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The influence of food on the pharmacokinetics of CGP 6140 (amocarzine) after oral administration of a 1200 mg single dose to patients with onchocerciasis

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Eleven male patients from Mali with *Onchocerca volvulus* infections received in random order a 1200 mg single oral dose of CGP 6140 after an overnight fast and after food intake. The concentrations of CGP 6140 and of its *N*-oxide metabolite, CGP 13231, were measured in plasma and urine. Mean (± s.d.) AUC CGP 6140 values were 67.0 ± 10.8 μmol l^{-1} h in fed and 22.0 ± 17.2 μmol l^{-1} h in fasting patients. The mean maximum concentrations (C_{max}) in plasma ± s.d. were 12.7 ± 2.8 μmol l^{-1} in fed and 4.7 ± 4.1 μmol l^{-1} in fasting patients. The median time to C_{max} was 3 h in fed and 2 h in fasting patients. Mean (± s.d.) AUC of the *N*-oxide metabolite was 59.9 ± 10.7 μmol l^{-1} h in fed and 23.4 ± 16.2 μmol l^{-1} h in fasting patients. The urinary recovery was less than 0.5% of dose for CGP 6140 in both fed and fasting conditions. It was 30.1 ± 11.5 and 11.4 ± 8.0% of the dose for the *N*-oxide metabolite in fed and fasting conditions, respectively. Variability in plasma concentrations and urinary recovery of CGP 6140 and of the *N*-oxide metabolite was greater in fasted patients. The low solubility of CGP 6140 in aqueous solutions at neutral pH and its higher solubility at acidic pH might explain the increase in bioavailability after food intake. The administration of CGP 6140 after food intake is therefore recommended for an optimal systemic effect.

Keywords CGP 6140 amocarzine patients *Onchocerca volvulus* food bioavailability

Introduction

The pharmacokinetics of CGP 6140 (proposed International Nomenclature Name (INN): amocarzine) [4-nitro-4′-(*N*-methyl-piperazinyl-thiocarbonyl-amido)-diphenylamine] after single 100–1600 mg oral doses are reported in a companion paper (Lecaillon *et al.*, 1990).

The aim of the present paper was to describe the influence of food on the pharmacokinetics of the drug and of its *N*-oxide metabolite CGP 13 231 after oral administration of a single 1200 mg dose of CGP 6140 to patients with *Onchocerca volvulus* infections.

Methods

Patients

Eleven male patients infected with *Onchocerca volvulus* participated in the study. They received a full clinical examination prior to the study and

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a complete parasitological, haematological and biochemical profile was determined. The patients were fully informed of the objective and protocol of the study which was approved by the World Health Organisation's Secretariat Committee on Research involving Human Subjects (SCRIHS). Prior to participation each patient had to give his informed consent.

Experimental design

The study was of a randomised cross-over design where each patient received a 1200 mg single oral dose of CGP 6140 on days 1 and 5 either after an overnight fast (A) for the first administration followed by a postprandial state (B, large breakfast) for the second administration (sequence AB) or *vice versa* (sequence BA). The two doses of CGP 6140 were given each as six 200 mg film coated tablets with 100 ml of water. For fed patients. a large standard breakfast (500 ml of coffee with milk, 200 g of meat with bones and 200 g of noodles) was served before dosing. Fasting subjects took a standard breakfast (rice with milk) 2 h after dosing. At 4 h after dosage, a standard meal (rice with sauce, 200 g of meat with bones and salad) was served to all eleven patients.

Blood (about 10 ml) was withdrawn into lithium heparin tubes before and at 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 h after drug administration. Plasma was separated by centrifugation, frozen in liquid nitrogen and stored at −20° C until analysis.

Urine was collected by fractions before and from 0 to 48 h after the first administration, and from 0 to 144 h after the second administration. The volume of each fraction was measured and a 5 ml sample was frozen and stored at −20° C.

Analytical measurements

CGP 6140 and its *N*-oxide metabolite, CGP 13 231, were measured in plasma by column-switching high-performance liquid chromatography (Lecaillon *et al.*, 1987).

The limit of assay was 50 nmol of CGP 6140 and of the *N*-oxide metabolite per litre of plasma (about 20 ng ml^{-1}) (coefficient of variation, CV = 10%). In urine, the limit of assay was 250 nmol l^{-1} (about 100 ng ml^{-1}) (CV = 8%).

Pharmacokinetic analysis

The following pharmacokinetic parameters were calculated:

AUC (0,48 h)	Measured by the linear trapezoidal rule.
C_{max}	Peak concentration.
t_{max}	Time to peak concentration.
$t_{½,z}$	Terminal elimination half-life in plasma determined from the log-linear segment of the concentration-time curve.
Ae (0,48 h)	Cumulative urinary excretion over 48 h (% of dose).
CL_R	Renal clearance, calculated as *Ae* (0,48 h)/AUC (0,48).

Results

The mean (± s.d.) concentrations of CGP 6140 in plasma are shown in Figure 1a and indicate a rapid absorption of the drug. The plasma drug concentrations were higher in fed compared with fasting patients. A greater intersubject variability as shown by the s.d. of the plasma drug concentrations was also observed after administration to fasting patients. The concentrations of the *N*-oxide metabolite CGP 13 231 were similar to those of the unchanged drug (Figure 1b).

The urinary recovery of CGP 6140 ranged from 0.01 to 0.54% of the dose in fasting and from 0.06 to 0.18% of the dose in fed patients. The urinary recovery of the *N*-oxide metabolite ranged from 2.97 to 27.2% of dose in fasting and from 12.4 to 48.3% of dose in fed patients.

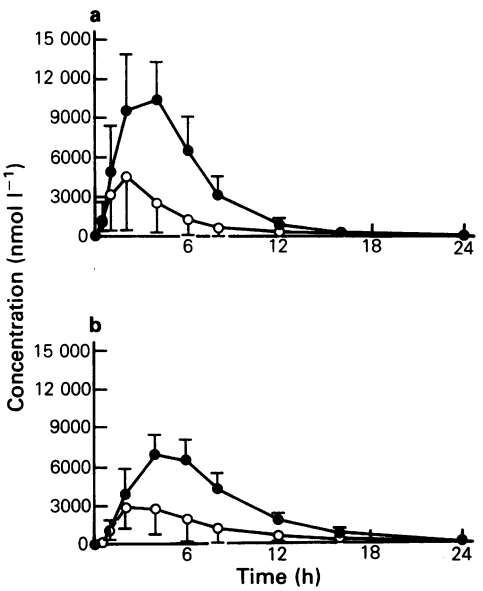

Figure 1 Mean (± s.d.) plasma concentrations of a) CGP 6140 and b) its *N*-oxide metabolite CGP 13 231 after a 1200 mg single oral dose of CGP 6140 to fasting (○) and fed patients (●) (n = 11).

Table 1 Pharmacokinetic parameters of CGP 6140 and its *N*-oxide in plasma (values of t_{max} are given as median values).

Dosing condition	*Patient number*	C_{max} *(μmol l^{-1})*	t_{max} *(h)*	*AUC (0,48 h) (μmol l^{-1} h)*	$t_{½,z}$ *(h)*	Ae *(0, 48 h) (% of dose)*	CL_R *(ml min^{-1})*
CGP 6140							
Fasting	1	0.76	2	6.03	5.3	0.01	–
	2	14.40	2	56.10	4.0	0.14	–
	3	5.64	2	29.00	4.0	0.16	–
	4	1.27	2	4.48	4.3	0.02	–
	5	4.56	1	18.80	5.4	0.04	–
	6	7.21	2	25.70	3.9	0.13	–
	7	1.88	1	8.85	5.2	0.54	–
	8	7.70	4	48.10	3.0	0.07	–
	9	5.17	2	25.00	3.6	0.03	–
	10	1.70	2	11.40	3.8	0.05	–
	11	1.38	1	8.34	6.1	0.05	–
	Mean	4.70		22.00	4.4	0.11	
	± s.d.	± 4.07		± 17.20	± 0.9	± 0.15	
	Median		2				
Fed	1	10.20	1	53.10	4.1	0.06	–
	2	14.20	4	77.80	3.3	0.11	–
	3	10.20	4	57.20	3.4	0.08	–
	4	17.50	2	72.40	3.8	0.13	–
	5	10.10	4	79.30	3.9	0.14	–
	6	14.20	2	57.70	3.4	0.08	–
	7	9.42	2	59.20	4.1	0.13	–
	8	16.80	4	84.10	3.9	0.16	–
	9	12.00	2	60.20	3.6	0.15	–
	10	13.00	2	74.60	3.6	0.17	–
	11	11.80	4	61.30	3.5	0.18	–
	Mean	12.70		67.00	3.7	0.13	
	± s.d.	± 2.75		± 10.80	± 0.3	± 0.04	
	Median		3				
N-*oxide*							
Fasting	1	0.95	2	9.58	4.6	3.0	167
	2	4.78	4	38.60	3.9	27.2	379
	3	4.41	4	32.70	4.2	21.1	347
	4	1.59	2	6.63	3.1	4.6	376
	5	2.71	2	17.00	5.1	9.7	308
	6	5.43	2	31.00	3.4	20.8	361
	7	1.82	2	11.50	5.9	6.8	319
	8	6.83	4	59.90	3.2	11.2	101
	9	3.17	4	26.50	3.6	10.3	208
	10	1.40	4	11.90	4.7	6.2	283
	11	1.72	2	12.40	5.4	4.7	203
	Mean	3.16		23.40	4.3	11.4	277
	± s.d.	± 1.93		± 16.20	± 0.9	± 8.0	± 94
	Median		2				
Fed	1	5.67	4	47.10	3.4	12.4	141
	2	5.77	4	48.50	3.4	26.6	295
	3	6.50	4	53.70	3.2	30.5	306
	4	10.70	4	73.00	3.5	48.3	356
	5	6.74	6	65.20	3.5	16.9	140
	6	7.98	4	55.70	3.0	45.0	435
	7	8.42	6	67.70	3.3	36.3	289
	8	9.40	6	78.00	3.3	40.5	279
	9	5.94	4	51.50	3.3	27.3	285
	10	6.56	4	50.80	3.8	20.2	214
	11	8.29	4	67.80	3.1	27.2	216
	Mean	7.45		59.90	3.3	30.1	269
	± s.d.	± 1.64		± 10.70	± 0.2	± 11.5	± 88
	Median		4				

The individual and mean pharmacokinetic parameters (± s.d.) are given in Table 1 for CGP 6140 and for the *N*-oxide metabolite. The plasma concentrations (C_{max} and AUC) of CGP 6140 and of the *N*-oxide metabolite were compared by variance analysis (Grieve, 1980) using treatment A (fasting) as reference.

No significant difference was detected between the treatment sequences AB or BA, the periods and the subjects (significance level, $P = 0.05$). C_{max} and AUC values of CGP 6140 were significantly lower in fasting than in fed patients ($P = 0.01$). The variation coefficient of pure error of the CGP 6140 AUC was 52% of the mean AUC in fasting patients.

The ratio fed/fasting for mean AUC of CGP 6140 was 3.0 (range 1.3–16.2). It was 2.6 for the AUC (range 1.3–11.0) and the urinary recovery (range 1.0–10.5) of the *N*-oxide metabolite.

Discussion

Intersubject variability in plasma concentrations of CGP 6140 and its *N*-oxide metabolite in fasting subjects has already been reported (Lecaillon *et al.*, 1990), this variability being larger at higher doses. In the fasting patients of the present study, AUC values were lower than those found previously and this was due mainly to the low AUC recorded in several patients, ten times lower than expected from previous data in fasting patients. The low urinary recovery of the *N*-oxide metabolite in the subjects presenting with a low AUC of CGP 6140 indicates that the reduction in bioavailability might be attributed to a reduced absorption of CGP 6140 in fasting subjects. Such irregular and unpredictable absorption patterns must be avoided in patients with onchocerciasis where the killing of microfilariae is dose dependent and may lead to undesirable host reactions (Mazzotti reaction).

The half-lives of elimination of the drug and of the *N*-oxide metabolite as well as the renal clearance of the metabolite (Table 1) were not modified by food.

The pKa of CGP 6140 is close to 6.8. Its low solubility in aqueous solutions at neutral pH (solubility of 14 mg l^{-1} in simulated intestinal fluid, pH 6.8, 37° C) and the higher solubility under acidic conditions (solubility of 200 mg l^{-1} in 0.1 mol l^{-1} HCl, pH 1.2, 37° C) might explain the observed differences in bioavailability. Thus, acidic secretions and slower gastric emptying after food intake (Toothaker & Welling, 1980) might improve the dissolution of CGP 6140.

Bile secretion in the duodenum is activated by food and may also accelerate the dissolution of compounds that have a poor aqueous solubility. The partition coefficient of CGP 6140 between n-octanol and aqueous solution is 1.9 with 0.1 mol l^{-1} HCl, 15 with 0.067 mol l^{-1} phosphate buffer (pH 5.2) and 525 with 0.067 mol l^{-1} phosphate buffer (pH 7.4). The poor bioavailability which was mostly observed after high doses of CGP 6140 given to fasting patients also suggests that the low solubility of the drug at neutral pH is the major factor influencing the absorption of the drug. The systemic availability of other antiparasitic compounds, albendazole and mebendazole, is also increased when these drugs are taken with a fatty meal (Lange *et al.*, 1988; Muenst *et al.*, 1980). The influence of gastric and bile secretions and the increase of hepatic blood flow by food were proposed to explain this increase in bioavailability. The administration of CGP 6140 after food intake is therefore recommended for an optimal systemic effect. The results of this study subsequently led to the development of an efficient and well tolerated low dose repeat regimen given postprandially, which has been used successfully in 300 patients in Latin America (Guderian *et al.*, 1989; Zea-Flores *et al.*, 1990).

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