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Discovery of altered pharmacokinetics of CGP 15 210 G in poor hydroxylators of debrisoquine during early drug development

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The pharmacokinetics of CGP 15 210 G, a new 5-HT uptake inhibitor in poor and extensive metabolisers of debrisoquine, give indirect evidence of an association between its metabolism and polymorphic hydroxylation of the debrisoquine type.

Keywords genetic hydroxylation polymorphism debrisoquine CGP 15 210 G

Introduction

During the first phases of drug development, when only a few volunteers are involved, the selection of participating subjects should be stringent in order to reach valid conclusions. We believe that it is desirable ethically to attempt to assess the drug metabolising capability of individuals before experimentation with new drugs. Unwanted dynamic effects or unusual kinetic behaviour of new drugs could be related to drug metabolism. Therefore, for example, by examining prospectively the oxidation phenotype of volunteers it may be possible to protect them from unwanted effects due to drug accumulation. Such testing *at an early stage* during drug development has been suggested by Idle *et al.* (1983) and by Lennard *et al.* (1984). In all healthy volunteers entering phase 1 studies at the Human Pharmacology Institute (HPI) we are using the debrisoquine hydroxylation test for determination of the genetic expression of oxidative drug metabolising capacity.

According to previous population studies (Mahgoub *et al.*, 1977; Idle & Smith, 1979; Dick *et al.*, 1982) our healthy volunteers can be divided into a majority of extensive metabolisers (EM) and a minority of poor metabolisers (PM). Using a ratio of debrisoquine (D)/4-OH-debrisoquine (OHD) above 20 as the index of poor metabolism (Lennard *et al.*, 1977; Evans *et al.*, 1980) 7% of 122 subjects tested were found to be PM.

In an initial dose finding study with a new 5-hydroxytryptamine (5-HT) uptake inhibitor, CGP 15 210 G (bis[cis-3-hydroxy-4-(2,3-dimethylphenoxy)-piperidine] sulphate), the highest plasma concentrations and area under the plasma drug time curve were found in one PM of debrisoquine. Therefore, the pharmacokinetics of CGP 15 210 G were studied more extensively in both phenotypes. A preliminary summary of our results has been presented elsewhere (Antonin *et al.*, 1984). The metabolic pathway of CGP 15 210 G and the extent of absorption are still unknown in man.

Methods

The study was approved by the Ethics Committee of the HPI Ciba-Geigy, Tübingen. Each subject gave written informed consent.

Five EM (one female and four males, mean age 25 years, mean body weight 71 kg) and five PM (two females and three males, mean age 30 years, mean body weight 69 kg) took part. After a 12 h fast they received a single oral dose of 25 mg CGP 15 210 G. Blood samples were drawn as shown in Figure 1. Plasma was

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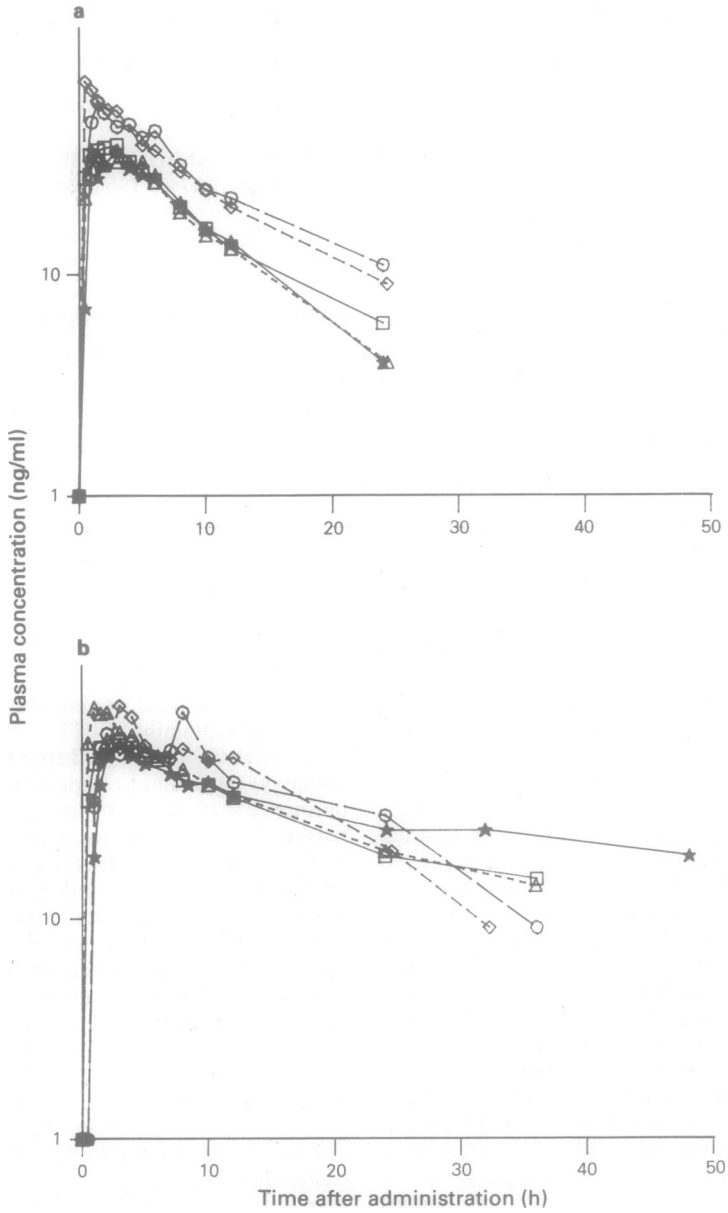

Figure 1 Plasma concentrations of CGP 15 210 G after a 25 mg oral dose in (a) extensive metabolisers and (b) poor metabolisers.

analysed for CGP 15 210 G by extraction with toluene under alkaline conditions, acylation with HFBA and gas chromatography with electron-capture detection (Schneider & Dubois, 1982). Concentrations down to 15 ng/ml can be determined with a coefficient of variation of <10 % in aliquots of 1 ml plasma.

The area under the plasma concentration time

Table 1 Pharmacokinetic parameters of CGP 15 210 G in poor (PM $n = 5$) and extensive (EM $n = 5$) metabolisers of debrisoquine

Volunteer	*Phenotype*	*D/4–OHD*	C_{max} *(ng/ml)*	*AUC (0,24) (ng ml^{-1} h)*	$t_{1/2}$ *(h)*
1	EM	0.58	36	389	6.0
2	EM	0.53	34	385	5.8
3	EM	0.36	38	409	5.9
4	EM	0.71	73	639	7.1
5	EM	0.28	59	635	6.8
Mean		0.49	48	491	6.3
± sd		0.17	17	133	0.6
6	PM	57	61	875	36.3
7	PM	36	89	1001	15.5
8	PM	31	63	886	16.8
9	PM	35	91	1122	12.1
10	PM	60	85	1073	18.2
Mean		44	78	991	19.8
± sd		14	15	110	9.5

D/4 – OHD = urinary ratio of debrisoquine/4-hydroxydebrisoquine
C_{max} = maximal plasma concentration
AUC (0,24) = area under the curve 0–24 h, calculated by the trapezoidal rule
$t_{1/2}$ = elimination half-life, calculated by log-linear regression

The unpaired t-test (two-tailed) showed significant differences between AUC ($P < 0.001$) and $t_{1/2}$ ($P < 0.05$) of poor and extensive hydroxylators.

curve was calculated according to the trapezoidal rule, the half-life of elimination by log-linear regression (Ritschel, 1980).

Results

The five PM of debrisoquine had higher and more sustained plasma concentrations of CGP 15 210 G than the five EM subjects (Figure 1). Thus, CGP 15 210 G was detectable in the plasma only of PM at 36 h after drug ingestion. The area under the plasma drug concentration-time curve was found to be approximately two-three fold larger and the elimination half-life two-three times longer in PM than in EM (Table 1).

Discussion

These data suggest that the metabolism of the new 5-HT uptake inhibitor CGP 15 210 might provide a further example of polymorphic drug metabolism. With the early knowledge of polymorphic control of metabolism of this drug subsequent subchronic multiple-dose tolerance studies can be designed more appropriately without exposing healthy subjects to unnecessary risks. For participation in a presently running subchronic study only EM of debrisoquine were selected. The same applies to clinical studies later during drug development when therapeutic efficacy has to be shown. Given the present 'state of the art' in clinical pharmacology it seems desirable to anticipate genetic polymorphism in drug metabolism during early phase I studies.

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