Clopamide: Plasma concentrations and diuretic effect in humans

Clopamide pharmacokinetics were determined after oral doses of 5, 10, and 20 mg in normal volunteers. Maximum plasma concentrations occurred within 2 hours and were followed by a monoexponential decline with an elimination half-life of approximately 10 hours. There was an approximately linear relationship between dose and the AUC. Urinary sodium, chloride, and potassium excretion rates indicated that the peak diuretic activity corresponded with peak plasma drug concentrations and probably continued for 12 to 24 hours. There was little difference between the total sodium and chloride output after each dose of clopamide, suggesting that 5 mg may have been close to the top of the dose-response curve. Chlorothiazide, 500 mg, caused less sodium and chloride output with similar potassium loss. During chronic administration to patients with hypertension, hypokalemia was more marked with clopamide, 10 mg daily, than with clopamide, 5 mg, or chlorothiazide, 500 mg daily. (CLIN PHARMACOL THER 1987;42: 299-304.)

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Clopamide is an oral diuretic agent that shares the same aromatic sulfonamide base as the thiazide diuretics but is without the double-ring structure characteristic of these compounds.[1] It has proved effective in the treatment of hypertension and cardiac failure in a recommended daily dose of 5 to 20 mg/day.[2-6]

Pharmacokinetic and dose-response studies of clopamide have been limited by the lack of a sensitive assay technique. In this study a new HPLC assay is described that has allowed an examination of the pharmacokinetic disposition of clopamide after single oral doses and an investigation of the relationship between plasma levels of the drug and its effects on water and electrolyte excretion. A single dose of chlorothiazide was used as a reference compound. Because of concern that high doses of thiazide diuretics may have adverse biochemical effects, including elevations of serum lipids and hypokalemia, a clinical trial was also undertaken to compare biochemical changes of placebo with chronic administration of two doses of clopamide, 5 and 10 mg daily, and 500 mg daily doses of chlorothiazide.

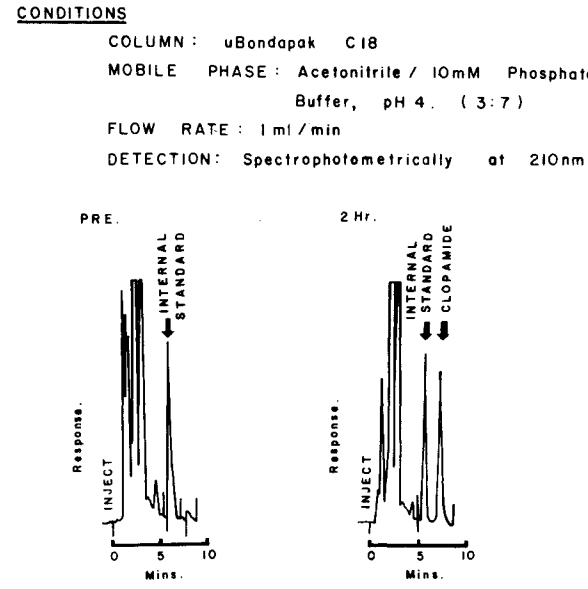

Fig. 1. HPLC of clopamide and internal standard, chlorthalidone.

METHODS

Pharmacokinetic study. Eight subjects (six men and two women) aged 20 to 23 years participated in the study. All subjects had normal clinical examinations

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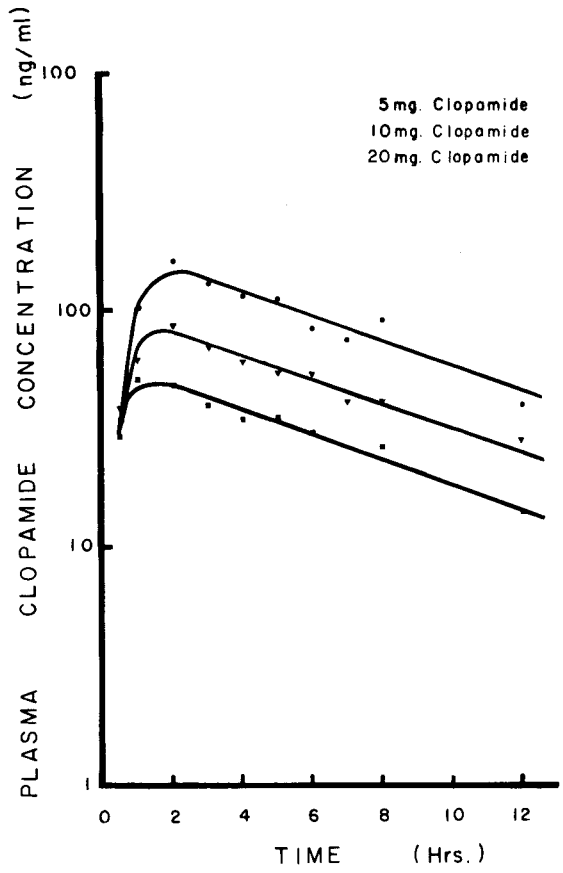

Fig. 2. Plasma concentrations of clopamide after oral administration of three doses of the drug (■, 5 mg clopamide; ▼, 10 mg clopamide; ●, 20 mg clopamide).

Table I. Pharmacokinetic parameters after acute administration of clopamide

	Clopamide		
	5 mg	*10 mg*	*20 mg*
C_{max} (ng/ml)	63 ± 9	91 ± 5	175 ± 13
t_{max} (hr)	1.9 ± 0.5	2.5 ± 0.5	1.8 ± 0.2
AUC (ng/ml/hr)	543 ± 87	862 ± 79	1538 ± 61
$t_{1/2}$ (hr)	11.6 ± 2.9	10.0 ± 1.4	8.1 ± 1.8

and were free from significant past or intercurrent illnesses. Biochemical and hematologic profiles taken 1 week before the beginning of the study were also within normal limits. Subjects were instructed to maintain a constant diet throughout the course of the study. The subjects were studied on four occasions 3 to 7 days apart. On each occasion either oral clopamide (in a dose of 5, 10, or 20 mg) or oral chlorothiazide, 500 mg,

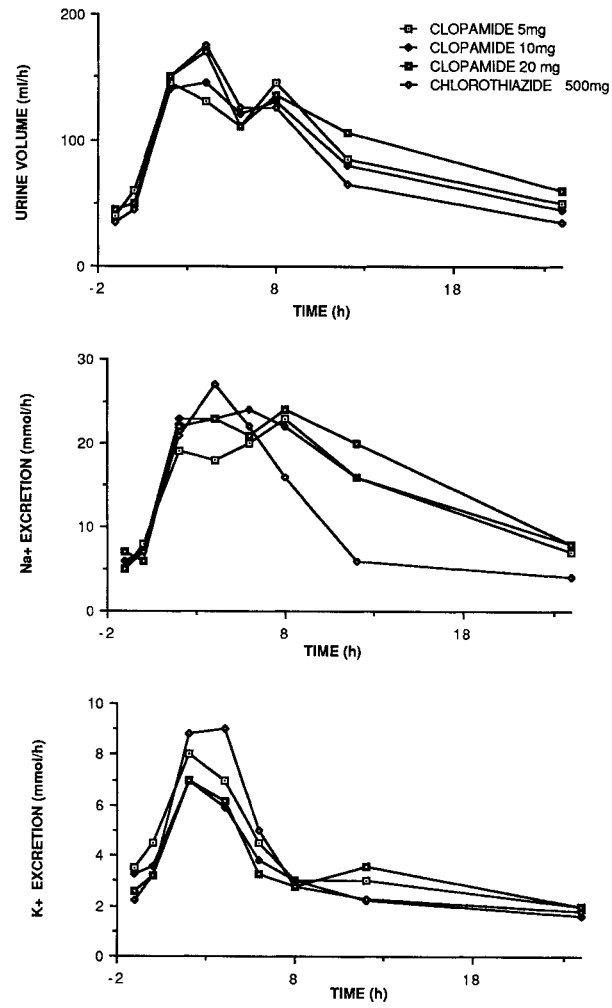

Fig. 3. Excretion rate of urine *(top)*, sodium *(middle)*, and potassium *(bottom)* after oral administration of clopamide and chlorothiazide. The excretion rates represent the average during the collection interval and have been plotted at the midpoint of the interval. Sodium excretion rates during the 12- to 24-hour interval were different as shown by one-way ANOVA ($P < 0.01$). Student-Newman-Keuls tests indicated that clopamide produced a greater excretion of sodium in this interval than did chlorothiazide ($P < 0.05$). Potassium and urine excretion rates did not vary significantly between treatments.

was administered in randomized order. No alcohol or other medications were allowed from 2 days before until after the completion of each study.

On each study day subjects consumed a standard breakfast at 8 AM after an overnight fast. Two 1-hour urine samples were collected as a baseline between 8 AM and 10 AM and after administration of the drug

Table II. Cumulative amount of urine and electrolytes excreted in 24 hours after oral acute administration of clopamide and chlorothiazide

	Clopamide			*Chlorothiazide, 500 mg*
	5 mg	*10 mg*	*20 mg*	
Urine	2163 ± 177	2051 ± 244	2349 ± 214	1901 ± 182
Sodium	329 ± 32	374 ± 27	384 ± 27	249 ± 18*
Chloride	331 ± 27	351 ± 22	400 ± 32	250 ± 24*
Potassium	88 ± 9	76 ± 5	92 ± 9	86 ± 8

*One-way ANOVA indicated a significant difference in the cumulative amount of electrolyte excretion after the four treatments. Student-Newman-Keuls procedure indicated that the subjects given chlorothiazide excreted less electrolytes than those given clopamide ($P < 0.05$).

with 200 ml water. At 10 AM further timed urine collections were made 2, 4, 6, 8, 12, and 24 hours after drug administration. Urine volumes (V_{ur}) were measured and samples were stored at 4° C until analyzed for electrolytes and creatinine. Blood samples for drug estimation were collected 0, ½, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours after administration and the centrifuged plasma was stored at −20° C until assayed. For the first 8 hours of the study, fluid intake was restricted to water (200 ml 2, 4, 6, and 8 hours after administration), and standard meals were provided at midday and 6 PM.

The protocol was approved by the University and Hospital Ethics Committees and informed written consent was obtained from each participant.

Measurement of clopamide in plasma. HPLC, consisting of a solvent delivery system (M 6000, Waters Associates, Milford, Mass.), an automatic injector (Waters Intelligent Sample Processor), a Waters data module, and a variable wavelength ultraviolet detector operating at 210 nm (M450, Waters Associates) were used. The column was a stainless steel μBondapack phenyl column with a mobile phase consisting of acetonitrile/10 mmol/L potassium dihydrogen phosphate, pH 4.0 in the proportion 3:7. Flow rate was 1 ml/min. Under these conditions the retention times of clopamide and the internal standard, chlorthalidone, were 7.2 and 5.9 minutes, respectively (Fig. 1).

Standards were prepared by spiking clopamide to drug-free plasma in the concentration range of 10 to 500 ng/ml. To 1 ml plasma sample or standard, 50 μl of chlorthalidone internal standard (500 ng) was added and the pH was adjusted to 8.5 with 1 mol/L sodium hydroxide solution. The samples were then extracted with 10 ml dichloromethane on a reciprocating shaker for 10 minutes and briefly centrifuged (1000 g maximum for 5 minutes). The dichloromethane was then transferred to a clean extraction tube and evaporated to dryness under a gentle stream of nitrogen at 40° C. The residue was reconstituted with 100 μl mobile phase and an aliquot (usually 25 μl) was injected into the HPLC.

Clopamide levels were calculated by comparing ratios of clopamide and chlorthalidone in unknown plasma samples with those in standards. The coefficients of variation for within-assay reproducibility were 4.5% (50 ng/ml) and 8% (250 ng/ml) and for interassay reproducibility 10% (200 ng/ml). The minimum detectable concentration was 10 ng/ml plasma.

Pharmacokinetic analysis. The elimination half-life ($t_{1/2}$) of clopamide was determined from graphs relating the log of the plasma-drug concentration of each individual to time after drug administration. The curve of best fit was determined for each data set by nonlinear least-squares regression with the computer package AUTOAN-2 (Ann Arbor, Mich.). Data were not weighted and first-order absorption and elimination were assumed. Cases in which the fit of the curves to measured plasma levels was poor ($R < 0.6$) were not included in the calculation of average values.

AUCs were calculated with the trapezoidal rule. Estimates of areas beyond the last measured plasma concentration (C) were obtained from the expression C/β, where β is the slope of the terminal exponential of drug disposition.

Clinical trial. Sixteen patients (nine men and seven women) aged 32 to 68 years participated in the study. All had essential hypertension previously treated with a diuretic as the sole antihypertensive therapy. All patients had normal biochemical and hematologic indexes and none were receiving chronic drug treatment that might affect either blood pressure control or electrolyte balance. To enter the study, subjects were required to have a supine diastolic blood pressure within the range of 90 to 110 mm Hg and plasma potassium levels >3.5 mmol/L 2 weeks after ceasing previous medication. The protocol was approved by the Hospital Ethics Committee and informed, written consent was obtained from each participant.

Table III. Plasma biochemistry (mean ± SD) during chronic administration of clopamide and chlorothiazide to 16 hypertensive patients

	Placebo (mmol/L)		*Clopamide, 5 mg (mmol/L)*		*Clopamide, 10 mg (mmol/L)*
	3 Wk	*5 Wk*	*3 Wk*	*5 Wk*	*3 Wk*
Potassium	3.9 ± 0.1	4.0 ± 0.5	3.5 ± 0.1	3.6 ± 0.1	3.4 ± 0.1
Sodium	140 ± 0.5	140 ± 0.5	140 ± 0.4	140 ± 0.5	139 ± 0.8
Bicarbonate	27 ± 2.6	27 ± 3.3	30 ± 3	29 ± 3	31 ± 2
Urea	5.7 ± 1.0	6.0 ± 1.3	6.1 ± 1.2	6.3 ± 1.0	6.6 ± 1.5
Creatinine	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.02	0.09 ± 0.01	0.1 ± 0.01
Calcium	2.3 ± 0.1	2.3 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.07
Fasting glucose		5.8 ± 1.9		5.3 ± 2.0	
Cholesterol		6.2 ± 1.0		6.4 ± 0.9	

*One-way ANOVA of the data at 5 weeks indicated a significant linear relationship between potassium levels with placebo and clopamide, 5 and 10 mg ($P < 0.0001$). There was also a significant difference between the four treatment groups ($P < 0.001$), and subsequent comparisons using Student-Newman-Keuls procedure indicated that placebo differed from the other three treatments ($P < 0.05$).

The study was conducted as a double-blind Latin square crossover trial balanced for carryover effects. Two weeks after ceasing previous medication, subjects who met the entry criteria were randomly assigned to treatment with either placebo, clopamide, 5 mg or 10 mg, or chlorothiazide, 500 mg daily, for 5 weeks. Subsequent active drug periods of 5 weeks' duration were interspersed with 2-week washout periods during which all subjects received potassium supplements. Plasma potassium levels were measured 3 and 5 weeks after the start of each treatment period. If these were <3.0 mmol/L at the 3-week visit, potassium supplementation (18 mEq potassium/day) was introduced. Plasma sodium, urea, creatinine, and bicarbonate values were also determined 3 and 5 weeks after the start of each treatment. Plasma cholesterol and fasting plasma glucose levels were determined at the 5-week point.

Statistical analysis. All data have been expressed as means ± SE unless otherwise indicated. The V_{ur} and the quantity of sodium, potassium, chloride, and creatinine appearing in the urine have been presented as excretion rates averaged over 24 hours. The effects of the four different drug regimens on water and electrolyte excretion were analyzed by one-way ANOVA. If this procedure indicated differences between the regimens, subsequent multiple comparisons were carried out by the Student-Newman-Keuls procedure.

RESULTS

Average plasma concentrations of clopamide after administration of three dose levels of the drug are shown in Fig. 2. Pharmacokinetic parameters derived from these data are shown in Table I. The drug was absorbed rapidly with maximum plasma levels achieved within 2 hours of administration. Average AUCs increased approximately in proportion to the dose administered (0.6:1.8). The average elimination $t_{1/2}$s were around 10 hours and did not differ significantly between doses.

Average amounts of creatinine excreted during the collection periods were similar after each of the drug doses, indicating similar completeness of urine collection. The rates of urine output per hour during the baseline period and after administration of the drugs are shown in Fig. 3. Both clopamide and chlorothiazide increase the rate of urine production to a maximum 2 to 4 hours after administration. Output was still significantly higher than baseline levels during the 12- to 24-hour collection period. No significant difference existed in the total V_{ur} after each of the four treatments (Fig. 3; Table II).

The rate of sodium excretion (U_{na}) was also maximal 2 to 4 hours after drug administration. During the first 8 hours U_{na} was similar after each of the four drug doses (Fig. 3), but beyond this time the U_{na} produced by 500 mg chlorothiazide returned to basal levels whereas the effect of all three doses of clopamide remained high. However, no relationship existed between doses of clopamide administered and the U_{na} and no clinically or statistically significant differences were apparent during any of the collection periods or when the cumulative amount of U_{na} over 24 hours was compared. The excretion rate of chloride ions and the cumulative output of chloride (Table II) showed a pattern similar to that of U_{na}.

Clopamide also increased the excretion rate of potassium, although in contrast to its effect on U_{na} this

Clopamide, 10 mg (mmol/L)	*Chlorthiazide, 500 mg (mmol/L)*	
5 Wk	*3 Wk*	*5 Wk*
3.4 ± 0.1	3.8 ± 0.1	3.7 ± 0.1*
139 ± 0.7	140 ± 0.4	139 ± 0.4
29 ± 3	29 ± 0.5	28 ± 0.6
6.3 ± 1.5	6.0 ± 1.3	6.1 ± 1.6
0.09 ± 0.01	0.09 ± 0.02	0.09 ± 0.02
2.4 ± 0.06	2.4 ± 0.13	2.4 ± 0.09
5.6 ± 1.3		5.4 ± 1.2
6.1 ± 1.6		6.3 ± 0.8

effect had declined to near baseline levels by the time of the 6- to 8-hour urine collection. The excretion rates and the cumulative amount of potassium excreted were again similar after chlorothiazide and the three doses of clopamide (Fig. 3; Table II).

In the crossover trial, daily administration of clopamide produced a significant dose-dependent reduction in plasma potassium levels compared with placebo (Table III). In eight subjects receiving 10 mg clopamide, plasma potassium levels were <3.5 mmol/L after 3 weeks of treatment compared with two subjects in both the 5 mg clopamide and 500 mg chlorothiazide groups and none in the placebo group. In three patients receiving 10 mg clopamide daily, plasma potassium levels were <3 mmol/L 3 weeks after beginning treatment, and thereafter they received potassium supplementation.

There were no significant changes in any of the other biochemical parameters measured (Table III).

DISCUSSION

Diuretic agents such as clopamide are widely used for the treatment of hypertension and cardiac failure. Despite their long use, controversy still exists about appropriate doses to be used in these conditions.[7] This debate has been stimulated by the results of recent large-scale trials such as the Multiple Risk Factor Intervention Study, which raised the possibility that high doses of diuretics might be harmful.[8]

It has been suggested recently that the benefit to side effect ratio of several widely used diuretic agents might be improved by lowering the recommended dose.[7] This notion has been supported by studies of chlorthalidone that produced a substantial incidence of hypokalemia when administered in a dose of 50 to 100 mg daily.[9] Since the recommended dose was reduced to 12.5 to 25 mg daily, this problem appears to have been largely resolved. Such problems may have arisen because the recommended doses of these agents were determined before modern methods of dose-response evaluation were introduced.

Clopamide is a thiazide-like diuretic agent whose recommended dose in hypertension has been up to 20 mg/day and in cardiac failure up to 60 mg/day. Like many other agents of this type, its pharmacokinetics have never been evaluated, largely because of the lack of an adequate assay. In the present study a new HPLC procedure has enabled plasma concentrations of the drug to be measured for up to 24 hours after administration. Sodium, potassium, and chloride excretion were used as a measure of the pharmacodynamic effect of the drug. The results demonstrated that clopamide is absorbed rapidly and, after attaining peak levels, plasma concentrations declined in a monoexponential fashion with $t_{1/2}$s on the order of 10 hours. Over the dose range of 5 to 20 mg the AUC increased roughly in proportion to the dose, and the elimination $t_{1/2}$ remained unaltered.

Despite the linearity of the pharmacokinetic behavior of the drug there was little evidence of dose dependency in the effect of single doses on water and electrolyte excretion. In 24 hours the 20 mg dose of clopamide resulted in only 17% greater loss of sodium and 9% greater excretion of water than the 5 mg dose. This suggests that 5 mg clopamide is close to the upper plateau of the dose-response curve and it is possible that even lower doses will provide a maximal diuretic effect. Alternately, because thiazide and thiazide-like diuretics act on renal tubules from within the nephron, it is possible that renal excretion and hence urinary drug concentration was maximal at the 5 mg dosage level. Because urinary clopamide levels were not measured in the present study, this possibility cannot be excluded. However, the apparently linear relationship between dose and AUC makes this possibility less likely. In addition, it must be emphasized that this study was conducted with single doses given to young, healthy volunteers. Older subjects receiving chronic treatment or those with sodium-retaining conditions might prove more refractory to the diuretic and natriuretic effects of the drug.

Although the increased U_{na} and water excretion persisted into the 12- to 24-hour observation period, the effect on potassium had disappeared by 8 hours. Possibly a higher concentration of clopamide is required to trigger potassium excretion. If so it might be expected that with repetitive administration and accumulation of

clopamide in plasma the potassium loss might be relatively greater than was apparent in this single-dose study.

The question of potassium excretion with chronic administration of clopamide was investigated in more detail with a crossover trial in hypertensive patients. Evidence from this study indicated that at the 10 mg daily dose level there was a lower average potassium level and a higher number of patients with potassium levels <3.5 mmol/L despite a larger number of subjects receiving potassium supplements. Thus despite evidence from the single-dose study that potassium excretion was similar at the 5, 10, and 20 mg dose level, with chronic administration evidence of hypokalemia was more apparent at the higher dose. The explanation for this discrepancy may lie in an accumulation of plasma clopamide concentrations with chronic administration. However, the presence of hypokalemia during chronic administration confirms previous reports that even small doses of long-acting thiazide-like diuretics may produce some degree of hypokalemia.

It is interesting that during chronic administration to hypertensive patients no significant effect of diuretic therapy on plasma cholesterol or fasting blood glucose levels was observed. This may have reflected the relatively small number of patients investigated or the short duration of the study.

In summary, this study has suggested that single doses of 5 mg clopamide are virtually as effective in their natriuretic and diuretic effect as 10 and 20 mg doses. The kaliuretic effect, although similar at the three dose levels, was briefer, suggesting that higher drug concentrations might be necessary to trigger potassium loss. This suggestion received some support from the results of the chronic dosing study, which suggested a higher frequency of hypokalemia after 10 mg clopamide than after 5 mg clopamide or 500 mg chlorothiazide.

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