimination half-life $t_{\frac{1}{2}\beta}$ of proguanil in the ulcer patient subjects from 14.2 ± 2.7 h to 23.1 ± 8.2 h in plasma. This change is statistically significant ($P<0.05$) Plasma clearance was significantly reduced ($P<0.05$) after the cimetidine administration. There was no significant change in the volume of distribution (Table 2(a). Cimetidine did not affect proguanil absorption in these patients, this might be due to previous exposure to antacids or H_2-antagonist. The pathologic condi-

Table 2
Pharmacokinetic parameters and profiles of proguanil, cycloguanil and 4-CPB in four ulcer patients following 200 mg proguanil before and after cimetidine

(a) Pharmacokinetic parameters of proguanil in four ulcer patients following 200 mg proguanil before and after cimetidine

Parameter	Proguanil ($n=6$)		Proguanil/cimetidine	
	Mean ± SD		Mean ± SD	
$t_{1/2a}$ (h)	1.54	0.45	1.46	0.45
T_{max} (h)	4.5	1.7	5.3	1.5
C_{max} (ng ml^{-1})	347.1	54.0	481.45	69.80
AUCo-∞ (ng ml^{-1} h^{-1})	8261	1198	12155	2127*
V_D(l kg^{-1})	7.30	1.09	7.94	2.22
$t_{1/2\beta}$ (h)	14.22	2.75	23.06	8.17**
$Cl_{T/f}$ (ml min^{-1} kg^{-1})	6.00	0.74	4.11	0.68

(b) Pharmacokinetic profile of cycloguanil in four ulcer patients following 200 mg proguanil before and after cimetidine

	Plasma	
	Before	After
	Mean ± SD	Mean ± SD
T_{max} (h)	6.0 ± 4.0	8.0 ± 1.7
C_{max} (ng ml^{-1})	38.8 ± 1.8	26.1* ± 21
AUCo-∞ (ng ml^{-1} h^{-1})	459 ± 261	462.0 ± 152

(c) Pharmacokinetic profile of 4-Chlorophenylbiguanide (4-CPB) in four ulcer patients following 200 mg oral proguanil before and after 400 mg cimetidine

	Plasma	
	Before	After
	Mean ± SD	Mean ± SD
T_{max} (h)	7.5 ± 4.0	6.0 ± 1.7
C_{max}(ng ml^{-1})	9.8 ± 6.7	5.6 ± 0.3
AUCo-∞ (ng ml^{-1} h^{-1})	160.0 ± 50	125* ± 44

* $P<0.05$, Significant.
** $P<0.005$.

tions of this group of subjects might have modulated the effect of cimetidine.

The prolongation of the elimination half-life of proguanil might be due to the effect of cimetidine on the metabolic pathways. There was significant decrease ($P<0.05$) in C_{max} and AUCo-∞ of cycloguanil in plasma after cimetidine treatment (Table 2(b). There was a corresponding decrease in plasma concentration 4-CPB after the cimetidine (Table 2(c).

A comparison of the normal pharmacokinetic profiles of the subjects and the ulcer patients before the cimetidine administration shows that the values of C_{max} and AUCo-∞ of proguanil were larger in the ulcer patients while the elimination half-life was smaller than those of the normal subjects. These differences might be due to previous exposure of patients to a CP450 inhibitor or any of the H_2-receptor antagonists. The effect of gastric pH might also be a factor since the patients are likely to have more acid in the gut than the normal subjects and therefore an enhanced absorption.

In conclusion, co-administration of proguanil

and cimetidine in both healthy and peptic ulcer patients cimetidine induced a significant increase in bioavailability of proguanil and a significant fall in total body clearance of proguanil. These interactions led to a fall in availability of the active metabolite, cycloguanil. Therefore the interaction between these two common drugs may have therapeutic implications when administered concurrently for a length of time.

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