Influence of mild liver impairment on the pharmacokinetics of tezosentan, a drug excreted unchanged into bile

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Aims

To investigate the effect of mild liver impairment on the pharmacokinetics of tezosentan.

Methods

Eleven patients with mild liver impairment and eight healthy subjects received an intravenous infusion of 50 mg h⁻¹ tezosentan for 1 h. Plasma and urine concentrations were determined during and following termination of the infusion.

Results

The pharmacokinetic parameters presented as geometric means [95% confidence interval (CI)] for clearance, volume of distribution and terminal half-life were 30 (22, 40) and 42 (36, 48) l h⁻¹, 28 (19, 42) and 19 (16, 23) l, and 4.5 (2.9, 7.0) and 3.6 (2.9, 4.5) h in liver patients and healthy subjects, respectively. The ratios (liver patients/healthy subjects) of these geometric means (95% CI) were 0.71 (0.47, 1.1), 1.5 (0.87, 2.6), and 1.3 (0.69, 2.3), respectively. A two-compartment model accurately fitted the concentration–time data. In both groups approximately 4% of the dose was excreted unchanged into urine.

Conclusions

Although there was a slight trend towards a decreased clearance, the pharmacokinetics of tezosentan in patients with mild liver impairment were similar to those in healthy subjects. Therefore, no dose adaptation seems to be needed in this patient population.

Introduction

Endothelin-1 has potent and long-lasting vasoconstrictive properties and has been implicated in numerous (patho)physiological processes [1]. Endothelin receptors have become attractive targets for drug discovery because circulating concentrations of endothelin-1 are elevated in various disease states.

Tezosentan, a dual competitive endothelin receptor antagonist formulated for parenteral use, is currently in development for the treatment of acute heart failure [2]. A two-compartment model with disposition half-lives of

0.1 and 3 h describes its pharmacokinetic profile [3]. Tezosentan is not metabolized to any major extent, and is excreted almost exclusively into the bile [4].

Heart failure is commonly associated with liver hypoxia, leading to sinusoidal congestion and hypoperfusion [5, 6]. Such liver impairment could affect the pharmacokinetics of tezosentan, a drug with a moderate to high hepatic extraction ratio. Furthermore, endothelin-1 may play a role in the pathogenesis of ascites in cirrhosis and portal hypertension [7], which suggests a potential indication for endothelin antago-

nists in liver disease. These considerations prompted us to investigate the effect of liver impairment on the pharmacokinetics of tezosentan.

Methods

Subjects

Eight healthy subjects and 11 patients with mild liver impairment (Child–Pugh class A) were studied. Originally, 12 Child–Pugh class A (score 5 or 6) patients were recruited but one was later shown to be a Child–Pugh class B patient (score 7). All patients had a documented history of liver cirrhosis (based on a complete physical examination, laboratory test results, ultrasound examination and/or laparoscopy and/or a histological diagnosis after biopsy). Liver impairment was quantified using the Child–Pugh classification [8, 9]. Apart from age (25 ± 2 and 52 ± 9 years), no relevant differences existed between the two groups.

The study was conducted according to the principles of the Declaration of Helsinki, was approved by an ethics committee (Ethik-Kommission Regionales Departement Innere Medizin Beider Basel, Basel, Switzerland), and all subjects gave written informed consent. Administration of intravenous tezosentan (50 mg h^{-1} for 1 h) was performed using a calibrated infusion pump. A sample of the infusion solution was taken for accurate determination of the dose administered.

Blood samples and urine were collected up to 24 h after the start of the infusion. Concentrations of tezosentan in the infusion solution, plasma and urine were determined using narrow-bore liquid chromatography coupled to tandem mass spectrometry [3]. The limit of quantification was 1.0 ng ml^{-1} in urine and plasma, and 4.0 ng ml^{-1} in the infusion solution samples. Intra- and interassay inaccuracy and imprecision were $<15\%$ for all three matrices.

Pharmacokinetic parameters were calculated by model-dependent and model-independent methods using WinNonlin (Pharsight Corp., Mountain View, CA, USA). For the model-dependent analysis, a two-compartment model with a weighting factor of $1/Y^2$ provided good fits to the data. Data from the study groups were compared by one-way analysis of variance (ANOVA) after log-transformation and dose normalization of C_{max} and AUC. Disposition half-lives, CL and V_{ss} were logarithmically transformed before statistical comparison.

Results

The mean plasma concentration–time curves for tezosentan in the two groups are shown in Figure 1.

Figure 1

Plasma concentration–time profiles of tezosentan in healthy subjects ($\circ$, $n = 8$) and patients with mild hepatic impairment ($\blacksquare$, $n = 11$). Subjects and patients received a 50-mg h^{-1} intravenous infusion of tezosentan for 1 h. Data are presented as arithmetic mean $\pm$ SD on a semilogarithmic and linear (insert) scale

Following termination of the infusion, the plasma concentrations of the drug decreased rapidly in a biphasic pattern in both healthy subjects and patients, but at a slightly lower rate in the latter. Derived and calculated pharmacokinetic parameters obtained by model-independent and -dependent methods are given in Table 1. All were similar in patients with liver disease and healthy subjects, although there was a trend to a smaller clearance and a greater volume of distribution in the patients. Comparison by ANOVA yielded a statistically significant difference only for the half-life of the second disposition phase. Total urinary recovery of unchanged tezosentan was approximately 4% of the dose in both groups. The Child–Pugh class B patient had an $\text{AUC}_{0-\infty}$ of $5586 \text{ ng h ml}^{-1}$, a clearance of 7.9 l h^{-1} , a renal clearance of 1.6 l h^{-1} and a urinary recovery of 21%. Few adverse events were reported and none was serious or severe. Headache and fatigue/somnolence were the most frequent events in both groups.

Discussion

Tezosentan is excreted almost completely unchanged by the liver into the bile [4] and therefore impaired liver function might be expected to influence its pharmacokinetics. Liver impairment may affect the pharmacokinetics of drugs because of changes in hepatic blood flow, biliary excretion, liver enzyme activity and/or plasma protein binding [10].

The results show that in patients with mild liver

Table 1
Pharmacokinetic parameters of tezosentan using noncompartmental and compartmental analysis in healthy subjects and in patients with mild hepatic impairment

Analysis/population	AUC _{0-∞} (ng h ml ⁻¹)	C _{max} (ng ml ⁻¹)	t _{1/2z} (h)	t _{1/2} (α) (h)	t _{1/2} (β) (h)	CL (l h ⁻¹)	V _{ss} (l)	CL _R (l h ⁻¹)	Urinary recovery (% of dose infused)
<i>Noncompartmental</i>									
Healthy subjects (n = 8)	1198 (1007, 1424)	1279 (1082, 1512)	3.6 (2.7, 4.7)			42 (35, 50)	19 (15, 24)	1.7 (1.5, 2.0)	4.1 (3.1, 5.3)
Patients (n = 11)	1689 (1185, 2408)	1570 (1142, 2158)	4.5 (2.7, 7.4)			30 (21, 42)	28 (18, 45)	1.0 (0.57, 1.8)	3.4 (1.8, 6.6)
Ratio of mean	1.4 (0.93, 2.1)	1.2 (0.84, 1.8)	1.3 (0.69, 2.3)			0.71 (0.47, 1.1)	1.5 (0.87, 2.6)	0.59 (0.31, 1.1)	0.84 (0.39, 1.8)
<i>Compartmental</i>									
Healthy subjects (n = 8)	1151 (974, 1360)	1085 (923, 1275)		0.10 (0.08, 0.12)	1.4 (1.2, 1.6)	43 (37, 51)	13 (11, 16)		
Patients (n = 11)	1526 (1072, 2173)	1368 (1003, 1866)		0.14 (0.11, 0.18)	2.7 (1.9, 3.6)	33 (23, 47)	19 (14, 27)		
Ratio of mean	1.3 (0.88, 2.0)	1.3 (0.87, 1.8)		1.4 (0.99, 2.0)	2.0 (1.3, 2.8)	0.76 (0.50, 1.1)	1.4 (0.94, 2.2)		

Data are expressed as geometric mean (and 95% confidence interval). AUC_{0-∞} and C_{max} are normalized to a dose of 50 mg.

impairment the pharmacokinetics of tezosentan after a single i.v. infusion are essentially unaltered. There was a trend towards a decreased clearance in liver patients, but this was not statistically significant. Since steady-state conditions had not been attained following 1 h of tezosentan infusion, possible differences in V_{ss} should be interpreted with caution. This study was conducted on a limited number of subjects and therefore a larger study could have revealed statistically significant differences. The highest exposure to and renal excretion of tezosentan was observed in the patient with moderate liver impairment. This suggests that exposure to tezosentan may be increased in patients with more marked liver impairment. When comparing the results obtained with model-independent and model-dependent methods, it was noted that the model consistently predicted lower values for C_{max} and AUC. This may be due to (i) the infusion duration of 1 h, which was probably too short to attain steady-state conditions, and (ii) the limited number of samples taken during the initial disposition phase following termination of the infusion.

Alterations in plasma protein binding only result in relevant changes in unbound drug exposure for drugs with a high extraction ratio given intravenously, and changes are clinically relevant only for drugs with a narrow therapeutic index [6, 11]. Tezosentan is a moderate to high clearance drug but has a wide therapeutic index [3]. For these reasons, plasma protein binding experiments were not performed in the present study.

Valsartan is a compound that shares some pharmacokinetic characteristics with tezosentan. Both undergo little metabolic conversion, show high plasma protein binding, have a small volume of distribution (approximately 20 l) and, at physiological pH, are dianions [2, 12]. Therefore, both may be substrates of the canalicular multispecific organic anion transporter cMOAT (also termed MRP2), enabling their excretion from the liver into the bile [13–15]. Involvement of P-glycoprotein is less likely based on data for the structural analogue bosentan [16]. Exposure to valsartan is shown to be approximately doubled in patients with mild liver impairment [17]. Bilirubin, in the form of its di-glucuronide, is a dianion and is also excreted into the bile by cMOAT [18]. It has been reported that a patient with a plasma bilirubin concentration six times above the upper limit of normal had a markedly increased exposure to valsartan [17]. The Child–Pugh class B patient in the present study, who showed the highest exposure to tezosentan, also had the highest bilirubin concentration (2.5 times the upper limit of normal), whereas the other patients had values that did not differ from those in the healthy subjects.

In conclusion, the pharmacokinetics of tezosentan in patients with mild liver impairment are similar to those observed in healthy subjects. Thus, no dose adaptation for tezosentan seems necessary in this patient population. Pharmacokinetic studies with tezosentan in patients with more advanced stages of liver disease (Child–Pugh class B and C) are warranted. In addition, it may be worthwhile to investigate the relationship between exposure to tezosentan and bilirubin concentrations.

The clinical part of this study was performed at the Department of Gastroenterology, University Hospital, Basel, Switzerland with Professor Christoph Beglinger as the principal investigator.

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