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Clinical pharmacokinetics of pioglitazone

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Summary: Pioglitazone is a thiazolidinedione antidiabetic agent that increases insulin sensitivity and decreases hepatic gluconeogenesis. Administered once daily without regard to meals, it is well absorbed, and is metabolised by the hepatic cytochrome P450 enzyme system. The half-life of the drug is approximately 9 hours, but two active metabolites (M-III and M-IV) contribute to extended glucose-lowering effects. In animals, after absorption the highest concentrations are found in the liver, plasma, and kidney. The mean absolute bioavailability is 83%, t_{max} is 1.5 (range 0.5–3.0) hours, and the absorption rate constant ranges from 0.04 to 1.17 hr^{-1}. Mean clearance is 2.4 (range 1.72–4.17) L/hr. With single oral doses between 2 and 60 mg, C_{max} and area-under-the-curve (AUC) increased linearly with dose: no changes were observed upon repeated administration. The AUC is not affected by food. The volume of distribution is 0.253 L/kg, probably due to extensive protein binding (>97%). Drug interaction studies have not shown inhibition or induction of any cytochrome P450 enzymes involved in drug metabolism, thus the potential for drug interactions is low. The pharmacokinetics of pioglitazone do not differ significantly between healthy volunteers and patients with type 2 diabetes. Dosage adjustment is not necessary in patients with renal failure, or in those undergoing haemodialysis. In hepatic insufficiency, volume of distribution was increased, and C_{max} was reduced. Age and gender appear to have no significant effect on the pharmacokinetics of pioglitazone, and there do not appear to be any differences between races.

Introduction

Pioglitazone is a thiazolidinedione antidiabetic agent that increases insulin sensitivity in target tissues and decreases hepatic gluconeogenesis. It is a peroxisome proliferator-activated receptor (PPARγ) agonist that increases transcription of insulin-responsive genes and increases insulin sensitivity (Füchtenbusch et al., 2000). Like other thiazolidinediones, pioglitazone ameliorates insulin resistance associated with type 2 diabetes without stimulating insulin release from pancreatic β-cells, thus lowering the risk of hypoglycaemia.

Administered once daily without regard to meals, pioglitazone is well absorbed and extensively metabolized via the hepatic cytochrome P-450 enzyme system. Although the parent compound has a half-life of approximately 9 hours, two active metabolites (M-III and M-IV) contribute to glucose-lowering effects. This review addresses the pharmacokinetic characteristics of pioglitazone, including those in special patient populations and drug interaction studies.

Preclinical studies

In animals, pioglitazone is well absorbed with the highest concentrations distributed into the liver, plasma, and kidney. Pioglitazone is extensively bound to plasma protein both in animals and in humans (free fraction <3%). Furthermore, serum protein binding is independent of drug concentration in the range of 0.05 to 5 μg/mL. Pioglitazone undergoes significant hepatic metabolism by hydroxylation of aliphatic methylene groups to form three metabolites (designated M-I, M-II, and M-IV), by the oxidation of the methyl group to form an additional metabolite (M-V), and by the oxidation of one metabolite (M-IV) to be converted to another metabolite (M-VI). The metabolic pathway of the parent compound and six metabolites is shown in Figure 1. Only small amounts of unchanged pioglitazone are excreted in urine, bile, and faeces.

An important feature of pioglitazone is that it is an enantiomeric drug (see Figure 1), which is administered as a racemate. A number of studies have focused on chiral interconversion, both *in vitro* and *in vivo*. The *in vitro* chiral conversion of pioglitazone was investigated in both rat and human plasma. The ratio of the enantiomer composition [(+)/(−)] was approximately 2:3 for rat and 1:1 for human plasma. Furthermore, chiral conversion was also observed *in vivo* after intravenous and oral administration of both the R- and the S-enantiomer to rats. The conversion reached equilibrium at about 3 hours postdose. In

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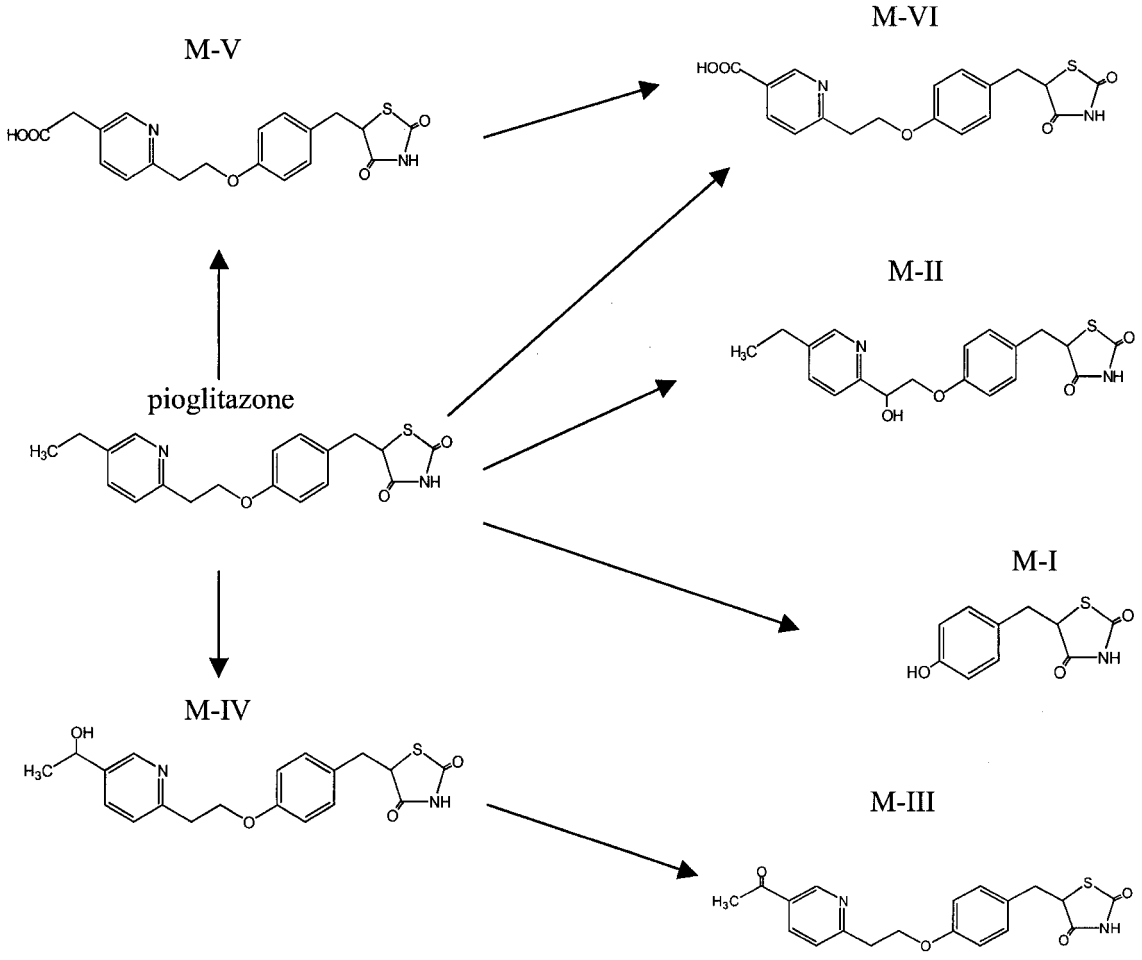

Fig. 1 Metabolic pathway of pioglitazone in dogs, rats, and monkeys

addition, in terms of pharmacokinetics, no detectable differences between the two enantiomers were observed after either intravenous or oral administration of either enantiomer. Based on these results, it is inferred that chiral interconversion of pioglitazone also occurs in humans. This justifies the practice to characterise the pharmacokinetics of pioglitazone based on the total concentrations of both enantiomers.

An important factor is the contribution of the metabolites of pioglitazone to its pharmacological actions. Three of the metabolites, M-III, M-IV, and to a lesser extent, M-II, were shown to have pharmacological activity in diabetic animal models. In rat models, the relative hypoglycaemic potency (ED_{50}) of these metabolites was 40% to 60% of that of pioglitazone. The potency for the triglyceride-lowering effect of M-II was nearly twice that of the parent compound, while the potency of metabolites M-III and M-IV was slightly less than pioglitazone.

High-performance liquid chromatographic methods for the determination of pioglitazone in dog plasma (Zhong and Lakings, 1989), in human serum (Zhong and Williams, 1996; Yamashita et al., 1996), and in urine (Yamashita et al., 1996) have been developed. Typically, these assays do not differentiate between the two enantiomers of pioglitazone. The limit of quantification of these assays is 25–50 ng/mL, which is sufficient for characterisation of the pharmacokinetics in clinical studies. Evaluation of the pharmacokinetics of pioglitazone in clinical studies required determination of the metabolites as well as parent drug (Zhong and Williams, 1996; Yamashita et al., 1996).

Clinical studies

The pharmacokinetics of pioglitazone and its metabolites were evaluated in studies of single and multiple doses administered to healthy subjects and to patients with type 2 diabetes mellitus conducted in the United States, Europe, and Japan. The pharmacokinetic data of pioglitazone and its active metabolites (M-III and

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M-IV) are presented individually, as are those of the total active compound (pioglitazone + M-IV + M-III). M-II is found in relatively low concentrations in man (about 10% of M-III metabolite) and does not significantly contribute to total active compounds.

Pharmacokinetics in healthy subjects

Absorption

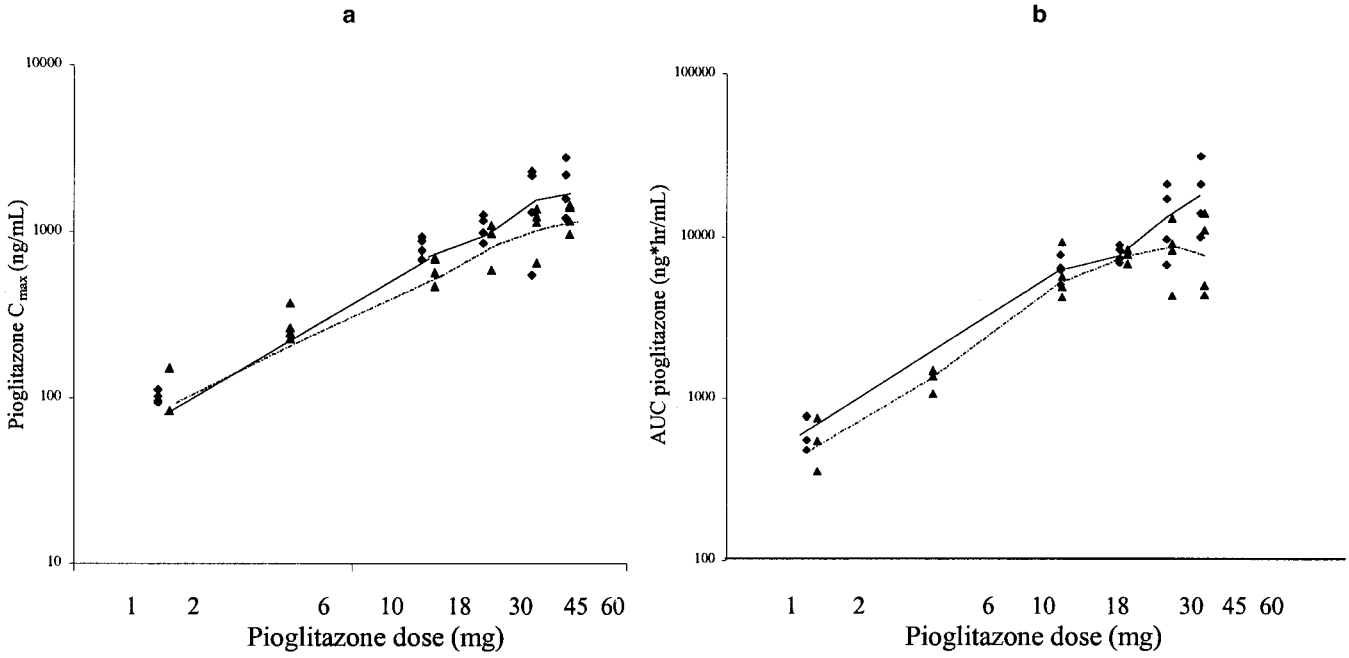
The absolute bioavailability of pioglitazone was determined in a 2-way crossover study of 8 healthy subjects. Pioglitazone was administered in an intravenous infusion of 5 mg (30 vol% propylene glycol solution) over 2 hours and as a single oral tablet (7.5-mg tablet equal to market image tablet). Since pioglitazone is insoluble, a special formulation had to be used and only a relatively low dose could be infused intravenously. For this reason, also a low oral dose was chosen that would result in comparable plasma levels to the intravenous arm. Data from the 7 subjects who completed the study show that pioglitazone was rapidly absorbed: median time to maximal serum concentration (t_{max}) was 1.5 hours (range 0.5–3.0 hours). A one-compartment pharmacokinetic model with first-order absorption successfully analysed the data following oral administration. The value of the absorption rate constant (k_a) ranged from 0.40 to 1.17 hr^{-1}, supporting rapid absorption. The mean absolute bioavailability was 83% (95% CI: 74%–93%).

The dose and time dependency of the pharmacokinetics of pioglitazone were studied after administration of single and multiple doses varying between 2 and 60 mg in healthy volunteers. At each dose level, t_{max} of the parent compound was usually between 1 and 3 hours. For single oral doses between 2 and 60 mg, both C_{max} and AUC increased linearly with dose. C_{max} ranged from 101 to 3500 ng/mL (Fig. 2). Furthermore, no changes in these parameters were observed upon repeated administration, indicating the absence of major dose and time dependencies in the absorption of pioglitazone.

A separate study focused on the effect of food on the absorption of pioglitazone. Food slightly delayed the rate of absorption of pioglitazone (median t_{max} 3 hours vs. 2 hours), but the extent of absorption was not altered as demonstrated by comparable AUC values. Therefore, pioglitazone may be taken without regard to meals (Geerlof et al, 2000).

Distribution

The volume of distribution of pioglitazone was determined following intravenous administration in 7 healthy male subjects in the absolute bioavailability study. The volume of distribution was rather small, between 0.199 and 0.299 L/kg, mean 0.253 L/kg. This is most probably attributable to extensive binding to plasma protein, particularly albumin. The free fraction of pioglitazone in plasma is <3%, and the binding is independent of concentration in the concentration range of 34-2000 ng/mL (which includes the therapeutic range). No information is available on the volume of distribution of the metabolites since these have not been administered separately. The active metabolites M-III and M-IV, however, are also highly protein bound, with free



Individual values with line through median, single dose (◆), multiple dose (▲)

Fig. 2 **a** C_{max} after single or multiple doses of pioglitazone; **b** AUC after single or multiple doses of pioglitazone

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fractions between 0.3% and 0.9%. Therefore, their volume of distribution is likely equally small.

Metabolism

In vitro studies with human liver microsomes have shown that multiple cytochrome P-450 isoenzymes are involved in the metabolism of pioglitazone to 5 primary metabolites (M-I, M-II, M-IV, M-V, and M-VI) (Fig. 1). One of the metabolites, M-IV, may be further oxidised to form an additional metabolite, M-III. M-VI may be formed either directly from the parent compound or from another metabolite, M-V. Multiple cytochrome P-450 isoenzymes (1A1, 1A2, 2C8, 2C9 [Arg and Cys], 2C19, 2D6, and 3A4) are involved in the metabolism of pioglitazone to M-II and M-IV. The most important isoenzymes appear to be CYP2C8/9 and CYP3A4, which contribute approximately 40% and less than 20%, respectively, to the total metabolism of pioglitazone. The involvement of CYP3A4 suggests the possibility of a wide interindividual variability in the pharmacokinetics of pioglitazone, and that its metabolism may be subject to inhibition by compounds such as ketoconazole. The minor role of CYP2D6 in the metabolism indicates that the pharmacokinetics are probably not subject to genetic polymorphism. Indeed, no evidence has yet indicated the existence of such a genetic polymorphism.

A separate *in vitro* study that evaluated multiple thiazolidinediones reported that pioglitazone, unlike troglitazone, did not inhibit any of the P450 isoenzymes involved in drug metabolism (Yamazaki et al, 2000). This suggests that, compared to other thiazolidinediones, pioglitazone may have a reduced interaction potential.

In man, as in animals, pioglitazone has three active metabolites: M-II, M-III, and M-IV (based on data derived from healthy subjects). The main active metabolites of pioglitazone in man, however, are M-III and its precursor, M-IV (Fig. 1); M-II is present at about 10% the concentration of M-III, and 2% of M-IV. Each active metabolite has a considerably longer serum half-life ($t_{1/2}$) than does the parent compound (Table 1).

Elimination

Pioglitazone is slowly cleared from the blood, despite a relatively small volume of distribution. In the study of absolute bioavailability, clearance of an intravenous dose of 5 mg pioglitazone varied between 1.72 and 4.17 L/hr (mean 2.4 L/hr). Thus, pioglitazone is eliminated with a low hepatic extraction ratio, which may be partly explained by the extensive binding to plasma proteins. In several other investigations, the oral clearance (CL/F) of unchanged pioglitazone was low and independent of dose for doses between 2 and 60 mg. Corrected for oral bioavailability (83%), oral clearance of unchanged pioglitazone in other studies was similar to that in the absolute bioavailability study. Thus, saturation of the hepatic enzymes involved in the metabolism of pioglitazone does not occur in the therapeutic dose range (15–60 mg). Furthermore, no important changes in pharmacokinetics were observed upon repeated dosing for 9 days. Thus, the pharmacokinetics of pioglitazone appear to be both dose and time independent. After oral

Table 1 Pharmacokinetic data of serum pioglitazone, active metabolites M-III and M-IV, and total active compounds from three studies

Compound		C_{max} (ng/mL)	t_{max}* (hr)	$AUC_{0-\infty}$ (ng · hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr/kg)
Pioglitazone						
	a	1482 ± 499.7	3 (2–5)	13854 ± 4996	9.2 ± 7.5	0.038 ± 0.0128
	b	1491 ± 672.9	4 (2–5)	14458 ± 7434	8.8 ± 5.4	0.0529 ± 0.0249
	c	1552 ± 708.0	3 (2–5)	14071 ± 5727	9.5 ± 4.5	0.0478 ± 0.0149
M-III						
	a	168 ± 50.7	16 (8–48)	9314 ± 2828	29.4 ± 8.6	
	b	188 ± 71.4	12 (6–24)	9616 ± 3320	26.7 ± 8.7	
	c	181 ± 39.8	20 (8–24)	10581 ± 3042	28.8 ± 10.8	
M-IV						
	a	639 ± 188.9	16 (6–24)	35074 ± 9011	27.2 ± 6.6	
	b	636 ± 209.1	16 (12–24)	34200 ± 10305	27.4 ± 10.8	
	c	614 ± 192.4	14 (5–24)	32971 ± 9049	27.8 ± 8.6	
Total active compounds						
	a	1865 ± 605.3	4 (3–5)	56895 ± 15561	24.0 ± 5.7	
	b	1903 ± 785.1	4 (3–5)	56946 ± 19815	23.6 ± 8.4	
	c	1928 ± 846.0	4 (2–5)	56022 ± 15651	23.8 ± 5.7	

All data reported as mean ± SD except * median + range. All three studies (2-treatment, 2-period, crossover) were conducted in healthy subjects and evaluated a single oral dose 45 mg administered after breakfast; a comparison of pharmacokinetics after administration of 1 tablet of 45 mg vs 3 tablets of 15 mg (n=24); b comparison of a suspension vs. a tablet formulation (n=24); c pharmacokinetics in fasted vs. fed state (n=23)

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administration, pioglitazone is extensively oxidized, and renal excretion of the parent drug and the metabolite, M-III, is not detectable. The main compound excreted in the urine is M-V, followed by M-VI and M-IV (Table 2).

The terminal elimination half-life of pioglitazone after intravenous administration of 5 mg ranged from 3.5 to 9.0 hours (mean 5.8 hours). After oral administration, the terminal half-life was in the same range, consistent with a rapid absorption from the GI tract. The terminal half-life of the active metabolites, M-III and M-IV, is considerably longer (26–28 hours). Both M-III and M-IV serum levels decline slowly with parallel terminal slopes, suggesting that conversion from M-IV to M-III is rate limited. Slower elimination of the active metabolites presumably contributes to an extended pharmacological activity and allows for once-daily administration of pioglitazone.

Table 2 Cumulative urinary excretion of Pioglitazone and metabolites in healthy subjects

	% Dose excreted in the urine over 48 hours
Pioglitazone	Not detected
M-I	0.5 ± 1.2
M-II	0.7 ± 2.5
M-III	Not detected
M-IV	5.8 ± 1.7
M-IV sulfate	1.9 ± 0.7
M-V	12.4 ± 2.5
M-VI	7.8 ± 1.9
Total (0–24 hr)	19.9 ± 3.9
Total (0-48 hr)	29.6 ± 5.9

Data reported for patients who received 30-mg tablets of pioglitazone. Data are reported as mean ± SD

Pharmacokinetics in type 2 diabetes

In patients with type 2 diabetes, changes in the clearance of pioglitazone might be expected because of changes in plasma protein binding, either directly as a result of elevated serum free fatty acid concentrations, or indirectly as a result of impaired renal function, which is common in these patients. Table 3 shows the pharmacokinetic parameters from an early study where patients were given 15, 30, or 60 mg pioglitazone. These can be compared with the pharmacokinetic parameters shown in Table 1, where healthy volunteers were given 45 mg pioglitazone. Although there appear to be differences in AUC and C_{max} of pioglitazone, these are not significant in the context of the variability seen in man. Further, the concentration of metabolites seems similar in patients and healthy volunteers. The most important variable determining drug concentration in man is clearance of drug, and the values in patients (expressed as L/hr) and volunteers (expressed as L/hr/kg) are similar.

Table 3 Pioglitazone pharmacokinetics in patients with type 2 diabetes

Dose	15 mg	30 mg	60 mg
Pioglitazone			
$AUC_{0\text{-}24}$ (ng · hr/mL)	3425 ± 1261	7652 ± 3139	10000 ± 3404
C_{max} (ng/mL)	327 ± 106	715 ± 216	972 ± 266
t_{max} (hr)	2.1 ± 1.1	2.5 ± 1.18	2.6 ± 0.966
CL/F (L/hr)	4.93 ± 1.73	4.64 ± 2.22	6.74 ± 3.46
Total active compounds			
$AUC_{0\text{-}24}$ (ng · hr/mL)	18000 ± 5910	34000 ± 9582	52000 ± 13000
C_{max} (ng/mL)	1052 ± 377	1940 ± 597	2884 ± 536
t_{max} (hr)	5.6 ± 4.03	5.4 ± 2.5	6.3 ± 3.2
M-III			
$AUC_{0\text{-}24}$ (ng · hr/mL)	4719 ± 1613	7110 ± 2161	12000 ± 3989
M-IV			
$AUC_{0\text{-}24}$ (ng · hr/mL)	10000 ± 3595	19000 ± 5876	30000 ± 8235

Data are reported as mean ± SD

Overall, the pharmacokinetics of pioglitazone in patients with diabetes are similar to those in healthy volunteers.

Pharmacokinetics in special populations

Renal insufficiency

A well-described and common complication of diabetes mellitus is nephropathy. Therefore, a study was conducted to investigate the pharmacokinetics of pioglitazone in patients with diabetes mellitus with renal impairment (Edwards and Eckland, 1999). This was an open-label study in patients with severe renal impairment (n = 12; CL_{CR} mean = 14 mL/min) or moderate renal impairment (n = 9; CL_{CR} mean = 46 mL/min) and healthy age- and gender-matched controls with normal renal function (n = 6, CL_{CR} mean = 100 mL/min). A single dose of pioglitazone was administered, followed by 10 once-daily doses of 45 mg. The concentration-time profile of these groups is shown in Figure 3. The C_{max} and $AUC_{(0\text{-}120)}$ of pioglitazone and metabolites M-III and M-IV were decreased in patients with impaired renal function (Fig. 3). The C_{max} and $AUC_{(0\text{-}120)}$ of pioglitazone and metabolites M-III and M-IV were also decreased in these patients. This may be explained by reduced protein binding, which is common in patients with renal impairment, resulting in an increased free fraction of pioglitazone. Because pioglitazone elimination is primarily hepatic, the intrinsic clearance is

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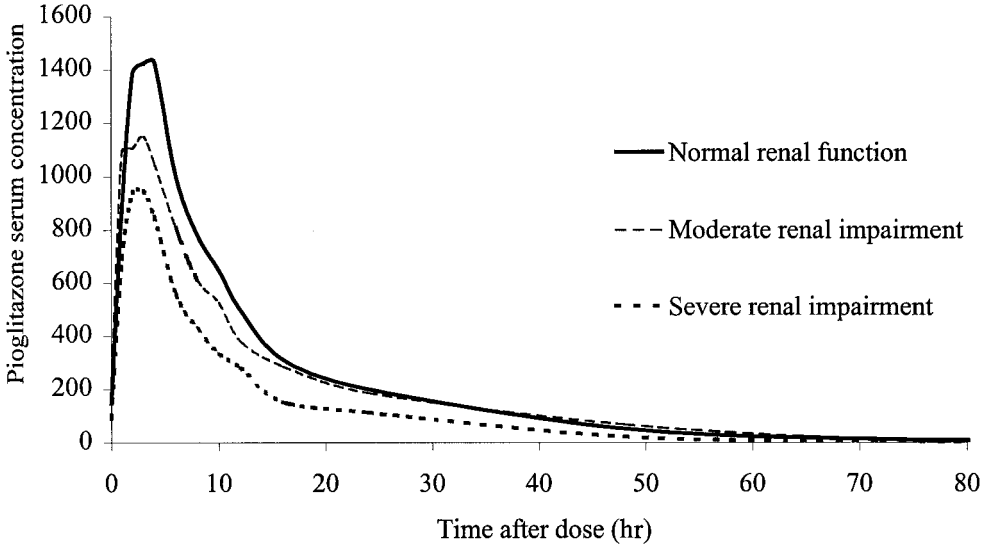

Fig. 3 Serum concentration profile of pioglitazone in renally impaired patients. Normal renal function, n=6; moderate renal impairment, n=9; severe renal impairment, n=12. Serum concentrations measured after 10 days of repeated dosing with pioglitazone

probably unaffected, resulting in reduced exposure to total pioglitazone, but similar free drug (therapeutically effective) concentrations. Furthermore, as might be expected, there is no relationship between terminal elimination half-life of pioglitazone and creatinine clearance (over the range, 4.3-120 mL/min) in this study. Therefore, adjustment of starting and maintenance doses of pioglitazone is unnecessary in patients with renal failure.

A population model was developed to describe the clinical pharmacokinetics of pioglitazone and its main metabolites in patients with renal or hepatic impairment. It is a two-compartment model with linear elimination (Cl=4.28 L/hr from the central compartment V_d=37 L). On the basis of this model it was predicted that haemodialysis has only a marginal (<1%) influence on the plasma concentrations of pioglitazone and metabolites. Therefore, no dose adjustment would be required in patients undergoing haemodialysis.

Hepatic insufficiency

In clinical use, pioglitazone is administered chronically, and doses will be selected for patients based on therapeutic effect. The single-dose pharmacokinetics of an oral dose of 30 mg pioglitazone were evaluated in a study of 12 male patients with chronic liver insufficiency (Child-Pugh class B or C) compared with 12 healthy male subjects. The concentration-time profiles are shown in Figure 4. The mean AUC and total clearance were similar in the two groups. However, volume of distribution of pioglitazone was increased by 55% in the patients with hepatic insufficiency, and mean C_{max} of pioglitazone in these patients was approximately 57% of that reported in healthy subjects (Fig. 4). This is consistent with a decreased degree of plasma protein binding. The free fraction of drugs that are extensively bound to plasma protein is often increased in patients with hepatic impairment. This was most likely also the case in the present study population since before administration of pioglitazone, mean serum albumin levels were 4.5 $\pm$0.289 g/dL in healthy subjects versus 3.18$\pm$0.453 g/dL in patients with hepatic impairment. The AUC of M-IV was slightly increased and serum levels of M-III were substantially lower in patients with hepatic impairment compared with healthy subjects. This also suggests impaired oxidative biotransformation of M-IV to M-III in patients with hepatic insufficiency.

This increase may explain the greater volume of distribution and lower C_{max}. The increase in free fraction would also result in an increase in total clearance if the intrinsic hepatic clearance were unaffected. Because the total clearance of pioglitazone was not affected in patients with severe hepatic impairment, the intrinsic hepatic clearance must be reduced. Since this clearance determines free (therapeutically relevant) plasma concentration in the body, free pioglitazone may accumulate.

Elderly

Two studies were conducted to evaluate possible age-related differences in the pharmacokinetics of pioglitazone, one in the United States and one in Japan. The U.S. study was an open-label, single-dose study in 12 healthy non-elderly subjects (age range: 35–49 years) and 11 healthy elderly subjects (age range: 65–

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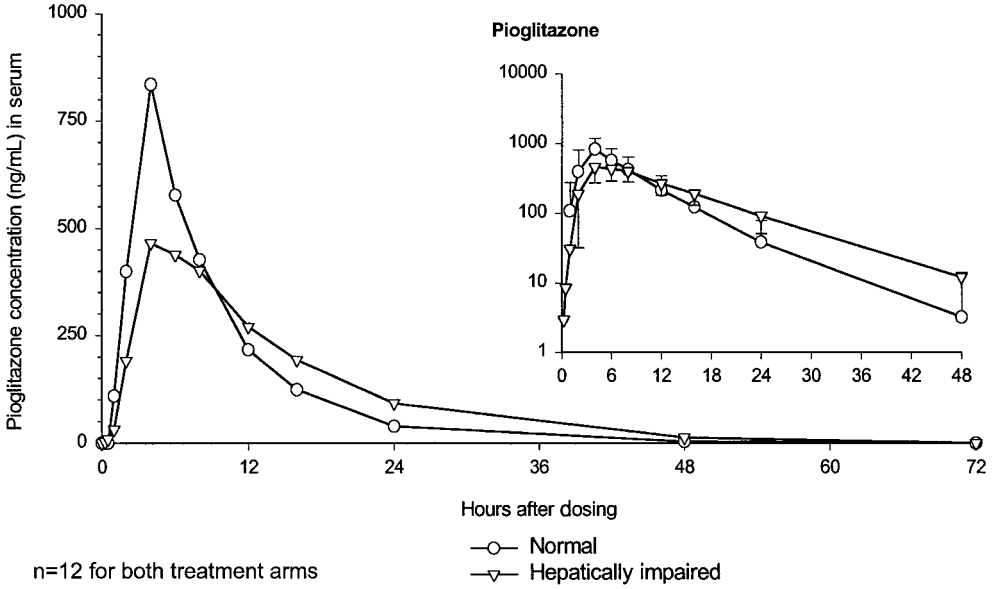

Fig. 4 Pioglitazone serum concentration time profiles in normal and hepatically impaired subjects

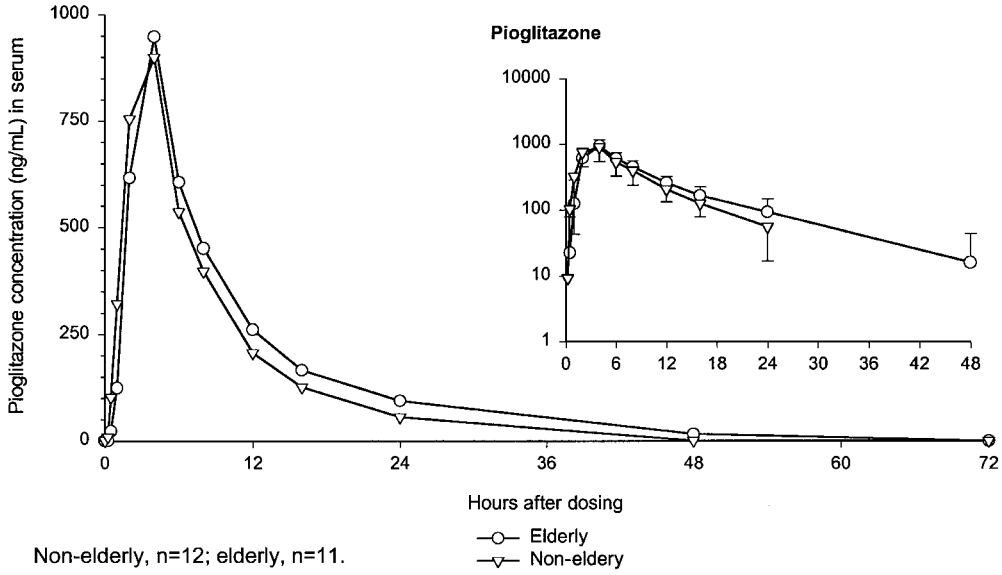

Fig. 5 Mean concentrations (ng/ml) of pioglitazone in serum, comparing elderly and non-elderly subjects

73 years). Subjects received a single 30-mg dose of pioglitazone after breakfast. Although the C_{max} was similar in each group, there was an increase in total exposure (in terms of AUC) of approximately 20% in the elderly, which could be explained by an 18% reduction in oral clearance (Fig. 5).

In the Japanese study, data obtained in the elderly were compared to data from a single-blind, multiple-dose study in non-elderly, healthy, Asian male subjects. Elderly patients had lower C_{max} and AUC values than did non-elderly patients, but other pharmacokinetic parameters were similar. The composition of metabolites in the serum at steady state was also similar for elderly and non-elderly patients.

The results of these investigations seem to indicate that in the elderly there are no profound changes in pharmacokinetics of pioglitazone as result of the aging process *per se*. This does not exclude the possibility that in individual elderly patients profound changes in pharmacokinetics may have occurred because of, for example, concomitant other diseases, drug interaction, and other factors.

Overall, in the context of clinical use, there was no significant change in pharmacokinetics in elderly patients.

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Other

Although no formal studies have been conducted, data from pharmacokinetic studies including both male and female healthy subjects allow for a comparative evaluation. In three separate studies, females had slightly higher C_{max} and AUC and delayed t_{max} values compared with males. These differences were small and are not clinically significant.

No pharmacokinetic data in children are available for pioglitazone.

No formal studies have been conducted to evaluate the effect of ethnicity on the pharmacokinetics of pioglitazone. However, no major differences are apparent from inspection of meta-analysis data from Caucasian, African-American and Japanese patients.

Drug-drug interactions

Since pioglitazone is extensively metabolised via the cytochrome P450 system, and patients with diabetes are commonly subjected to polypharmacy, there could be a potential for drug-drug interactions.

In vitro studies have shown that pioglitazone does not inhibit the P450 isozymes involved in drug metabolism (Yamazaki et al., 2000).

Specific studies have addressed the potential for induction of P450 isozymes by pioglitazone. CYP3A4 (the isozyme most commonly responsible for drug metabolism) is not induced by pioglitazone dosed for 10 days as shown by a lack of change in urinary 6β hydroxycortisol:cortisol ratio (a sensitive marker of CYP3A4 induction). In this study 6 healthy subjects received pioglitazone 45 mg once daily. The 6β-hydroxycortisol/free cortisol ratio was measured in urine. The mean ratios (±SD) before and after repeated dosing of pioglitazone were 4.99 ± 1.92 and 5.11 ± 2.01, respectively. These study results clearly suggest that pioglitazone does not induce the hepatic CYP3A4 enzyme system. Furthermore, pioglitazone does not influence the pharmacokinetics of exogenously administered female sex steroids (either oral contraceptives or hormone replacement therapy), unlike other thiazolidinediones, which induce CYP3A4 (Carey and Liu, 2000).

In another study, the effect of repeated dosing of pioglitazone on the steady-state concentrations of the R and S enantiomers of warfarin and the resultant anticoagulant status were assessed. Pioglitazone had no effect either on warfarin enantiomer concentrations or on anticoagulant status. The enantiomers of warfarin are good markers for CYP1A1/2 and 2C9, suggesting that neither of these isozymes was induced by pioglitazone. Additional drug interaction studies have been undertaken with phenprocoumon, glipizide, metformin, and digoxin, all in healthy volunteers (Crijns-Kortboyer and Eckland, 1999). There was no interaction between pioglitazone and any of these drugs, each of which may be commonly used in patients with diabetes. Since multiple P450 isozymes are involved in the metabolism of pioglitazone, the potential for other drugs to inhibit the metabolism of pioglitazone to a clinically significant extent must be very small.

Conclusion

Pioglitazone is rapidly absorbed after oral administration (81%–94%), and reaches peak concentration in approximately 2.5 hours in patients with type 2 diabetes. It is extensively metabolised in the liver, and most is excreted as inactive metabolites in the faeces. Although the parent compound, pioglitazone, has a half-life of approximately 9 hours, its chief active metabolites, M-III and M-IV, have half-lives of approximately 26–30 hours. Pioglitazone is administered once daily.

The absence of parent compound in the urine suggests that the oral clearance of pioglitazone is metabolic. This observation, coupled with slow clearance from the blood, justifies the conclusion that pioglitazone has a low hepatic extraction ratio and is subject to restrictive elimination. This means that clearance is sensitive to changes in both the intrinsic capacity of the liver and the free fraction in the plasma.

Pioglitazone and its metabolites do not inhibit any of the P-450 isoenzymes involved in drug metabolism. Pioglitazone does not affect, inhibit, or induce the metabolism of commonly co-administered drugs.

Age and gender appear to have no significant effect on the pharmacokinetics of pioglitazone. In patients with renal failure, no adjustment to the starting dose of pioglitazone is required, since elimination is primarily hepatic.

No pharmacokinetic data in children are available for pioglitazone. No formal studies have been conducted to evaluate the effect of ethnicity on the pharmacokinetics of pioglitazone. However, comparison of meta-analysis data from a U.S. study showed no differences between white and black subjects in the absorption, distribution, and excretion of pioglitazone. Similarly, data from several studies with white and Asian subjects show no clinically relevant differences between races.

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