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PHARMACOKINETICS AND DISPOSITION

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Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man

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Abstract *Objective*: The pharmacokinetics of orally and intravenously administered valsartan were determined in two studies. In a first pilot study, three i.v. doses of valsartan were given in an ascending manner (5, 10 and 20 mg) to evaluate tolerability and basic pharmacokinetics of the i.v. formulation. In a second study, the absolute bioavailability of 80 mg valsartan from a capsule and a buffered solution was compared with a 20 mg i.v. dose.
Methods: The concentrations of valsartan in plasma and urine were measured using HPLC. The disposition of valsartan after an i.v. dose was characterized by biphasic decay kinetics, with a distribution phase (half-life 1.0 h), followed by a longer elimination phase (half-life 9.5 h). The volume of distribution at steady state was 16.9 l, and the total body clearance 2.2 $l \cdot h^{-1}$. 29% of the i.v. dose was recovered unchanged in the urine.
Results: Plasma levels peaked 2 h after oral administration of the 80 mg capsule. Thereafter, plasma levels declined biexponentially with a terminal $t_{1/2}$ of 7.0 h. C_{max} was reached 1 h after administration of the solution, and $t_{1/2}$ was 7.5 h. On average 7.3% (capsule) and 12.6% (solution) of the dose was excreted in the urine as the unchanged drug. The fraction of dose absorbed and systemically available after oral administration was 0.23 for the capsule and 0.39 for the solution, based on AUC. Absorption appeared to follow two first-order processes. The first phase was rapid, with a half-life of 0.5 h and 0.9 h for solution and capsule, respectively. The slower absorption phase was characterized by a half-life of 6.5 h for the solution and 3.5 h for the capsule. Most of the drug was absorbed during the period 0.4 h to 3 h post-dosing, and 90% of the fraction absorbed from the capsule was absorbed within 5 h.

Key words Valsartan; pharmacokinetics, deconvolution, healthy volunteers, bioavailability

Introduction

Valsartan, (*S*)-*N*-valeryl-*N*-{[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl}-valine, is a potent, highly selective antagonist of the angiotensin II (Ang II) AT_1-receptor [2, 3] and lowers the blood pressure in hypertensive patients. In 1982, Furukawa et al. [4] reported that derivatives of imidazole-5-acetic acid attenuated vasoconstriction induced by Ang II. These compounds were later improved and gave rise to losartan, which was the first orally active antagonist of the AT_1-receptor subtype [5]. In valsartan, the heterocyclic imidazole of losartan has been replaced with a nonplanar, acylated amino acid [6]. After oral or intravenous administration, losartan is converted, by oxidative transformation, to a pharmacologically active metabolite [7]. In contrast, valsartan is only slightly metabolized [8]. In healthy volunteers, valsartan is well tolerated after single and multiple dosing [9]. The studies presented here were conducted, in healthy volunteers, to obtain information regarding the pharmacokinetics of valsartan after parenteral administration and to determine its absolute bioavailability after oral administration of a solid dosage form and a solution. Before the main study was done, three i.v. doses were given to healthy male volunteers in a pilot study.

A preliminary account of this work was presented as a poster at the Sixth European Congress of Biopharmaceutics and Pharmacokinetics, Athens, April 1996 [1]

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Materials and methods

Study 1 (pilot study)

Study design and population

The pilot study was performed to investigate the tolerance to an intravenous formulation and the pharmacokinetics of valsartan after parenteral administration, as well as to select the dose and the timing of blood sampling in the main study (absolute bioavailability study). Three doses were given in an ascending manner (5, 10, 20 mg). Nine healthy men, ranging in age from 23 to 53 years and in weight from 61.7 to 88.0 kg, were included in and completed the study. Other medications were not permitted during the trial. The study was approved by an ethical review board and the subjects gave written informed consent.

An open dose escalation approach was chosen. The number of subjects was restricted to three per dose level. The i.v. formulation contained 10 mg valsartan/ml isotonic aqueous solution (pH 7.0). The doses (5, 10 and 20 mg) were diluted with sterile, pyrogen-free aqueous 0.9% NaCl to a total volume of 10 ml. The 10 ml volume was injected over a period of 30 s, followed by 5 ml of 0.9% saline solution to flush the cannula. Blood samples (5 ml) were collected before and 2.5, 5, 10, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 h after the end of the injection. The plasma was separated from the blood, frozen and stored at −18 °C. Urine was collected before administration of the drug and at the following times thereafter: 0–2, 2–4, 4–8, 8–12 and 12–24 h. The weight of each urine fraction was recorded and a 10 ml aliquot was stored at −18 °C until assayed.

Drug analysis

Valsartan in the plasma was assayed by HPLC and fluorescence detection and in the urine by HPLC and UV detection. After the internal standard (CGP 48791) had been added to the samples, valsartan and the internal standard were isolated by solid-phase extraction on a Bond-Elut CH cartridge, with methanol as the final eluent. After evaporation of the solvent, the residue was dissolved in the mobile phase (0.1% trifluoroacetic acid in acetonitrile/H_2O; 45/55; v/v) and chromatographed on a 250 mm × 4 mm i.d. column packed with Nucleosil C18/10 μm. Chromatography was achieved by a binary isocratic elution (0.1% trifluoroacetic acid in acetonitrile/H_2O; 45/55; v/v), and the flow rate of the mobile phase was 1 ml · min^{-1}. In extracts from plasma, valsartan and the internal standard were detected by fluorescence monitoring. Excitation was set at 265 nm and emission at 378 nm. In extracts from urine, UV detection at 215 nm was used; otherwise, both the sample preparation and chromatography were identical for plasma and urine.

Study 2 (main study)

Study design and population

This was a single-center study with an open, randomized three-way cross-over design. The ethical standards were the same as described for the pilot study. Single oral doses of 80 mg of valsartan as a capsule formulation and as a buffered solution, and 20 mg of valsartan as an i.v. bolus injection, were given to 12 healthy male volunteers. The drug-free interval between treatment periods was at least 1 week. The 12 subjects had an average age of 28 years (range 22–44 years), a mean body weight of 73.9 kg (range 58–86 kg) and a mean height of 179 cm (range 169–187 cm). The same i.v. formulation of valsartan (10 mg · ml^{-1}) used for the pilot study was available for the main study. Blood samples were collected as described for the pilot study before and at the following time points after i.v. administration: 2.5, 5, 10, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h; after oral administration of the solution: 10, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h; and after oral administration of the capsule: 0.5, 1, 2, 3, 4, 6, 7, 12, and 24 h. Urine was collected as described in the pilot study. The analyses were performed by HPLC as described above. The method was validated by analysis of spiked human plasma and urine samples together with the samples from this study. The limit of quantitation was 0.13 mg · l^{-1} in plasma and 0.65 mg · l^{-1} in urine.

Pharmacokinetic evaluation

Noncompartmental analysis. The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal method [10]. For AUC calculations, after the i.v. dose, the concentration at time 0 (C_0) was equated with the concentration measured at 2.5 min after injection. Slopes of log-linear regression lines from the plasma concentration-time curves were used to calculate half-lives characterizing the concentration decay. The half-life of the terminal phase ($t_{1/2\lambda 2}$) after p.a. and i.v. dosing was calculated from the concentrations at 6–8 h and 24 h. After i.v. dosing, the half-life of the distribution phase ($t_{1/2\lambda 1}$) was obtained from the concentrations between 10 min and 4–6 h, using the method of residuals. Because of the low concentrations observed 24 h after dosing, it was not necessary to extrapolate the terminal elimination half-life to infinity, therefore AUC (0–24 h) is considered to be equal to the total AUC. CL, the total plasma clearance, i.e. the sum of all partial clearances, was calculated from: CL = dose/AUC. V_{ss}, the volume of distribution at steady state, was calculated as: CL·MRT. The mean residence time (MRT), a model-independent parameter, was determined by the ratio of AUMC to AUC, where AUMC is defined as the area under the first moment of the concentration-time curve. The renal clearance (CL_R) of valsartan was estimated from the ratio of the amount of unchanged drug excreted in urine (A_e) to the corresponding plasma AUC. The ratio of AUC after oral and i.v. administration, corrected by the corresponding doses, was used to calculate the fraction of the administered dose which was systemically available (f).

Deconvolution. Evaluation of the absorption process was performed by deconvolution [11, 12] (PCDCON, software written by W.R. Gillespie, University of Texas at Austin, USA). The input response data were fitted using an interpolating cubic spline to the raw data. The same procedure was performed with the i.v. data. The result of deconvolution was given as a cumulative input and transformed in to a percentage of the fraction of the dose remaining to be absorbed. The slopes of the rapid and slow absorption phases (k_a) were determined using Excel 4.0. The bioavailability, estimated from deconvolution (f_{Dcon}), was calculated as a mean value of the estimated cumulative amount absorbed from the time point when an apparent plateau was reached.

Results

Pilot study

Mean (SD) concentration-time profiles for valsartan are shown in Fig. 1. The mean AUC values were 2.1, 4.1, and 12.1 mg · l^{-1} · h at dose levels of 5, 10 and 20 mg, respectively. AUC values increased in a dose proportional manner between doses of 5 and 10 mg, although there was a tendency towards a disproportional increase in the AUC after the highest dose of 20 mg. Between 17% and 22.4% (mean values) of the drug dose was excreted unchanged from 0 to 24 h. A complete phar-

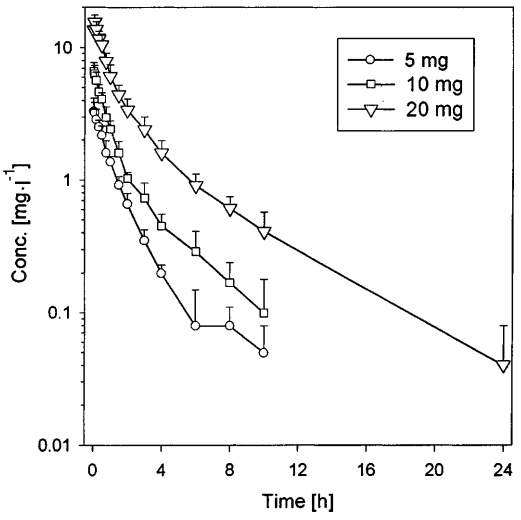

Fig. 1 Mean (SD) plasma concentration-time curves after 5, 10 and 20 mg of valsartan, administered as an intravenous bolus to three healthy volunteers

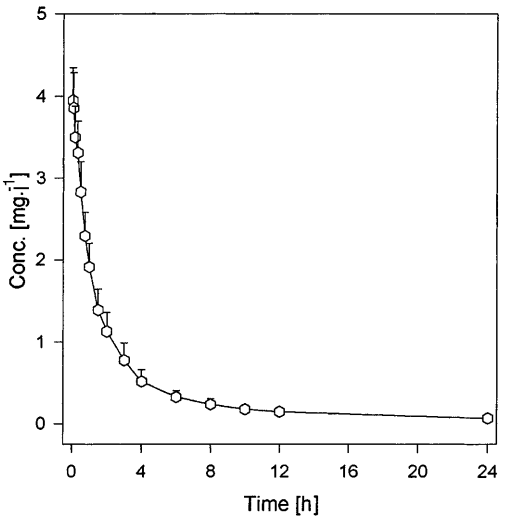

Fig. 2 Mean (SD) plasma concentration-time curve after 20 mg of valsartan, administered as an intravenous bolus to 12 healthy volunteers

macokinetic evaluation was not performed because the blood sampling schedule was not optimal. There were no adverse experiences, and no changes in clinical laboratory determinations which could be attributed to the drug. As the 20 mg i.v. dose gave plasma concentrations comparable to those observed previously after an oral dose of 80 mg, these two doses were selected for the main study.

Main study

The individual and mean (SD) model-independent pharmacokinetic parameters after i.v. administration are presented in Table 1. Figure 2 shows the mean (SD) profile for valsartan after the intravenous dose. After an i.v. bolus, the plasma concentration-time curve declined in a biexponential manner with a marked alpha-phase in the first 2 h: Plasma clearance of valsartan was 2.19 (0.39) $l \cdot h^{-1}$, V_{ss} was 16.9 (6.90) l, and MRT was 7.82 (3.32) h. The mean half-life for the distribution phase was 1.01 h and the terminal half-life was 9.45 (3.83) h. The percentage of the intravenous dose excreted in the urine intact was 29.0 (5.82)% (Fig. 4). Mean renal clearance after i.v. administration was 0.62 (0.15) $l \cdot h^{-1}$.

Figure 3 shows the mean (SD) profile for valsartan after oral dosing. After administration of the 80 mg capsule, C_{max} occurred at 2 h. Plasma concentrations declined biexponentially, with a mean terminal $t_{1/2}$ of 7.0 h. After oral administration of the solution, C_{max} was reached after only 1 h, and the mean terminal $t_{1/2}$ was 7.5 h. Based on AUC values, the bioavailability of the capsule and the solution was 23% and 39% of the dose, respectively. The mean amounts excreted in the urine after oral administration are given in Tables 1–3 and shown graphically in Fig. 4. On average 7.3% and 12.6% of an oral dose (capsule and solution, respectively) was excreted in the urine unchanged (Fig. 4). The major proportion was excreted within 12 h after dosing.

Table 1 Summary of pharmacokinetic data after 20 mg of valsartan, administered as an intravenous bolus to 12 healthy volunteers

Subject no.	C_{max} ($mg \cdot l^{-1}$)	AUC ($mg \cdot l^{-1} \cdot h$)	$t_{1/2\lambda1}$ (h)	$t_{1/2\lambda2}$ (h)	CL ($l \cdot h^{-1}$)	MRT (h)	V_{ss} (l)	CL_R ($l \cdot h^{-1}$)	A_e (% of dose)
1	3.42	8.38	0.83	5.48	2.39	4.88	11.64	0.81	33.75
2	4.66	9.81	0.87	8.26	2.04	7.23	14.74	0.45	21.84
3	4.43	7.34	1.03	9.25	2.72	6.06	16.51	0.54	19.94
4	3.77	8.76	1.10	15.30	2.28	12.10	27.62	0.56	24.64
5	3.93	7.25	0.96	9.50	2.76	7.65	21.11	0.70	25.34
6	3.61	7.33	1.09	7.16	2.73	4.93	13.45	0.82	30.00
7	4.03	9.79	1.16	15.07	2.04	12.69	25.94	0.67	32.73
8	4.57	9.82	0.80	4.89	2.04	4.12	8.39	0.72	35.51
9	4.09	13.15	1.07	6.54	1.52	6.16	9.37	0.59	39.09
10	4.40	10.45	0.98	5.75	1.91	4.86	9.30	0.51	26.76
11	3.41	10.48	1.19	14.50	1.91	13.26	25.30	0.61	32.06
12	3.91	10.06	1.08	11.65	1.99	9.84	19.56	0.51	25.72
Mean	4.02	9.39	1.01	9.45	2.19	7.82	16.91	0.62	28.95
SD	0.43	1.70	0.13	3.83	0.39	3.32	6.90	0.12	5.82

Table 2 Summary of pharmacokinetic data after 80 mg of valsartan, administered as an oral capsule to 12 healthy volunteers

Subject no.	C_{max} ($mg \cdot l^{-1}$)	t_{max} (h)	AUC ($mg \cdot l^{-1} \cdot h$)	$t_{1/2\lambda 2}$ (h)	A_e (% of dose)	f	k_a (h^{-1})	f D_{con}
1	1.15	2	8.52	8.08	7.85	0.26	0.43	0.26
2	1.40	2	8.94	7.37	6.93	0.23	0.50	0.23
3	1.61	2	6.55	6.81	5.66	0.23	0.78	0.22
4	2.09	2	9.88	8.28	8.38	0.28	1.50	0.29
5	2.64	1.5	9.93	4.20	9.88	0.35	1.59	0.37
6	0.88	2	5.42	8.64	4.03	0.19	0.54	0.19
7	0.70	1.5	4.02	7.00	3.59	0.10	1.00	0.11
8	2.18	2	12.90	4.69	13.48	0.33	0.57	0.33
9	1.98	1.5	10.02	7.59	9.95	0.19	1.73	0.20
10	1.66	3	9.14	6.40	3.92	0.22	1.26	0.22
11	1.00	2	5.81	9.61	5.15	0.14	0.95	0.24
12	2.41	2	11.33	5.90	9.27	0.28	0.84	0.30
Mean	1.64	2	8.54	7.05	7.34	0.23	0.97	0.24
SD	0.63	Median	2.61	1.58	3.02	0.07	0.45	0.07

Table 3 Summary of pharmacokinetic data after 80 mg of valsartan, administered as an oral solution to 12 healthy volunteers

Subject no.	C_{max} ($mg \cdot l^{-1}$)	t_{max} (h)	AUC ($mg \cdot l^{-1} \cdot h$)	$t_{1/2\lambda 2}$ (h)	A_e (% of dose)	f	k_a (h^{-1})	f D_{con}
1	2.17	1	10.44	7.86	13.40	0.31	0.97	0.32
2	3.48	1.5	15.44	6.63	12.46	0.40	1.79	0.41
3	2.91	1	12.72	9.39	9.43	0.44	0.78	0.44
4	4.71	1	18.59	8.24	15.90	0.54	1.58	0.61
5	2.61	1	9.60	5.58	9.38	0.34	1.29	0.35
6	2.50	1.5	11.40	10.61	12.46	0.39	0.96	0.40
7	3.13	1.5	13.82	8.51	14.40	0.36	1.55	0.56
8	4.40	1.5	18.63	4.12	16.13	0.48	1.47	0.36
9	3.75	1	20.46	7.26	15.09	0.39	1.49	0.40
10	2.49	1	12.15	6.29	6.17	0.29	1.50	0.30
11	4.25	1.5	16.27	7.28	15.23	0.39	2.24	0.39
12	2.62	1	12.34	8.25	10.16	0.31	1.54	0.32
Mean	3.25	1	14.32	7.50	12.55	0.39	1.43	0.41
SD	0.85	Median	3.53	1.73	3.10	0.07	0.40	0.09

Deconvolution of the plasma levels, measured after administration of the two oral formulations, with the intravenous bolus dose as the unit impulse response, gave the following results: The final average cumulative amount of valsartan absorbed was 24% for the capsule and 41% for the solution (Tables 2, 3). After intake of the capsule, 50% of the total absorbed was absorbed within 1.6 h and 90% after 4.6 h (Table 4). After administration of the solution, one-half of the amount

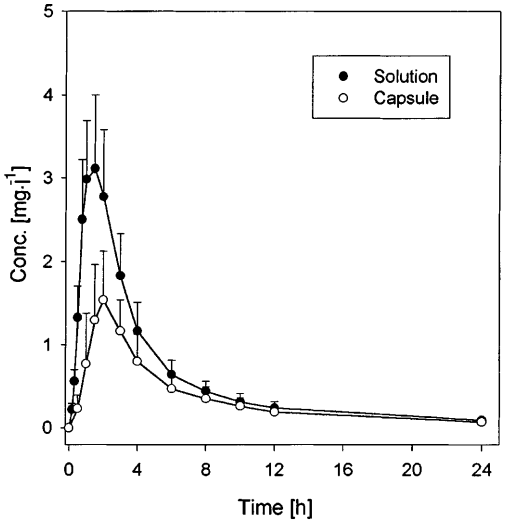

Fig. 3 Mean (SD) plasma concentration-time curves after 80 mg of valsartan, administered as a capsule and solution to 12 healthy volunteers

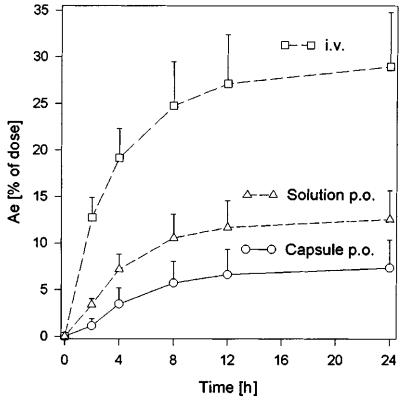

Fig. 4 Mean (SD) total urinary excretion after 20 mg of valsartan, administered as an intravenous bolus, and 80 mg of valsartan, administered as a capsule and solution to 12 healthy volunteers

Table 4 Time needed to reach 50% and 90% of the available fraction to be absorbed (f) after 80 mg of valsartan, administered as an oral capsule and solution to 12 healthy volunteers

Subject no.	Capsule 50% of f	Capsule 90% of f	Solution 50% of f	Solution 90% of f
1	1.8	8.6	0.7	4.1
2	1.8	8.2	0.8	1.7
3	1.8	4.3	0.8	3.5
4	1.3	2.2	0.7	1.7
5	1.1	1.9	0.7	1.9
6	1.9	2.8	1	4.2
7	1.1	2.8	1	2
8	1.7	6.5	1.1	2.2
9	0.8	5.8	0.7	1.8
10	1.8	5.0	0.7	1.4
11	1.8	2.8	1	1.8
12	1.7	3.7	0.7	2
Mean	1.55	4.55	0.83	2.36
SD	0.37	2.29	0.15	0.98

absorbed was absorbed and systemically available within 0.8 h, and 90% within 2.4 h. Cumulative input plots of valsartan for the solution and capsule dosage forms are shown in Figs. 5 and 6, respectively. Plots representing the fraction of the dose remaining to be absorbed (Fig. 7) show that absorption from the capsule and from the solution can be described by two first-order processes. A rapid absorption phase with a half-life of 0.5 h from the solution and of 0.9 h from the capsule is evident in the first 2 h. Thereafter, a much slower phase predominates. The half-life of the slower absorption phase is 6.5 h and 3.5 h for the solution and the capsule, respectively. The slight delay in the onset of rapid absorption for the capsule formulation most probably represents dissolution of the active ingredient.

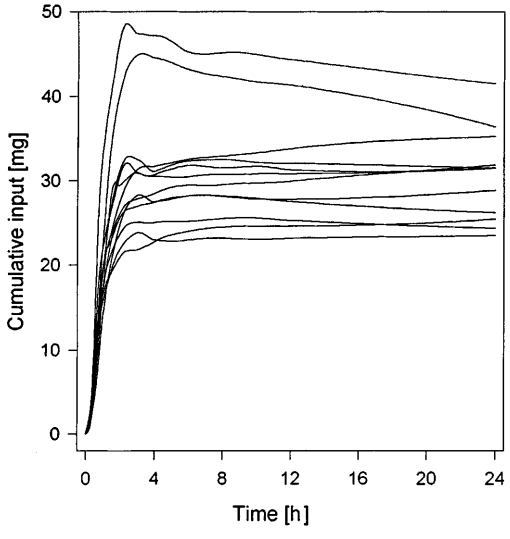

Fig. 5 Calculated input of valsartan, using deconvolution, after 80 mg of valsartan, administered as an oral solution to 12 healthy volunteers

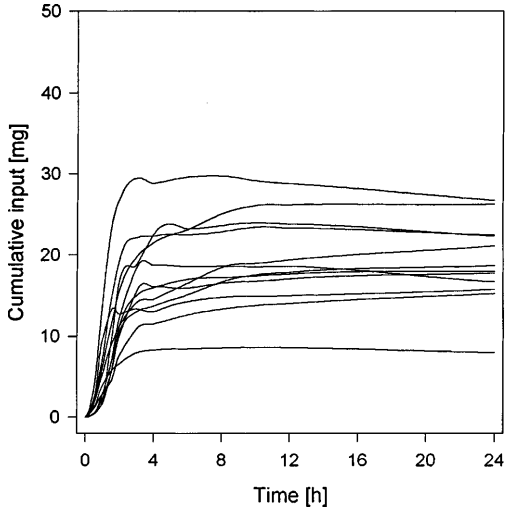

Fig. 6 Calculated input of valsartan, using deconvolution, after administration of 80 mg as an oral capsule to 12 healthy volunteers

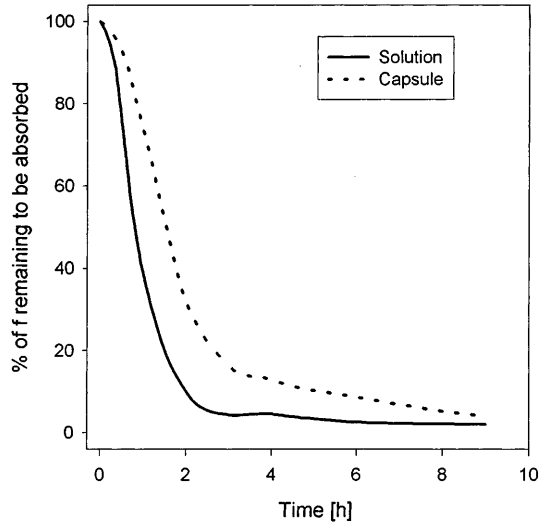

Fig. 7 Average percentage of the fraction of the dose remaining to be absorbed after 80 mg of valsartan, administered as an oral capsule and solution to 12 healthy volunteers

Discussion

The results reported here characterize the pharmacokinetics after parenteral and oral administration of valsartan in healthy volunteers. Plasma clearance (CL) of valsartan (about $2\,l \cdot h^{-1}$) was relatively slow when compared with the flow of plasma to the liver (about $30\,l \cdot h^{-1}$). The estimated volume of distribution at steady state was also low (about 17 l) and, for a hydrophilic molecule, less than the body water. One explanation for this observation is that valsartan is highly bound to plasma proteins (94–97%), allowing only limited distribution outside the plasma compartment. Renal excretion of valsartan ($0.62\,l \cdot h^{-1}$) represents only 30% of the total plasma clearance. Thus, renal excretion is a minor

pathway for the elimination of valsartan. Indeed, it has been shown that valsartan is eliminated mainly by non-renal routes. Most of it is excreted largely unchanged in the bile and is metabolized only slightly [8].

The compound is absorbed rapidly: 50% of the absorbed fraction of the capsule is absorbed within 1.6 h. The absorption is characterized by two sequential first-order phases, indicating a passive diffusion process. The difference of 0.4 h in the absorption half-life of the two oral formulations is probably due to the disintegration of the solid formulation and, more importantly, to solubilization of the drug.

The absolute bioavailability of valsartan was assessed from plasma data by two different methods. Based on the oral to intravenous AUC ratio, corrected for the administered dose, bioavailability was 23% and 39% for the capsule and solution, respectively. The use of deconvolution techniques confirmed these results. The final average cumulative amount reaching the systemic circulation was 24% from the capsule and 41% from the solution, although in some cases there was variation in the cumulative amounts. Based on urinary excretion, the estimated bioavailability is 25% and 43% for the capsule and solution, respectively. From the amount excreted in the urine, the ratio of urinary excretion after oral treatments (solution/capsule) is 1.7, and thus identical to the mean ratio of absolute systemic availability (f) from the two oral formulations.

Valsartan is a tetrazole derivative containing acid (pKa = 4.73) and carboxylic (pKa = 3.9) groups which make the compound soluble in the neutral pH range. The drug exists mainly in the ionized (highly soluble) form at physiological pH. The reduction in relative bioavailability of the capsule formulation compared with a phosphate buffered solution may be understood when these physicochemical properties are taken into account. Under nonbuffered or acidic conditions (pH 1.0, e.g. fasting stomach), the dissolution of valsartan is likely to be limited by its low solubility. In contrast, dissolution of valsartan capsules is both rapid and complete at pH 5.0 and above, and will not be rate limiting for the absorption of the compound. The phosphate buffered solution of valsartan is obviously not a practicable dosage form. However, it is likely to deliver valsartan to the upper GI tract in a well-dispersed and solubilized form, which can take advantage of the rapid absorption in this segment of the GI tract: the pH at the site of absorption could not be measured, but is likely to have been in the range 6–7. The observed reduction in availability for the capsule compared with a buffered solution of valsartan could therefore be attributed to solubility limitations for valsartan under nonbuffered conditions as well as the effect of pH on transport of valsartan across the intestinal epithelium. Deconvolution of the plasma concentration-time data for the two oral treatments is consistent with this hypothesis. Further evidence to support the existence of an initial rapid absorption phase is available from a study where valsartan was administered after pre-treatment with cimetidine (E. Schmidt, unpublished data). Under these conditions, C_{max} for valsartan was increased, although the extent of absorption (AUC) was unchanged. This is consistent with an increase in the initial rate of absorption, and was attributed to greater solubilization of valsartan in a pH range optimal for rapid absorption. Solubility and lipophilicity are physicochemical characteristics of the compound which cannot be influenced by the formulation itself. In the present study, the capsule formulation shows extremely rapid dissolution when solubility is not limiting and can be considered optimal in terms of in vitro pharmaceutics for this compound.

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References

1. Flesch G, Mueller Ph, Hell F, Degen P, Howald H, Dieterle W (1996) Absolute oral biovailability of valsartan in healthy volunteers. Eur J Drug Metab Pharmacokinet: 60 (abstract 163)
2. Criscione L, Bradley WA, Buehlmayer P, Whitebread S, Glazer R, Lloyd P, Mueller P, DeGasparo M (1995) Valsartan: preclinical and clinical profile of an antihypertensive angiotensin-II antagonist. Cardiovasc Drug Rev 13: 230–250
3. Criscione L, De Gasparo M, Buehlmayer P, Whitebread S, Ramjoué HP, Wood JM (1993) Pharmacological profile of valsartan: a potent, orally active nonpeptide antagonist of the angiotensin II AT_1-receptor subtype. Br J Pharmacol 110: 761–771
4. Furukawa Y, Kishimoto S, Nishikawa K (1982) Hypotensive imidazole-5-acetic acid derivatives. Patent issued to Takeda Chemical Industries, Ltd, Osaka, Japan. US patent 4–340, 598 and 4–355, 040
5. Buehlmayer P, Criscione L, Fuhrer W, Furet P, DeGasparo M, Stutz S, Whitebread S (1991) Nonpeptidic angiotensin II antagonists: synthesis and in vitro activity of a series of novel naphthalene and tetrahydronaphthalene derivativies. J Med Chem 34: 3105–3114
6. Duncia JV, Carini DJ, Chiu AT, Johnson AL, Price WA, Wong PC, Wexler RR, Timmermans PB (1992) A potent, orally active nonpeptide angiotensin II receptor antagonist. Med Res Rev 12: 149–191
7. Lo MW, Goldberg MR, McCrea JB, Lu H, Furtek CI, Bjornsson TD (1995) Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite EXP 3174 in humans. Clin Pharmacol Ther 58: 641–649
8. Waldmeier F, Müller Ph, Flesch G, Winkler T, Kriemler HP, Bühlmayer P, DeGasparo M (1997) Pharmacokinetics, disposition and biotransformation of valsartan (CGP 48 933) in healthy male volunteers after a single oral dose of 80 mg ^{14}C-radiolabelled preparation. Xenobiotica 27: 59–71
9. Flesch G, Müller Ph, Degen P, Lloyd P, Dieterle W (1993) Repeated dose pharmacokinetics of valsartan, a new angiotensin-II antagonist, in healthy subjects. Eur J Drug Metab Pharmacokinet 18 (abstract 256)
10. Gibaldi M, Perrier D (1982) Pharmacokinetics. Dekker, New York
11. Veng Pedersen P (1988) Linear and nonlinear system approaches in pharmacokinetics: how much do they have to offer? I. General considerations. J Pharmacokinet Biopharm 16: 413–472
12. Cutler VHL (1978) Linear systems analysis in pharmacokinetics. J Pharmacokinet Biopharm 6: 265–282