Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite EXP3174 in humans

The pharmacokinetics of the angiotensin II receptor antagonist losartan potassium and its active carboxylic acid metabolite EXP3174 were characterized in 18 healthy male subjects after administration of intravenous losartan, intravenous EXP3174, and oral losartan. In these subjects, the average plasma clearance of losartan was 610 ml/min, and the volume of distribution was 34 L. Renal clearance (70 ml/min) accounted for 12% of plasma clearance. Terminal half-life was 2.1 hours. In contrast, the average plasma clearance of EXP3174 was 47 ml/min, and its volume of distribution was 10 L. Renal clearance was 26 ml/min, which accounted for 55% of plasma clearance; terminal half-life was 6.3 hours. After oral administration of losartan, peak concentrations of losartan were reached in 1 hour. Peak concentrations of EXP3174 were reached in 3½ hours. The area under the plasma concentration–time curve of EXP3174 was about four times that of losartan. The oral bioavailability of losartan tablets was 33%. The low bioavailability was mainly attributable to first-pass metabolism. After intravenous or oral administration of losartan the conversion of losartan to the metabolite EXP3174 was 14%. (CLIN PHARMACOL THER 1995:58:641-9.)

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One of the most important regulators of blood pressure is the renin-angiotensin system.[1] Interruption of this hormonal system has provided a means for controlling hypertension, as shown by the efficacy of the angiotensin converting enzyme (ACE) inhibitors captopril[2] and enalapril.[3] However, it is becoming increasingly clear that both ACE and renin[4] have other substrates, some outside the renin-angiotensin system. For example, ACE also cleaves the vasodepressor and inflammatory nonapeptide bradykinin into inactive fragments. A side effect that can be associated with ACE inhibitors is a dry cough, possibly the result of bradykinin potentiation,[5] thus showing the need for a more specific mechanism for the treatment of hypertension.

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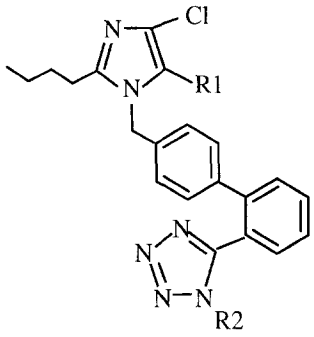

	R1	R2
Losartan potassium	CH_2OH	K
EXP3174	COOH	H

Structures of losartan potassium and EXP3174.

Recently a new class of drugs has been developed to inhibit the action of angiotensin II at its receptor. Losartan potassium (2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt; see Structure), is a highly selective

Table I. Summary pharmacokinetics of losartan and EXP3174 after a 50 mg losartan tablet and a single 20-minute intravenous infusion of 20 mg losartan in 12 healthy male subjects in study 1*

	Losartan								
Subject No.	C_{max} *(ng/ml)†*	t_{max} *(hr)*	$t_{1/2}$ *(hr)*	*AUC (ng · hr/ml)†*	V_{ss} *(L)*	*CL (ml/min)*	CL_R *(ml/min)*	*%Dose in urine*	*Oral F (%)*
50 mg oral dose of losartan									
1	649	0.5	1.8	727	—	—	69.9	6.6	66.6
2	250	0.5	3.6	586	—	—	48.5	3.5	37.2
3	178	2.0	2.3	355	—	—	84.2	4.0	30.7
4	89	1.3	2.3	307	—	—	89.0	3.3	25.1
5	416	0.8	3.7	766	—	—	62.6	5.7	42.8
6	733	1.3	2.3	690	—	—	60.6	4.8	59.4
7	49	1.3	2.3	184	—	—	55.2	1.3	12.1
8	76	1.8	2.0	282	—	—	56.7	2.3	20.6
9	195	1.3	1.8	484	—	—	103.0	6.5	39.9
10	317	0.8	2.2	608	—	—	43.7	3.4	37.5
11	235	0.5	1.7	254	—	—	89.8	2.8	24.4
12	370	0.5	1.5	464	—	—	101.3	6.1	33.3
Mean	296	1.0	2.1‡	476	—	—	72.0	4.2	35.8§
SD	217	0.5	0.5‡	200	—	—	20.6	1.7	15.5
20 mg intravenous dose of losartan									
1	—	—	2.4	436	39.9	763.8	83.1	10.9	—
2	—	—	1.6	630	21.2	529.3	38.6	7.9	—
3	—	—	1.4	462	24.0	721.4	95.0	13.9	—
4	—	—	2.1	489	31.8	681.1	89.8	13.6	—
5	—	—	2.9	716	31.0	465.5	54.2	12.1	—
6	—	—	2.1	465	28.5	717.3	61.9	9.8	—
7	—	—	2.0	610	16.0	546.2	73.2	13.9	—
8	—	—	1.7	549	22.1	607.5	58.9	10.3	—
9	—	—	3.9	485	65.9	687.3	104.6	15.1	—
10	—	—	1.7	647	19.0	514.9	44.7	9.4	—
11	—	—	1.1	417	20.8	799.1	73.8	10.9	—
12	—	—	1.4	557	20.2	598.1	88.0	16.0	—
Mean	—	—	1.8‡	539	28.4	636.0	72.1	12.0	—
SD	—	—	0.6‡	95	13.6	107.4	20.8	2.5	—

C_{max}, Peak plasma concentration; t_{max}, time to reach C_{max}; $t_{1/2}$, half-life; AUC, area under the plasma concentration–time curve; V_{ss}, steady-state volume of distribution; CL, plasma clearance; F, bioavailability.

*The assayed potencies of the losartan tablet and the mean intravenous dose were 49.1 mg and 19.7 mg as losartan potassium, respectively.

†Data normalized to 20.0 mg intravenous and 50.0 mg oral dose on the basis of assayed potency.

‡Harmonic mean and pseudo standard deviation.

§Geometric mean is 32.6%.

AT_1-subtype, non-peptide, orally active angiotensin II receptor antagonist.[6] It has been shown to be active in animal models of hypertension[6] and to be antihypertensive in humans.[7-10] This mechanism would be expected to be free of the actions of ACE inhibitors that are due to bradykinin potentiation, such as cough, while maintaining clinical efficacy and general tolerability.

Characterization of activity of losartan in animals revealed that the 5-carboxylic acid of losartan, EXP3174 (Structure), is an active metabolite that contributes to the overall in vivo activity of losartan in animals[11] and humans.[12] However, losartan is not a pro-drug because losartan itself is a potent angiotensin II antagonist. In vitro human microsomal investigations have suggested that the conversion of losartan to EXP3174 is catalyzed by two cytochrome P450 subfamilies: CYP3A4 and CYP2C9.[13] Pharmacokinetics of losartan in humans after oral administration have been described.[14,15]

To understand the relationship between the pharmacokinetics of losartan and its clinical activity, it is necessary to investigate its disposition after oral and intravenous administrations and to examine the disposition of the active metabolite. In this article, the pharmacokinetics of losartan after both oral and intravenous ad-

EXP3174					
C_{max} (ng/ml)†	t_{max} (hr)	$t_{1/2}$ (hr)	AUC (ng · hr/ml)†	CL_R (ml/min)	%Dose in urine
387	2.0	3.9	2174	21.3	5.9
271	4.0	7.6	2333	27.4	7.9
258	6.0	8.4	2197	32.5	8.8
198	4.0	6.5	1872	21.9	5.2
189	3.0	14.0	1370	23.1	3.7
189	4.0	5.1	1414	19.3	3.6
241	4.0	8.7	1694	18.4	3.7
154	7.0	4.9	1316	25.8	4.3
249	6.0	6.0	2187	37.0	10.0
391	3.0	8.4	3187	18.0	7.2
249	2.0	8.9	1751	28.7	6.2
217	4.0	4.5	1487	37.7	7.0
249	4.1	6.4‡	1915	25.9	6.1
74	1.6	2.3‡	538	6.9	2.1
45	4.0	3.2	464	22.4	3.5
137	4.0	4.4	1241	24.4	9.8
89	4.0	3.6	766	29.5	7.6
61	4.0	4.5	623	32.7	6.4
57	4.0	6.5	693	27.2	5.7
48	4.0	4.9	500	33.0	5.2
71	4.0	6.3	718	20.1	4.3
45	6.0	5.4	579	26.7	4.8
99	4.0	3.7	934	38.2	11.7
125	4.0	10.3	1279	19.6	7.3
72	4.0	4.1	572	34.5	6.2
69	4.0	3.6	562	32.1	5.8
76	4.2	4.6‡	744	28.4	6.5
30	0.6	1.3‡	272	6.0	2.3

ministrations (study 1) is described. In addition, because EXP3174 contributes to the pharmacodynamics of losartan, the metabolite's pharmacokinetics after intravenous administration and the extent of conversion of oral and intravenous losartan to EXP3174 (study 2) was studied. The in vitro blood-to-plasma concentration distribution ratios of losartan and EXP3174 were also determined.

MATERIAL AND METHODS

Study design

Study 1. The study was a two-period, randomized, open crossover study to investigate the intravenous disposition and oral bioavailability of losartan tablets. On two occasions after an overnight fast, 12 healthy male subjects (age range, 21 to 36 years; mean weight, 75.6 kg) were given losartan potassium salt either as a single 50 mg tablet orally or as a 20 mg, 20-minute, constant-rate intravenous infusion in saline solution. A minimum 7-day washout period separated the treatments.

Blood samples were collected in heparinized tubes at 0, 15, 30, and 45 minutes and at 1, 1¼, 1½, 1¾, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30, and 36 hours after the administration of oral losartan, as well as at 0, 5, 10, 15, 20, 23, 26, 30, 45, 60, and 90 minutes and at 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, and 30 hours after initiation of administration of intravenous losartan. Total urine voided for 48 hours after drug administration was collected at the following intervals: predose and at 0 to 3, 3 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours.

Study 2. This was an open, three-period crossover study in six different healthy male subjects (age range, 22 to 30 years; mean weight, 78.6 kg) to study the conversion of losartan to EXP3174, the intravenous disposition of losartan and EXP3174, and the oral bioavailability of losartan solution. All doses were administered after an overnight fast. A solution of losartan (^{14}C-radiolabeled) was administered in a randomized sequence in the first and third periods as a single 100 mg oral dose and as a single 30 mg, 20-minute, constant-rate intravenous infusion in saline solution. During the second treatment period, EXP3174 was administered as a single 20 mg, 20-minute, constant-rate intravenous infusion in saline solution. Each period was separated by at least 7 days. Blood samples were collected in heparinized tubes at 0, 15, 30, and 45 minutes and at 1, 1½, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after the administration of oral losartan; at 0, 10, 20, and 30 minutes and at 1, 1½, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after initiation of the administration of intravenous losartan; and at 0, 10, and 20 minutes and at 1, 2, 4, 6, 9, 12, 18, 24, 30, and 36 hours after the initiation of the administration of intravenous EXP3174. Total urine voided for 96 hours after the losartan doses was collected at the following intervals: predose and 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 18, 18 to 24, 24 to 36, 36 to 48, 48 to 72, and 72 to 96 hours. For intravenous EXP3174, total urine was collected for 48 hours at the following intervals: predose and 0 to 3, 3 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours.

Sample assays

Plasma and urine samples were analyzed for losartan (as potassium salt) and EXP3174 (as free acid) simultaneously by a validated HPLC assay with

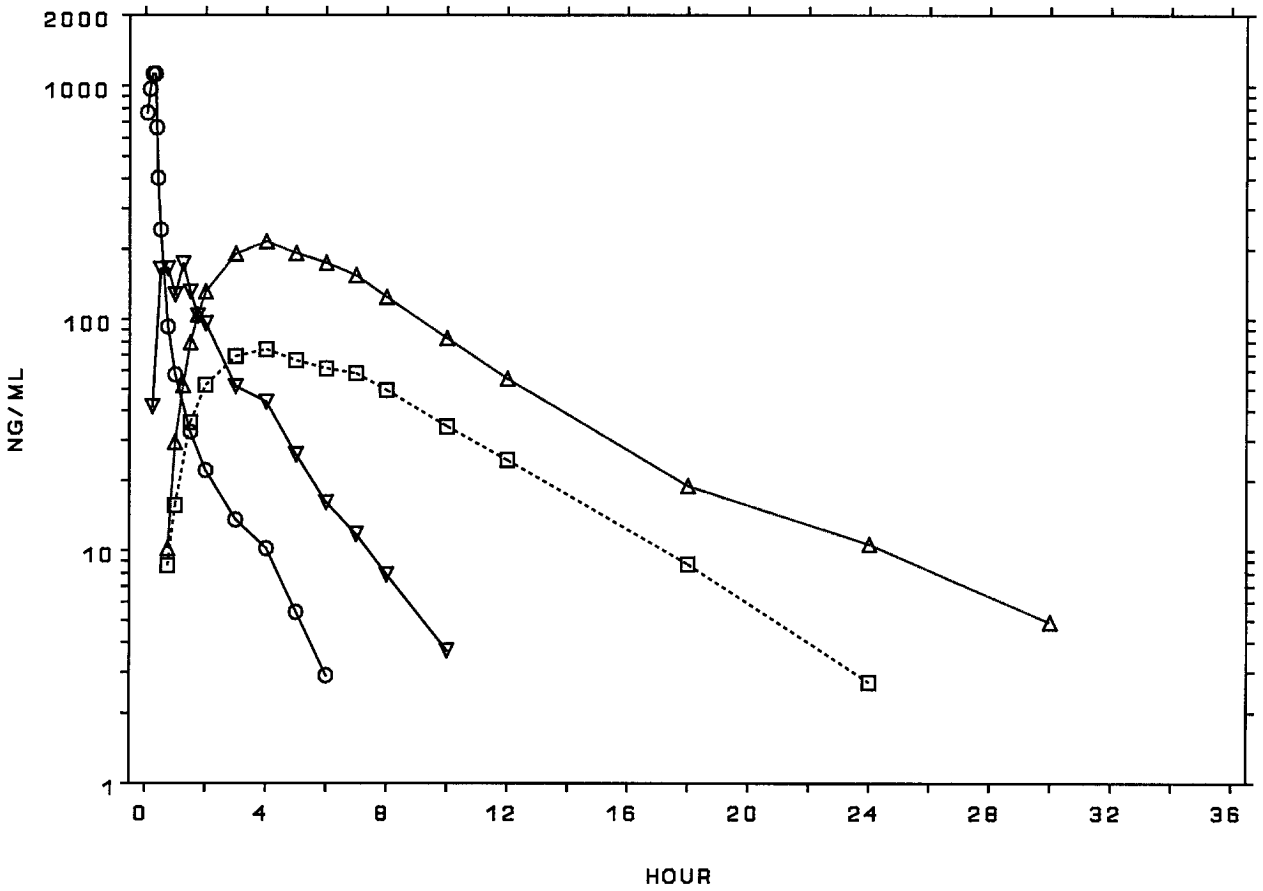

Fig. 1. Mean plasma concentrations (in nanograms per milliliter) of losartan and EXP3174 in 12 subjects after the administration of a single 20-minute intravenous infusion dose of 20 mg losartan (*open circles,* losartan; *squares,* EXP3174) and a single 50 mg oral dose of losartan (*inverted triangles,* losartan; *triangles,* EXP3174) in study 1.

ultraviolet detection.[16] The limits of quantification for losartan or EXP3174 were 5 ng/ml in plasma and 10 ng/ml in urine. Quality control samples for losartan and EXP3174 in plasma and urine (at concentrations of 20, 80, and 800 ng/ml for plasma and 40, 160, and 1600 ng/ml for urine) were included in each analytic run and the interday coefficients of variation throughout the study assay periods were <5%.

Blood-to-plasma concentration distribution ratio

The blood-to-plasma distribution ratios of losartan and EXP3174 were measured in fresh human blood from four donors. Losartan and EXP3174 were added to whole blood to give final concentrations of 20, 200, and 800 ng/ml (in triplicate at each concentration). After incubation at 37° C for 30 minutes, samples were centrifuged, and the concentrations of losartan and EXP3174 in plasma were determined by HPLC. The blood to plasma concentration distribution ratio was calculated as the nominal concentrations in blood to the found concentrations in plasma.

Pharmacokinetic analyses

The area under the plasma concentration–time curve (AUC) up to the last measured time point [AUC(0-t)] for both losartan and the metabolite EXP3174 were calculated with use of the linear trapezoidal method for ascending concentrations and the log-trapezoidal method for descending concentrations. Values for AUC(0-∞) were obtained by summing AUC(0-t) and AUC(t-∞); the latter was obtained by dividing the last measured plasma concentration by the terminal disposition rate constant (λ) which was estimated by regression of the terminal log-linear plasma concentration time points. Terminal disposition half-life ($t_{1/2}$) was calculated as the quotient of the natural log of 2 and λ. Harmonic mean half-lives and their pseudo standard

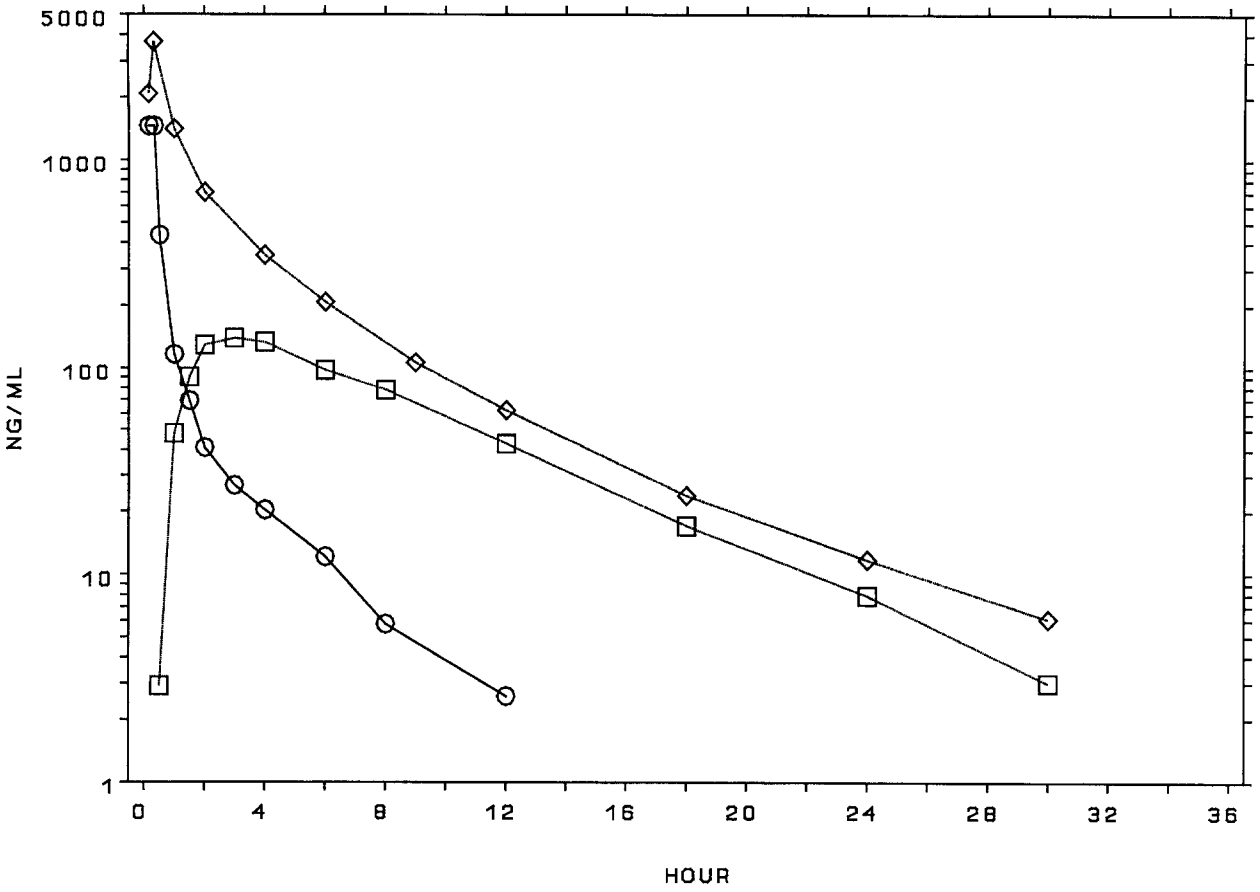

Fig. 2. Mean plasma concentrations of losartan and EXP3174 in six subjects after the administration of a single 20-minute intravenous infusion of 30 mg losartan (*circles*, losartan; *squares*, EXP3174 formed from losartan), and a single 20-minute intravenous infusion dose of 20 mg EXP3174 (*diamonds*, EXP3174), study 2.

deviations were calculated according to the method of Lam et al.[17] Volume of distribution at steady-state (V_{ss}) after infusion was calculated according to the method of Perrier and Mayersohn.[18] Urinary recoveries of losartan and EXP3174 were expressed as the percentage of dose administered, with EXP3174 being corrected for molecular weight (MW 461.015 for losartan potassium and 436.905 for E-3174 free acid). Renal clearance of losartan and EXP3174 was calculated as the quotient of the amount excreted in urine and the corresponding plasma AUC over the same time interval.

The fraction of the intravenous dose of losartan converted systemically to EXP3174 (f_{iv}) was calculated as follows[19]:

$$f_{iv}=AUC_{EXP3174,Div} \cdot CL_{EXP3174}/D_{iv} \cdot MW_{los}/MW_{EXP3174}$$

in which $AUC_{EXP3174,Div}$ is the area under the metabolite EXP3174 plasma concentration–time curve after intravenous administration of the parent drug losartan, $CL_{EXP3174}$ is the systemic clearance of EXP3174, D_{iv} is the intravenous dose of parent drug losartan, and MW_{los} and $MW_{EXP3174}$ are the molecular weights of losartan and EXP3174, respectively. Similarly, the overall fraction of an oral dose of losartan that is converted to EXP3174 by both presystemic and systemic mechanisms (f_{po}) was estimated by the following expression:

$$f_{po}=AUC_{EXP3174,Dpo} \cdot CL_{EXP3174}/D_{po} \cdot MW_{los}/MW_{EXP3174}$$

in which $AUC_{EXP3174,Dpo}$ is the area under the metabolite EXP3174 plasma concentration–time curve after oral administration of the parent drug losartan, and D_{po} is the oral dose of losartan. The contributions of presystemic and systemic conversion after oral losartan were estimated as follows. Because bioavailability (F) and systemic conversion (f_{iv}) could be estimated,

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