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Pharmacokinetics of CGP 6140 (amocarzine) after oral administration of single 100–1600 mg doses to patients with onchocerciasis

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The concentrations of CGP 6140 [4-nitro-4′-(*N*-methyl-piperazinylthiocarbonylamido)-diphenylamine] and of its *N*-oxide metabolite, CGP 13 231, were measured in plasma and urine after single oral dose of 100–1600 mg of CGP 6140 to 41 fasted Ghanaian patients with *Onchocerca volvulus* infections. The absorption of CGP 6140 was rapid and its terminal elimination half-life was about 3 h. The plasma concentrations of CGP 6140 were essentially proportional to the dose. A greater variability in plasma concentrations was apparent after the 800 and 1600 mg doses indicating a poor bioavailability of the drug administered in fasting conditions to several patients. In plasma, the concentrations of CGP 13 231 were similar to those of CGP 6140. The amount of CGP 13 231 excreted in urine was 25–40% of the dose of CGP 6140 whereas only 1.5% was excreted as unchanged drug. If a single dose of drug is used for the treatment, the plasma concentration would be maintained for 3–4 h at a high level. At 8 h, the concentration falls to about 10% of the C_{max}. If sustained plasma concentrations of the drug are needed for efficacy, twice daily administration would maintain the minimum concentration at about 10% of the C_{max}.

Keywords CGP 6140 amocarzine *Onchocerca volvulus* patients pharmacokinetics

Introduction

Onchocerciasis is a filarial infection of man that affects several million people in Africa and there are foci in Central and South America as well as in the Saudi Arabian peninsula. The microfilariae of *Onchocerca volvulus* which are produced by macrofilariae and are predominantly located in subcutaneous nodules, migrate to the skin and the eyes. The host response to the microfilariae results in skin alterations and blindness. Drugs used against *O. volvulus* kill microfilariae (diethyl-carbamazine, ivermectine) or macrofilariae (suramin). The Onchocerciasis Control Programme (OCP) in West Africa identified the development of a macrofilaricide as a priority for its Onchocerciasis Chemotherapy Project (OCT) since suramin as a parenteral drug with repeat administration is not suitable for mass therapy in a control programme.

Following evidence of a micro- and macrofilaricidal activity of CGP 6140 in experimental filariasis (Striebel *et al.*, 1982), this compound was selected for joint development between

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Ciba-Geigy Limited, Basle and OCT. The proposed International Nomenclature Name (INN) for CGP 6140 is amocarzine.

In patients, preliminary results indicated that CGP 6140 rapidly induced a microfilarial reduction lasting several months after single oral doses or short term repeated dose regimens. Effects on macrofilariae in a large series with a repeated postprandial regimen are still under investigation. The pharmacokinetics of the drug in healthy volunteers after single oral administration of a 100 mg dose have been described previously (Lecaillon *et al.*, 1987a). The mean plasma elimination half-life was 2.6 h. It was 2.9 h for the *N*-oxide metabolite of CGP 6140, CGP 13 231. CGP 6140 was metabolized extensively and the urinary excretion of CGP 13 231 represented 35% of the dose of CGP 6140.

The aim of the present study was to investigate the dose dependency of the pharmacokinetics of the drug and of its *N*-oxide metabolite in fasted patients infected with *O. volvulus*.

Methods

Patients

Forty-one adult Ghanaian male patients infected with *O. volvulus* participated in the study. The patients received a full clinical examination prior to the study and 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 World Health Organization's Secretariat Committee on Research involving Human Subjects (SCRIHS). Prior to participation each patient had to give his informed consent.

Experimental design

The patients were given one of the following single oral doses as capsules containing 100 mg each of micronized CGP 6140 (median particle size < 2.0 μm), in the morning after an overnight fast: 100 mg (six patients), 200 mg (six patients), 400 mg (six patients), 600 mg (three patients), 800 mg (eight patients), 1200 mg (six patients) and 1600 mg (six patients).

Blood (about 10 ml) was withdrawn into lithium heparin tubes before and at 0.5, 1, 2, 4, 8, 16 and 24 h after administration. Additional samples were collected up to 96 h following the 100 mg dose. Plasma was separated and stored at −20° C until analysis.

Urine was collected before and from 0 to 72 h after administration of the 200–1600 mg doses and from 0 to 168 h after the 100 mg dose. The volume of each fraction was measured and 5 ml samples were stored at −20° C until analysis.

Analytical measurements

CGP 6140 and CGP 13 231 concentrations were measured by column-switching high-performance liquid chromatography (Lecaillon *et al.*, 1987b). CGP 13 231 was measured after administration of 100, 1200 and 1600 mg doses, only. The limit of assay (coefficient of variation < 10%) was about 50 nmol l^{-1} (20 ng ml^{-1}) in plasma and 250 nmol l^{-1} (100 ng ml^{-1}) in urine.

The synthetic reference compounds CGP 6140, CGP 13 231 and the *N*-desmethyl derivative, were provided by Ciba-Geigy Limited, Basle, Switzerland. The *N*-acetyl *N*-desmethyl and desulphurated derivatives of CGP 6140, of interest as potential metabolites, were provided by Hindustan Ciba-Geigy Limited, Research Centre, Bombay (Anjanneyulu, 1987).

Results

Concentrations in plasma and urine

The mean concentrations of CGP 6140 and CGP 13 231 in plasma after the 100 and 1200 mg doses are shown in Figure 1. Neither CGP 6140 or CGP 13 231 was detected in plasma at 24 h after the 100 mg dose in most patients. Low concentrations of unchanged drug were found in urine up to 24 h. High concentrations of CGP 13 231

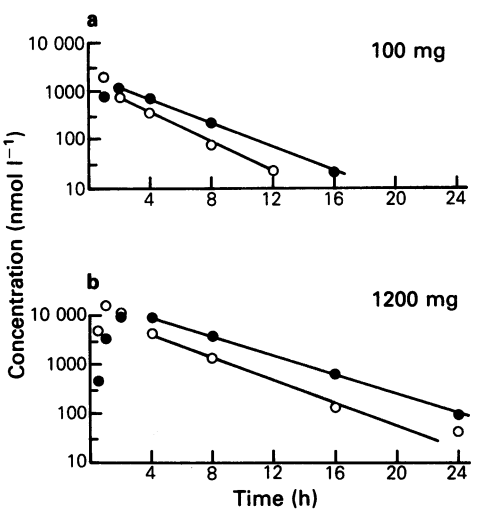

Figure 1 Mean plasma concentration-time courses ($n = 6$) of CGP 6140 (○) and of CGP 13 231 (●) after a) 100 mg and b) 1200 mg doses.

were measured in urine for the first 24 h and the metabolite could be detected up to 72 h. One of the subjects receiving an 800 mg dose had very low plasma (C_{max} = 556 nmol l^{-1} and AUC = 3320 nmol l^{-1} h) and urine drug concentrations. These data were not included in the calculation of mean pharmacokinetic parameters.

Pharmacokinetics and dose dependency

The mean pharmacokinetic parameters (± s.d.) in plasma and urine at each dose level are listed in Table 1 for CGP 6140 and CGP 13 231.

The C_{max} values for each dose were recorded at 1 h for most of the patients.

The terminal elimination half-life ($t_{½,z}$) of CGP 6140 increased slightly with doses up 800 mg. The mean values were 2.1 h at the 100 mg dose and 3.9 h at the 800 mg dose. The plasma concentration of CGP 6140 was essentially proportional to the dose although a greater variability in AUC (measured using the linear trapezoidal rule) was apparent after the 800 and 1600 mg doses. At these dose levels, several patients had low concentrations of CGP 6140 and its metabolite.

CGP 6140 is largely metabolised in the body since urinary recovery (Ae(0,72 h)), of unchanged drug was less than 1.5% of the dose.

In plasma, the concentrations of the *N*-oxide metabolite were similar to those of the unchanged drug. The AUC ratio of CGP 13 231/CGP 6140 was independent of dose. The mean $t_{½,z}$ of the metabolite was similar to that of parent drug indicating that the kinetics of the metabolite are formation-rate limited. The urinary recovery of CGP 13 231 represented 25–40% of the dose of CGP 6140 in most patients. A lower amount was recovered in patients with relatively low AUC values for unchanged drug and CGP 13 231.

No *N*-desmethyl, acetylated *N*-desmethyl or desulphurated derivatives of CGP 6140 were detected in plasma at 4 h post-dosing or in the urine (t = 0–16 h) of patients receiving the 800 mg dose.

Discussion

The absorption of the CGP 6140 appeared to be rapid since C_{max} values were recorded at 1 h. However, C_{max} values were not proportional to dose (1.95 μmol l^{-1} for the 100 mg dose and 16.8 μmol l^{-1} for the 1200 mg dose) whereas AUC values appeared to be (Table 1). Furthermore, the decrease in concentration after C_{max} was slower following high doses (Figure 1) suggesting a more prolonged absorption. The longer $t_{½,z}$ associated with higher doses may reflect the longer time over which the drug could be assayed.

After the 800 and 1600 mg doses about half of the patients had plasma concentrations of CGP 6140 less than predicted from other doses. These subjects also presented with a low excretion of the *N*-oxide metabolite in urine. A probable explanation for these observations might be some reduction in the amount of drug absorbed after administration of high doses of CGP 6140. The clinical implications of these pharmacokinetic results could be twofold.

Firstly, the variable absorption from the 800 and 1600 mg doses raises questions about a reproducible efficacy and an evaluation of the tolerability of CGP 6140 given in single high

Table 1 Pharmacokinetic parameters of CGP 6140 and its *N*-oxide metabolite, CGP 13 231, in plasma (mean ± s.d., t_{max} values are medians)

Dose (mg)	C_{max} *(nmol l^{-1})*	t_{max} *(h)*	*AUC(0,24 h) (nmol l^{-1} h)*	*AUC (0,24 h)* normalised for 100 mg dose (nmol l^{-1} h)*	$t_{½,z}$ *(h)*	Ae*(0,72 h) (% of dose)*
CGP 6140						
100	1950 ± 508	1	4270 ± 1180	4270 ± 1180	2.1 ± 0.2	
200	1520 ± 547	1	5590 ± 1180	2795 ± 590	2.4 ± 0.5	
400	7450 ± 2720	1	22400 ± 5490	5600 ± 1370	2.4 ± 0.7	
600	10900 ± 2970	1	34600 ± 6030	5770 ± 1000	3.1 ± 0.4	
800	8963 ± 4163	1	26887 ± 11869	3360 ± 1483	3.9 ± 1.2	
1200	16800 ± 5930	1	55700 ± 9630	4640 ± 800	3.3 ± 0.8	
1600	11800 ± 9450	1	44500 ± 28800	2780 ± 1800	3.7 ± 1.5	
CGP 13231						
100	1250 ± 172	1.5	5940 ± 880	5940 ± 880	2.5 ± 0.4	34.8 ± 9.0
1200	10400 ± 2840	2	75500 ± 18900	6290 ± 1575	3.1 ± 0.5	26.9 ± 2.3
1600	7230 ± 2750	3	49500 ± 23400	3090 ± 1950	3.4 ± 0.5	15.9 ± 5.7

* : AUC(0, 24 h) × 100/dose (mg).

doses and in the fasting state. The variability of the absorption of the drug at the high doses of 1200 mg when given to patients in fasting state was confirmed (Lecaillon *et al.*, 1990). Thus, the administration of high doses of the drug under fasting conditions is not recommended. Lecaillon *et al.* (1990) showed significant improvement in the absorption of CGP 6140 when a 1200 mg dose of the drug was administered to fed patients.

Secondly, if a single dose of drug is used for therapy, the plasma drug concentration would be maintained at a high level for only 3–4 h. At 8 h after dosing, the concentration in plasma falls to a value which is close to or below 10% of the C_{max}. With high single doses, high and short lived peak drug concentrations are sometimes reached, which may induce rapid killing of *O. volvulus* microfilariae with undesirable host reactions due to the liberation of parasite antigens (Mazzotti reaction). On the other hand, such short lived peak drug concentrations may be insufficient to cause a macrofilaricidal effect. Thus, sustained plasma concentrations of the drug may be needed for efficacy, and hence repeated administration would be more appropriate. Considering the elimination half-life of about 3 h, twice daily administration would maintain the minimum concentration at about 10% of the maximum concentration.

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