Absorption and Excretion of Cinepazide (Vasodilator) after Single and Multiple Oral Doses in Man

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Summary

The concentrations of cinepazide in human plasma and urine were studied by using high-performance liquid chromatography. Each of 7 healthy, male volunteers received 200 and 400 mg of cinepazide on separate occasions for single dose experiments. In the case of the 200 mg single dose, a rapid peak of plasma concentration at 2.8–4.9 $\mu\text{g/ml}$ was observed at 1–3 hr, and 57.6% of the cinepazide was excreted in urine within 24 hr. The peak plasma level increased proportionally with the dose of cinepazide, whereas the extent of cinepazide excretion increased slightly with the dose.

In multiple dose experiments, each of these volunteers received, on two separate occasions, 200 mg of cinepazide t. i. d. at 9 : 00 am, 1 : 00 pm and 5 : 00 pm each day for 1 day and 5 days, respectively. The results on the peak and valley plasma levels of multiple dose cinepazide indicated reproducible absorption in comparison with values predicted using a computer program describing a one compartment, open pharmacokinetic model. The extent of cumulative urinary excretion of cinepazide was nearly constant during multiple dose experiments. No side effects were noted.

Key Words : Cinepazide, Plasma concentration, Urinary excretion, Human pharmacokinetics, HPLC determination

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Cinepazide, 4-(3, 4, 5-trimethoxycinnamoyl)-1-(1-pyrrolidinyl) carbonylmethylpiperazine maleate was developed by Delalande Co., Ltd. (France) as a vasodilator (Pourrias, B. et al., 1974a, Pourrias, B. et al., 1974b, Marmo, E. et al., 1973). The chemical structure is shown in Fig. 1. The compound was found to be the most active vasodilator of several substituted cinnamoylpiperazines (Fauran, C. et al., 1969, Huguet, G. et al., 1969). The drug has been used to treat peripheral and cerebral vascular disorders (Bremer, C., 1974, Garrigues, A., 1975). The metabolism of cinepazide in animals and human has been previously studied by Cameron, B. D. et al. (1976), Oliver, M. C. et al. (1977), Tsumura, M. et al. (1979) and Nomura, H. et al. (1979). Cameron, B. D. et al. (1976), showed that cinepazide- ^{14}C was absorbed well and that more than 60% of the radioactivity was excreted within 24 hr in rats, dogs and man. For several hours more than 60% of the radioactivity in the plasma was due to the unchanged drug. Further, cinepazide was essentially excreted in urine, partly unchanged, in all three species. Oliver, M. C. et al. (1977) studied the plasma level and urinary excretion of cinepazide in man. Less information could be available on the absorption and excretion of cinepazide after single and multiple oral doses in man. In the present study, the pharmacokinetics of cinepazide was studied in man after single and multiple oral doses by using high performance liquid chromatographic determination of the unchanged drug in the plasma and urine. The

results of laboratory tests before and after drug administrations were also shown.

Materials and Methods

1. Materials

Cinepazide tablets (Daiichi Seiyaku Co., Ltd.) containing 200 mg of cinepazide maleate were used.

2. Volunteers

Descriptions of the several healthy, male volunteers are shown in Table 1. The subjects were confirmed to be submitted to the laboratory tests before and after drug administrations.

3. Trial procedure

Single oral dose : Seven volunteers took on separate occasions 200 mg (Step 1) and 400 mg (Step 2) of cinepazide with a small amount of water 30 min after a standard breakfast. Heparinized plasma specimens were obtained at 0, 0.5, 1, 1.5, 2, 3, 5, 7 and 24 hr after drug ingestion. Urine collections were also carried out at 0, 2, 4, 6, 8 and 24 hr.

Multiple oral dose : Seven volunteers took

Table 1 Description of Volunteers^{a)}

Subject	Age (yrs)	Body weight (kg)
A	38	61.0
B	41	61.5
C	42	62.0
D	31	59.0
E	36	59.5
F	29	55.5
G	32	61.7

a) All were Japanese males.

Fig. 1 Structure of cinepazide.

Table 2-1 Clinical Values

		Hematological test				Serum biochemical test						
		RBC ($\times 10^6/\text{mm}^3$)	Hb (g/dl)	Ht (%)	WBC ($\times 10^3/\text{mm}^3$)	GOT (I.U.)	GPT (I.U.)	ALP (K.A.U.)	BUN (mg/dl)	Crea (mg/dl)	Na ⁺ (mEq/l)	K ⁺ (mEq/l)
A	1	3.85	15.0	43.5	4.5	23	0	6.4	17.0	0.84	135	4.6
	2	4.18	15.5	46.2	4.3	23	7	7.2	17.4	0.98	134	3.5
	3	3.95	15.1	45.5	5.4	19	10	7.7	17.5	0.87	132	3.5
	4	3.69	14.7	43.5	5.5	18	6	6.8	19.6	0.77	135	4.8
	5	3.71	13.8	42.5	5.6	17	6	6.8	16.5	0.68	135	3.9
B	1	5.06	18.3	54.5	7.1	25	13	4.4	21.7	0.81	131	4.4
	2	5.19	17.7	50.0	8.0	23	17	4.9	25.7	0.95	135	4.5
	3	5.15	18.2	53.0	7.4	19	18	5.2	26.3	0.86	131	4.1
	4	4.62	17.2	47.0	5.8	18	13	5.2	24.9	0.77	138	4.7
	5	4.67	17.2	48.5	5.4	21	7	5.3	20.8	0.75	132	3.9
C	1	4.08	15.8	42.5	5.5	29	4	3.6	22.5	0.95	134	4.3
	2	4.21	15.9	38.9	7.2	22	13	4.4	26.9	1.03	133	4.9
	3	4.39	15.3	46.0	6.8	22	16	4.5	23.9	1.02	131	3.9
	4	4.06	15.2	43.5	5.0	20	11	3.7	23.1	0.95	137	4.9
	5	4.04	15.3	43.0	4.9	26	11	3.9	21.0	0.70	135	3.8
D	1	4.90	16.1	45.0	6.1	22	5	6.5	17.5	0.81	140	5.0
	2	5.14	16.9	46.5	5.0	21	26	6.8	17.2	0.82	134	4.4
	3	4.67	16.1	46.5	5.7	19	28	6.6	17.8	0.65	131	3.8
	4	4.68	15.7	46.0	5.6	14	10	5.2	15.0	0.74	136	5.2
	5	4.32	15.0	47.0	5.9	18	11	6.7	13.6	0.65	129	4.6
E	1	4.58	16.4	47.5	5.4	24	24	6.8	14.3	0.56	131	4.3
	2	4.82	17.3	46.4	6.3	22	21	7.6	19.0	0.78	136	4.8
	3	4.44	15.9	45.5	5.0	22	24	8.1	17.5	0.74	133	3.8
	4	4.39	16.2	47.8	4.7	20	17	7.2	20.1	0.74	138	4.9
	5	4.31	15.7	47.5	5.4	25	25	7.7	15.7	0.60	136	4.0
F	1	4.93	16.2	48.0	9.6	20	0	7.5	14.6	0.84	130	4.7
	2	4.90	16.1	44.8	10.7	19	12	9.8	14.9	1.53	135	4.9
	3	4.86	16.3	49.0	7.0	15	11	8.4	22.0	1.23	133	3.5
	4	4.86	16.0	48.0	9.0	16	10	6.7	15.8	1.08	138	4.8
	5	4.57	15.4	46.5	8.3	17	7	6.6	15.1	0.65	137	4.0
G	1	5.18	16.9	45.0	4.6	18	11	4.2	13.1	0.67	131	4.0
	2	5.16	17.9	48.4	5.9	28	17	4.6	14.6	0.76	134	4.7
	3	4.60	16.5	45.5	3.8	15	18	6.6	17.1	0.77	132	4.1
	4	4.77	16.0	46.0	4.6	18	15	4.3	13.9	0.67	134	5.0
	5	4.33	15.7	44.0	3.9	17	13	4.4	14.9	0.56	134	3.9

1 : before step I , 2 : after step I , 3 : after step II , 4 : after step III , 5 : after step IV

meals at 8 : 30, 12 : 30, and 16 : 30 and received a tablet containing 200 mg of cinepazide 30 min after each meal for 1 day (Step 3). Heparinized plasma specimens were obtained at 1.5, 8, 9, 9.5,

10, 24, and 32 hr after the first administration, and urine was also collected at 0, 4, 8, 24, and 32 hr.

A similar protocol was followed when cine-

Table 2-2 Clinical Values (Continued)

		Serum biochemical test			Urinalysis					BP	HR	ECG
		Cl ⁻ (mEq/l)	CHO (mg/dl)	TP (g/dl)	PH	Protein	Glucose	Urobili- nogen	Sediments			
A	1	105.8	215	7.06	6.0	Tr.	—	±	O.B.	140/74	56	O.B.
	2	96.6	208	7.12	6.5	Tr.	—	+	O.B.	150/90	58	O.B.
	3	96.9	213	7.28	5.5	+	—	+	O.B.	142/88	76	O.B.
	4	102.6	212	6.90	5.5	—	—	±	O.B.	136/94	55	O.B.
	5	102.1	177	6.74	5.5	Tr.	—	+	O.B.	134/88	50	O.B.
B	1	99.8	230	6.81	6.5	—	—	±	O.B.	134/90	90	O.B.
	2	94.8	221	6.40	6.0	Tr.	—	±	O.B.	124/86	82	O.B.
	3	100.3	237	6.65	5.5	—	—	±	O.B.	130/80	88	O.B.
	4	103.7	197	5.99	6.0	—	—	±	O.B.	126/94	74	O.B.
	5	101.9	184	6.13	5.5	—	—	±	O.B.	106/80	76	O.B.
C	1	107.3	199	6.96	5.5	Tr.	—	±	O.B.	128/90	57	O.B.
	2	93.9	198	6.99	6.0	—	—	±	O.B.	126/90	54	O.B.
	3	95.8	203	7.25	6.5	—	—	±	O.B.	124/90	62	O.B.
	4	101.7	199	7.02	7.5	Tr.	—	+	O.B.	128/82	52	O.B.
	5	100.1	171	6.90	6.0	—	—	±	O.B.	118/82	53	O.B.
D	1	99.8	249	6.98	5.5	—	—	±	O.B.	114/72	51	O.B.
	2	96.3	201	6.88	6.0	Tr.	—	±	O.B.	108/70	47	O.B.
	3	97.7	236	7.07	5.5	Tr.	—	±	O.B.	118/70	56	O.B.
	4	98.5	229	6.57	5.5	—	—	±	O.B.	112/70	53	O.B.
	5	94.3	193	6.93	6.0	—	—	±	O.B.	110/71	52	O.B.
E	1	103.2	143	7.66	5.0	Tr.	—	±	O.B.	124/86	58	O.B.
	2	97.0	131	7.78	6.0	—	—	±	O.B.	118/82	55	O.B.
	3	96.9	143	7.31	5.5	—	—	±	O.B.	124/80	46	O.B.
	4	102.6	139	6.97	5.5	—	—	±	O.B.	140/88	55	O.B.
	5	103.8	121	6.94	6.0	—	—	±	O.B.	126/84	54	O.B.
F	1	107.1	201	6.86	5.5	Tr.	—	±	O.B.	110/78	70	O.B.
	2	97.8	174	6.65	6.0	Tr.	—	±	O.B.	118/68	58	O.B.
	3	99.4	194	6.85	5.5	Tr.	—	±	O.B.	108/61	62	O.B.
	4	102.1	186	6.52	5.5	Tr.	—	±	O.B.	108/74	70	O.B.
	5	102.9	172	6.45	5.5	Tr.	—	+	O.B.	114/72	68	O.B.
G	1	103.6	202	7.34	6.0	—	—	±	O.B.	124/88	81	O.B.
	2	96.8	148	7.21	6.0	—	—	±	O.B.	100/62	58	O.B.
	3	96.8	168	7.06	5.5	—	—	±	O.B.	112/74	62	O.B.
	4	95.4	165	6.98	5.5	—	—	±	O.B.	112/74	67	O.B.
	5	102.1	145	6.95	6.0	—	—	±	O.B.	118/78	66	O.B.

pazide was administered t. i. d. for 5 days (Step 4). Heparinized plasma specimens were obtained at 0, 1.5, 8 and 9.5 hr after the first administration of the drug on days 1, 2, 3, and 4.

Samples were taken at 0, 1.5, 8, 9.5, 10 and 11 hr on day 5 and at 0 and 8 hr on day 6. Total urine was collected every 24 hr for 5 days, and then at 8 hr on day 6. Samples were stored at -20°

until analysis.

4. Analytical methods

Sample preparation

Plasma : To a 50 ml glass stoppered centrifuge tube were added 1.0 ml of plasma and 1 ml of M/15 phosphate buffer solution (pH 7.3). The samples were extracted with 10 ml of chloroform containing 1 μ g/ml of α -naphthol, the internal standard. An 8 ml aliquot-of-chloroform layer was transferred to a 10 ml glass-stoppered centrifuge tube and evaporated to dryness under a stream of dry nitrogen. The residue was dissolved in 200 μ l of 0.01N-HCl-methanol (50/50, v/v) and 10 μ l was then subjected to high-performance liquid chromatography.

Urine : Urine samples were diluted 5–40 fold with water, if necessary. To a 50 ml glass-stoppered centrifuge tube were added 1.0 ml of diluted urine and 1 ml of M/15 phosphate buffer (pH 7.3). The samples were extracted with 10 ml of chloroform containing 10 μ g/ml of α -naphthol, the internal standard. A 5 ml aliquot-of-chloroform layer was transferred to a 10 ml glass-stoppered centrifuge tube and evaporated to dryness under a stream of dry nitrogen. The residue was dissolved in 1 ml of 0.04 N-HCl- methanol (50/50, v/v) and 10 μ l was

then subjected to high-performance liquid chromatography.

High performance liquid chromatography :

A Hitachi 635 liquid chromatograph was used for analyzing of all samples. A stable reversed-phase stationary phase, Lichrosorb RP-18 (5 μ m diameter, Merck), was packed into a 150 $\times$ 2.1 mm i. d. stainless steel column using a balance density slurry. The mobile phase was 0.1% (NH₄)₂CO₃-methanol (50/50, v/v). The operating temperature was ambient and the flow rate of the eluate was 0.3 ml/min. The effluent was monitored continuously at 305 nm, with a full scale deflection of 0.02–0.08 AUFS. Concentrations of unknown plasma and urine samples were calculated by comparing the peak height ratio of the extracted samples to processed standards. This method was found to be practical for determining unchanged cinepazide in plasma or urine. The performance of the assay is summarized in Table 3.

5. Pharmacokinetic Analysis

The plasma level versus time profile for cinepazide could be described adequately by viewing the body as consisting of one compartment, with the drug being absorbed, distributed and eliminated from the body through a series of first-order process. Fitting a double-expo-

Table 3 Performance Characteristics of the HPLC Assay

Feature	Capability	
	cinepazide in human plasma and urine	
applicability	plasma	urine
efficiency	102.0% recovery	102.6% recovery
precision	$\pm 0.27 \mu\text{g/ml}$ S.D. (5 $\mu\text{g/ml}$ plasma)	$\pm 1.96 \mu\text{g/ml}$ S.D. (50 $\mu\text{g/ml}$ urine)
range	0 ~ 10 $\mu\text{g/ml}$	0 ~ 100 $\mu\text{g/ml}$
specificity	separates known metabolites	
assay time	up to 30 samples per day manually	

nential curve to observed cinepazide concentrations in plasma was carried out by using the modification program of Lowenthal, W. et al. (1967).

$$C = \frac{ka A_o}{Vd(ka - kd)} (e^{-kd(t-t_o)} - e^{-ka(t-t_o)})$$

C : plasma concentration at time t ($\mu\text{g/ml}$)

Ao : dose (mg/kg)

Vd : apparent volume of distribution (l/kg)

ka : absorption rate constant (hr^{-1})

kd : disappearance rate constant (hr^{-1})

t : time after drug administration (hr)

t_o : lag time for absorption (hr)

Prediction of plasma levels after a given number of doses was carried out according to the assumption that the rate constant for absorption and disappearance is the same as that following the single dose for each dose of the multiple-dose regimen. The physiological characteristics of individuals are such that cinepazide concentrations at any given time are not normally distributed. Consequently, the median of a group may be a better choice than the mean for the simulation of plasma levels (Muller, F. W. et al., 1969).

Results

Cinepazide was administered in single 200 or 400 mg oral doses. The peak concentration was obtained at 1-3 hr and averaged 3.7 (range 2.8-4.9) and 8.1 (range 6.4-10.3) $\mu\text{g/ml}$, respectively (Table 4, Table 5). Interindividual variation in plasma level was rather large at 0.5-1 hr after drug ingestion. The peak plasma level increased proportionally with the dose of cinepazide. Next, there was a rapid fall in the plasma level at both dose levels. The biological half-life varied from subject to subject over the range 0.9-2.7 hr and was independent of the dose, as shown in Table 6.

The plasma levels were not measurable by the assay method after 24 hr with the 200 mg dose. The mean plasma level at 24 hr was 0.02 $\mu\text{g/ml}$ following the 400 mg oral dose. Urinary excretion after 200 and 400 mg of cinepazide is shown in Fig. 2. Approximately 54 to 64 % (mean 57.6 %) of the 200 mg dose was excreted in urine within 24 hr, and 62 to 76 % (mean 66.8 %) of the 400 mg dose was excreted in urine within 24 hr. The extent of urinary excretion increased slightly with the dose. Fig. 3 shows the relationship between the plasma level of

Table 4 Plasma Levels of Unchanged Cinepazide after Single Oral Administration of 200 mg of Cinepazide to Human Subjects

Subject	Plasma level ($\mu\text{g/ml}$)							
	0.5	1.0	1.5	2.0	3.0	5.0	7.0	24.0(hr)
A	0.2	1.8	2.6	2.9	2.3	1.0	0.4	0.0
B	0.1	4.9	4.3	3.5	2.4	1.0	0.5	0.0
C	1.2	4.4	3.5	2.9	2.0	0.9	0.4	0.0
D	2.7	3.4	3.5	3.7	2.9	1.3	0.6	0.0
E	0.4	3.5	3.7	3.5	2.5	1.3	0.5	0.0
F	0.4	2.8	2.7	2.6	2.5	1.1	0.6	0.0
G	0.1	1.3	2.5	3.0	3.5	1.2	0.5	0.0
Mean ±S.E.	0.73 ±0.36	3.16 ±0.49	3.26 ±0.25	3.16 ±0.15	2.59 ±0.18	1.11 ±0.06	0.50 ±0.03	0.0

Table 5 Plasma Levels of Unchanged Cinepazide after Single Oral Administration of 400 mg of Cinepazide to Human Subjects

Subject	Plasma level ($\mu\text{g/ml}$)							
	0.5	1.0	1.5	2.0	3.0	5.0	7.0	24.0(hr)
A	4.5	7.1	7.0	6.8	5.2	2.2	0.9	0.0
B	0.1	0.5	8.2	8.6	6.2	2.6	1.1	0.03
C	0.0	1.2	2.7	5.8	7.0	3.5	1.6	0.06
D	2.3	8.4	8.5	8.4	7.7	3.9	1.5	0.0
E	0.5	0.6	6.4	5.9	6.2	3.9	2.1	0.06
F	7.0	9.1	7.7	6.5	5.1	2.5	1.0	0.0
G	2.6	10.3	9.3	6.1	6.2	2.9	1.1	0.0
Mean	2.43	5.31	7.11	6.87	6.23	3.07	1.33	0.02
$\pm$ S.E.	± 0.98	± 1.65	± 0.82	± 0.44	± 0.35	± 0.26	± 0.16	± 0.01

Table 6 Parameters for Cinepazide Pharmacokinetics

200mg/man									
	A	B	C	D	E	F	G	mean	fit to medians
Ka(hr ⁻¹)	0.715	1.585	1.255	0.756	1.070	0.800	0.715	0.985	1.120
Kd(hr ⁻¹)	0.704	0.753	0.590	0.617	0.605	0.616	0.699	0.655	0.594
t _{1/2} (hr)	0.98	0.92	1.17	1.12	1.15	1.13	0.99	1.07	1.17
t ₀ (hr)	0.42	0.50	0.25	0.00	0.42	0.42	0.83	0.41	0.42

400mg/man									
	A	B	C	D	E	F	G	mean	fit to medians
Ka(hr ⁻¹)	0.785	1.870	0.915	0.731	1.973	1.291	1.251	1.259	0.726
Kd(hr ⁻¹)	0.663	0.362	0.278	0.702	0.255	0.582	0.608	0.493	0.708
t _{1/2} (hr)	1.05	1.91	2.49	0.99	2.72	1.19	1.14	1.64	0.98
t ₀ (hr)	0.08	0.92	0.83	0.33	0.92	0.08	0.33	0.50	0.33

cinepazide and the urinary excretion rate. The experimental results here show that the urinary excretion rate of unchanged cinepazide is directly proportional to the plasma level of cinepazide in human volunteers. Fig. 4 shows the plasma levels of unchanged cinepazide after 1 day of multiple oral administration (t. i. d. 200 mg). The individual plasma levels at 7 : 00 pm (2 hr after the 3 rd administration) were 2.6~5.6 $\mu\text{g/ml}$ (mean 4.6 $\mu\text{g/ml}$). This mean plasma level was slightly higher than the peak plasma level

after a single oral dose of 200 mg of cinepazide. At 24 hr after the final dose, the plasma cinepazide levels were nearly zero. Table 7 shows the result of urinary excretion of unchanged cinepazide following 1 day of multiple oral doses (t. i. d. 200 mg).

Approximately 41 to 69 % (mean 53.5 %) of the dose was excreted in urine over 24 hr after the initial administration. In comparison with the urinary excretion after a single oral dose, a nearly equal percentage of the unchanged drug

Fig. 2 Mean cumulative urinary excretion of unchanged cinepazide after single oral administrations.
 —●— : 200 mg/man, —○— : 400 mg/man
 Mean values $\pm$ S. E. are given.

Fig. 3 Plasma levels and urinary excretion rates of unchanged cinepazide after a single oral administration.
 200 mg/man (—●—: plasma level, —●—: urinary excretion rate), 400 mg/man (—○—: plasma level, —○—: urinary excretion rate)

was excreted. Fig. 5 shows the plasma levels of unchanged cinepazide following multiple oral administration (t. i. d. 200 mg) for five days. The daily peak and valley plasma cinepazide level profile coincided with that of the 1-day multiple dosing. Table 8 shows the urinary excretion of unchanged cinepazide following 5 days of multiple oral administration (t. i. d. 200

Fig. 4 Plasma level of unchanged cinepazide during and after multiple oral administration to human subjects (200 mg, t. i. d., for one day). Dotted line for one-compartment open model fit to medians.
 ○ : mean value $\pm$ S. E., ● : median

mg). The extent of the cumulative urinary excretion was nearly equal each day. In comparison with the urinary excretion of 1 day of multiple oral dosing, here, a slightly larger amount of the unchanged drug was excreted daily. Table 2 shows the results of laboratory tests of volunteers before and after drug administrations. These subjects showed normal laboratory values. No side effect was seen during these experiments.

Discussion and Conclusion

Some knowledge of pharmacokinetic data for single and multiple oral dosing is necessary to develop an optimum dosage schedule which would balance patient convenience with proper body content of drug. In the present investigation, the peak plasma levels of cinepazide were observed at 1-3 hr following single oral doses. Oliver, M. C. et al. (1977) reported that the peak plasma level of cinepazide occurred at 30-45 min following a single 200 mg oral dose in the fasting state. The difference might be due to the gastric emptying rate. The variation in plasma levels at 0.5-1 hr could also be related to variability in the onset of absorption among

Table 7 Urinary Excretion of Unchanged Cinepazide during and after Multiple Oral Administration to Human Subjects (200 mg, t. i. d., for one day)

Subject	Excretion in urine (mg)				
	0 ~ 4	4 ~ 8	8 ~ 24	24 ~ 32	0 ~ 32 (hr)
A	77.4	88.6	106.4	5.0	277.4
B	82.9	149.6	179.2	3.1	414.8
C	77.3	89.8	79.1	4.9	251.1
D	78.8	128.9	138.4	7.9	354.0
E	51.1	134.5	151.5	5.8	342.9
F	65.7	99.5	127.5	8.5	301.2
G	86.4	123.7	130.0	4.0	344.1
Mean $\pm$ S. E.	74.23 $\pm$ 4.55	116.37 $\pm$ 9.00	130.30 $\pm$ 12.06	5.60 $\pm$ 0.75	326.50 $\pm$ 20.63
Accumulated mean value $\pm$ S. E.	74.23 $\pm$ 4.55	190.60 $\pm$ 10.07	320.90 $\pm$ 20.84	326.50 $\pm$ 20.63	$\left[\begin{array}{c} 54.42 \\ \pm 3.44 \\ (\% \text{ of dose}) \end{array} \right]$

Fig. 5 Mean plasma level of unchanged cinepazide during and after multiple administration (200 mg, t. i. d., for five days). Mean $\pm$ S. E. are given.

volunteers, because of malabsorption of cinepazide (basic drug) in the stomach. Of practical importance is the fact that the presence of food appeared to delay the absorption of cinepazide. The peak plasma level increased proportionally with the therapeutic dose of cinepazide. In the multiple dose study, peak and valley plasma cinepazide levels were predicted using a com-

puter program describing an one compartment, open linear pharmacokinetic model. Correlation between the assayed and the computer-predicted median values was 0.964 after 1-day dosage; with 5 day dosage, the correlation was 0.981. The results indicated that plasma cinepazide concentration-time profiles following p.o. doses of the drug could be represented by a

Table 8 Urinary Excretion of Unchanged Cinepazide during and after Multiple Oral Administration to Human Subjects (200 mg, t. i. d., for 5 days)

Subject	Excretion in urine (mg)						
	1	2	3	4	5	6	0 ~ 6 (day)
A	291.6	349.4	309.7	303.6	216.3	4.0	1474.6
B	414.9	428.8	429.5	379.9	346.7	5.4	2005.2
C	253.4	305.0	317.5	307.0	297.5	3.6	1484.0
D	257.9	453.8	421.6	437.6	313.5	7.5	1891.9
E	436.8	461.7	485.5	422.6	369.6	5.8	2182.0
F	386.8	330.5	398.0	438.2	280.1	5.3	1838.9
G	470.0	447.0	452.8	419.8	320.6	4.7	2114.9
Mean $\pm$ S. E.	358.77 $\pm$ 33.87	396.60 $\pm$ 24.92	402.09 $\pm$ 25.06	386.96 $\pm$ 22.32	306.33 $\pm$ 18.75	5.19 $\pm$ 0.49	1855.93
Accumulated mean value $\pm$ S. E.	358.77 $\pm$ 33.87	755.37 $\pm$ 51.09	1157.46 $\pm$ 74.67	1544.41 $\pm$ 92.11	1850.74 $\pm$ 106.74	1855.93 $\pm$ 107.02	
Accumulated mean per cent of dose $\pm$ S. E.	59.80 $\pm$ 5.65	62.95 $\pm$ 4.26	64.30 $\pm$ 4.15	64.35 $\pm$ 3.84	61.69 $\pm$ 3.56	61.86 $\pm$ 3.57	

linear pharmacokinetic system with reproducible absorption. This multiple dosing schedule using the same dose (200 mg every 4 hr for three doses) produced a peak level at 4.7 μ g/ml after the 3rd administration, falling to barely measurable quantities prior to the next day's dose. The total excretion in the urine was 115 and 267 mg during 24 hr collection period for the 200 and 400 mg single doses, respectively. The extent of urinary excretion was larger than that reported by Oliver, M. C. et al. (1977).

The extent of urinary excretion of cinepazide increased slightly with increased dosing. This tendency might be due to the slow metabolism of cinepazide at higher dose. The cumulative urinary excretion of cinepazide was nearly constant during the experiments. This result suggested reproducible absorption and excretion of cinepazide during multiple dose experiments. The experimental results presented here show that the urinary excretion rate of unchanged cinepazide is directly proportional to

the plasma level in human subjects. It thus would appear that plasma cinepazide was mainly excreted in the urine without significant transformation.

In conclusion, cinepazide is well-absorbed orally. The onset of absorption is delayed by food. Cinepazide is mainly excreted in the urine as the intact compound. The peak plasma level of cinepazide is dose dependent in the therapeutic dose range. Urinary excretion of unchanged cinepazide is slightly larger in higher doses. No difference is observed in the plasma level and urinary excretion patterns during the ordinary dosage schedule (200 mg t. i. d.). No accumulation of the drug and no side-effect are expected following repetitive oral dosing in the clinical trials.

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