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The influence of the sparteine/debrisoquine genetic polymorphism on the disposition of dexfenfluramine

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1 To determine whether dexfenfluramine is a substrate of cytochrome P450 2D6 (CYP2D6), its disposition has been studied in nine extensive (EM) and eight poor metabolizers (PM) of debrisoquine.

2 Following a 30 mg dose of dexfenfluramine hydrochloride, urine was collected in all subjects for 96 h post-dose and plasma samples were collected in 11 subjects (six EMs and five PMs). Dexfenfluramine and nordexfenfluramine were measured in urine by h.p.l.c. and in plasma by g.c.

3 Urinary recovery of dexfenfluramine was greater in PMs than EMs (4136 ± 1509 μg *vs* 1986 ± 792 μg; 95% CI of difference 926–3374; $P < 0.05$) whereas that of nordexfenfluramine was similar in both phenotypes (PM: 1753 ± 411 μg *vs* 1626 ± 444 μg).

4 Dexfenfluramine AUC was higher in PMs (677 ± 348 μg l^{-1} h) than EMs (359 ± 250 μg l^{-1} h). The apparent oral clearance of dexfenfluramine was greater in EMs than PMs (93.6 ± 42.4 l h^{-1} *vs* 45.6 ± 19.5 l h^{-1}; 95% CI of difference 1.2–94.7; $P < 0.05$). The renal clearance was similar in both phenotypes (EMs: 5.88 ± 2.83 l h^{-1}; PMs 6.60 ± 2.01 l h^{-1}), indicating that the higher urinary recovery of dexfenfluramine in PMs reflects higher plasma concentrations, rather than phenotype differences in the renal handling, of dexfenfluramine.

5 The apparent nonrenal clearance of dexfenfluramine was substantially lower ($P < 0.05$; 95% CI of difference 3.0–94.1) in PMs (39.0 ± 19.5 l h^{-1}) than EMs (87.6 ± 41.2 l h^{-1}).

6 There was a significant inverse correlation ($r_s = -0.776$ 95% CI -0.31–-0.94; $n = 11$; $P = 0.005$) between the debrisoquine metabolic ratio and the apparent nonrenal clearance of dexfenfluramine.

7 PMs had a higher incidence of adverse effects (nausea and vomiting) than EMs.

8 In conclusion, the metabolism of dexfenfluramine is impaired in PMs. Thus CYP2D6, the isoenzyme deficient in poor metabolizers of debrisoquine, must catalyse at least one pathway of dexfenfluramine biotransformation.

Keywords dexfenfluramine cytochrome P450 genetic polymorphism debrisoquine

Introduction

Dexfenfluramine, the S-enantiomer of the racemate fenfluramine, is used as an anorectic drug to assist weight loss in the obese [1]. Recently, dexfenfluramine has also been used to improve diabetic control in obese patients with Type II diabetes [2]. Dexfenfluramine is eliminated principally by metabolism (Figure 1), with approximately 9% of the dose excreted in the urine as unchanged drug [3, 4]. Considerable interindividual variation in the elimination half-life of dexfenfluramine and the racemate fenfluramine has been reported [1]. For many drugs such interindividual variation is attributable to differences in the activity of drug metabolizing enzymes. Cytochrome P450 2D6 (CYP2D6) metabolizes many widely used drugs [5]

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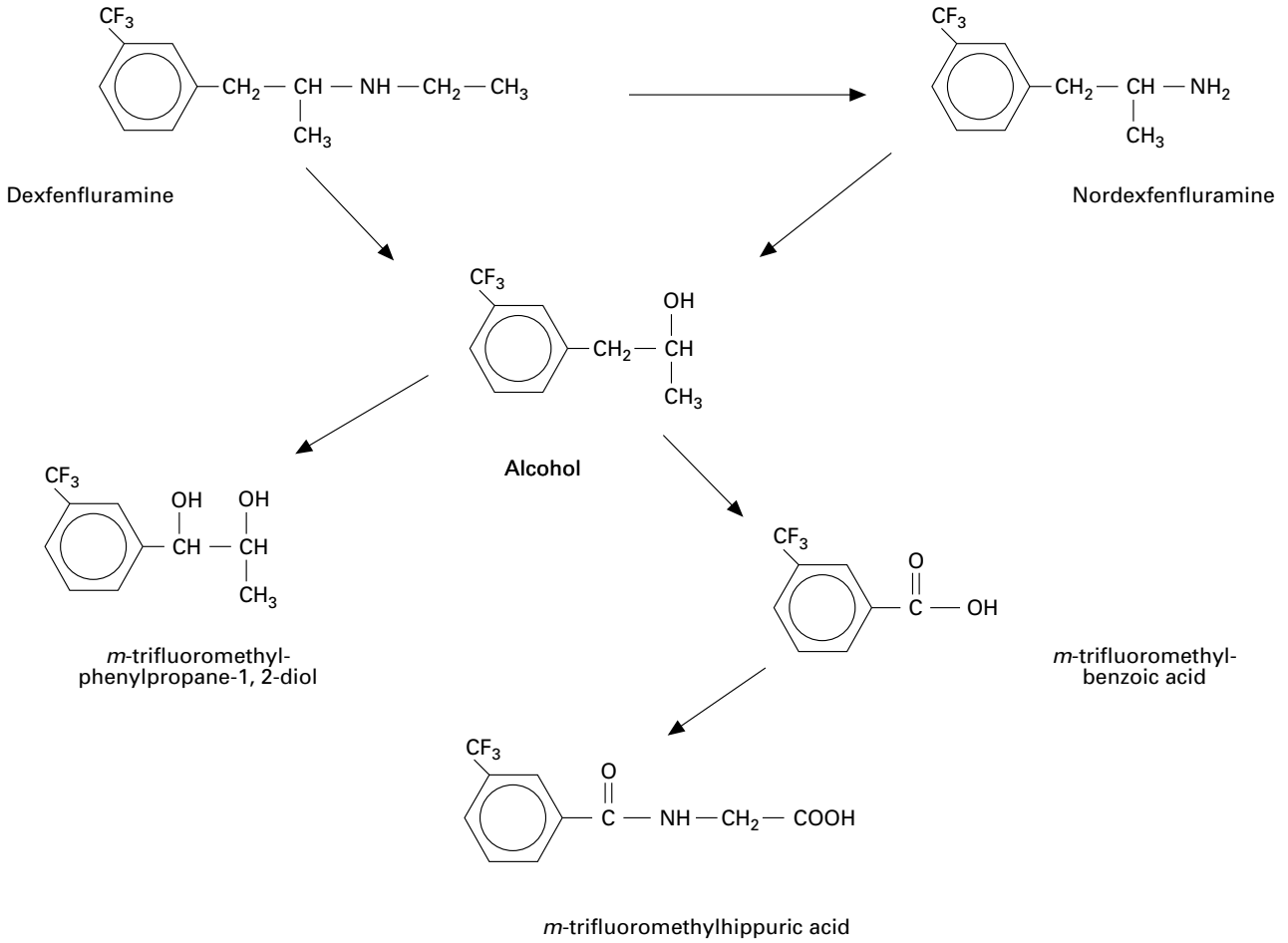

Figure 1 Metabolic pathways of dexfenfluramine in man as proposed by Campbell *et al.* [3] and Richards *et al.* [4] on the basis of the urinary recovery of dexfenfluramine metabolites.

and displays a genetic polymorphism. Certain individuals in the population (poor metabolizers or PMs) lack the functional enzyme and do not metabolize substrates of CYP2D6, such as sparteine and debrisoquine, in the usual manner. The remainder of the population are termed extensive metabolizers (EMs). Clinical consequences of the absence of the functional enzyme depend on the significance of the impaired pathway of metabolism to the overall elimination of the drug in addition to the therapeutic index of the substrate. Poor metabolizers can be at increased risk of adverse effects when administered standard drug doses, as has been observed for phenformin and perhexiline [5].

Dexfenfluramine is a phenylethylamine and has structural similarities to substrates of CYP2D6 such as methoxyamphetamine [6], MDMA [7] and selegeline [8]. In human liver microsomes two reactions catalysed by CYP2D6, the metabolism of codeine to morphine (Gross & Mikus, unpublished observation) and the oxidation of dextromethorphan to dextrorphan [9], are inhibited by dexfenfluramine (K_i 2 μM and 1.8 μM, respectively). The findings indicate that dexfenfluramine has an affinity for CYP2D6 but the relevance of the *in vitro* observation to the disposition of dexfenfluramine in poor metabolizers cannot be predicted. Therefore, a phenotyped panel study has been performed to determine whether the disposition of dexfenfluramine differs in poor and extensive metabolizers of debrisoquine.

Methods

Subjects

This study was approved by the Medical Research Ethics Committee, Royal North Shore Hospital, Sydney. All volunteers were healthy as assessed by routine medical examination and biochemical tests of liver and renal function, and gave written informed consent prior to participating in the study. Seventeen healthy subjects were recruited, nine extensive metabolizers (EM; six female and three male; age 29 ± 7 years; weight 65 ± 7 kg) and eight poor metabolizers (PM; six female and two male; age 34 ± 6 years; weight 59 ± 6 kg) of debrisoquine, a marker for the activity of CYP2D6. Debrisoquine metabolizer phenotype was determined using standard techniques following an oral 10 mg dose of debrisoquine [10]. One subject (PM4) was a cigarette smoker and two subjects (EM3 and PM3) were taking oral contraceptives.

Protocol

A 30 mg dose of dexfenfluramine hydrochloride (two 15 mg Adifax® Capsules, Servier Laboratories, Australia; dose 25.92 mg base or 112 μmol) was administered under medical supervision at 08.00 h with 100 ml water

after an overnight fast. All subjects refrained from any medication for 1 week and from alcohol for 24 h prior to and during the study. For the initial 4 h post-dose each subject rested and was encouraged to drink 150 ml water per hour. Subjects were given a standard light lunch 4 h post-dose and dinner 6 h later. All subjects were asked to spontaneously report any symptoms experienced at any time after the dose of dexfenfluramine. If any effects were reported, the subjects were also asked to state when they abated.

All urine voided for 96 h post-dose was collected over the following intervals: 0–2, 2–3, 3–4, 4–5, 5–7, 7–9, 9–11, 11–13, 13–24, 24–36, 36–48, 48–60, 60–72, 72–84 and 84–96 h. The pH and volume of all urine samples was measured and an aliquot stored at -20°C pending analysis. In eleven subjects (six EM and five PM) venous blood samples were also collected. An indwelling cannula was inserted prior to the dexfenfluramine dose and 10 ml blood samples were taken pre-dose, and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 14 h post-dose. Additional samples were taken by venepuncture at 24, 25, 32, 35, 36, 48, 49, 60, 72, 84 and 96 h. Blood samples were transferred to tubes containing lithium heparin and centrifuged at 2200 *g* for 10 min. Aliquots of plasma were then stored at -20°C pending analysis.

Analysis of dexfenfluramine and nordexfenfluramine

The concentrations of dexfenfluramine and nordexfenfluramine in urine were measured using a high performance liquid chromatographic technique developed for this study [11]. The concentrations of dexfenfluramine and nordexfenfluramine in plasma were measured by Dr S. Dawling, Poisons Unit, Guy's Hospital, according to the method of Richards *et al.* [12]. The limit of quantitation of the plasma assay for both analytes was 2 $\mu g\, l^{-1}$. All concentrations are reported in terms of the respective bases, and when appropriate have been converted to molar values using the molecular weights of dexfenfluramine (231.3) and nordexfenfluramine (203.2).

Data analysis

Noncompartmental pharmacokinetic parameters were calculated using standard equations [13]. The urinary half-life of dexfenfluramine was calculated from the terminal slope of the relationship between log rate of urinary excretion *vs* midpoint time curve by extended least squares nonlinear regression [14].

The maximum serum concentration (C_{max}) and the time at which it was attained (t_{max}) were noted from the observed plasma concentration-time data. The terminal elimination rate constant (λ_z) was calculated as the slope of the terminal log serum concentration *vs* time data [14]. The terminal half-life of dexfenfluramine ($t_{1/2}$) was calculated as $0.693/\lambda_z$. The area under the plasma concentration-time curve (AUC(0, t)) was calculated using the trapezoidal rule during the portion of the curve where successive concentrations were increasing and the log trapezoidal rule during the portion of the curve where successive serum concentrations were decreasing [14]. The area under the curve of dexfenfluramine was extrapolated to infinity (AUC) by adding C_{last}/λ_z. The apparent oral clearance of dexfenfluramine (CL_O) was calculated as DOSE/AUC. Dexfenfluramine renal clearance (CL_R) was calculated as the amount of dexfenfluramine recovered in the urine divided by the AUC, and apparent nonrenal clearance (CL_{NR}) as the difference between the CL_O and CL_R.

Based on the variability in dexfenfluramine clearance in healthy volunteers reported by Cheymol *et al.* [15] and using at least five subjects per group, this study could detect a phenotype difference in dexfenfluramine clearance of 25 $l\, h^{-1}$ with a power of 0.8 at an α of 0.05 (two-tailed test). Results are reported as mean and standard deviation (s.d.), except for half-life which is reported as the harmonic mean. Differences in parameters between EMs and PMs were assessed using the Mann-Whitney U-test [16]. Relationships between variables were assessed according to the value of the Spearman rank correlation coefficient and the 95% confidence interval is also reported. A probability of less than 5% was considered significant. For parameters where phenotype differences were observed, the 95% confidence interval of the difference between the population means (95% CI of difference) is also reported.

Results

Urinary recovery

In all subjects urinary pH was within the range 4.8 and 7.4 and there was no difference between EMs and PMs. The mean 96 h urinary recovery of dexfenfluramine was greater ($P<0.05$; 95% CI of difference 3.6–13.0) in PMs (16.0 ± 5.8% dose) than in EMs (7.7 ± 3.1% dose). The mean urinary half-life of dexfenfluramine was longer ($P<0.05$; 95% CI of difference 0.3–15.6) in PMs (17.8 h) than in EMs (9.9 h).

The 96 h urinary recovery of nordexfenfluramine was similar ($P=0.63$) in EMs (7.1 ± 1.9% dose) and PMs (7.7 ± 1.8% dose). Nordexfenfluramine was still being excreted in the majority of subjects at 96 h. Therefore the total urinary recovery of nordexfenfluramine was underestimated. The sum of the urinary recoveries of dexfenfluramine plus nordexfenfluramine was higher in PM (23.7 ± 5.7%) than EM (14.8 ± 3.9%) ($P<0.05$, 95% CI of difference 3.9–13.9).

A phenotype difference in the urinary recovery of dexfenfluramine was also observed (95% CI of difference 0.8–4.1) in the 11 subjects in whom plasma concentrations of dexfenfluramine were also measured (Table 1). In these 11 subjects the urinary recovery of dexfenfluramine was similar to that observed in all 17 volunteers, indicating that the disposition of dexfenfluramine in this subgroup appropriately reflects the disposition of dexfenfluramine in all 17 subjects studied.

Table 1 Dexfenfluramine pharmacokinetic parameters (mean ± s.d.) calculated in extensive (EM) and poor metabolizers (PM) of debrisoquine.

Subject	*MR*	C_{max} ($\mu g l^{-1}$)	t_{max} (*h*)	λ_z (h^{-1})	$t_{1/2}$ (*h*)	*AUC* (0, t) ($\mu g\ l^{-1}\ h$)	*AUC* ($\mu g\ l^{-1}\ h$)	CL_o ($l\ h^{-1}$)	*Ae* (*mg*)	CL_R ($l\ h^{-1}$)	CL_{NR} ($l\ h^{-1}$)
EM											
EM 3	0.3	15.9	3.5	0.0397	17.4	265	343	75.6	0.94	2.75	72.8
EM 4	3.7	29.8	4.5	0.0233	29.7	720	853	30.4	2.14	2.51	27.9
EM 5	0.2	18.1	4.0	0.0596	11.6	220	287	90.3	2.32	8.09	81.4
EM 7	0.8	12.5	6.0	0.0609	11.4	190	222	116.6	2.02	9.10	107.4
EM 8	0.8	16.1	5.1	0.0564	12.3	243	286	90.8	2.19	7.66	83.1
EM 9	0.2	10.2	5.0	0.0639	10.9	139	164	157.9	0.85	5.18	152.7
Mean		17.1	4.7	0.0506	13.7*	296	359	93.6	1.74	5.88	87.6
s.d.		6.8	0.9	0.0158		212	250	42.4	0.66	2.83	41.2
PM											
PM 1	136	29.3	5.0	0.0222	31.3	1098	1256	20.6	4.92	3.92	16.7
PM 3	53	28.3	4.5	0.0346	20.0	596	688	37.7	6.16	8.96	28.7
PM 6	56	20.5	5.0	0.0326	21.3	511	609	42.6	4.60	7.55	35.0
PM 7	54	16.7	5.0	0.0463	15.0	314	355	73.1	1.85	5.21	67.9
PM 8	24	18.6	4.5	0.0400	17.3	403	478	54.2	3.52	7.36	46.8
Mean		22.7	4.8	0.0351	19.7*	584†	677†	45.6†	4.21†	6.60	39.0†
s.d.		5.8	0.3	0.0090		306	348	19.5	1.62	2.01	19.5

* harmonic mean. † $P < 0.05$ EM *vs* PM

Plasma concentrations

Log plasma concentration–time profiles of both dexfenfluramine and nordexfenfluramine in representative EM and PM subjects are shown in Figure 2. The pharmacokinetic parameters of dexfenfluramine are given in Table 1.

Considerable interindividual variation in dexfenfluramine disposition was observed in the 11 subjects in whom plasma concentrations were measured. For example, C_{max} varied threefold (10–30 $\mu g\ l^{-1}$) and AUC varied more than 10-fold. Poor metabolizers tended to have a higher C_{max} (mean values: EM 17 $\mu g\ l^{-1}$; PM 22.7 $\mu g\ l^{-1}$) and a longer dexfenfluramine half-life (EM 13.7 h; PM 19.7 h). However, these differences were not statistically significant. Dexfenfluramine AUC was twofold greater ($P < 0.05$) in PMs ($677 \pm 348\ \mu g\ l^{-1}\ h$) than EMs ($359 \pm 250\ \mu g\ l^{-1}\ h$), and consequently the apparent oral clearance was lower ($P < 0.05$; 95% CI of difference 1.2–94.7) in PMs ($45.6 \pm 19.5\ l\ h^{-1}$) than EMs ($93.6 \pm 42.4\ l\ h^{-1}$). The renal clearance of dexfenfluramine was similar in EMs and PMs, indicating that the higher urinary recovery of dexfenfluramine in PMs reflects phenotype differences in nonrenal clearance rather than in renal drug handling. The apparent nonrenal clearance of dexfenfluramine was substantially lower ($P < 0.05$; 95% CI of difference 3.0–94.1) in PMs ($39.0 \pm 19.5\ l\ h^{-1}$) than EMs ($87.6 \pm 41.2\ l\ h^{-1}$), indicating that the elimination of dexfenfluramine by metabolism is impaired in PMs relative to EMs. There was a significant inverse correlation ($r_s = -0.776$; 95%CI -0.31 – -0.94; $P = 0.005$) between the debrisoquine metabolic ratio and the apparent nonrenal clearance of dexfenfluramine (Figure 3).

The C_{max} (EM: $8.4 \pm 0.4\ \mu g\ l^{-1}$; PM: $7.0 \pm 1.8\ \mu g\ l^{-1}$),

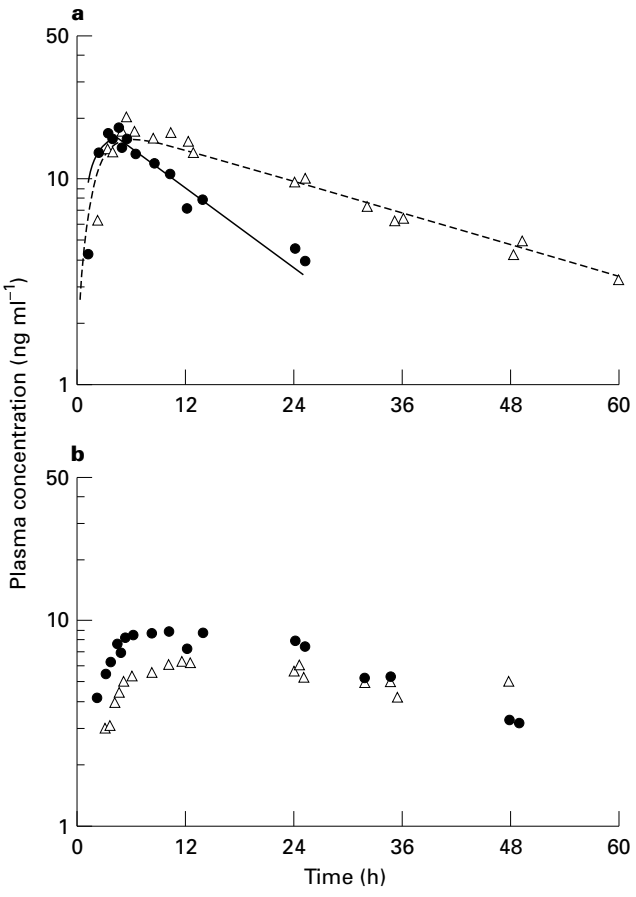

Figure 2 Plasma concentration-time profile of a) dexfenfluramine and b) nordexfenfluramine in representative extensive (EM 5, ●) and poor (PM 6, △) metabolizers.

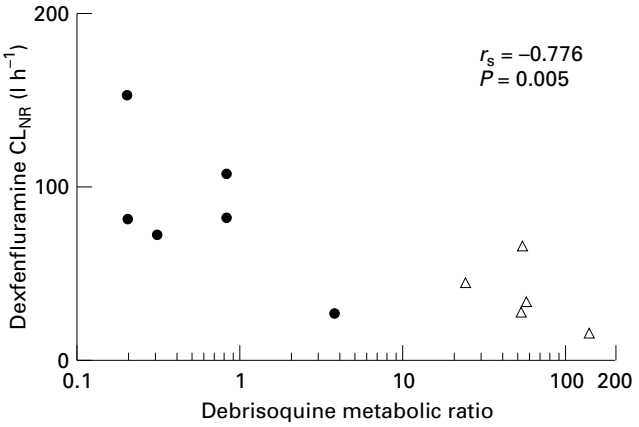

Figure 3 Relationship between the $\log_{10}$ metabolic ratio of debrisoquine and the apparent nonrenal clearance of dexfenfluramine in extensive (●) and poor (△) metabolizers.

t_{max} (EM: 12 ± 6 h; PM: 18 ± 9 h) and AUC (EM: 301 ± 55 μg l^{-1} h; PM 336 ± 136 μg l^{-1} h) of nordexfenfluramine were similar ($P > 0.05$) in the EMs and PMs. Therefore, this pathway of metabolism is not impaired in poor relative to extensive metabolizers.

Adverse effects

A number of adverse effects were noted in both the extensive and poor metabolizers. All subjects felt very cold for some time within the first 3 h of taking dexfenfluramine. The other adverse effects and the number of volunteers spontaneously reporting their reactions are given in Table 2. Poor metabolizers experienced more nausea, vomiting and headaches. The nausea and headaches experienced by the PMs were of later onset, greater severity and longer duration than those experienced by extensive metabolizers.

Discussion

The disposition of dexfenfluramine has been studied in healthy volunteers in whom the activity of the polymorphic enzyme CYP2D6 is known. The mean apparent oral clearance of dexfenfluramine was substantially lower in poor than in extensive metabolizers. The renal clearance of dexfenfluramine was comparable in the two groups and therefore the difference in apparent oral clearance reflects phenotype differences in the apparent nonrenal clearance of dexfenfluramine. Metabolism is the major pathway of nonrenal dexfenfluramine elimination [1] and the twofold difference in apparent nonrenal clearance reflects a twofold difference in metabolic capacity. Consequently, the metabolism of dexfenfluramine is diminished in poor metabolizers of debrisoquine, which indicates that the metabolism of dexfenfluramine is catalysed in part by CYP2D6. The significant correlation between the debrisoquine metabolic ratio and dexfenfluramine apparent nonrenal clearance supports a role for CYP2D6 in the metabolism of dexfenfluramine.

Table 2 Adverse effects reported in extensive (EM) and poor metabolizers (PM) following a 30 mg dose of dexfenfluramine. The number of individuals reporting each symptom is given.

Symptom	*EM* ($n=9$)	*PM* ($n=8$)
Nausea	2	7
Vomiting	0	4
Headache	4	6
Light-headedness	5	4
Diarrhoea	1	1

Nordexfenfluramine pharmacokinetic parameters including C_{max}, t_{max}, AUC and urinary recovery were all similar in poor and extensive metabolizers. The formation of this metabolite therefore does not appear to differ in EMs and PMs. This observation suggests that a different pathway of dexfenfluramine metabolism must be impaired in poor metabolizers. It has been suggested that *m*-trifluoromethylphenylpropan-1,2-diol and *m*-trifluoromethylbenzoic acid are formed independently of nordexfenfluramine [3, 17]. Thus metabolism to one of these compounds may be mediated by CYP2D6.

Structural requirements for compounds to interact with the active site of CYP2D6 have been proposed by comparing the structures of known substrates of this enzyme [18–20]. Dexfenfluramine, with a basic nitrogen atom and a hydrophobic coplanar region, is a candidate for interaction with CYP2D6. Oxidation at 5 or 7 Å from the nitrogen atom, at the *meta*- or *para*- position of the benzene ring would be predicted from the proposed models for substrate oxidation by CYP2D6. However, this pathway of metabolism could be hindered by the electron-rich *meta*-trifluoromethyl group. CYP2D6 catalyses aromatic and aliphatic hydroxylation, *O*-dealkylation and *O*-demethylation [21] and *N*-demethylation [22]. Additional pathways of metabolism catalysed by CYP2D6 have recently been identified, including carbamic ester cleavage of tiracizine [23] and the oxidative *N*-dealkylation of selegeline at sites only 2.5 Å from the basic nitrogen atom [8]. Selegeline is structurally related to dexfenfluramine, and this latter observation using stably expressed CYP2D6 is clearly at variance with the proposed models for substrate oxidation by CYP2D6. A role of CYP2D6 in dexfenfluramine metabolism therefore can not be rejected simply on the grounds that the compound does not conform to the substrate models currently proposed. Studies using recombinant CYP2D6 or analysis of the urinary recovery of all dexfenfluramine metabolites in EMs and PMs would indicate which metabolic pathway is mediated by CYP2D6.

Interindividual variation in the disposition of dexfenfluramine was observed within both phenotypes. Overall a tenfold variation in the apparent nonrenal clearance of dexfenfluramine was observed and there was some overlap between the poor and extensive metabolizers. Thus, CYP2D6 activity is only one of the factors contributing to the interindividual variation in dexfen-

fluramine disposition observed in the healthy volunteers studied. Subject EM4, who had a debrisoquine metabolic ratio of 3.7 and therefore lower CYP2D6 activity than the other extensive metabolizers, had a longer half-life, and lower apparent oral and nonrenal clearances of dexfenfluramine relative to the other EMs.

The adverse effects noted in this study in healthy volunteers were similar to those reported previously in patients administered dexfenfluramine [25]. The high frequency of adverse effects observed is partly related to the single 30 mg dose of dexfenfluramine given because the drug is usually administered as a 15 mg dose twice daily [1]. Nevertheless, adverse effects were more frequent in poor than in extensive metabolizers. Dexfenfluramine t_{max} was much earlier than the time of onset of adverse effects. Therefore, unless there is a substantial delay in the equilibration of dexfenfluramine across the blood–brain barrier, these effects are unlikely to be related to the higher plasma concentrations of dexfenfluramine in the poor metabolizers. Peak nordexfenfluramine concentrations were similar in extensive and poor metabolizers and are thus also unlikely to contribute to the greater severity of adverse reactions observed in the poor than extensive metabolizers. Dexfenfluramine administration has been associated with the development of pulmonary hypertension in a small number of patients [1]. However, as this adverse drug reaction has not been linked to high dexfenfluramine plasma concentrations, it is unlikely that PMs will be at increased risk of this complication. Further studies in patients prescribed dexfenfluramine would be required to confirm whether any adverse effects noted at standard doses during routine therapy are related to an individual's CYP2D6 phenotype.

In conclusion, in healthy normal weight subjects the pharmacokinetics of dexfenfluramine differ in poor and extensive metabolizers of sparteine/debrisoquine. The apparent nonrenal clearance is lower in PMs, consistent with impaired metabolism. Therefore metabolism catalysed by CYP2D6 contributes to dexfenfluramine elimination. Even if phenotype differences in dexfenfluramine steady-state concentrations are confirmed in obese patients prescribed dexfenfluramine, there is only a weak relationship between dexfenfluramine plasma concentrations and weight loss [26]. It is therefore unlikely that the differences in disposition observed between extensive and poor metabolizers would have consequences for the efficacy of dexfenfluramine.

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