Figure 3 shows the mean blood propranolol levels in rats after the nasal administration of the sustained-release formulations as compared to those obtained previously (4) after intravenous, oral, and nasal administration of an isotonic solution of the drug.

The pharmacokinetic parameters calculated for the different formulations and for the different administration routes are shown in Table III.

Figure 4 shows the mean plasma level in dogs after the nasal administration of the solution and two sustained-release formulations as well as the intravenous and oral solutions. Table IV shows the pharmacokinetic parameters in dogs calculated for the different formulations and for the different administration routes.

DISCUSSION

The oral administration of propranolol to human subjects resulted in low and variable plasma drug levels compared to intravenous administration (1). Similar results were obtained in rats and dogs after the oral administration of propranolol solution (Figs. 3 and 4). However, the data in Figs. 3 and 4 clearly show that the nasal administration of the drug solution in both rats and dogs resulted in plasma drug levels similar to those of an intravenous administration. The data in Figs. 3 and 4 show that the sustained-release formulations resulted in lower initial blood levels of the drug. However, the drug level in the blood was maintained longer. Furthermore, the blood drug profile from the sustained-release formulations administered to rats correlated with the *in vitro* (Fig. 2) release of the drug from these formulations.

The pharmacokinetic parameters for the different formulations and different administration routes obtained for both rats and dogs are shown in Tables III and IV, respectively. The maximum blood levels of the drug observed after administration of the sustained-release formulations were much lower than those observed after administration of the nasal solutions. However, the bioavailability calculated from the area under the blood level curves was identical.

The results of this study strongly suggest that the nasal administration of propranolol is superior to the oral route and as effective as the intravenous route. A study is underway on the bioavailability of propranolol from nasal dosage forms in humans.

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Pharmacokinetics of Phenylbutazone in Healthy Subjects after Oral Administration of Single and Multiple Doses

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Received December 10, 1979, from the **Biopharmaceutical Research Center and the* ‡*Medical Department, Ciba-Geigy, Rueil-Malmaison, France,* and the §*Department of Rheumatic Diseases, Antoine Béclère Hospital, Clamart, France.* Accepted for publication June 23, 1980.

Abstract □ Plasma concentration profiles were studied after single oral doses of phenylbutazone of 100, 300, and 600 mg in cachets to six healthy volunteers. The pharmacokinetics of phenylbutazone can be described by a two-compartment open model. The drug is absorbed rapidly and distributed partially into an extravascular compartment; about one-third remains in the plasma. The mean elimination half-life was 77 hr (54–99 hr), and there was a linear relationship between the dose and the area under the plasma concentration curve. In a multiple-dose study, six healthy volunteers received 150 mg of phenylbutazone in cachets twice daily every 11–13 hr for 17 days. A steady state was reached after ~200 hr of chronic treatment. The resultant steady-state plasma concentrations were about four times higher than the peak concentration produced by a single 150-mg dose. The half-lives corresponding to the apparent elimination rate constant for the first and last administrations did not differ in each subject. The theoretical minimum concentrations are higher than the pseudosteady state reached during chronic treatment.

Keyphrases □ Phenylbutazone—pharmacokinetics after single and multiple oral doses □ Pharmacokinetics—phenylbutazone, single and multiple oral doses □ Anti-inflammatory agents—phenylbutazone, pharmacokinetics after single and multiple oral doses

Phenylbutazone has been used as an anti-inflammatory agent for about 25 years. After oral administration, it is completely and rapidly (1) absorbed and almost completely metabolized (1–3). Its half-life in plasma ranges from 1 to 3 days (1, 2, 4–6) and shows large interindividual differences. Phenylbutazone is highly protein bound (~99%) (1). The drug is eliminated mainly in the urine (60–70%) (1, 2).

The single-dose kinetics of phenylbutazone have been studied (1, 7, 8), and two-compartment model was proposed for it (8). There is an almost linear relationship between the dose and the area under the plasma concentration curve (*AUC*) (9).

No precise information is available on multiple-dose kinetics. The steady-state plasma levels of phenylbutazone were measured by several investigators (1, 10–14) and were predicted by Orme *et al.* (12) from knowledge of the half-lives of antipyrine in individual subjects but not from the single-dose kinetics of phenylbutazone. The discrepancy between predicted and measured steady-state plasma levels of phenylbutazone has been discussed, and it was suggested that an increase in the volume of distribution occurs after multiple dosing (14).

Recent advances in analytical methodology (15) have made possible the investigation of the pharmacokinetics of phenylbutazone in humans in greater detail. This report describes the plasma concentration profiles obtained after the oral administration of phenylbutazone in single doses of 100, 300, and 600 mg and after repeated administration of 150 mg twice daily for 17 days.

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EXPERIMENTAL

Subjects—Six healthy volunteers were instructed to take no drugs of any kind for at least 1 week prior to the study and no drugs other than phenylbutazone during the experiment.

Five males and one female, 23–29 years and 58–95 kg, participated in the single-dose study. Subjects 2, 3, and 5 took part in the later multiple-dose study together with three additional volunteers. The subjects in this group of four males and two females were 22–29 years old and 59–80 kg.

Procedure—Phenylbutazone was given as the pure active ingredient in cachets without any excipient.

Single-Dose Study—Each subject received 100, 300, and 600 mg at 4-week intervals according to the crossover design. The doses were given to the fasting subjects with 100 ml of water at ~8 am, 2 hr before a light standardized breakfast. A standard lunch was given 4 hr later.

Blood samples (5 ml) were collected in heparinized tubes before and 0.5, 1, 2, 3, 4, 6, 8, 24, 48, 72, 96, and 168 hr after drug administration. The 48-hr sample was omitted after the 600-mg single dose, but additional samples were collected after 240 and 336 hr. Plasma was separated by centrifugation and kept at −20° until analysis.

Multiple-Dose Study—Each subject received one 150-mg dose on the 1st and 22nd days and 150 mg twice daily from the 5th day until the 21st day. The interval after the first dose was allowed so that the total plasma concentration curve of the first dose could be plotted over 96 hr. Morning doses were taken at ~9 am during breakfast. Evening doses were taken during the meal at ~8 pm.

Blood samples were collected in heparinized tubes at various times after the first and last administrations and just before each morning dose during chronic treatment. Plasma was obtained by centrifugation and kept at −20° until the time of analysis.

Drug Assay—Phenylbutazone was assayed in plasma samples from the single-dose study by a GLC method using a flame-ionization detector that measured concentrations as low as 250 ng/ml of plasma. All samples were assayed in duplicate.

In the meantime, a new GLC method (15) was developed using an electron-capture detector capable of determining concentrations down to 10 ng/ml of plasma with the same extraction procedure as used in the flame-ionization technique. Plasma samples from the multiple-dose study were analyzed for phenylbutazone by the electron-capture GLC method. All samples were assayed in duplicate.

Both methods yielded similar results for the same set of samples. Two spiked plasma solutions were prepared (250 and 2500 ng of phenylbutazone/ml of plasma) and analyzed six times by the flame-ionization method and six times by the electron-capture method for each concentration. The results were 250.8 ± 3.6 ($CV\%$, n = 6) and 2473.3 ± 4.3 with flame-ionization detection and 249.8 ± 5.0 and 2483.0 ± 5.3 with electron-capture detection.

Moreover, the three unconjugated metabolites of phenylbutazone in plasma (15) were tested by the flame-ionization and electron-capture methods. None of these metabolites interfered with phenylbutazone chromatography.

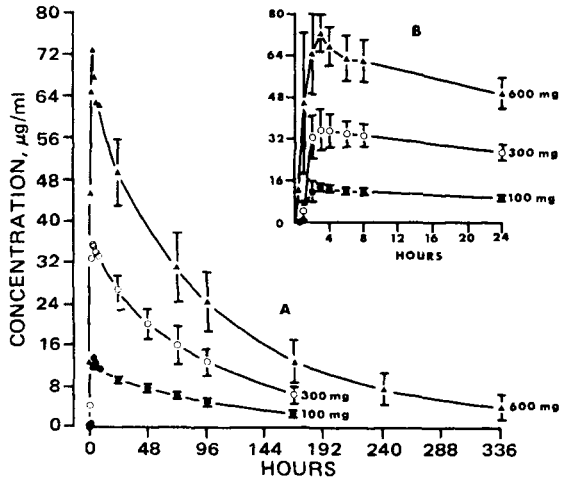

Figure 1—*Mean plasma phenylbutazone concentrations* (±SD) *in six healthy volunteers for doses of 100* (●), *300* (○), *and 600* (▲) *mg. Curve A shows concentrations up to 168 hr for 100 and 300 mg and up to 336 hr for 600 mg. Curve B shows concentrations up to 24 hr.*

Table I—Individual Pharmacokinetic Parameters of Phenylbutazone from Single-Dose Study [a]

Dose, mg	Subject	C_{max}, μg/ml	T_{max}, hr	$T_{1/2}$, hr	AUC_∞, (μg hr)/ml
100	1	12.48	1.81	99.0	1188
	2	17.05	2.88	74.5	1496
	3	14.25	3.22	73.7	1080
	4	12.63	7.03	83.5	1596
	5	13.80	2.90	66.0	1167
	6	15.32	1.81	63.6	1108
	Mean	14.25		76.7	1272
	SD	1.73		13.0	217
	Median		2.89		
300	1	35.05	3.29	86.6	3470
	2	42.96	5.09	54.1	3050
	3	30.77	5.86	74.5	3461
	4	46.33	1.85	78.7	4046
	5	35.43	3.23	82.5	3362
	6	39.97	2.86	70.7	3083
	Mean	38.41		74.5	3412
	SD	5.73		11.5	360
	Median		3.26		
600	1	51.18	6.38	92.4	6615
	2	81.44	3.57	70.0	6349
	3	81.34	2.35	82.5	7430
	4	83.30	2.96	94.8	9734
	5	88.11	1.73	62.4	5629
	6	65.87	0.99	70.0	4441
	Mean	75.20		78.7	6700
	SD	13.94		13.2	1795
	Median		2.65		

[a] C_{max}, T_{max}, and k_E values were calculated from the multiexponential equation giving the best fit to the experimental results. The $T_{1/2}$ values were derived from k_E, and the AUC values were extrapolated to time infinity according to the $T_{1/2}$ values.

Mathematical Methods—The calculations, curve fitting, and statistical analysis were carried out with the aid of a computer[1] equipped with a plotter[2].

RESULTS

Single-Dose Study—*Plasma Concentration–Time Curves*—The curves were obtained by using a multiexponential computer program that selects the equation giving the best fit to the experimental results. The individual curves, as well as the average curves (Fig. 1), exhibited a two-phase decline of the plasma concentration as a function of time. This finding indicates a distribution phase that is sufficiently slow, as compared to the absorption phase, to be visible after absorption is almost completed.

The pharmacokinetics of phenylbutazone, therefore, can be described by a two-compartment open model. With the assumption that all transfer processes, including absorption, are first order, such a model corresponds to a three-term exponential equation. In fact, 16 of the 18 individual curves fitted such an equation.

The equations of the average curves are as follows. For the 100-mg dose:

$$C = -88.00e^{-1.651t} + 12.22e^{-0.5606t} + 10.74e^{-0.0093t} \quad \text{(Eq. 1)}$$

For the 300-mg dose:

$$C = -180.00e^{-1.802t} + 4.87e^{-0.0920t} + 30.78e^{-0.0101t} \quad \text{(Eq. 2)}$$

For the 600-mg dose:

$$C = -152.38e^{-0.994t} + 5.94e^{-0.4005t} + 55.67e^{-0.0092t} \quad \text{(Eq. 3)}$$

The individual equations permitted the calculation of the pharmacokinetic parameters shown in Table I.

Absorption—Phenylbutazone was absorbed rapidly, with the maximum concentration being reached ~3 hr after administration. Nevertheless, the individual values of T_{max} were scattered, and there was a variable delay in some subjects before absorption started (lag time).

In six of 18 cases, the rate of absorption appeared to be slow initially and then increased gradually. This finding indicates that drug absorption was fast enough to have little, if any, effect on the other two phases, *i.e.*, distribution and elimination.

[1] Wang 720 C.
[2] IBM.

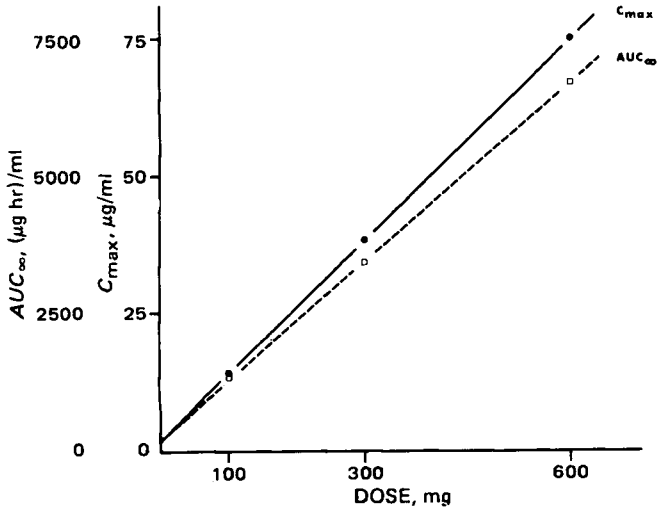

Figure 2—*Relationship between dose and* C_{max} (●) *and between dose and* AUC_∞ (□) *for phenylbutazone in a single-dose study.*

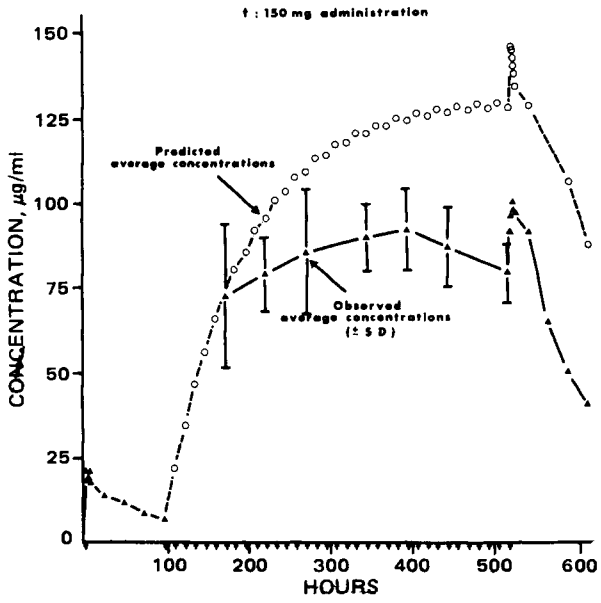

Figure 3—*Predicted* (○) *and observed* (▲) *average plasma concentrations of phenylbutazone during chronic treatment.*

Distribution—The apparent volume of distribution can be estimated from the area under the plasma concentration curve (AUC) and the elimination rate constant (k_E):

$$V_{area} = \frac{F \text{ dose}}{k_E AUC} \qquad \text{(Eq. 4)}$$

where F is the fraction of the dose absorbed.

The average value of the apparent volume of distribution (V_{area}) for all doses was 10.2 liters, assuming that $F = 1$. The volume of plasma (calculated on the basis of 41 ml/kg of body weight) was 2.9 liters. Since F is ≤ 1, ~30% of the administered phenylbutazone remained in the plasma.

Elimination—The overall elimination rate constant, k_E (Table I), clearly was independent of the dose. The mean elimination half-life for all doses was 77 hr, but the individual values varied from 54 to 99 hr. The intrasubject variation was less but was not negligible.

Dose Dependency of Pharmacokinetic Parameters—As shown in Fig. 2, there was a satisfactory linear relationship between the dose and C_{max} and between the dose and AUC_∞ (AUC extrapolated to infinity).

Multiple-Dose Study—Phenylbutazone elimination half-lives ($T_{1/2}$) estimated from the slope of the terminal linear segment of log–linear plots of the plasma concentration were similar at the beginning and end of the chronic treatment. Mean values (±SD) were 65.5 (±8.9) and 66.8 (±12.0) hr, respectively. The areas under the concentration profiles following administration of the first dose were measured by the trapezoidal rule and extrapolated to time infinity using the $T_{1/2}$ values. Their mean value (±SD) was 1697 (±231) (μg hr)/ml, which was in good agreement with the value calculated from the single-dose study [1706 (μg hr)/ml].

The AUC values after single doses were larger than those for a dose interval after multiple dosing; the mean values for the six subjects were 1697 (μg hr)/ml for AUC_0^∞ after a single dose and 1140 (μg hr)/ml for AUC_{504}^{516} after multiple doses. (Plasma levels after 516 hr were estimated roughly by interpolation from the 512- and 528-hr values.) The ratio of these two mean AUC values is similar to the ratio of the measured (~90 μg/ml) to the predicted (~130 μg/ml) steady-state plasma levels (~0.7).

As chronic treatment proceeded, the plasma phenylbutazone concentration measured just before the morning dose increased progressively up to values about four times higher than the peak concentration following the administration of the first dose of the treatment (mean value ± SD, 24.7 ± 6.2 μg/ml). Theoretical phenylbutazone concentrations just before the morning dose were obtained by the superposition technique and were distinctly higher than the corresponding experimental values (Fig. 3).

DISCUSSION

The pharmacokinetics of single doses of phenylbutazone can be described by a two-compartment open model. The drug was absorbed rapidly after oral administration in a single dose. It was distributed partially to an extravascular compartment, but at least one-third of the absorbed drug remained in the plasma. This finding is in agreement with the data reported by Burns *et al.* (1). The mean elimination half-life of phenylbutazone was ~77 hr, with individual values varying from 54 to 99 hr, which are within the reported range (1, 2, 4–6). There was a satisfactory linear relationship between the dose and the AUC. This finding is in agreement with the results reported by Lukas *et al.* (9); the fourfold increase of the dose did not cause a qualitative change in the elimination kinetics of phenylbutazone.

Single doses showed a linear relationship of AUC, C_{max}, and dose up to 600 mg, whereas upon multiple dosing, the plasma levels were lower than would be expected from a linear superposition of single-dose kinetics.

The differences found between single-dose predictions and actual steady-state concentrations cannot be correlated to the fact that two analytical procedures were used for the two phases of the study. Both methods yielded similar results for the same samples, and there was no interference between phenylbutazone and its three metabolites in the two methods.

In the multiple-dose study, the half-lives corresponding to the apparent elimination rate constant in each subject did not differ greatly for the first and last administrations. The theoretical minimum concentrations were much higher than the pseudosteady-state concentrations reached during chronic treatment in healthy volunteers.

The same effects were noticed by Edström (8) in patients with ankylosing spondylitis and by Orme and coworkers (12, 13) in patients with rheumatoid arthritis.

Burns *et al.* (1) showed that, after multiple dosing, increases in the dosage of phenylbutazone did not produce a proportional increase in plasma levels, which tended to reach a limiting concentration. Moreover, when phenylbutazone was administered intravenously to a subject whose plasma level was at this limiting concentration, the drug disappeared rapidly from the plasma until the level declined to the limiting value; after this level was reached, the concentration decreased at a much slower rate. Burns *et al.* (1) assumed that this phenomenon was due to a greatly increased rate of metabolism at higher dosages. The present results are not in agreement with this assumption; the half-life is at least as long at the end of chronic treatment as at the beginning.

On the condition that absorption is complete after multiple dosing, the present data show an increase in drug clearance from the plasma, since the steady-state levels are lower than predicted. However, since the elimination half-life is unchanged, the volume of distribution probably is increased. This is reasonable since phenylbutazone has a low extraction ratio and is highly protein bound. An increase in the free fraction at high concentrations (12, 13) would explain the increase in the clearance and the volume of distribution with no change in the half-life.

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Bioavailability and Pharmacokinetics of a New, Slow-Release Potassium Chloride Capsule

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Abstract □ The bioavailability of a new, slow-release potassium chloride product consisting of coated beads in a hard gelatin capsule was compared with the bioavailability of two marketed products, an elixir and a slow-release tablet, by determining the urinary excretion of potassium. Twelve healthy male volunteers were dosed with a total of 80 mEq of potassium, in a single dose for the capsule and tablet and in three 26.6-mEq doses at 6-hr intervals for the elixir. Mean recoveries in 24-hr urine potassium levels from all three dosage forms after subtracting normal urine potassium excretion levels were 50.8% from the capsule, 53.9% from the elixir, and 63.1% from the tablet. Maximum excretion rates were reached at 2.0 hr for the elixir, 6.8 hr for the capsule, and 4.0 hr for the tablet. Fewer side effects were reported with the capsule than with the elixir and tablet.

Keyphrases □ Potassium chloride—bioavailability and pharmacokinetics of slow-release capsule □ Bioavailability—potassium chloride in slow-release capsule □ Pharmacokinetics—potassium chloride in slow-release capsule

Potassium chloride is indicated for the treatment of hypokalemic alkalosis associated with various cardiovascular disorders. Aqueous solutions of potassium chloride are effective potassium supplements when taken as prescribed; however, because of an unpleasant taste due to the chloride ion, patient compliance during long-term therapy has been a problem. More palatable forms of potassium salts, such as the gluconate or mixtures of bicarbonate, citrate, and acetate, are available, but the chloride ion has been shown to be a prerequisite for effective treatment (1).

BACKGROUND

A new, slow-release potassium chloride preparation containing 600 mg (8 mEq) of potassium chloride[1] in the form of small, nearly spherical beads enclosed in a hard gelatin capsule was developed to avoid or minimize a high localized concentration of potassium within the GI tract. The potassium chloride crystals are specially coated to permit a uniform, controlled *in vivo* release over 8–10 hr. Extensive toxicity testing in animals was carried out to compare the new capsule preparation with a marketed wax-matrix tablet[2]. The results indicated a marked difference in the ulcerogenic potential of the tablet and capsule dosage forms (2). Based on the animal toxicity data, it was concluded that the new capsule dosage form is not likely to cause local irritation of the GI mucosa.

Certain pharmacokinetic characteristics of potassium make accurate determination of bioavailability difficult. Up to 98% of the physiological potassium in humans is distributed within the intracellular space. The major elimination pathway of potassium is *via* urinary excretion; the secondary elimination pathway is *via* the feces and perspiration. Bioavailability estimates derived from serum potassium levels are inaccurate because of the homeostatic mechanisms that maintain serum potassium levels within a relatively narrow range (3).

Attempts to determine the bioavailability of potassium preparations by measuring urinary potassium levels have been reported (4–6). To achieve any success, the bioavailability study must be conducted where there can be careful control of the diet, fluid intake, physical activity, and urine collection. Fixed menus with a known potassium content should be given throughout the study. Strenuous exercises that might cause

Table I—Cumulative Potassium Recovery from 12 Subjects after 24 hr

Subject	Mean[a] Control Potassium Level, mEq	Net Increase in Urine Potassium in 24 hr, mEq		
		Elixir	Capsule	Tablet
1	51.0 ± 7.3	46.6	22.0	49.1
2	47.9 ± 6.1	48.4	38.3	55.4
3	52.9 ± 8.2	43.3	40.1	53.8
4	61.7 ± 5.6	51.0	37.2	61.6
5	66.7 ± 6.3	42.1	31.0	65.1
6	52.9 ± 4.1	52.5	39.0	52.1
7	45.8 ± 10.1	56.0	42.4	45.3
8	41.6 ± 12.0	50.6	61.0	41.6
9	64.2 ± 1.3	12.3	38.7	42.9
10	48.8 ± 3.2	37.3	32.9	42.6
11	52.2 ± 12.8	37.6	62.5	44.8
12	54.1 ± 5.9	39.2	42.2	51.9
Mean ± *SD*	53.3 ± 7.5	43.1 ± 11.4	40.6 ± 11.4	50.5 ± 7.6

[a] Average of 3 control days (Days 0, 4, and 8).

[1] Berlex Laboratories Inc., Cedar Knolls, N.J.

[2] Slow-K, Ciba Pharmaceutical Co., Summit, N.J.

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