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The effects of human CYP2C8 genotype and fluvoxamine on the pharmacokinetics of rosiglitazone in healthy subjects

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Aims
To determine the effect of *CYP2C8* genotype and of fluvoxamine on the pharmacokinetics of rosiglitazone.

Methods
Twenty-three healthy subjects with the following genotypes were included in a two-phase, open-label, cross-over trial: *CYP2C8*3/*3* (n = 3), *CYP2C8*1/*3* (n = 10) and *CYP2C8*1/*1* (n = 10). In Phase A, the subjects were given 4 mg rosiglitazone as a single oral dose. In Phase B, the subjects were treated with multiple oral doses of 50 mg fluvoxamine maleate for 3 days prior to the single oral administration of 4 mg rosiglitazone. Plasma concentrations of rosiglitazone and relative amounts of *N*-desmethylrosiglitazone were measured in both phases for 24 h after drug administration.

Results
The pharmacokinetics of rosiglitazone and *N*-desmethylrosiglitazone were not significantly different between the *CYP2C8* genotypic groups. Fluvoxamine caused a statistically significant (P = 0.0066) increase in the $AUC_{0-\infty}$ of rosiglitazone, with a geometric mean ratio of 1.21 [95% confidence interval (CI) 1.06–1.39]. The elimination half-life ($t_{1/2}$) was also significantly higher (P = 0.0203) with a geometric mean ratio of 1.38 [95% CI 1.06–1.79]. The coadministration of fluvoxamine had no influence on the pharmacokinetics of *N*-desmethylrosiglitazone.

Conclusion
The importance of the *CYP2C8*3* mutation in the *in vivo* metabolism of rosiglitazone could not be confirmed. Fluvoxamine increased the $AUC_{0-\infty}$ and $t_{1/2}$ of rosiglitazone moderately and hence may be a weak inhibitor of CYP2C8.

Introduction

Rosiglitazone maleate is an oral agent in the thiazolidine dione class used in the treatment of Type 2 diabetes mellitus. The thiazolidine diones are highly selective and potent agonists for the peroxisome proliferator-activated receptor gamma (PPARγ), which decrease blood glucose levels by sensitizing peripheral tissues to insulin [1–3]. The bioavailability of rosiglitazone is approximately 99% after oral dosing in tablet form and the absorption is rapid, reaching maximal concentration (C_{max}) within 1 h [4]. The major products of metabolism following incubation of rosiglitazone with human liver microsomes are para-hydroxy- and *N*-desmethylrosiglitazone. These pathways are catalysed mainly by CYP2C8, with a minor contribution from CYP2C9 [5]. The *in vivo* metabolism of rosiglitazone is complex,

with many *N*-demethylated and hydroxylated metabolites being identified in both nonconjugated and conjugated form [4]. The quantitative importance of *N*-demethylation of rosiglitazone *in vivo* has been verified by several studies [6–9]. Thus, the CYP2C8- and CYP2C9-inhibitor gemfibrozil [6, 7] increases the AUC of rosiglitazone and prolongs its $t_{1/2}$, decreases the *N*-desmethylrosiglitazone/rosiglitazone AUC ratio and prolongs the time to maximum concentration (t_{max}) of *N*-desmethylrosiglitazone [8]. Furthermore, trimethoprim, which is an inhibitor of CYP2C8, raises the AUC of rosiglitazone and decreases the formation of *N*-desmethylrosiglitazone [9]. It has also been shown that the antifungal agent ketoconazole causes a slight increase in the AUC and C_{max} of rosiglitazone in humans [10] and that rifampicin decreases the AUC by inducing CYP2C8 [9, 11].

CYP2C8 catalyses the metabolism of a number of other clinically used drugs, such as the anticancer drug paclitaxel [12] and the antimalarial drug amodiaquine [13]. Several allelic variants of CYP2C8 have been described (http://www.imm.ki.se/cypalleles), namely *CYP2C8*1A–C* [14, 15], *CYP2C8*2–3* [16], *CYP2C8*4* [15] and *CYP2C8*5–10* [17]. *CYP2C8*3* has a reported allele frequency of 0.10–0.23 in the Caucasian population [18].

A study by Bidstrup *et al.* 2006 described no significant effect of the *CYP2C8*3* genotypes on the *in vivo* metabolism of a therapeutic dose of repaglinide, a known substrate of CYP2C8 [19]. On the other hand, Niemi *et al.* [20, 21] reported that plasma concentrations of repaglinide were lower in subjects with the CYP2C8*1/*3 genotype. A study by Martinez *et al.* showed differences in the AUC and $t_{1/2}$ of (R)-ibuprofen between subjects with the *CYP2C8*3/*3*, *CYP2C8*1/*1* and *CYP2C8*1/**3 genotypes [22] and the combined effect of *CYP2C8* and *CYP2C9* genotypes on racemic ibuprofen pharmacokinetics was described by Garcia-Martin *et al.* [23].

CYP2C9 is among the most important drug-metabolizing enzymes in humans. Substrates include phenytoin, tolbutamide, torsemide, S-warfarin and numerous nonsteroidal anti-inflammatory drugs [24, 25]. The two most significant mutant alleles are *CYP2C9*2* (C_{430}>T: Arg144→Cys) and *CYP2C9*3* (A_{1075}>C: Ile359→Leu) and have been shown to affect drug metabolism [26–28]. Garcia-Martin *et al.* found that ibuprofen clearance was determined not only by *CYP2C8* genotype but also by the *CYP2C9* genotypes **1/*1*, **1/*2*, **1/*3*, **2/*2*, **2/*3* and **3/*3* [23]. Despite the high degree of homology in amino acid sequence, the crystal structures of human CYP2C8 [29] and CYP2C9 [30] reveal structural differences in the active site, which determine substrate specificity. A linkage between the *CYP2C8* and *CYP2C9* genetic polymorphism in the Caucasian population has been observed. Yasar *et al.* have reported that approximately 96% of the subjects with the *CYP2C8*3* allele also carried *CYP2C9*2* and 85% of the subjects possessing the *CYP2C9*2* variant also carried *CYP2C8*3* [31].

Fluvoxamine is an antidepressant drug that belongs to the class of selective serotonin reuptake inhibitors (SSRI). It is a potent inhibitor of the *in vitro* CYP2C9-mediated 4-methylhydroxylation of tolbutamide and the 7-hydroxylation of (S)-warfarin in human liver microsomes [32]. *In vivo*, fluvoxamine is also a moderate inhibitor of CYP2C19 and CYP2C9 [33–35] and a potent inhibitor of CYP1A2 [34, 36], but its possible effect on the metabolism of CYP2C8 substrates has never been described. Walsky *et al.* investigated 209 drugs as potential inhibitors of CYP2C8, but fluvoxamine was not tested [37].

The aims of this study were to investigate the effect of (i) the *CYP2C8*3* allele and (ii) multiple doses of fluvoxamine on the pharmacokinetics of rosiglitazone.

Methods

Subjects

Twenty-three healthy Caucasians gave written informed consent to participate in the trial. Subjects were divided into three groups based on their *CYP2C8* genotype. Their demographic information and *CYP2C8* and *CYP2C9* genotypes are shown in Table 1. All subjects were free of cardiovascular, hepatic, renal or gastrointestinal disease, drug abuse or alcohol dependence assessed by physical examination and a review of medical history. In addition, blood pressure and the results of laboratory tests (blood chemistry, haematology and immunology) were required to be within the normal range.

Genotyping

The DNA was extracted from peripheral leucocytes using a PUREGENE™ genomic DNA purification kit according to the guidelines of the manufacturers (Gentra Systems, Minneapolis, MN, USA). *CYP2C8* genotype with regard to the **3* mutation was determined by Professor A. Rane (Department of Medical Laboratory Sciences and Technology, Division of Clinical Pharmacology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden) by a previously published method [31]. The subjects were chosen from a Caucasian population [38], which had been screened with respect to their *CYP2C9* genotype [39].

Table 1
Demographic information and *CYP2C* genotypes of the subjects

Subject no.	Sex	Age, years	Weight, kg	Height, cm	CYP2C8 genotype	CYP2C9 genotype
1	M	23	76	189	*3/*3	*2/*2
2	F	27	60	162	*3/*3	*2/*2
3	M	24	74	184	*3/*3	*2/*2
Median (range)	–	24 (23–27)	74 (60–76)	184 (162–189)	–	–
4	M	25	80	180	*1/*1	*1/*1
5	M	26	80	184	*1/*1	*1/*1
6	M	29	78	176	*1/*1	*1/*1
7	M	26	78	174	*1/*1	*1/*1
8	M	26	98	199	*1/*1	*1/*1
9	M	26	66	175	*1/*1	*1/*1
10	M	27	84	183	*1/*1	*1/*1
11	M	25	117	185	*1/*1	*1/*1
12	M	26	97	190	*1/*1	*1/*1
13	M	25	88	190	*1/*1	*1/*1
Median (range)	–	26 (25–29)	82 (66–117)	183.5 (174–199)	–	–
14	M	25	89	180	*1/*3	*1/*2
15	M	26	70	178	*1/*3	*1/*2
16	M	26	81	186	*1/*3	*1/*2
17	M	25	79	188	*1/*3	*1/*2
18	M	25	67	181	*1/*3	*1/*2
19	M	26	71	176	*1/*3	*1/*2
20	M	29	82	180	*1/*3	*1/*2
21	M	25	72	170	*1/*3	*1/*2
22	M	28	80	195	*1/*3	*1/*2
23	F	23	56	159	*1/*3	*1/*2
Median (range)	–	25.5 (23–29)	75.5 (56–89)	180 (159–195)	–	–

Design

The study was registered in the European Clinical Trials Database (EudraCT no. 2004-003978-28). It was approved by The Danish Medicines Agency, The Danish Data Protecting Agency and the Regional Ethical Committee of Vejle and Funen Counties, and was conducted in accordance with Good Clinical Practice (GCP) and monitored by the GCP-Unit, Odense University Hospital. Drug use was monitored to ensure good compliance. Sample size calculations were based on the primary outcome represented by differences in AUC between subjects with *CYP2C8*1/*3* and *CYP2C8*1/*1* genotypes. It was estimated that a true difference of 35% could be detected, given a two-sided level of significance (α) of 0.05 and a power (β) of 80%, using 10 subjects in each group. The number of subjects with the *CYP2C8*3/*3* genotype is small and only three could be recruited.

The study was conducted as an open-label, two-phase, cross-over trial with a wash-out period of at least 2 weeks between the phases. The volunteers fasted from 8 h before to 1 h after rosiglitazone administration.

Phase A At 08.00 h, the subjects were given a single 4-mg rosiglitazone tablet (Avandia®; GlaxoSmithKline Pharma A/S, Brondby, Denmark).

Phase B The subjects were given 50-mg fluvoxamine maleate tablets (Fevarin®; Solvay Pharmaceuticals B.V., Weesp, Holland) at 08.00 h and 20.00 h for 3 days. On day 4, both a 4-mg Avandia® tablet and a 50-mg Fevarin® tablet were administered at 08.00 h.

Sample analysis

In both phases, blood samples were drawn from an i.v. cannula in a forearm vein at 0, 20, 40, 60, 80 min and at 2, 3, 4, 6, 8, 10 and 24 h after rosiglitazone administration. Blood samples containing ethylenediaminetetraacetic acid as anticoagulant were centrifuged for 10 min at 2400 *g*. Plasma was separated and stored at −20 °C until analysis. The plasma concentrations of rosiglitazone were determined in duplicate by a validated high-performance liquid chromatography (HPLC) method which also detects *N*-desmethylrosiglitazone

[40]. The limit of quantification was 1 ng ml^{-1} and the detection limit was 0.25 ng ml^{-1} for rosiglitazone in human plasma. The intra- and interday precision coefficients of variation did not exceed 8.7% [40]. Only relative concentrations of *N*-desmethylrosiglitazone could be determined, since the pure reference substance was not available. Structural identification of rosiglitazone and *N*-desmethylrosiglitazone was made by an IonSpec Ultima Fourier Transform Mass Spectrometer with a 4.7-T magnet using electrospray ionization. The molecular ions of rosiglitazone (m/z = 358) and *N*-desmethylrosiglitazone (m/z = 344) were found in fractions, collected from the HPLC eluent. This is similar to the LS/MS data described by Cox *et al.* [4].

Data analysis

The pharmacokinetic parameters were determined using a noncompartmental model (WinNonlin® Professional, version 4.1; Pharsight Corporation, Mountain View, CA, USA). The $AUC_{0-\infty}$ was calculated using the linear trapezoidal method. The values of C_{max} and t_{max} were read directly from the concentration–time curve. The terminal elimination half-life ($t_{1/2}$) was calculated from the equation $t_{1/2} = \ln 2/\lambda$, where λ is the terminal slope calculated by linear regression of the time *vs.* log concentration. Prior to statistical analysis, $AUC_{0-\infty}$, $t_{1/2}$ and C_{max} data were transformed to their natural logarithm to justify a Gaussian distribution. Statistical analysis was performed using GraphPad QuickCalcs (GraphPad Software, Inc., San Diego, CA, USA), StatXact-3 (Cytel Software Corporation, Cambridge, MA, USA) and Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA, USA).

$AUC_{0-\infty}$, C_{max} and $t_{1/2}$ values were compared between genotypes using unpaired *t*-test. The geometric ratio of means with their 95% confidence intervals (CIs) and *P*-values were then calculated. Effects on t_{max} were determined using unpaired Hodges–Lehman estimates of median differences with exact 95% CIs and *P*-values. The effects of fluvoxamine on the $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ of rosiglitazone were analysed using the paired test.

Results

One subject with the *CYP2C8*3/*3* genotype (no. 1) developed a superficial venous thrombosis 1 day after the first trial day following i.v. catheterization. He was successfully treated with locally applied heparinoid, but was excluded from the study. One of the *CYP2C8*1/*3* genotypes (no. 15) experienced general malaise, nausea, tiredness, insomnia, constipation, accommodation and miction difficulties 1 day after the initiation of fluvoxamine treatment. The latter was stopped immediately, the subject withdrew from the study and the symptoms gradually disappeared.

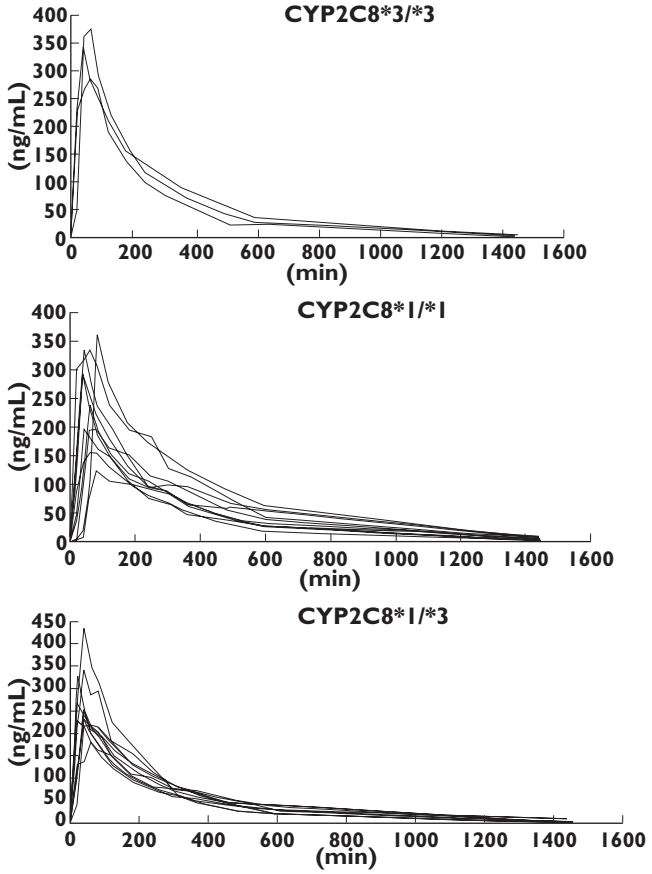

Figure 1
Phase A, plasma drug concentration–time curves in subjects with the *CYP2C8*3/*3* (n = 3), *CYP2C8*1/*1* (n = 10) and *CYP2C8*1/*3* (n = 10) genotypes after a single oral dose of 4-mg rosiglitazone

The plasma concentration–time curves of the three genotypes in each phase are shown in Figures 1 and 2. Large variations are seen within each genotype and, in particular, one of the *CYP2C8*1/*3* subjects (no. 23) displayed a higher $t_{1/2}$ (19.4 h) and $AUC_{0-\infty}$ (3455 h ng ml^{-1}) than all the other subjects in phase B. Table 2 shows the median and range of the pharmacokinetic parameters of rosiglitazone and the metabolite *N*-desmethylrosiglitazone. In Phase A, the median $AUC_{0-\infty}$ of 1479 h ng ml^{-1} in *CYP2C8*3/*3* subjects was 22% higher than in *CYP2C8*1/*1* (1210 h ng ml^{-1}) and *CYP2C8*1/*3* (1208 h ng ml^{-1}) subjects. The median C_{max} in Phase A was 28% and 26% higher in *CYP2C8*3/*3* (335 ng ml^{-1}) compared with *CYP2C8*1/*1* (265 ng ml^{-1}) and *CYP2C8*1/*3* (260 ng ml^{-1}) subjects, respectively. The same trends were seen during Phase B. Thus, the median $AUC_{0-\infty}$ in *CYP2C8*3/*3* subjects

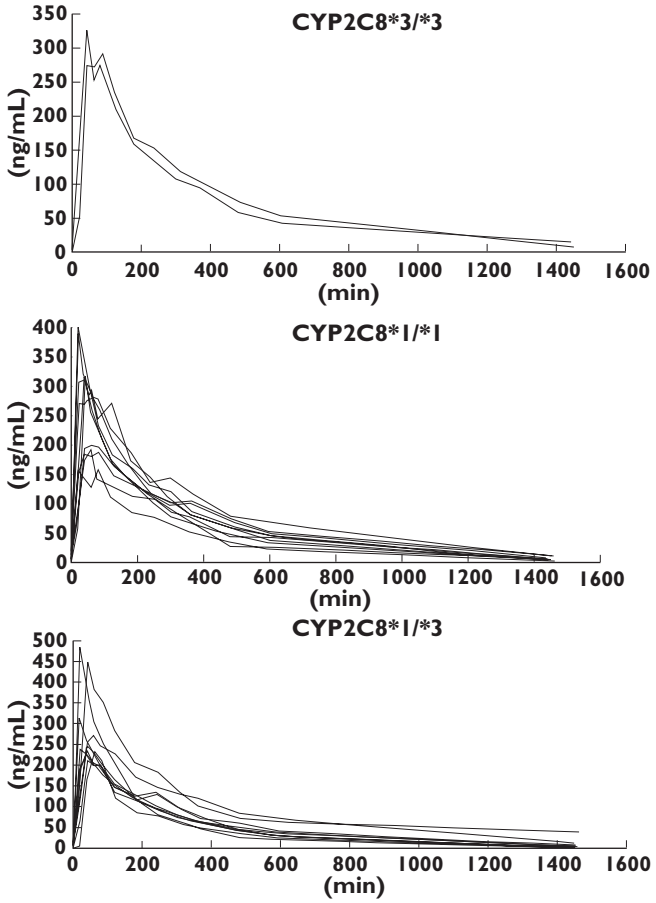

Figure 2

Phase B, plasma drug concentration–time curves in subjects with the *CYP2C8*3/*3* ($n = 2$), *CYP2C8*1/*1* ($n = 10$) and *CYP2C8*1/*3* ($n = 9$) genotypes after a single oral dose of 4-mg rosiglitazone and coadministration of fluvoxamine

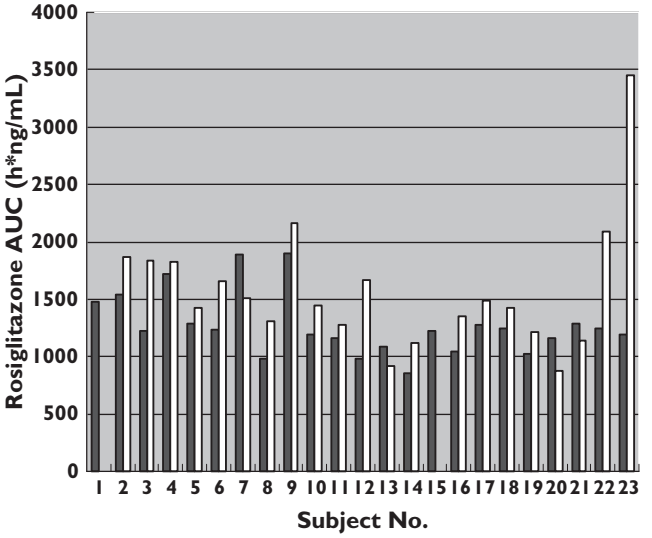

Figure 3

The area under the rosiglitazone concentration–time curves ($AUC_{0-\infty}$) for each subject in Phase A (■, baseline) and Phase B (with fluvoxamine, □)

was 1851 h ng ml^{-1}, 1478 h ng ml^{-1} in *CYP2C8*1/*1* and 1353 h ng ml^{-1} in *CYP2C8*1/*3* subjects. The corresponding median values for C_{max} were 309 ng ml^{-1}, 303 ng ml^{-1} and 245 ng ml^{-1}. However, these differences between genotypes were not statistically significant. Furthermore, no differences in $AUC_{0-\infty}$ and t_{max} were found for the metabolite *N*-desmethylrosiglitazone. The longer t_{max} and $t_{1/2}$ of *N*-desmethylrosiglitazone made it impossible to calculate precise values of the latter within the 24-h sampling period.

The interaction with fluvoxamine in Phase B resulted in higher rosiglitazone median $AUC_{0-\infty}$ in all three genotypes (Figure 3). Values were increased by 25% in *CYP2C8*3/*3*, 22% in *CYP2C8*1/*1* and 12% in *CYP2C8*1/*3* subjects. The overall ($n = 21$) geometric mean ratio was 1.21 with a 95% CI of 1.06, 1.39, a result that is statistically significant ($P = 0.0066$). The difference in $AUC_{0-\infty}$ was also significantly different without the outlier (subject no. 23) with an overall ($n = 20$) geometric mean ratio of 1.16, a 95% CI of 1.05–1.29 and a *P*-value of 0.0067. The $t_{1/2}$ was also significantly higher in Phase B with a geometric mean ratio of 1.38, a 95% CI of 1.06–1.79 and a *P*-value of 0.0203. Without subject no. 23 ($n = 20$) the difference in $t_{1/2}$ was also significant ($P = 0.0078$), giving a geometric mean ratio of 1.24 (1.07–1.44).

Discussion

The pharmacokinetic characteristics of rosiglitazone and *N*-desmethylrosiglitazone were found to be similar to previously published data [4, 8]. One explanation for the large interindividual variation seen in the pharmacokinetic parameters could be the prsence of other known and unknown mutations of *CYP2C8*. However, since the frequencies of the other known allelic variants are relatively low in the Caucasian population, other factors probably contribute to the variability. Another explanation may be that other enzymes or excretory mechanisms are involved in the disposition of rosiglitazone. In the present study, the subjects in each group of *CYP2C8* genotypes where chosen to have the same *CYP2C9* genotype to ensure that any possible contribution by CYP2C9 to rosiglitazone metabolism was approximately the same in all three groups. This was made easy because of the allelic linkage between *CYP2C8*3* and *CYP2C9*2* [31]. Thus, since the *CYP2C9* genotypes were identical in each group, differences in CYP2C9

Table 2
Median and range of the pharmacokinetic parameters of rosigltazone and *N*-desmethylrosiglitazone in each genotype in study Phase A and B

	Phase A			Phase B		
	CYP2C8*3/*3 *n* = 3	CYP2C8*1/*1 *n* = 10	CYP2C8*1/*3 *n* = 10	CYP2C8*3/*3 *n* = 2	CYP2C8*1/*1 *n* = 10	CYP2C8*1/*3 *n* = 9
Rosiglitazone						
$t_{1/2}$, h	3.2 (2.9–5.0)	3.9 (2.9–7.8)	3.1 (1.7–6.3)	6.7 (4.9–8.6)	5.0 (4.2–6.4)	4.2 (3.1–19.4)
t_{max}, h	1.1 (0.7–1.1)	1.0 (0.6–1.4)	0.7 (0.3–1.0)	1.1 (0.7–1.5)	0.9 (0.3–1.4)	0.7 (0.3–1.0)
C_{max}, ng ml^{-1}	335 (285–374)	265 (124–361)	260 (179–435)	309 (292–326)	303 (158–400)	245 (210–485)
$AUC_{0-\infty}$, h ng ml^{-1}	1479 (1221–1537)	1210 (980–1903)	1208 (852–1288)	1851 (1838–1863)	1478 (918–2160)	1353 (876–3455)
N-*desmethyl-rosiglitazone*						
$t_{1/2}$, h	16.7 (12.4–20.4)	16.4 (12.6–22.4)	15.4 (7.0–35.5)	24.7 (15.6–33.7)	34.6 (20.1–79.0)	19.3 (12.2–23.6)
t_{max}, h	6.0 (5.1–8.0)	6.1 (4.0–10.1)	6.0 (3.1–8.0)	6.1 (6.0–6.1)	8.0 (4.0–10.0)	8.0 (4.1–10.0)
AUC_{0-24}, relative area units	400 (333–478)	399 (325–476)	456 (136–544)	435 (379–490)	395 (248–446)	450 (376–627)

activity probably did not contribute to the variation in rosiglitazone pharmacokinetics within each group.

Although the median values of $AUC_{0-\infty}$ and C_{max} were ≥20% higher in the subjects homozygous for the *CYP2C8*3* allele, these findings were not statistically significant. A greater number of homozygous *CYP2C8*3* subjects are probably needed to detect a possible real difference between subjects with *CYP2C8*3/*3* compared with *CYP2C8*1/*1* and/or *CYP2C8*1/*3* genotypes. Only three subjects homozygous for the *CYP2C8*3* allele were included in the study due to its low frequency in the population. According to the Hardy–Weinberg equation, only 1–5% of the Caucasian population have the *CYP2C8*3/*3* genotype and thus the recruitment of sufficient numbers of subjects is problematic. The study revealed no significant pharmacokinetic differences between the groups with the *CYP2C8*1/*1* and *CYP2C8*1/*3* genotypes. Data have been published on the *in vivo* effect of the *CYP2C8*3* genotypes on the metabolism of CYP2C8 substrates. Thus, ibuprofen clearance has been linked to the CYP2C8 and the CYP2C9 polymorphisms [22, 23]. Furthermore, it has been reported that the *CYP2C8*3* allele is associated with a lower AUC of repaglinide (compared with *CYP2C8*1*), whereas polymorphism in the *SLCO1B1* gene results in substantially higher plasma concentrations of the drug, suggesting that the activity of this transporter is an important determinant of repaglinide pharmacokinetics [20, 21]. In contrast, Bidstrup *et al.* found no significant differences in pharmacokinetics between subjects carrying the *CYP2C8*3* allele and subjects who were homozygous wild-type given therapeutic (2 mg) and subtherapeutic (0.25 mg) doses of repaglinide [19].

The present study does not demonstrate conclusively whether rosiglitazone is metabolized exclusively by CYP2C8 alone and that the *CYP2C8*3* allele expresses a totally inactive form of CYP2C8. If this were the case, larger differences in AUC and $t_{1/2}$ between the *CYP2C8*3* genotypes would be expected. Overall, the data for rosiglitazone, repaglinide and ibuprofen suggest that the *CYP2C8*3* allele does not affect the metabolism of these CYP2C8 substrates to an equal extent. The crystal structure of CYP2C8 reveals a large active site capable of binding substrates in multiple orientations [29], and site-directed mutagenesis studies show that active site residues differentially affect the binding and turnover of different substrates [41].

The higher rosiglitazone AUC and $t_{1/2}$ found in the present study during coadministration of fluvoxamine is much less than the effect of the CYP2C8 inhibitor gemfibrozil, which increased the AUC by 2.3-fold and prolonged the $t_{1/2}$ from 3.6 to 7.6 h. In addition, the *N*-desmethylrosiglitazone/rosiglitazone AUC ratio was decreased by 38% and the t_{max} of *N*-desmethylrosiglitazone prolonged [8]. Compared with the present study, the effects of the CYP2C8 inhibitors trimethoprim and ketoconazole were also larger, increasing the rosiglitazone AUC by 38% and 47%, respectively [9, 10]. These studies with the inhibitors gemfibrozil, trimethoprim

and ketoconazole confirmed that rosiglitazone is a CYP2C8 substrate, but they also demonstrated a difference in the degree of inhibition of rosiglitazone metabolism [6–10].

The coadministration of fluvoxamine increased the $AUC_{0-\infty}$ of rosiglitazone in 17 of the 21 subjects studied. This moderate effect was overall significant and is comparable to a previous study, where a daily dose of 75 mg fluvoxamine decreased the median clearance of the CYP2C9 substrate tolbutamide from 845 ml h^{-1} to 688 ml h^{-1} [36]. If steady state had been achieved for fluvoxamine (requiring 4 days of dosing), its effect on rosiglitazone pharmacokinetics might have been more pronounced.

We conclude that the presence of the *CYP2C8*3* and *CYP2C9*2* alleles did not influence the pharmacokinetics of rosiglitazone significantly at a dose used clinically. Fluvoxamine moderately increased the $AUC_{0-\infty}$ of rosiglitazone in subjects with the *CYP2C8*1/*1*, *CYP2C8*1/*3* and *CYP2C8*3/*3* genotypes.

Competing interests: None declared.

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