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PHARMACOKINETICS AND DISPOSITION

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Cyclosporin increases the exposure to tezosentan, an intravenous dual endothelin receptor antagonist

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Abstract *Objective*: To investigate in 12 healthy subjects the pharmacokinetics and tolerability of tezosentan, an endothelin receptor antagonist, when given concomitantly with cyclosporin.
Methods: Tezosentan was infused at a dose of 6.25 mg/h and 25 mg/h for 6 h either alone or following a single dose of 400 mg cyclosporin. Blood and urine samples were collected for pharmacokinetic determinations. Vital signs, electrocardiogram, adverse events, and clinical laboratory parameters were monitored to assess tolerability.
Results: Concomitant cyclosporin resulted in a fourfold increase in the exposure to tezosentan. Tezosentan alone was well tolerated. In combination with cyclosporin, and at both doses, all subjects reported headache, hot flushes and nausea/vomiting, some of which were of severe intensity.
Conclusion: The poor tolerability of the combination of cyclosporin and tezosentan is not correlated with the plasma concentrations of tezosentan.

Keywords Tezosentan · Cyclosporin · Pharmacokinetic interaction

Introduction

Endothelin-1 is one of the most potent known constrictors of human resistance and capacitance vessels [1], and, in several disease states such as heart failure, endothelin-1 levels are elevated in the plasma [2]. Tezosentan (Veletri; Ro 61-0612), an endothelin receptor antagonist specifically formulated for parenteral use [3], was well tolerated in healthy subjects, and its pharmacokinetics could be described using a two-compartment pharmacokinetic model. The drug was quickly eliminated from the systemic circulation with disposition half-lives of 6 min and 3 h [4]. This study evaluated the effect of cyclosporin on the pharmacokinetics and tolerability of tezosentan in healthy subjects.

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Methods

Twelve healthy [based on physical examination, vital signs, electrocardiogram (ECG) and clinical laboratory tests] male Caucasian subjects were recruited. They gave written informed consent, and the study was conducted according to the principles of the Declaration of Helsinki. Tezosentan was dissolved in water containing tris-aminomethane, ethylene diamine tetraacetic acid (EDTA) and NaCl and infused at a rate of 25 mg/h for 6 h alone (treatment A) or following the oral intake of 400 mg cyclosporin (Sandimmun, Optoral, Novartis; treatment B1) 1 h earlier. After six and four subjects had received treatments A and B1, respectively, it was noted that concomitant tezosentan and cyclosporin were poorly tolerated. Plasma samples were analysed, and it was decided to lower the dose of tezosentan to 6.25 mg/h for 6 h (treatment B2). Two further subjects were recruited who received treatments A and B2 with a 1-week washout. No improvement in tolerability was observed and the study was stopped prematurely.

Repeated blood (21) and urine (5) samples were collected over 48 h, and concentrations of tezosentan were determined by means of a narrow-bore liquid chromatography method coupled to tandem mass spectrometry (LC-MS/MS). The chromatographic system consisted of a Haipeek Clipeus Phenyl guard column (Higgins Analytical, Mountain View, Calif., USA), a Symmetry C18 analytical column (Waters, Rupperswil, Switzerland) and an API 365 triple quadruple mass spectrometer from Perkin-Elmer Sciex (Concord, Ontario, Canada). The limits of quantification were 1.0 ng/ml and 2.5 ng/ml in urine and plasma, respectively [4].

The pharmacokinetic parameters were calculated with model-dependent and model-independent methods using WinNonlin (Pharsight Corporation, Mountain View, Calif.). For the analysis of the pharmacokinetic data, treatment A data from all subjects were combined. Tolerability was assessed by the recording of adverse events, vital signs, and ECG and clinical laboratory tests. The tolerability data were evaluated descriptively. The two subjects who received the lower dose of tezosentan were treated separately.

Results

After infusion stop, tezosentan plasma concentrations quickly decreased with a biphasic profile. In the presence

of cyclosporin, the area under the plasma concentration–time curve (AUC) and the peak plasma concentration (C_{max}) of tezosentan increased three- to fourfold, whereas clearance, volume of distribution, and the renal excretion decreased three- to fourfold. Half-life and the renal clearance of tezosentan were unaffected (Table 1). Co-administration of the lower dose of tezosentan and cyclosporin resulted in plasma concentrations similar to those observed after the higher dose of tezosentan alone (data not shown).

The reported adverse events with their intensity are presented in Table 2. Subjects receiving tezosentan and cyclosporin reported more adverse events and of more severe intensity than subjects receiving tezosentan alone, regardless of the dose of tezosentan. All adverse events resolved spontaneously and without sequelae. No other treatment-related changes in tolerability parameters were observed.

Discussion

Tezosentan is almost exclusively excreted unchanged via the bile and given the fast initial disposition phase and the small volume of distribution, it is likely that active excretion of tezosentan occurs. Inhibition of drug transport proteins in the liver is the likely mechanism by which cyclosporin increases the exposure to tezosentan [5]. By inhibiting these proteins, cyclosporin might also limit the distribution of tezosentan into some tissues, thereby decreasing its volume of distribution. In a similar way as it affects tezosentan, cyclosporin has been shown to affect the pharmacokinetics of digoxin, a substrate of drug transport proteins [5], leading to significant digoxin toxicity in patients awaiting cardiac transplantation [6]. Tezosentan is strongly bound to plasma proteins and, therefore, an interaction with cyclosporin at this level cannot be entirely excluded. When the biliary route is inhibited by cyclosporin, renal excretion of tezosentan probably represents an alternative route of elimination as evidenced by increased urine concentrations of tezosentan in subjects treated with cyclosporin.

The evaluation of tolerability is hampered by the fact that cyclosporin was not given alone, the lack of a placebo arm, the small number of subjects and that cyclosporin levels were not measured. The adverse events reported are probably related to tezosentan as they are typical for this compound [4], they mainly occurred after infusion of tezosentan was started and that cyclosporin, at the single dose given, is well tolerated by healthy subjects [7]. It cannot be excluded, however, that acute cyclosporin toxicity occurred, which, at least in part, resembles the clinical picture observed in this study [8].

The observed adverse events are probably not correlated with the plasma concentrations of tezosentan because the two subjects receiving the lower dose of tezosentan and cyclosporin had plasma concentrations

Table 1. Pharmacokinetic parameters of tezosentan in healthy subjects in the presence or absence of cyclosporin. Data are expressed as geometric means (and 95% CI). *A* tezosentan 25 mg/h for 6 h alone, *B1* tezosentan 25 mg/h for 6 h + 400 mg cyclosporin. *AUC* area under concentration–time curve, C_{max} peak plasma concentration, $t_{1/2}$ half-life, *CL* clearance, *Vss* volume of distribution at steady state, CL_R renal clearance

Treatment	$AUC_{0-\infty}$ (ng·h/ml)	C_{max} (ng/ml)	$t_{1/2}$ (α) (h)	$t_{1/2}$ (β) (h)	CL (l/h)	Vss (l)	CL_R (ml/min)	Urine recovery (% of dose infused)
A ($n=8$)	3982 (3632, 4367)	881 (768, 1012)	0.11 (0.10, 0.13)	4.1 (3.2, 5.3)	37.7 (34.4, 41.3)	24.1 (19.9, 29.2)	33.8 (17.8, 64.1)	5.4 (2.9, 10.0)
B1 ($n=4$)	15779 (9281, 26827)	3118 (1908, 5095)	0.12 (0.05, 0.27)	4.4 (3.1, 6.3)	9.5 (5.6, 16.1)	8.4 (5.8, 12.0)	31.0 (17.3, 55.5)	19.6 (16.2, 23.5)

Table 2. Overview of reported adverse events (AEs) by treatment. *A* tezosentan 25 mg/h for 6 h alone, *B1* tezosentan 25 mg/h for 6 h + 400 mg cyclosporin, *B2* tezosentan 6.25 mg/h for 6 h + 400 mg cyclosporin

Treatment sequence[a]			A–B2 ($n=2$)	
Treatment Adverse event	A ($n=6$) No	B1 ($n=4$) No	A No	B2 No
Total subjects with at least one AE	1	4	1	2
Total number of AEs	1	17	1	9
Headache	1	4	1	$2^{\#\#}$
Hot flushes	–	4	–	2
Nausea	–	4^{***}	–	$2^{*\#}$
Vomiting	–	$3^{**\#}$	–	$1^{\#}$
Lower abdominal pain	–	1	–	–
Dizziness	–	–	–	$1^{\#}$
Loose stools	–	1	–	–
Sweating	–	–	–	1

*, #Indicate number of adverse events of severe or moderate intensity, respectively. All other adverse events were of mild intensity

[a]Applicable to the two subjects who received tezosentan alone and in combination with cyclosporin

of tezosentan similar to those measured after infusion of 25 mg/h for 6 h alone but tolerability was still poor. Drug transport proteins are an integral part of the blood–brain barrier [9]. They remove substances from the brain, and inhibition of this process may enhance the brain penetration of a particular drug. It is hypothesised that the observed poor tolerability in the presence of cyclosporin is related to increased concentrations of tezosentan in the brain. Cyclosporin has been shown to increase the cerebral uptake of a number of compounds [10] in rats. In man, loperamide, a potent opiate normally lacking centrally mediated side effects, was shown to cause respiratory depression [11] when co-administered with quinidine, a P-glycoprotein inhibitor [5].

In conclusion, the tolerability profile of tezosentan when given concomitantly with cyclosporin hampers the co-administration of both drugs in a clinical setting.

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