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The Effect of Age on the Pharmacokinetics of Valsartan

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ABSTRACT: Twelve young (mean age 23 years, range 18–28) and 12 elderly (mean age 76 years, range 65–89) volunteers were given a single oral dose of 80 mg valsartan after an overnight fast. Each group consisted of six male and six female subjects. Mean systemic exposure to valsartan was higher in the elderly when compared with the young (AUC(0–24 h), 52% increase and AUC(0–∞), 70% increase). Variability, as shown by the coefficient of variation (CV), was larger for the elderly subjects and ANOVA of the log transformed AUC showed a significant difference between the two groups. This difference was largely brought about by five elderly subjects (one male, four females), whose AUC was about 2-fold higher than the rest of the group. For the remaining elderly subjects, plasma valsartan AUC was similar to that observed for the young volunteers. This higher systemic exposure in five of the elderly subjects is not thought to be of clinical relevance when data from the patient population are considered. Other covariates—such as body weight, comedication, creatinine clearance, valsartan kinetics (absorption rate, distribution, and elimination)—did not explain the higher AUC in this subset of the elderly group. Data from the present study were compared with population kinetic data obtained from larger clinical trials including hypertensive patients in all age groups. Using this population approach, there was no difference in the pharmacokinetics of valsartan between male and female patients. Also, a relationship between plasma clearance of valsartan and age was established. The median age of patients in the hypertensive pool was 55 years. For an average 70-year-old patient, plasma clearance of valsartan is predicted to fall by 22% compared with an average 55-year-old. For the population, this difference is not sufficient to warrant initial dose adjustment based on age *per se*. The covariate age, does not completely explain the variability in the pharmacokinetics of valsartan within the general population. The treatment was well tolerated.

Key words: valsartan; young and elderly volunteers; single dose; pharmacokinetics

Introduction

Pharmacologically, valsartan (Figure 1) is an orally active, potent and specific competitive angiotensin II antagonist acting at the ATI receptor subtype.

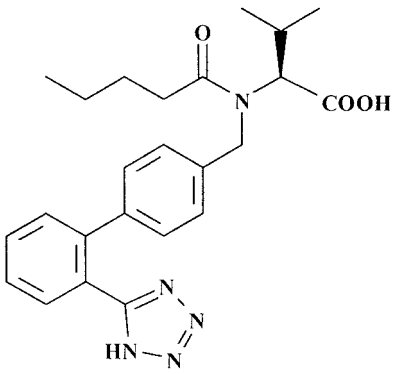

Figure 1. Chemical structure of valsartan

This receptor subtype mediates all the known effects of angiotensin II on the cardiovascular system. The preclinical and clinical efficacy and safety profile suggest that the compound is a well tolerated and efficacious antihypertensive drug [1,2].

Single and multiple dose Phase I studies were performed with a capsule formulation. After oral administration, valsartan is absorbed rapidly, with a T_{max} at 2 h. The plasma levels of valsartan decline in a biexponential manner, the two decay phases having mean half-lives of <1 h and 6–9 h, respectively. There is no change in the kinetics of valsartan on repeated once daily administration, and a limited accumulation of the drug is observed. Mean systemic exposure, as measured by the area under the curve (AUC), increased more or less in proportion to the dose in the tested range of 40–320 mg [2].

After an intravenous dose, the steady-state volume of distribution in humans was estimated to be 17 L and the plasma clearance about 2.2 L h^{-1}. Urinary excretion was not the main route of elimi-

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nation: 30% of an i.v. dose and about 10% of an oral dose was excreted unchanged in the urine, the rest of the dose was excreted in the bile. These excretion values of the intact drug agree with the absolute bioavailability of about 25% after oral administration [2].

Subjects and Methods

Subjects

A total of 24 healthy subjects were included, with six males and six females in each group, young and elderly. The 12 young subjects had a mean age of 23 years (range 18–28) and the 12 elderly had a mean age of 76 years (range 65–89). Two previous pharmacokinetic studies provided estimates of the inter-subject coefficient of variation (CV) of AUC (log transformed) amounting to 0.35 and 0.44, respectively. Based on a weighted average CV estimated as 0.39, a sample size of 12 volunteers per age group was determined in order to provide an 80% power of detecting about 40% difference in AUC due to age.

Since most elderly people take some medication, concomitant medication which was unlikely to interact with valsartan was allowed in the elderly group. In this regard, the conclusions of the study are more general and more likely to extrapolate to the elderly population.

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki, Venice and Hong Kong amendments 1983 and 1989, and good clinical practice (GCP). The study protocol and the subject informed consent forms were approved by an Ethical Review Board (ERB), and written informed consent for each subject was obtained prior to initiating any study procedures.

Dosage Form

Capsule containing 80 mg valsartan.

Study Design

This was an open-label, parallel group trial with single oral administration of 80 mg valsartan to 12 young and 12 elderly healthy volunteers after a 14-day run-in period. All volunteers were advised to maintain the same normal dietary habits during the trial period, and they were fasted for at least 12 h prior to the administration of valsartan. Subjects were asked to avoid caffeine containing beverages from 48 h before drug administration until 24 h thereafter, and smoking was not permitted while the volunteers were in the trial center. A single 80 mg oral dose (one capsule) was administered to each volunteer under supervision. The capsule was administered with 200 mL water, and a further 100 mL of water was provided at 1 and 3 h postdosing. Light meals—a snack, lunch and dinner—were provided at 2, 4 and 10 h postdosing.

Blood (10 mL) was collected into lithium heparinized vacutainer tubes just before administration of the drug and at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h postdosing. The blood samples were immediately centrifuged and the plasma samples were stored at $-20°C$ until analysis.

Analytical Method

Plasma concentrations of valsartan were determined using a fully automated high-performance-liquid-chromatography method with fluorimetric detection [3]. Liquid–solid extraction was performed automatically on a C8 reversed phase column using the Gilson ASPEC system. The on-line chromatography was performed on an ODS Hypersil C_{18} 5 μm column. The mobile phase, acetonitrile–pH 2.8 phosphate buffer (50:50 v/v), was used at a flow-rate of 1.3 mL min^{-1}. The fluorimetric excitation and emission wavelengths were set at 265 and 378 nm, respectively. The limit of quantitation was 0.005 mg L^{-1}. The method was validated during the analysis by running a series of drug-free human plasma samples spiked with known amounts of valsartan.

Pharmacokinetic Data Evaluation, Statistical Methodology and Population Pharmacokinetic Analysis

Body surface area (BSA) was calculated from height and body weight [4]. C_t (plasma concentration at t h postdosing), C_{max} (highest observed plasma concentration) and T_{max} (time to C_{max}) were obtained directly from the experimental data. AUC(0–24 h) (area under the plasma concentration–time curve) was calculated by the trapezoidal rule, $t_{1/2}\alpha$ (half-life associated with the α rate constant of the exponential term) was calculated by the incremental method [5] with $t_{1/2}\alpha = \ln 2/\alpha$, and $t_{1/2}\beta$ (apparent terminal elimination half-life) was obtained by linear regression from the terminal phase (β) of the semilogarithmic plot of the plasma concentration–time curve. At least three concentration–time points were used for the calculations of $t_{1/2}\beta$ (except for subject 6, two points). AUC(0–∞) (area under the plasma concentration–time curve up to infinity) was calculated with the following formula:

$$\text{AUC(0–24 h)} + \frac{C_{24}}{\ln 2} \times t_{1/2}\beta.$$

The absorption rate of valsartan was estimated from the plasma concentration–time curve using the incremental method fitted to a two-compart-

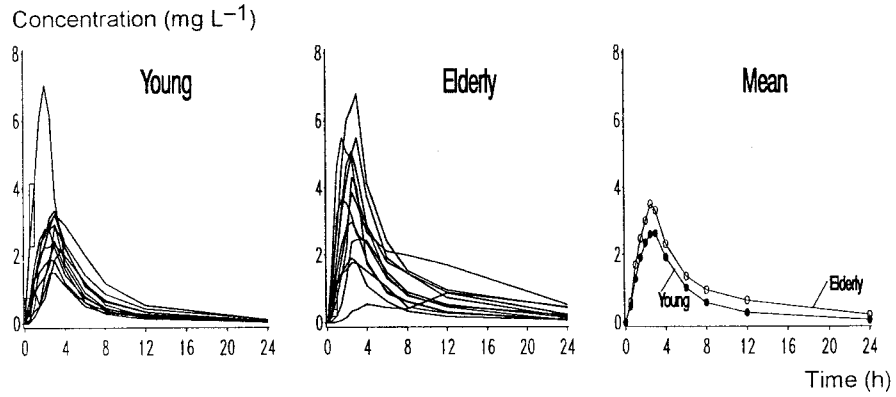

Figure 2. Individual and mean valsartan plasma concentrations ($n = 12$)

ment model [5]. The time required for 10, 50 and 90% of the absorbed fraction to be absorbed was calculated from either individual or mean plasma profiles. Prediction of valsartan plasma concentrations at steady-state was performed using the superposition technique [6] and the mean plasma profiles in each group.

An analysis of variance (ANOVA) considering group (elderly/young), sex (m/f) and interaction group/sex as factors was performed using the GLM procedure of SAS [7]. This was independently applied to the log transformed values AUC(0–24 h), AUC(0–∞), C_{max}, C_8, C_{12}, C_{24}, $t_{1/2}\beta$ and to CL_{cr} (creatinine clearance calculated according to the formula of Cockroft [8]), BSA, ALT (alanine–leucine transferase) and bilirubin values. When using the log transformed data, the root of the mean square error (MSE) was taken as an estimate of the variability in comparison to the mean value for a given parameter (coefficient of variation, CV).

For population pharmacokinetic analysis, the data previously obtained from healthy volunteers and patients were compared to the present study. Data were available from plasma concentration–time profiles of valsartan for 118 healthy subjects (1298 concentration data points), with each subject providing between five and 13 plasma samples, and the last sampling point being measured between 24 and 48 h after dosing. The dose of valsartan ranged from 80 to 200 mg, and dosing conditions were similar to the present study (single dose, fasted, food allowed 2 h after dosing). Concentration data from 92 hypertensive patients were also available. These data were obtained on days 1, 14 and 28 following repeated administration of a single daily dose of 10, 40, 80 or 160 mg of valsartan. Sampling times were at 0, 2, 4 and 6 h following drug intake. NONMEM (version IV level 1.0, implemented with double precision) was used in all analyses and the conditional estimation method was employed.

Results

Valsartan Pharmacokinetics in Plasma

Individual and mean valsartan plasma concentration–time profiles are given in Figure 2. At all sampling time-points, mean concentrations were higher in the elderly compared with the young subjects.

Individual and mean valsartan pharmacokinetic parameters are shown in Table 1. The mean AUC(0–24 h) was 52% higher in elderly than in young volunteers, and variability, as reflected by the CV and the range, was larger in the elderly. In young subjects, comparable mean values were recorded for men (14.7 mg·h L^{-1}) and women (16.5 mg·h L^{-1}), whereas in elderly, the mean value in women (27.3 mg·h L^{-1}) was higher than that in men (20.7 mg·h L^{-1}). Similarly, the mean AUC(0–∞) value in elderly (27.3 mg·h L^{-1}) was 70% higher than that in young (16.1 mg·h L^{-1}), and elderly women presented mean AUC values higher than those in elderly men or young subjects (Figure 3).

Also, mean C_{max} was 24% higher in the elderly than in the young, but the variability of the individual values, as reflected by the CV, was similar, and median T_{max} was comparable between the two groups (Table 1).

A biexponential decay described the fall in plasma levels of valsartan. $t_{1/2}\alpha$ of the mean profiles was 1 h for young and 1.1 h for the elderly. The median value for the terminal elimination half-life ($t_{1/2}\beta$) was 45% higher in elderly (7.4 h) than in the young (5.1 h) (Table 1), and Figure 3 shows the $t_{1/2}\beta$ (median, mean and range) for both sexes and both groups.

Statistical Evaluation

ANOVA applied to log-transformed kinetic parameters showed a significant difference between groups, i.e. between elderly and young subjects for AUC(0–∞), AUC(0–24 h), $t_{1/2}\beta$, C_{12}, C_{24}. The difference was marginally significant ($p = 0.0544$) for C_8.

Table 1. Individual and mean pharmacokinetic parameters for valsartan

Subject		C_{max}	T_{max}	AUC(0–24 h)	AUC(0–∞)	$t_{1/2}\beta$
No.	Sex	(mg L^{-1})	(h)	(mg·h L^{-1})	(mg·h L^{-1})	(h)
Young						
4	M	2.28	4.0	13.5	14.0	5.02
6	M	2.35	3.0	13.4	13.9	5.98
7	M	3.34	3.0	20.9	21.7	5.58
8	F	2.93	3.0	18.3	18.8	4.95
9	F	1.50	3.0	8.5	9.1	6.52
11	F	2.91	3.0	13.1	13.7	6.09
12	F	3.24	3.0	23.7	24.5	4.87
13	F	7.06	2.0	23.3	23.5	4.58
14	F	2.44	3.0	12.4	12.5	4.28
15	M	2.80	2.0	12.9	13.3	5.10
16	M	1.90	2.5	9.8	10.0	5.39
21	M	3.22	3.0	17.6	18.0	4.42
Mean		3.00		15.6	16.1	
S.D.		1.40		5.1	5.1	
CV%		47		33	32	
Median			3.0			5.06
Elderly						
1	F	5.10	2.5	30.4	31.7	5.21
2	M	2.98	2.5	16.2	16.6	4.70
3	M	1.78	2.5	12.8	13.8	7.41
5	M	0.88	12.0	12.1	—	*
10	M	2.46	3.0	18.7	19.9	5.96
17	M	3.87	2.5	38.8	46.0	8.86
18	F	5.49	3.0	35.5	42.2	10.2
19	F	6.79	3.0	41.6	47.3	9.15
20	F	1.92	2.5	10.5	11.3	7.37
22	F	5.49	1.5	28.5	31.2	8.86
23	F	4.30	2.5	17.3	18.0	5.65
24	M	3.66	1.5	22.0	22.4	4.43
Mean		3.73		23.7	27.3	
S.D.		1.79		10.9	13.1	
CV%		48		46	48	
Median			2.5			7.37

—, Not calculated; * ill defined.

A significant difference due to sex was noticed for C_{max}. It was marginal for $t_{1/2}\beta$ ($p = 0.0924$). The interaction factor was never significant.

Coefficients of variation of the ANOVA were high for all kinetic parameters (41–66%) except for $t_{1/2}\beta$ (23%) reflecting a large inter-subject variability and a possible lack of power for the analysis.

Population Pharmacokinetics

Data from 118 healthy volunteers with around 1300 concentration data points following a single oral dose of valsartan were successfully modelled by a two compartment model with zero order absorption rate. This model appeared to have fit and explained the data better than the same model with a first order rate. A suitable estimate of absorption was possible by a first order process with an estimated lag time between drug intake and onset of absorption of about 0.63 h (CV = 37%). However, it was noticed that 70% of the subjects had their concentration levels at 0.5 h averaging at about 0.38 mg L^{-1} (S.D. = 0.38). This would then cast doubts on the suitability of the first order absorption process with lag time. Thus an alternative, namely, a zero order process was considered. The duration of the zero order input had been approximated by the time maximum concentration was achieved. Undoubtedly, using a zero order or a first order process for absorption would have some effects on the estimation of other rates, e.g. disposition rates. However, the more important physiological parameter, clearance, is generally unaffected. It was estimated that clearance for a volunteer weighing 70 kg was about 1.96 L h^{-1} under a two-compartment model with first order absorption. That under a two-compartment model with zero order absorption was estimated to be 1.84 L h^{-1}. Therefore, the use of clearance or distribution volume for exploring subgroup differences is likely to remain valid in either models. Median clearance was estimated as 1.92 L h^{-1} and median volume of distribution (V) was

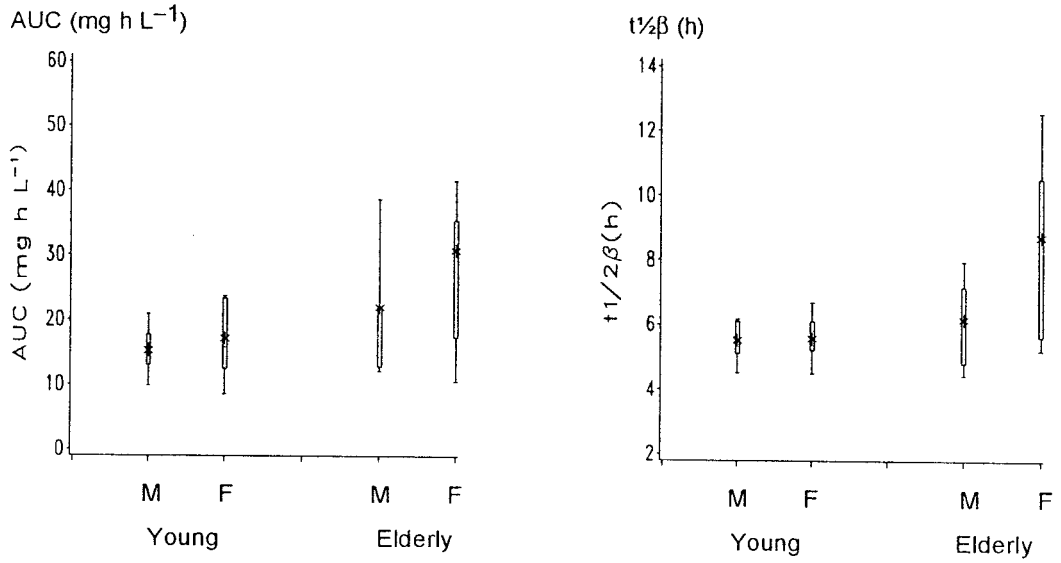

Figure 3. AUC and $t_{1/2}\beta$ in young and eldely men (M) and women (F). (Boxes indicate the 25–75 percentiles and whiskers the total range of values. The stars represent the mean value)

about 9.5 L. The corresponding between-subject coefficients of variation were about 56 and 24%. Body weight had an increasing effect on volume by a factor of 0.13 L kg^{-1}.

Ninety-two patients provided concentration data at steady state conditions. Due to the small number of sampling points (only four per patient per visit), a one compartment model was used and provided a reasonable fit to the data. Median clearance for this data set was estimated as 1.44 L h^{-1} and the median volume of distribution was estimated as 9 L.

The corresponding between-patient coefficients of variation were approximately 47 and 69%. Due to fitting the reduced (one compartment) model, variation of V was much higher than that observed in the healthy volunteer studies; age had a decreasing effect on both clearance and volume (CL = 76/age and V = 515/age). Body weight and gender had no effect on either clearance or volume.

Safety and Tolerability

Safety and tolerability were assessed from reported adverse experiences and routine laboratory tests. No abnormal findings were recorded during the trial and the treatment was well tolerated.

Discussion

Mean systemic exposure to valsartan was higher in elderly than in young volunteers. This difference was mainly due to five elderly subjects (one male and four females). AUC(0–24 h) values ranged from 28.5 to 41.6 mg·h L^{-1} for these five subjects, and from 10.5 to 22.0 mg·h L^{-1} for the remaining elderly subjects. The mean systemic exposure for the seven remaining elderly subjects was equal to that of the 12 young subjects (AUC(0–24 h) = 15.6 mg·h L^{-1}).

Possible factors explaining the higher systemic exposure in this subset of five elderly subjects were investigated.

Absorption

The time required for 90% of the absorbed dose to be absorbed was around 3.5 and 3 h for the young and elderly, respectively.

Distribution

$t_{1/2}\alpha$ was 1 h for the young and 1.1 h for the elderly.

Elimination

AUCs for two of the elderly subjects (nos. 1 and 22) were similar, although their respective $t_{1/2}\beta$ differed by about 70% (Table 1). A slower elimination would therefore not be the only factor responsible for the observed difference in systemic exposure.

The disposition of valsartan was investigated in six healthy male volunteers who received a single oral dose of 80 mg of a ^{14}C-labelled preparation as a neutral buffered solution [8].

Valsartan was excreted largely as unchanged compound and was only minimally metabolized. This result may be explained by the fact that valsartan, at physiological pH, is a hydrophilic di-anion. Therefore it may be a poor substrate for metabolizing enzymes. The pronounced biliary elimination suggests active involvement of an anion transporting system in the liver, presumably of the canalicular multispecific organ anion transporter (cMOAT),

which is responsible for biliary elimination of many anionic endo- and xenobiotics, particularly of di-anions.

Valsartan was metabolized to a small extent only. The only notable inactive metabolite in plasma, urine and faeces was the valeryl-4-hydroxy-valsartan (M1). It was neither an N- nor an O-glucuronic acid conjugate nor a sulphate conjugate. In particular, since alkaline treatment had no effect on this metabolite, an acyl glucuronide could be ruled out. Various spectroscopic data provided evidence that the metabolite was a hydroxylated derivative of valsartan formed by oxidation [8].

The radioactivity in selected plasma samples was analysed by radio-HPLC. In plasma collected at 1 h (T_{max}), unchanged valsartan was the only detectable radioactive compound. In plasma samples collected at 8 h, in addition to valsartan, a metabolite was detected which accounted for approximately 10% of the radioactivity. Essentially identical chromatograms were obtained following direct analysis of plasma samples without preparatory protein precipitation [8], thus denoting that no acyl glucuronide of valsartan or its minor metabolite was available or could be reverting back to the aglycone under appropriate conditions.

The mean total of valsartan in urine and faeces amounted to 81% of dose, and that of metabolite M1 was 9% [8]. Accordingly, the formation and excretion of valeryl-4-hydroxyvalsartan (metabolic clearance of valsartan) represents a minor additional elimination process which is a minor contribution to the total systemic clearance of valsartan.

Sex

Four out of the five elderly subjects presenting the highest AUC values were women. This might suggest a difference in systemic exposure of elderly subjects related to sex. However, this is not supported by population data in patients.

Age

The highest three AUC values were recorded in the oldest three subjects (nos. 17, 18, 19; 88–89 years). Subject nos. 1 and 22, who also presented high AUC values, were of the same age as the other seven elderly subjects (65–80 years). An effect of age on the exposure could not be definitely established from the present study, although a small decrease in clearance with age is supported by the population data (see below).

Creatinine Clearance

Four out of the five highest AUC values were also related to the lowest CL_{cr} values, although low AUCs were also observed at comparable CL_{cr}. Less than 10% of an oral dose is excreted in the urine as unchanged valsartan [8], which represents about 30% of the absorbed dose. Therefore, a change in valsartan kinetics related to a reduction in the glomerular filtration rate (reflected by CL_{cr}) due to age, would be unlikely. This is confirmed by a study on the effect of renal function on the pharmacokinetics of valsartan [9]. In order to cover the full spectrum of renal function, a total of 19 subjects with normal renal function and various degrees of renal dysfunction, as determined by creatinine clearance, were assigned to four groups: normal renal function ($CL_{cr} > 90$ mL min^{-1}), and mild (CL_{cr} 61–90 mL min^{-1}), moderate (CL_{cr} 30–60 mL min^{-1}) and severe ($CL_{cr} < 30$ mL min^{-1}) renal dysfunction. Creatinine clearance was determined following a 24-h time collection just prior to drug administration. Each subject received a single oral dose of 80 mg of valsartan (capsule) after an overnight fast. Blood samples were collected at frequent intervals up to 48 h postdose and plasma valsartan concentrations were determined. Pharmacokinetic parameters were calculated. Statistical analysis using a cubic polynomial regression function was performed to examine a relationship between renal function and the pharmacokinetic parameters of valsartan.

Scatter plots of pharmacokinetic parameters did not indicate any clear relationship with creatinine clearance. The regression coefficients of linear, quadratic and cubic terms for the AUC and C_{max} of valsartan versus renal function were not significantly different from zero. Thus, the pharmacokinetics of valsartan did not correlate with renal function. In addition, no clinically significant adverse experiences were observed in this trial; the 80 mg dose of valsartan was well tolerated. Based on these observations, there is no rationale for dosage adjustment of valsartan in patients with impaired renal function.

Bilirubin and ALT Values

The values of these biological parameters which reflect hepatic function were all within the normal ranges, and they were comparable between both young and elderly groups.

Body Surface Area and Weight

Body weight for the five elderly subjects showing the highest AUC values were in the same range as those of the other elderly and the young subjects. The observed differences were not reduced by correcting AUC values for BSA or weight.

Comedication

Two of the elderly subjects (nos. 18 and 19) with high AUC were treated long-term with a combination of paracetamol and dextropropoxyphene. The

latter drug is reported to inhibit the hepatic metabolism of carbamazepine [10]. However, valsartan undergoes little in the way of biotransformation, and this is unlikely to explain the increased variability in the elderly.

If oxygenating cytochrome P450 enzymes are involved in the elimination of a drug, drug–drug interactions may occur via inhibition or induction of the involved enzymes. Such interactions are clinically relevant only if the affected metabolic process is a main elimination process for a drug. According to a recent review [11], a significant interaction potential exists only if one enzyme contributes at least 40–50% of the total clearance. In the case of valsartan, the metabolic clearance is low and therefore the total systemic clearance of valsartan will not be affected by enzyme inhibition to any significant extent.

Population Kinetics

Analysis of covariates from the 'conventional study with 12 subjects per group' did not reveal any factors which may explain the observed increase in pharmacokinetic variability in the elderly. To further explore this observation, pooled data from healthy volunteers were successfully fitted to a two compartment model, and more sparse data from patients to a one compartment model. The absorption rate was modelled as zero order with a duration of 2–3 h. Using this approach, age was the only covariate which showed any correlation with valsartan kinetics (Figure 4), the relationship being described by CL = 76/age. In patients, body weight and gender had no effect on either valsartan plasma clearance or volume of distribution.

None of the above-mentioned factors were found to completely explain the observed higher exposure in some elderly subjects.

Steady-state plasma levels to be achieved following repeated daily administration of 80 mg, as estimated by the superposition technique (which assumed a linear kinetics of the drug versus time and dose), would be comparable in young and elderly subjects. A limited accumulation, as already reported in young subjects [2], would also be observed in elderly subjects under chronic treatment.

In conclusion, the absorption of valsartan was not affected by age. Systemic exposure to valsartan in 7/12 elderly subjects appeared similar to that observed in 12 young subjects. A significant increase in AUC (up to 100%), mostly related to a slower elimination, was recorded for 5/12 elderly subjects. This increase in kinetic variability was confirmed using a population approach, and a relationship between plasma clearance of valsartan and age was established. The median age of patients in the hypertensive pool was 55 years. For an average 70-year-old patient, plasma clearance of valsartan is predicted to fall by 22% compared with an average 55-year-old. For the population, this difference is not sufficient to warrant initial dose adjustment based on age *per se*. Other factors, which could not be identified, probably contribute more to the kinetic variability of valsartan than age itself. The treatment was well tolerated.

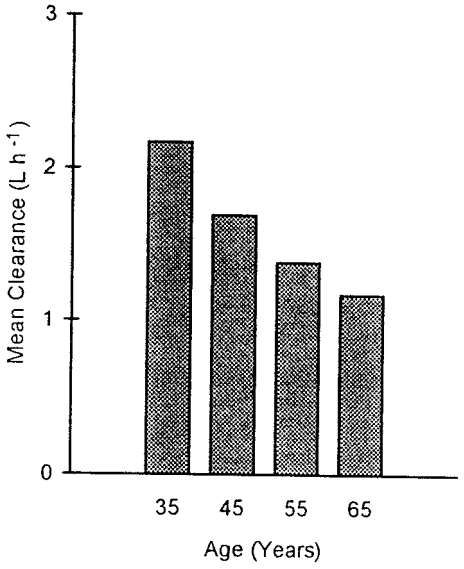

Figure 4. Mean clearance versus age (population data—hypertensive patients)

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