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SCIENTIFIC REVIEW

BIOAVAILABILITY FILE: VALSARTAN

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Bioavailability File: Valsartan

Summary

Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. Valsartan has much greater affinity (about 20000 fold) for the angiotensin II type 1 (AT1) receptor than for the angiotensin II type 2 (AT2) receptor, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow. Valsartan is rapidly absorbed after oral administration. Plasma levels peak 2-4 h after oral administration and then decline with a terminal half-life reported in various studies in the range of 6–9 h. A peak plasma concentration (C_{max}) of 1.64 mg/L occurred after oral administration of a single 80 mg dose of valsartan. A higher dose (200 mg) produced a proportionately higher C_{max} (3.46 mg/L) at a similar time post-dose. 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. The absolute bioavailability is 10-35%. Food decreases the exposure to valsartan (as measured by AUC) by about 40% and peak plasma concentration (C_{max}) by about 50%. There is considerable individual and between-subject variability (CV of 30%) in C_{max} and AUC (CV of 44%). Volume of distribution and plasma clearance have been estimated at 17 L and 2.2 L/h, respectively; the drug is extensively bound to plasma proteins (85 to 99%). In this paper, the physicochemical properties, analytical determination methods, bioavailability, and pharmacology of valsartan are reviewed.

Key Words: *Valsartan, pharmacokinetics, bioavailability, hypertension, angiotensin II receptor inhibitors.*

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Biyoyararlanım Dosyası: Valsartan

Özet

Valsartan yeni, potent, yüksek seçiciliğe sahip ve oral yoldan aktif anjiyotensin II tip-1 reseptör antagonist grubuna dahil antihipertansif bir ilaçtır. Valsartan'ın anjiyotensin II tip 1 reseptörüne afinitesi anjiyotensin II tip 2 reseptörüne olan afinitesinden yaklaşık 20000 kat daha fazladır. Bu sayede kan damarlarında gevşemeye ve kan basıncında düşmeye yol açmaktadır. Oral yoldan alımından sonra hızla absorbe olur. Maksimum kan konsantrasyonuna 2 - 4 saat sonra ulaşılır ve bu konsantrasyon çeşitli çalışmalarda kaydedilen 6-9 saat aralığında bir terminal yarı ömürle düşer. 80 mg dozda oral yoldan alındığında 1.64 mg/L olan maksimum konsantrasyona (C_{max}) ulaşır. Daha yüksek dozda (200 mg), orantılı olarak daha yüksek maksimum kan konsantrasyonu değerine (3.46 mg/L), doz sonrası benzer zamanda ulaşılmaktadır. Absorbe edilen doz fraksiyonu eğri altında kalan alan (AUC) üzerinden hesaplandığında, oral yoldan 0.23 ve çözelti şeklinde 0.39'dur. Mutlak biyoyararlanım % 10 - 35 arasında değişirken yiyecek etkisiyle biyoyararlanım (C_{max} % 50 ve AUC % 40) düşmektedir. Varyasyon maksimum kan konsantrasyonunda (CV % 30) ve eğri altında kalan alanda (CV % 44) bireyler arasında ve bireyler içinde yüksektir. Dağılım hacmi 17 L ve plazma klerensi 2.2 L/saattir. Valsartan yüksek derecede plazma proteinlerine bağlanmaktadır (% 85 - % 99). Bu çalışmada valsartana ait fizikokimyasal özellikler, analitik ölçüm metotları, biyoyararlanım ve farmakolojik özellikleri tartışılmıştır.

Anahtar Kelimeler: *Valsartan, farmakokinetik, biyoyararlanım, hipertansiyon, anjiyotensin II reseptör antagonistleri.*

INTRODUCTION

Most cardiovascular events are attributed to high blood pressure. High blood pressure is quantitatively the largest single risk factor for premature death and disability due to its extremely high prevalence in industrialized countries. Hence, antihypertensive therapy considerably reduces the risk of developing cardiovascular complications that cause a high mortality rate in patients with hypertension (1,2).

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Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. Valsartan inhibits angiotensin II receptors, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow (3-8). Valsartan is well tolerated after single and multiple dosing (5,9,10) following single oral doses up to 400 mg and after multiple dosing with 200 mg per day (10).

PHYSICOCHEMICAL PROPERTIES

Valsartan, N- valeryl- N[[2- (1H- tetrazol- 5- yl)biphenyl- 4- yl] methyl] valine (Fig. 1) has an empirical formula of $C_{24}H_{29}N_5O_3$ and a molecular weight of 435.5 g/mol [6,11,12]. It was synthesized in 10 steps and patented in 1990 (6). In another synthesis study, it was synthesized starting from L-valine methyl ester hydrochloride through four steps in an overall yield of 60%. The key step involves the palladium-catalyzed Suzuki coupling. This method overcomes many of the drawbacks associated with the previously reported syntheses and is more suitable for industrial production [13]. Valsartan is available as a white, microcrystalline powder with a melting range of 105-110°C. The specific rotation [α]D/20 in methanol is 68° (c = 1). The compound is the S enantiomer. The partition coefficient P is 0.033 (log P = 1.499), indicating that the compound has a rather hydrophilic character at physiological pH. Due to its fine particle size, valsartan adsorbs water reversibly from ambient atmosphere. The compound is stable when stored under dry conditions. Stable solutions can also be prepared in aqueous buffers of neutral pH (6). For ionizable molecules, pH plays a crucial role. The charge state that a molecule exhibits at a particular pH is characterized by the ionization constant (pKa) of the molecule. Buffers affect pH gradients in the unstirred water layers, which can dramatically affect both permeability and dissolution of ionizable molecules (14). Weakly basic drugs and weakly acidic drugs or salts thereof demonstrate pH-dependent solubility. For weak acids, as the pH value increases, the solubility of the acid increases due to the contribution from the ionized form (15,16). Valsartan contains two weakly acidic functions with pKa values of 3.9 and 4.7 and one asymmetric center and (co)exists in solution at physiological pH values as the undissociated acid, the mono-anion and the di-anion (6). A rise from pH 4 to pH 6 increases the solubility of valsartan by a factor of about 1000, but favors the anionic form and decreases lipophilicity. In vitro dissolution is rapid and complete at pH 5.0 and above and is solubility-limited at pH 3.0 and below. Since the solubility of valsartan increases in the pH range 4-8 and lipophilicity decreases in the same range, the rate of absorption of valsartan may be influenced by intestinal pH along the gastrointestinal (GI) tract. This has been demonstrated using an in vitro model of intestinal absorption (Caco-2 cells), where the absorption rate was observed to decrease as pH increased in the range 6-7.5. Thus, valsartan presents a special case (pH-dependent solubility) in a proposed general classification system, which categorizes drugs with respect to their biopharmaceutical and absorption properties (10). In the biopharmaceutics classification system (BCS) and biopharmaceutics drug disposition classification system (BDDCS), valsartan is a Class III drug with low permeability, poor metabolism and high solubility (17,18).

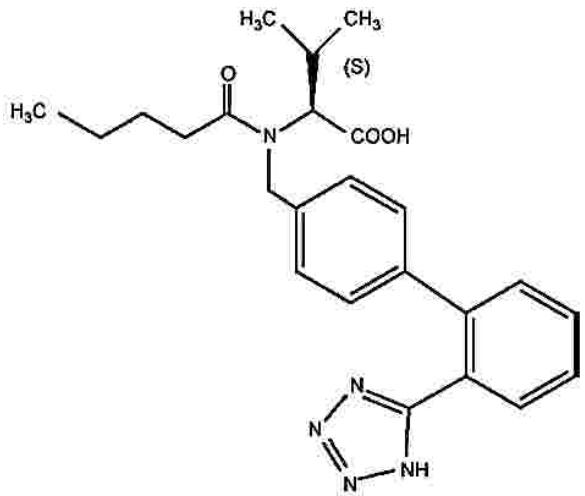

Figure 1: Chemical structure of valsartan.

Valsartan is soluble in water at 25°C to the extent of 0.18 g/L. In a buffered solution, the solubility is increased because the dianion salt is formed. In phosphate buffer (pH 8.0), valsartan is soluble at 25°C to the extent of 16.8 g/L, yielding a pH of 5.29 for the saturated solution (6).

QUANTIFICATION AND DETERMINATION METHODS

There have been few reports regarding the determination of valsartan in pharmaceutical dosage forms or in biological media including spectrophotometry (19). UV- and second derivative-spectrophotometric and high-performance liquid

chromatographic (HPLC) methods for the determination of valsartan in pharmaceutical formulations have been developed. It is reported that the proposed second derivative-spectrophotometric method assured a better precision and accuracy, and also determined a lower concentration of valsartan in capsules than the UV-spectrophotometric method. The main advantage of this method is significantly shortening analysis time, the low cost of analysis, and widespread access to the apparatus, while the HPLC procedure is rather time-consuming for routine assays, requires too many solvents and is also an expensive apparatus (19).

Analytical methods developed for the determination of valsartan in biological fluids mainly use the liquid chromatographic techniques. Several HPLC methods have been described in the literature for determination of valsartan (20-35) in biological fluids with photometric (36,37), fluorimetric (5,10,19,20,25) or mass spectrometric detection [38] after extraction from plasma. The existence of some fluorescent functional groups in the molecular structure of valsartan such as biphenyl, tetrazole, imidazole and benzimidazole also makes possible the development of a HPLC– fluorescence method for the determination of valsartan in biological fluids (20,39).

Very few methods have appeared in the literature for the determination of valsartan in biological media or in pharmaceutical dosage forms based on liquid chromatography–tandem mass spectrometry (LC-MS/MS) (40-42). The estimated calibration range of the LC-MS/MS method was 2–2000 ng/mL. The method was fully validated with intra-day mean accuracy and precision (as relative standard deviation) of 94.8–107% and 2.19–5.40% and inter-day mean accuracy and precision of 93.5–105% and 1.87–5.67%, respectively.

An electrochemical determination method for valsartan has also been reported. Differential-pulse adsorptive stripping and square-wave adsorptive stripping voltammetry for the valsartan determination were proposed and linearity was found in the range of $6.0x10^{8}$ to $4.0x10^{6}$ mol/L. The detection limits were $2.93x10^{9}$ and $3.27x10^{9}$ mol/L, respectively (11).

Direct UV–Vis spectrophotometric method is not suitable for simultaneous determination of drugs with spectral overlapping. Application of derivative technique of spectrophotometry offers a powerful tool for quantitative analysis of multi-component mixtures (43).

Over the years, many quantification methods for the simultaneous determination of valsartan and hydrochlorothiazide in biological matrices and pharmaceutical dosage forms have been reported, and these methods were based on HPLC (44,45) and UV-derivative spectrophotometry (2,35,44,45).

LC-MS/MS and capillary electrophoresis methods were used for simultaneous determination of hydrochlorothiazide and valsartan in pharmaceutical dosage forms (2,46). Reverse phase high-performance liquid chromatography (RP-HPLC) methods also have been developed for the determination of valsartan and amlodipine combination (32,47).

PHARMACOLOGY

Most cardiovascular events are attributed to high blood pressure. Serious and often fatal complications, including stroke, myocardial infarction, and renal failure, can develop if hypertension is not controlled (48). Hypertension is highly prevalent in diabetic and nondiabetic populations. Hence, antihypertensive therapy considerably reduces the risk of developing cardiovascular complications that cause a high mortality rate in patients with hypertension (1,2,49-55). Hypertension control even in treated hypertensive patients in most countries, including the Western world, is also inadequate, and has been reported as follows: United States 40% to 55%, Canada 47%, England 40%, Russia 33%, Greece 20% to 33%, Germany 30%, Argentina 29%, Brazil 29%, China 20% to 29%, Italy 28%, Sweden 21%, Spain 19%, and Turkey 8%. Control of isolated systolic hypertension, mainly in the elderly, remains a challenge, and elderly hypertensives have the poorest rate of blood pressure control in the United States (53).

Angiotensin antagonists are the first major innovation in hypertension management in over a decade. Their specificity of action and excellent side-effect profile provide good conditions for patient compliance as well as high and long-lasting effectiveness (56-61). Thus, the World Health Organization (WHO) Guidelines (1999) have recommended

the prescription of these drugs as a first-line treatment for essential hypertension (62). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis of aldosterone, cardiac stimulation, and renal reabsorption of sodium (12).

Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists (3,8,63-65). Valsartan has much greater affinity (about 20000 fold) for the angiotensin II type 1 receptor (AT_1) than for the angiotensin II type 2 receptor (AT_2) (6,8,12). Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis (12). A functional blockade of the AT_2 receptor was shown to occur in humans after 80 mg single doses of valsartan between 2 and 24 h after treatment (6,66-68). Single oral doses of valsartan at 1, 3, or 10 mg/kg decreased systolic blood pressure in a dose-dependent manner. The threshold dose was 1 mg/kg. The dose producing a decrease of 30 mmHg was calculated to be 1.4 mg/kg. The maximum blood pressure reduction was observed after 4 h and persisted for more than 24 h without evidence of reflex tachycardia (6).

The administration time–dependent antihypertensive efficacy of valsartan has been reported. Subjects were randomly assigned to receive valsartan (160 mg/day) as a monotherapy either on awakening or at bedtime. The highly significant blood pressure reduction after 3 months of treatment with valsartan was found similar for both treatment times. The findings confirmed that valsartan efficiently reduces blood pressure throughout the entire 24 hours, independent of treatment time (69).

The onset of action of valsartan was more rapid than that of losartan, which underwent hepatic transformation into a more active metabolite before the full effect was produced. Repeated daily treatment with valsartan lowered blood pressure reproducibly on each day of administration, without evidence of tolerance or accumulation. Heart rates in the valsartan-treated animals were not significantly different from those of the vehicle-treated controls (8).

In the single-dose studies, a dose-related increase in plasma renin activity and plasma AT_2 levels was observed. The drug plasma levels peaked at 2 h, and plasma renin activity (PRA) and AT_2 levels peaked between 4 and 6 h after dosing. After repeated administration of 200 mg of valsartan over 8 days, the effect on plasma AT_2 levels cumulated, whereas the pharmacokinetics remained unchanged (Fig. 2) (6). Based on an efficacy/tolerability profile of valsartan at various doses, it appears that 160 mg may be the optimal dose for initial therapy in patients with essential hypertension and in most patients with heart failure (7,70). It is also reported that only 160 mg valsartan provides sustained AT_1-receptor blockade over 24 hours (71).

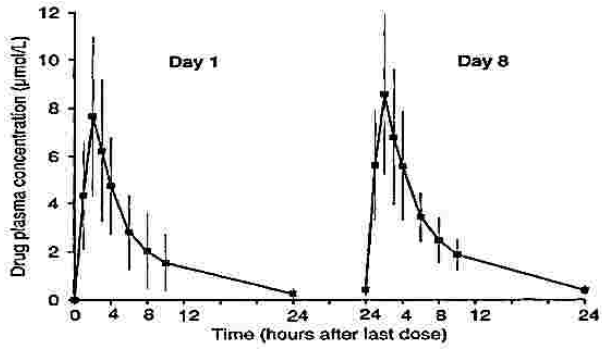

Figure 2: Drug plasma concentrations on days 1 and 8 of repeated once-daily administration of 200 mg valsartan to healthy subjects (6).

If angiotensin II receptor inhibitors are compared, candesartan and irbesartan block the receptor with insurmountable (noncompetitive) antagonism, whereas losartan, valsartan, and eprosartan are competitive antagonists. On the basis of elimination half-lives, losartan, valsartan, and eprosartan may be classified as shorter acting and candesartan cilexetil and irbesartan as longer acting (72). In a study, effects of 160 mg/day valsartan and 80 mg/day telmisartan were compared, and it was found that valsartan was also more effective in lowering arterial pulse pressure (73).

In the literature, a multitude of combination dosage forms with valsartan are reported (48,61,64,74-81). Furthermore, many comparison studies were performed with other angiotensin II inhibitors such as irbesartan, losartan, telmisartan, and other antihypertensive agents (64,72,73,81-87).

In a comparison study with losartan and telmisartan, valsartan induced significantly greater blood pressure reductions than did losartan and telmisartan at 2 weeks ($p<0.01$) and after 4 weeks ($p<0.05$) of treatment. From this study, it was concluded that treatment with valsartan resulted in an earlier, greater, and smoother antihypertensive effect compared with treatment with losartan or telmisartan; this differential effect was likely due to differences in the pharmacologic properties of these agents (87).

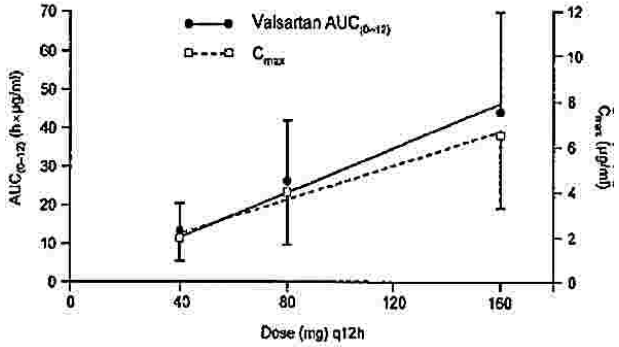

Figure 3: Dose versus mean (SD) valsartan area under the concentration-time curve in the dosing interval [$AUC_{(0-12\,h)}$] and C_{max} (90).

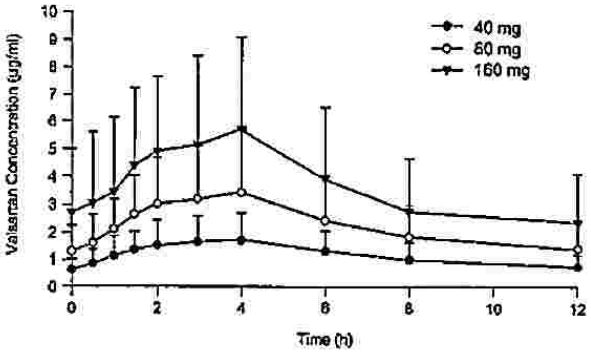

Figure 4: Mean (SD) plasma valsartan concentration-time profiles (90).

Another combination for valsartan is benazepril. Valsartan with or without benazepril remarkably decreased systolic and diastolic blood pressure in patients with essential hypertension within 6 weeks. Antihypertensive efficacy was weakened after long-term use of valsartan alone. The antihypertensive effect of the valsartan-benazepril group was the most remarkable and could avoid the side effects of high plasma angiotensin II (80).

Side Effects

In healthy volunteers, it is reported that valsartan is well tolerated after single and multiple dosing (5,9,10). No adverse signs or symptoms or changes in the clinical laboratory parameters were observed that could be associated with valsartan. Headache, cough, dizziness, and fatigue were the most common symptoms reported, and they were equally frequent and severe after active drug or placebo. Renal function, with regard to creatinine clearance, electrolyte excretion and uric acid excretion, was not influenced (6). Valsartan AT1 antagonists should be avoided throughout pregnancy (88,89).

PHARMACOKINETICS

Absorption

Valsartan is rapidly absorbed after oral administration (5,74,90). Measurable concentrations, i.e. above the limit of quantitation (LOQ), were observed 15 min or 30 min after dosing (10). Plasma levels peak 2-4 h after oral administration (3,5,12,74,90) and then decline with a terminal half-life reported in various studies in the range of 6–9 h (5,10,12,21,90,91).

Table 1. Mean (SD) pharmacokinetic parameters of valsartan (n = 18) (90)

Dose (mg q 12 h)	C_{max} (μg/ml)	T_{max}* (h)	C_{min} (μg/ml)	$AUC_{(0-12)}$ (μg · h/ml)	$t_{1/2}$ (h)
40	1.94 (1.0)	3	0.47 (0.3)	13.12 (7.2)	5.2 (1.9)†
80	3.95 (2.3)	2.5	1.05 (0.8)	25.94 (15.7)	6.5 (2.4)‡
160	6.40 (3.2)	3	1.98 (1.6)	43.54 (25.9)	6.6 (3.9)§

*Median value. $t_{1/2}$ values reported for patients with log concentration-time correlation coefficient ≥ 0.95: †n = 12, ‡n = 14, §n = 11.
$AUC_{(0-12)}$ = area under the concentration-time curve in the dosing interval.

A peak plasma concentration (C_{max}) of 1.64 mg/L occurred after oral administration of a single 80 mg dose of valsartan to volunteers (3,10,74). A higher dose (200 mg) produced a proportionately higher C_{max} (3.46 mg/L) at a similar time post-dose (3,74). A dose-proportionality assessment, based on a statistical power model, showed that doubling the dose increased the area under the concentration-time curve (AUC) and C_{max} 1.8 times (Fig. 3) (90). Valsartan plasma concentrations increased in a nearly proportional manner with dose, although the variability was high, with overlapping values across the 40 mg, 80 mg and 160 mg doses (Fig. 4, Table 1) (12,74,90). 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 (5). The absolute bioavailability is given as 25% (range: 10%-35%) in the literature (3,5,12,26,74,90). There

is considerable individual and between-subject variability in peak plasma concentrations (C_{max}) (CV of 30%) and AUC (coefficient of variation [CV] of 44%) (10,90). Food decreases the exposure to valsartan (as measured by AUC) by about 40% and peak plasma concentration (C_{max}) by about 50% (12,92). Patients should be advised to take valsartan 1 to 2 hours before or after meals (93). The pharmacokinetic properties of valsartan were relatively consistent during repeated administration of up to 200 mg daily doses to patients with hypertension, indicating that accumulation does not occur (12,90).

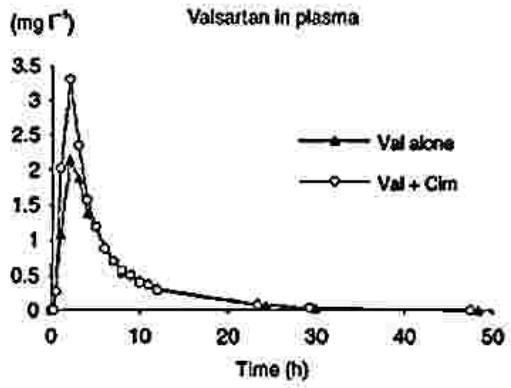

Figure 5: Mean plasma concentration-time curves for valsartan in 12 healthy male volunteers randomly assigned to single-dose treatment with 160 mg valsartan or 800 mg cimetidine or their combination (10).

The AUC and C_{max} values observed in heart failure patients were approximately 1.3–2 times higher than the values obtained in healthy subjects. These differences may be due to impaired cardiac function in heart failure patients compared with healthy subjects. However, the half-life was similar in both heart failure patients and healthy subjects, as was the high variability seen in pharmacokinetic parameters (90).

Mild or moderate hepatic impairment approximately doubled the area under the plasma concentration-time curve of valsartan compared with that seen in healthy volunteers; impaired renal function had no appreciable effect on the pharmacokinetic properties of the drug (3,90).

The influence of age on the pharmacokinetics of valsartan was examined among the 40 mg, 80 mg and 160 mg doses. The results suggested that the effect of age on the pharmacokinetics of valsartan was not significant at any dose level (Table 2) (90,91).

Distribution

Volume of distribution and plasma clearance of valsartan have been estimated at 17 L and 2.2 L/h, respectively; the drug is extensively bound to plasma proteins in the ratio of 85-99%. Its renal clearance is 0.62 L/h and it is about 30% of total clearance (5,12,74).

Table 2. Mean (SD) valsartan pharmacokinetic parameters by age group [90]

	≤65 y (n = 9)		>65 y (n = 9)	
Dose (mg q 12 h)	$AUC_{(0-12)}$ (h · μg/ml)	Clearance (ml/h/kg)	$AUC_{(0-12)}$ (h · μg/ml)	Clearance (ml/h/kg)
40	11.33 (5.7)	47.4 (23.1)	14.91 (8.4)	41.0 (20.7)
80	22.25 (9.7)	49.7 (36.7)	29.62 (19.9)	45.1 (23.8)
160	36.56 (20.6)	62.1 (32.1)	50.52 (29.9)	49.4 (24.4)

$AUC_{(0-12)}$ = area under the concentration-time curve in the dosing interval.

Metabolism and Elimination

The main elimination process for valsartan and its inactive metabolite is biliary elimination [94]. More than 70% of the drug is eliminated via biliary secretion (5,21,26,90). Renal excretion is largely complete 2 days post-dose, but substantial fecal elimination continues until days 4-7 (21,74).

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan (M1) and it is inactive on hypertension (12,21,74). The affinity of M1 for the ATI receptor is 200-fold lower than that of valsartan (6,12,21). This metabolite is formed by oxidative biotransformation and accounted for 9±3% of the dose in the excreta (21). The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes (12,21). Impaired renal function will not significantly change the clearance of valsartan (21,90). Therefore, impairment of hepatobiliary transport functions can have a marked impact on the pharmacokinetics of valsartan (90,94).

In one study, pharmacokinetic parameters for valsartan tablet and capsule formulations were compared. That study reported AUC values of 44.893 μg/mL.h and 44.963

Table 3. Pharmacokinetic parameters of valsartan and cimetidine after single oral doses of valsartan (160 mg) and cimetidine (800 mg), given alone or in combination to 12 healthy male volunteers (10)

Parameter	Valsartan			Cimetidine	
	Alone	+ Cimetidine	Ratio	Alone	+ Valsartan
$AUC_{0-48\ h}$ ($h \cdot mg \cdot l^{-1}$)	14.02 (6.10)	16.34 (9.79)		16.67 (2.68)	14.79 (2.73)
AUC ratio			1.12 (0.35)	0.90 (0.16)	
C_{max} ($mg \cdot l^{-1}$)	2.25 (1.07)	3.55 (2.13)		4.01 (0.76)	3.89 (0.78)
C_{max} ratio			1.70 (0.88)	1.00 (0.27)	
k_a (h)	0.85 (0.49)	1.78 (0.63)			
k_a ratio			2.69 (1.61)		
C_{max}/t_{max} ($mg \cdot l^{-1} \cdot h^{-1}$)	1.00 (0.52)	1.99 (1.48)			
C_{max}/t_{max} ratio			2.22 (1.36)		
t_{max} (h)	2.0 (2.0–3.0)	2.0 (1.0–3.0)		1.5 (0.5–3.0)	1.24 (0.5–4.0)
$t_{½}$ (h)	5.73 (0.87)	5.67 (1.24)		2.24 (0.23)	2.29 (0.47)

Pharmacokinetic parameters are expressed as means (SD); tmax is expressed as median (range).
AUC: area under curve, C_{max}: maximum concentration, k_a: absorption rate constant, t_{max}: time to reach maximum concentration, $t_{1/2}$: apparent terminal elimination half-life [10].

µg/mL.h, Cmax values of 6430.3 µg/mL and 5831.4 µg/mL, and t_{max} values 2 h and 2.5 h for tablets and capsules, respectively. The study showed no statistically significant differences in the plasma concentration levels after administration of the two formulations of valsartan: 80 mg tablets and 80 mg capsules (26).

Drug Interactions

A randomized, open, three-way crossover study was performed in 12 healthy male volunteers to determine the effect of a single oral dose of cimetidine on the pharmacokinetics and possible influence of cimetidine on the rate of absorption of a single oral dose of the angiotensin II receptor antagonist valsartan. The single-dose pharmacokinetics of valsartan was not essentially changed by co-administration of cimetidine, except for the increase in C_{max}, which, because of the wide margin of safety of valsartan, was judged not to be of clinical significance. This will not be different in the clinically relevant situation with multiple doses of cimetidine and the recommended once per day dose of valsartan (Fig. 5, Table 3) (10).

Formulation Types

The conventional tablet dosage forms and capsules of valsartan exist in commercially available forms. In addition, the pulsatile capsule dosage form for constant/ programmable chronotherapeutic controlled delivery has been prepared. The prepared system contains swellable polymer (L-hydroxypropyl cellulose (L-HPC), xanthan gum, polyethylene oxide or sodium alginate) together with drug tablet and erodible tablet (L-HPC or guar gum) in a pre-coated capsule (95).

CONCLUSION

In summary, valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. The most important property of valsartan is strongly pH-dependent solubility and decrease in absorption when it is taken with food. A rise from pH 4 to pH 6 increases the solubility of valsartan by a factor of about 1000. Food decreases the exposure to valsartan (as measured by AUC) by about 40% and peak plasma concentration (C_{max}) by about 50%. Another problem with valsartan is considerable inter- and intra-subject variation in C_{max} (30%) and $AUC_{0\pm48}$ h (44%) values. Despite its bioavailability problems, its specificity of action and excellent side-effect profile provide good conditions for patient compliance as well as high and long-lasting effectiveness, so it can be concluded that valsartan will become a more forthcoming drug in the angiotensin II type I receptor antagonist class of drugs.

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