The effects of hepatic impairment on the pharmacokinetics of fosfluconazole and fluconazole following a single intravenous bolus injection of fosfluconazole

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Aims

Fosfluconazole is a phosphate pro-drug of fluconazole (FLCZ). This study was conducted to determine the pharmacokinetics of fosfluconazole and FLCZ following a single intravenous injection of fosfluconazole in subjects with hepatic impairment and to compare them with healthy subjects.

Methods

Twenty-four subjects (12 with normal hepatic function and 12 with chronic stable mild to moderate impaired hepatic function) received a single 1000-mg bolus intravenous injection of fosfluconazole. Concentrations of fosfluconazole and FLCZ were determined in plasma and urine samples taken up to 192 h and 48 h postdose, respectively.

Results

The total clearance of fosfluconazole was higher and the $t_{1/2,z}$ and mean residence time were shorter in hepatically impaired subjects than in normal subjects. This may reflect more rapid conversion to FLCZ. The degree of protein binding of fosfluconazole (> 90%) and the amount of fosfluconazole excreted in the urine were similar in both groups. Slightly higher mean plasma concentrations of FLCZ were observed in the impaired group than in the normal group; however, hepatic impairment had no statistically significant effect on the FLCZ pharmacokinetic parameters apart from t_{max} . The t_{max} values were 4.8 h and 3.1 h in the normal and impaired subjects, respectively. The shorter t_{max} for FLCZ is also consistent with the more rapid conversion in the impaired subjects. The ratios (95% confidence intervals) for C_{max} and AUC of FLCZ (impaired/normal) were 106.0% (92.8, 121.2) and 115.6% (86.4, 154.7), respectively. There were no serious adverse events, and no discontinuations due to adverse events or laboratory test abnormalities. The adverse events reported were mostly mild in severity and no trend could be discerned between the groups.

Conclusions

Fosfluconazole was more rapidly converted to FLCZ in the hepatically impaired subjects but the FLCZ pharmacokinetic parameters (except t_{max}) were not statistically significantly affected by hepatic impairment. Fosfluconazole was well tolerated by both groups. These results suggest that there is no requirement to adjust the dose of fosfluconazole when administered to subjects with mild to moderate hepatic impairment.

Introduction

Fluconazole (FLCZ, Figure 1) is an antifungal agent which is efficacious in the treatment of patients with serious systemic fungal infections [1–3]. FLCZ is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug [4]. The current intravenous (i.v.) dosage form requires the administration of a high-volume infusion which is undesirable in critically ill patients in whom fluid overload must be avoided. There is, consequently, a need for a small-volume, high-dose formulation of FLCZ.

Fosfluconazole (Figure 1) is a phosphate pro-drug of FLCZ which is highly soluble ($>100 \text{ mg ml}^{-1}$) compared with FLCZ (4 mg ml^{-1}) [5]. *In vitro*, fosfluconazole is at least 25-fold less potent than FLCZ against single isolates of *Candida* species and *Cryptococcus neoformans*, but *in vivo* has similar efficacy to FLCZ in experimental models of fungal disease [6]. These observations are consistent with efficient conversion of fosfluconazole to FLCZ *in vivo*. Fosfluconazole is hydrolysed by alkaline phosphatase enzymes to FLCZ and free phosphate and is rapidly converted *in vitro* to FLCZ in homogenates of kidney, lung and liver of rat, dog and human.

In the previous clinical studies in healthy subjects [7–9], fosfluconazole was rapidly and almost completely converted to FLCZ. Only minor amounts of the administered dose of fosfluconazole were excreted unchanged in the urine and the majority was eliminated in the urine as FLCZ. Bolus i.v. injections of fosfluconazole were well tolerated at doses of up to 2000 mg in healthy subjects [7]. Renal impairment had marked effects on the FLCZ pharmacokinetics, but did not affect fosfluconazole pharmacokinetics, including its efficient conversion into FLCZ [10]. It is anticipated that fosfluconazole will be used for the treatment of systemic

fungal infections in patients who may have impaired hepatic function. It was therefore necessary to investigate whether the conversion of fosfluconazole to FLCZ is influenced by hepatic impairment to allow dosing recommendations to be made.

In this study, subjects with impaired hepatic function received a 1000-mg bolus i.v. injection of fosfluconazole to determine the pharmacokinetics of fosfluconazole and FLCZ and to compare them with those for healthy subjects.

Methods

Subjects

All male and female subjects gave their informed consent in writing prior to screening procedures. Female subjects had to be either postmenopausal (2 years after the last period) or surgically sterilized, and have a negative pregnancy test result at screening immediately prior to dosing. Subjects with impaired hepatic function should have stable mild to moderate hepatic impairment according to the Child–Pugh classification (category A and B) [11].

Volunteers were excluded if they had a history of clinically significant allergies; had received an experimental drug within the past 4 months; had evidence of drug abuse; were HIV+ or were hepatitis B surface antigen-positive. Subjects with hepatic impairment were excluded if they had evidence of clinically significant, acute, concurrent disease except those problems associated directly with the primary diagnosis of hepatic impairment; or had any clinically significant laboratory abnormality except for those parameters influenced by hepatic impairment. Subjects were also excluded if they were taking the drugs which are known to interact with FLCZ; had undergone porta-caval shunt surgery; or had a myocardial infarction within the 12 months prior to dosing. In addition, subjects with signs of hepatic encephalopathy greater than grade II portosystemic encephalopathy score; severe ascites and/or pleural effusion; acute exacerbation of liver disease; or haemoglobin $<8 \text{ mg dl}^{-1}$ were excluded.

Study design

This was an open single-dose study and all subjects received a 1000-mg bolus i.v. injection of fosfluconazole, supplied as 100 mg ml^{-1} solutions.

The study was performed at the Apex GmbH (Munich, Germany), in compliance with the ethical principles originating from the revised Declaration of Helsinki (South Africa, 1996). The clinical study protocol was approved by the ethics committee, Bayerische Landesärztekammer (Munich, Germany).

Figure 1
Chemical structures of fluconazole and fosfluconazole

Pharmacokinetic sampling

Blood samples (5 ml) for assay of fosfluconazole and FLCZ were collected at predose and at 5, 15, 30 and 45 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, 120, 144 and 192 h postdose. An additional 5 ml of blood was taken at 15 min and 1 h postdose for protein binding analysis. Within 1 h of collection the blood samples were centrifuged at $1500 \times g$ for 10 min and the plasma was stored at -70°C . Blood and plasma tubes were stored on ice prior to freezing.

Urine collections were made from predose, and 0–4, 4–8, 8–24 and 24–48 h following the start of the i.v. injection. A 10-ml aliquot for fosfluconazole and FLCZ analysis was stored at -70°C within 30 min of completion of the collection.

Drug assay

Plasma, urine and ultrafiltrate concentrations of fosfluconazole and FLCZ were determined at Maxxam Analytics Inc. (Mississauga, Ontario, Canada) using solid-phase extraction of the analytes with separation by liquid chromatography, followed by atmospheric pressure ionization and tandem mass spectrometric detection [7–10]. The lower limit of quantification was $0.2\ \mu\text{g ml}^{-1}$ in plasma and ultrafiltrates and $1.0\ \mu\text{g ml}^{-1}$ in urine.

The overall method imprecision values of quality control samples (coefficient of variation) were less than 13.8% for fosfluconazole and 11.6% for FLCZ at the following concentrations: plasma and ultrafiltrates 0.6, 6 and $12\ \mu\text{g ml}^{-1}$, urine 3, 30 and $80\ \mu\text{g ml}^{-1}$, respectively.

Pharmacokinetic analysis

The pharmacokinetic analysis of fosfluconazole and FLCZ plasma concentrations was performed by non-compartmental methods. The maximum observed plasma concentration (C_{max}) and the first time to C_{max} (t_{max}) of FLCZ were taken directly from the plasma concentration–time curve. The half-life of terminal exponential phase ($t_{1/2,z}$) was calculated as $\ln 2/\lambda_z$, where λ_z is the terminal elimination rate constant, calculated by ordinary least squares linear regression, using points in the linear terminal portion of the log concentration–time curve. The total area under the plasma concentration–time curve between time zero and infinity (AUC) was calculated as $\text{AUC}_t + (C_t/\lambda_z)$, where AUC_t is the area under the plasma concentration–time curve between time zero and the last quantifiable time, t , estimated from the linear trapezoidal method, and C_t is the last quantifiable concentration at time t , estimated by linear regression analysis. The mean residence time

(MRT) was estimated by AUMC/AUC , where AUMC is the area under the first-moment of concentration–time curve with extrapolation to infinity. The total plasma clearance (CL) of fosfluconazole was estimated as Dose/AUC . The volume of distribution at steady state (V_{ss}) of fosfluconazole was calculated as $\text{CL} \times \text{MRT}$. The cumulative amount of FLCZ excreted in the urine up to 48 h (Ae_{48}) was calculated and is reported as a percentage recovery of the dose administered [$Ae_{48}(\%) = 100 \times Ae_{48}/\text{dose}$]. This is reported as $Ae(\%)$ for fosfluconazole. Renal clearance (CL_R) of FLCZ was calculated as Ae_{48}/AUC_{48} .

The fraction of fosfluconazole unbound (f_u) was calculated as $[100 - (\text{ppb}_{0.25} + \text{ppb}_1)/2]/100$, where $\text{ppb}_{0.25}$ and ppb_1 are the percentages of protein bound at 15 min and 1 h.

The total plasma clearance of unbound fosfluconazole (CL_u) was calculated as CL/f_u .

Safety assessments

All observed or subjective adverse events were classified according to the Coding Symbol Thesaurus of Adverse Reaction Terms (COSTART).

Blood and urine samples for laboratory safety tests were collected at prestudy screening, predose, 48 h postdose and at follow-up. Laboratory test abnormalities were evaluated for clinical significance against sponsor-defined criteria based on normal ranges.

A 12-lead ECG, supine blood pressure and pulse rate were taken at screening, the day prior to dosing, 1, 2, 4, 8 and 48 h postdose and at follow-up. Cardiac rhythm was monitored continuously from 30 min predose until 1 h postdose.

Statistical analysis

The pharmacokinetic parameters of fosfluconazole and FLCZ were subjected to t -tests for unequal variances at the 5% significance level. The differences between the group means and the 95% confidence intervals (CIs) were calculated. AUC and C_{max} were log transformed prior to analysis, giving differences between the subject groups as ratio-estimates when back-transformed. The pharmacokinetic data for Child–Pugh category A group and B group revealed no evidence to suggest splitting the impaired subjects into these two groups, and therefore the impaired group as a whole was compared with the normal group. The sample size of 12 subjects per group was estimated to be sufficient to detect a difference of 20% in FLCZ AUC with a probability >0.8 when performing a two-sided test at the 5% level based upon data from a previous study in healthy volunteers.

Results

Demographics

Twenty-four subjects entered the study (Table 1) and all subjects completed the study. The two groups were matched as closely as possible with regard to age (± 5 years), weight (± 10 kg) and sex; however, two subjects in the normal group were 6 years older than their matched impaired subjects. In the impaired group there were six subjects each assigned to Child–Pugh category A and B. The mean values (ranges) of creatinine clearance in the normal and impaired groups were 122 (101–153) ml min⁻¹ and 126 (68–206) ml min⁻¹, respectively.

Pharmacokinetics

Fosfluconazole Higher mean plasma concentrations of fosfluconazole were observed in the normal group than in the impaired group (Figure 2). However, no fosfluconazole was detected in either group after 24 h postdose.

The pharmacokinetic parameters for fosfluconazole are summarized in Table 2. The mean CL was statistically significantly higher, and the mean $t_{1/2,Z}$ and MRT were lower ($P < 0.01$) in the impaired group than in the normal group. The mean AUC was higher in the normal group than in the impaired group. There was no statistically significant difference between the means for the two treatment groups for V_{ss} . The degree of protein binding for fosfluconazole was high ($>90\%$) in both groups and therefore the CL_u of fosfluconazole compared with the CL was consequently high. Mean CL_u was also higher in the impaired group as a whole compared with the normal group.

The A_e (%) of fosfluconazole was similar in both groups and occurred mostly over the first 0–4-h urine collection period.

Fluconazole After 24 h postdose, slightly higher mean plasma concentrations of FLCZ were observed in the impaired group than in the normal group (Figure 3).

Table 1

Mean (range) demographic characteristics

	Age (years)	Weight (kg)	Height (cm)	Body mass index (kg m ⁻²)
<i>Normal</i>				
Male ($n = 6$)	53.2 (44–59)	78.4 (69–88)	174.2 (170–181)	25.8 (24–29)
Female ($n = 6$)	57.9 (44–66)	66.8 (54–78)	164.7 (159–172)	24.6 (21–29)
Total ($n = 12$)	55.5 (44–66)			
<i>Impaired</i>				
Male ($n = 6$)	55.6 (48–62)	82.2 (71–98)	169.0 (160–177)	28.7 (26–31)
Female ($n = 6$)	54.3 (41–62)	71.5 (60–85)	164.0 (160–166)	26.6 (23–31)
Total ($n = 12$)	54.9 (41–62)			

Figure 2

Mean $\pm$ SD plasma concentration profiles of fosfluconazole after intravenous injection of fosfluconazole in subjects with normal hepatic function ($\circ$), $n = 12$; and impaired hepatic function ($\blacktriangle$), $n = 12$

Table 2

Comparison of fosfluconazole pharmacokinetic parameters after intravenous injection of fosfluconazole in subjects with normal and impaired hepatic function

Parameter	AUC ($\mu\text{g}\cdot\text{h ml}^{-1}$)	CL ($\text{ml min}^{-1} \text{kg}^{-1}$)	CLu ($\text{ml min}^{-1} \text{kg}^{-1}$)	Vss (l kg^{-1})	$t_{1/2,z}$ (h)	MRT (h)	Ae (%)
Normal ($n = 12$)	186.7 (180.7) $\pm$ 51.35	1.31 $\pm$ 0.280	24.41 $\pm$ 8.10	0.16 $\pm$ 0.025	2.4 $\pm$ 0.43	2.1 $\pm$ 0.36	1.4 $\pm$ 0.72
Impaired ($n = 12$)	118.2 (108.3) $\pm$ 57.23	2.14 $\pm$ 0.675	43.43 $\pm$ 16.83	0.16 $\pm$ 0.022	1.6 $\pm$ 0.53	1.4 $\pm$ 0.60	1.2 $\pm$ 0.85
Difference between means	NC	0.83	19.02	-0.01	-0.8	-0.7	NC
95% CIs	NC	0.38, 1.28	7.58, 30.46	-0.03, 0.01	-1.2, -0.3	-1.2, -0.3	NC

AUC, Total area under the plasma concentration–time curve between time zero and infinity; CL, total plasma clearance; CLu, total plasma clearance of unbound drug; Vss, volume of distribution at steady state; $t_{1/2,z}$, half-life of terminal elimination phase; MRT, mean residence time; Ae, cumulative amount excreted in the urine; NC, not calculated. The arithmetic mean (geometric mean) $\pm$ SD for AUC, and the arithmetic means $\pm$ SD and the difference (impaired – normal) between the means for all other parameters are presented.

Figure 3

Mean $\pm$ SD plasma concentration profiles of fluconazole after intravenous injection of fosfluconazole in subjects with normal hepatic function ($\circ$), $n = 12$; and impaired hepatic function ($\blacktriangle$), $n = 12$

FLCZ was detected in most subjects in both groups at 192 h postdose.

The pharmacokinetic parameters for FLCZ are shown in Table 3. The only FLCZ pharmacokinetic parameter that was statistically significantly different between the groups was $t_{\max}$, with the impaired group having a lower $t_{\max}$ than the normal group. The mean AUC, $t_{1/2,z}$ and MRT were higher in the impaired group than in the normal group. However, there was more variability in these pharmacokinetic parameters in the impaired subjects than in the normal subjects and this is mostly because of two subjects from the impaired group who had the greatest values. The other subjects in the impaired group had similar FLCZ pharmacokinetic values to those in the normal group.

The mean CL_R and Ae_{48} (%) were similar in both groups.

Safety

There were no serious adverse events, and no discontinuations due to adverse events or laboratory test abnormalities. Five adverse events reported by three normal subjects, and eight adverse events reported by seven impaired subjects were considered to be treatment related (Table 4). All adverse events were either mild or moderate in intensity and resolved without treatment.

Three subjects in both groups had clinically significant laboratory test abnormalities (according to the sponsor-defined criteria), but all were deemed either to

Table 3

Comparison of fluconazole pharmacokinetic parameters after intravenous injection of fosfluconazole in subjects with normal and impaired hepatic function

Parameter	AUC ($\mu\text{g}\cdot\text{h ml}^{-1}$)	C_{max} ($\mu\text{g ml}^{-1}$)	t_{max} (h)	$t_{1/2,z}$ (h)	MRT (h)	Ae_{48} (%)	CL_R ($\text{ml min}^{-1} \text{kg}^{-1}$)
Normal ($n = 12$)	795.6 (782.4) $\pm$ 154.40	13.4 (13.2) $\pm$ 2.52	4.8 $\pm$ 1.75	37.5 $\pm$ 5.80	56.1 $\pm$ 6.54	31.2 $\pm$ 4.02	0.13 $\pm$ 0.014
Impaired ($n = 12$)	992.1 (904.6) $\pm$ 484.73	14.0 (14.0) $\pm$ 1.47	3.1 $\pm$ 1.79	46.3 $\pm$ 25.08	68.2 $\pm$ 34.53	30.1 $\pm$ 10.78	0.12 $\pm$ 0.055
Ratio or difference between means	115.6%	106.0%	-1.7	8.8	12.1	NC	-0.01
95% CIs	86.4, 154.7%	92.8, 121.2%	-3.2, -0.2	-7.4, 25.0	-10.1, 34.2	NC	-0.05, 0.02

AUC, Total area under the plasma concentration–time curve between time zero and infinity; C_{max} maximum observed plasma concentration; t_{max} first time to C_{max} ; $t_{1/2,z}$ half-life of terminal elimination phase; MRT, mean residence time; Ae_{48} cumulative amount excreted in the urine up to 48 h; CL_R renal clearance; NC, not calculated. The arithmetic mean (geometric mean) $\pm$ SD and the ratio (impaired/normal) of the means for AUC and C_{max} and the arithmetic means $\pm$ SD and the difference (impaired – normal) between the means for all other parameters are presented.

Table 4

Incidence of adverse events and clinically significant laboratory test abnormalities after intravenous injection of fosfluconazole in subjects with normal and impaired hepatic function

Number of subjects with	Normal ($n = 12$)	Impaired ($n = 12$)
<i>Adverse events</i>		
All causality	4	7
Treatment related	3	7
Diarrhoea	3	3
Pruritus	0	2
Abdominal pain	1	0
Paraesthesia	1	0
Nausea	0	1
Asthenia	0	1
Dry mouth	0	1
<i>Clinically significant laboratory test abnormalities</i>		
With regard to normal baseline	3	3
Platelets ($<75 \times 10^3 \text{ mm}^{-3}$)	1	0
Urine blood ($\geq 1+$)	2	3
With regard to abnormal baseline	1	0
Urine blood (>1 +baseline)	1	0

be clinically insignificant or as a result of the subjects' hepatic impairment (Table 4).

Small changes in blood pressure and pulse rate were observed in both groups but there was no pattern across the time points or treatment groups. One normal subject and three impaired subjects had ECG abnormalities postdose, or a more abnormal ECG compared with baseline, but most of these subjects had ECG abnormalities at screening and all abnormalities were considered by the investigator to be clinically insignificant.

Discussion

Subjects with hepatic impairment had lower mean plasma concentrations of fosfluconazole than normal subjects. The CL of fosfluconazole was higher and the $t_{1/2,z}$ and MRT of fosfluconazole were shorter in the impaired group than in the normal group. Since fosfluconazole is converted to FLCZ this may reflect the more rapid conversion of fosfluconazole to FLCZ in hepatically impaired subjects. The shorter t_{max} for FLCZ is also consistent with the more rapid conversion in impaired subjects.

Aweeka *et al.* [12] have investigated the impact of hepatic disease on the pharmacokinetics of fosphenytoin (phosphate ester pro-drug of phenytoin) and phenytoin

following a single i.v. infusion for 30 min of fosphenytoin to subjects with hepatic cirrhosis and healthy subjects. Compared with the healthy subjects, the fosphenytoin CL was higher, $t_{1/2,Z}$ was shorter and $C_{\max}$ was lower in subjects with hepatic disease. The $t_{\max}$ for total phenytoin occurred earlier in subjects with hepatic disease. This finding is consistent with decreased binding of fosphenytoin to plasma proteins and increased fraction of unbound fosphenytoin resulting from decreased plasma protein concentrations associated with this disease state.

On the other hand, for fosfluconazole the degree of protein binding was also high in subjects with hepatic impairment and unaffected by hepatic impairment. The V_{ss} of fosfluconazole was similar to the extracellular volume (0.21 kg^{-1}) and fosfluconazole has insufficient lipophilicity to readily cross cell membranes passively. Fosfluconazole therefore is most likely to be efficiently hydrolysed in tissues where phosphatases are expressed extracellularly. The alkaline phosphatase activities in serum were higher in the impaired group (91.28 IU l^{-1}) than in the normal group (49.07 IU l^{-1}) of this study, suggesting the possibility that alkaline phosphatase in blood contributes to the conversion of fosfluconazole to FLCZ.

Slightly higher mean plasma concentrations of FLCZ were observed in the impaired group than in the normal group, but there was no statistically significant difference in the FLCZ pharmacokinetic parameters (except $t_{\max}$) between groups. These results suggest that no dosage adjustments are particularly recommended for the administration of fosfluconazole in Child–Pugh category A and B hepatically impaired patients, as is the case with FLCZ.

In conclusion, fosfluconazole was more rapidly converted to FLCZ in the hepatically impaired subjects, but the FLCZ exposure ($C_{\max}$ and AUC) were not affected by hepatic impairment. Fosfluconazole was well tolerated by both groups. These results suggest that there is no requirement to adjust the dose of fosfluconazole when administered to the subjects with mild to moderate hepatic impairment.

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