Nasal Absorption of Propranolol from Different Dosage Forms by Rats and Dogs

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Abstract □ The blood levels of propranolol in rats and dogs were compared after the administration of nasal, intravenous, and oral solutions. The results indicate that the blood drug levels after nasal and intravenous administration were identical, but the oral administration resulted in considerably lower blood levels. Sustained-release formulations of the drug also were administered nasally and resulted in low initial but prolonged blood levels. The bioavailability of the sustained-release formulation was identical to that of the intravenous administration.

Keyphrases □ Propranolol—nasal absorption from different dosage forms, rats and dogs □ Bioavailability—propranolol, comparison of sustained-release nasal formulation with intravenous administration, rats and dogs □ Absorption, nasal—propranolol from different dosage forms, rats and dogs

The oral administration of propranolol in human subjects resulted in considerable variation in plasma drug levels. Peak plasma levels in five subjects given 80-mg oral doses varied sevenfold, while 10-mg doses given intravenously to the same subjects varied only twofold (1). Furthermore, the bioavailability of an 80-mg oral dose in several subjects varied from 16 to 60% of that of a 10-mg iv dose. The variations in blood levels as well as the low bioavailability from oral doses have been attributed to extensive drug metabolism during absorption and first passage through the liver (1–3). A previous report (4) indicated that the blood levels of propranolol after intravenous and nasal administration of 1-mg doses in rats were identical but that oral administration of the same dose resulted in considerably lower blood levels.

This report presents the results on the nasal absorption of propranolol in rats and dogs after its administration in a solution and a sustained-release formulation.

Table I—Composition of Sustained-Release Dosage Forms of Propranolol Used in Rat Studies

Ingredient	Formulation		
	SR-A	SR-B	SR-C
Propranolol hydrochloride, mg	1	—	—
Propranolol (base), mg	—	0.88[a]	—
Propranolol stearate, mg	—	—	1.84[a]
Methylcellulose, mg	3	3	3
Saline, ml	0.1	0.1	0.1

[a] One milligram as propranolol hydrochloride.

Table II—Composition of Dosage Forms of Propranolol Used in Dog Studies

Ingredient	Intravenous	Oral	Nasal		
			Solution	SR-D	SR-E
Propranolol hydrochloride, mg	20	20	20	—	—
Propranolol stearate, mg	—	—	—	36.8[a]	36.8[a]
Methylcellulose, mg	—	—	—	—	15
Saline, ml	1	50	0.2	0.5	0.5

[a] Twenty milligrams as propranolol hydrochloride.

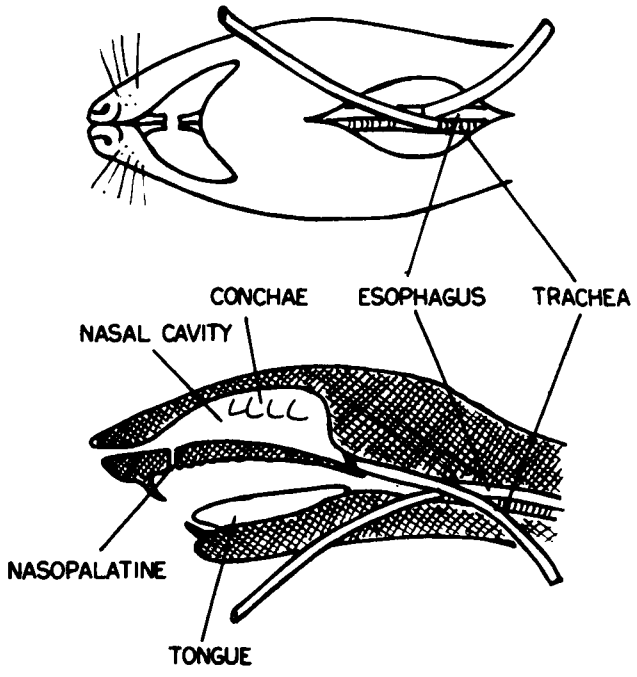

Figure 1—*Diagram of the surgical procedure of nasal absorption in the rat.*

EXPERIMENTAL

Materials—Propranolol hydrochloride USP[1], propranolol free base, and propranolol stearate were used. Propranolol free base and propranolol stearate were prepared from propranolol hydrochloride.

Composition of Formulations—The formulations used in the rat and dog studies are listed in Tables I and II, respectively.

***In Vitro* Dissolution**—The dissolution study was carried out using the USP rotating-basket method; 0.2 g of Formulation SR-A, SR-B, or SR-C was placed in the basket, which was lined from the inside with filter paper. (The filter paper was used as a barrier for the diffusion of methylcellulose.) The dissolution medium consisted of 500 ml of pH 7.4 isotonic buffer at 37°. The basket was rotated at 100 rpm. A 0.5-ml volume of the medium was withdrawn periodically, added to 0.2 ml of 0.1 *N* HCl, and assayed later.

Animal Studies—*Rats*—Male Sprague–Dawley rats, ~270 g, were anesthetized with pentobarbital (50 mg/kg). The surgical operation carried out on the rats was that described by Hirai *et al.*[2] (Fig. 1). An incision was made in the neck, and the trachea was cannulated with a polyethylene tube[3]. Another tube was inserted from the esophagus to the posterior part of the nasal cavity. The nasopalatine was closed with an adhesive agent[4] to prevent drainage of the drug from the nasal cavity to the mouth. The sustained-release preparation (equivalent to 1 mg of propranolol hydrochloride) was administered to the nasal cavity through the tube by means of a syringe. Blood (0.1–0.2 ml) was sampled from the femoral aorta periodically and analyzed later.

Dogs—Three beagle dogs, ~10 kg, were used in this crossover study.

[1] Ayerst Laboratories, New York, N.Y.

[2] S. Hirai, T. Yashiki, and T. Matsuzawa, presented at the 98th annual meeting of the Pharmaceutical Society of Japan, Okayama, Japan, April 1978.

[3] PE 260, Intramedic, Clay Adams, New York, N.Y.

[4] Super Glue, Woodhill Permetex, Cleveland, Ohio.

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Table III—Peak Blood Level (C_{max}), Time to Peak (T_{max}), and Area under Curve (AUC) after Nasal Administration of Sustained-Release Dosage Forms of Propranolol in Rats

Route	C_{max}, ng/ml[a]	T_{max}, min	$AUC_{0-\infty}$, (ng hr)/ml[a]	$\frac{AUC_{oral,nasal}}{AUC_{iv}}$
Intravenous	—	—	1033.8 ± 30.8	—
Oral	96.9 ± 18.6	50.0	196.9 ± 25.8	0.190
Nasal				
Solution	1161.4 ± 29.0	6.3	1033.0 ± 48.7	0.999
SR-A	949.0 ± 46.5	10.0	968.4 ± 15.4	0.936
SR-B	912.3 ± 88.3	13.3	1031.1 ± 42.1	0.997
SR-C	341.5 ± 35.5	71.2	1044.1 ± 30.5	1.009

[a] Mean ± SE (n = 3 or 4).

Table IV—Peak Plasma Level (C_{max}), Time to Peak (T_{max}), and Area under Curve (AUC) after Intravenous, Oral, and Nasal Administration of Propranolol in Dogs

Route	C_{max}, ng/ml[a]	T_{max}, min	$AUC_{0-\infty}$, (ng hr)/ml[a]	$\frac{AUC_{oral,nasal}}{AUC_{iv}}$
Intravenous	—	—	1892.1 ± 102.1	—
Oral	42.5 ± 7.2	50	130.1 ± 8.2	0.068
Nasal				
Solution	1539.2 ± 70.9	5	1942.1 ± 64.2	1.026
SR-D	236.6 ± 24.3	80	1902.3 ± 66.4	1.005
SR-E[b]	64.3 ± 5.6	180	—	—

[a] Mean ± SE (n = 3). [b] Not enough points to calculate $AUC_{0-\infty}$.

For the intravenous administration, the dogs were anesthetized with the intravenous injection of 30 mg of pentobarbital sodium/kg. The administered solution (20 mg of propranolol hydrochloride) was injected through the cubital vein. For the oral administration, the dogs were not anesthetized and the drug was administered by a stomach tube. For the nasal administration, the dogs were anesthetized and both the solution and the sustained-release preparation were administered to the nasal cavity through the nostrils with a micropipet and a syringe, respectively. Blood was sampled periodically from the cubital vein. After centrifugation, 0.5 ml of plasma was separated and analyzed later.

Analytical Method—Blood and plasma levels of propranolol were assayed spectrophotofluorometrically by a minor modification of the method of Shand *et al.* (1). Distilled water (0.5 ml) was added to 0.1–0.5 ml of blood or plasma. The mixture then was made alkaline with 0.5 ml of 1 *N* NaOH and extracted into 10 ml of heptane. After shaking and centrifugation, 8 ml of the heptane layer was extracted into 1.5 ml of 0.1 *N* HCl; the fluorescence of the acid layer was determined by a spectrophotofluorometer[5] (maximum excitation at 295 nm and maximum emission at 360 nm). The minimum detectable concentration was 3 ng/ml; pentobarbital did not interfere with the assay. Corrections were made for the blank.

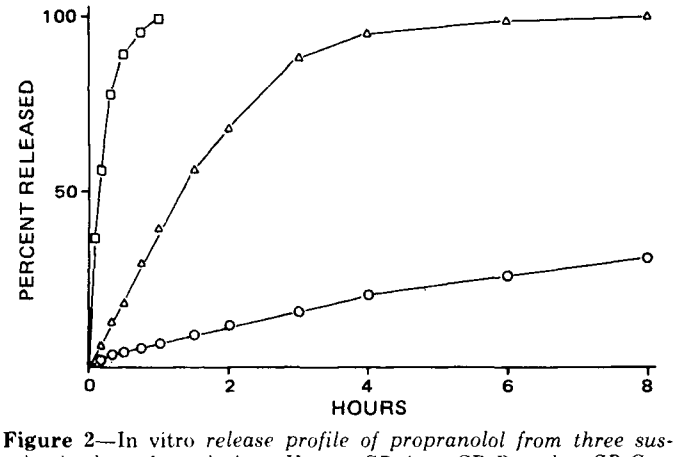

Figure 2—In vitro *release profile of propranolol from three sustained-release formulations. Key:* □, *SR-A;* △, *SR-B; and* ○, *SR-C.*

[5] Aminco-Bowman model 768 G, American Instrument Co., Silver Spring, Md.

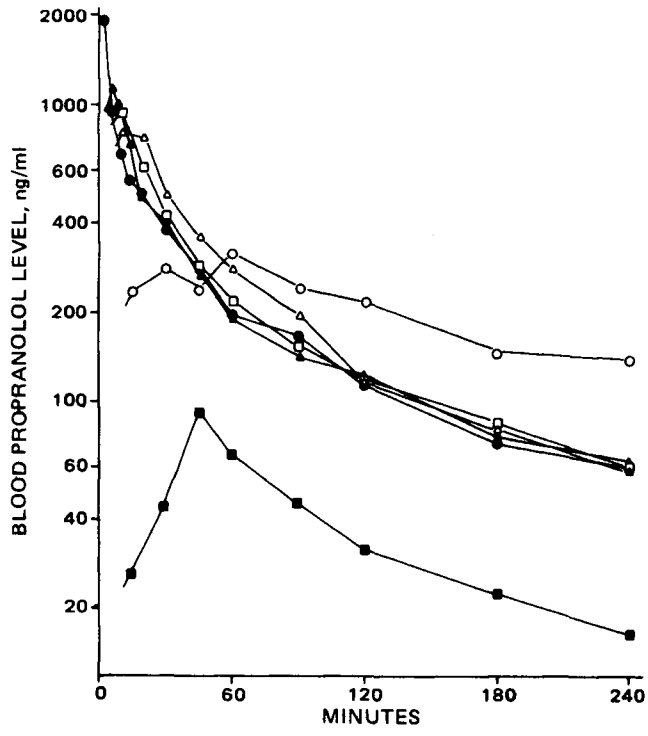

Figure 3—*Mean blood levels of propranolol in rats* (n = *3 or 4*). *Key:* □, *nasal SR-A;* △, *nasal SR-B;* ○, *nasal SR-C;* ▲, *nasal solution;* ●, *intravenous; and* ■, *oral.*

The samples of the *in vitro* dissolution study also were analyzed spectrophotofluorometrically.

RESULTS

Figure 2 shows the *in vitro* release profile of propranolol from three sustained-release formulations (SR-A, SR-B, and SR-C) administered nasally to rats.

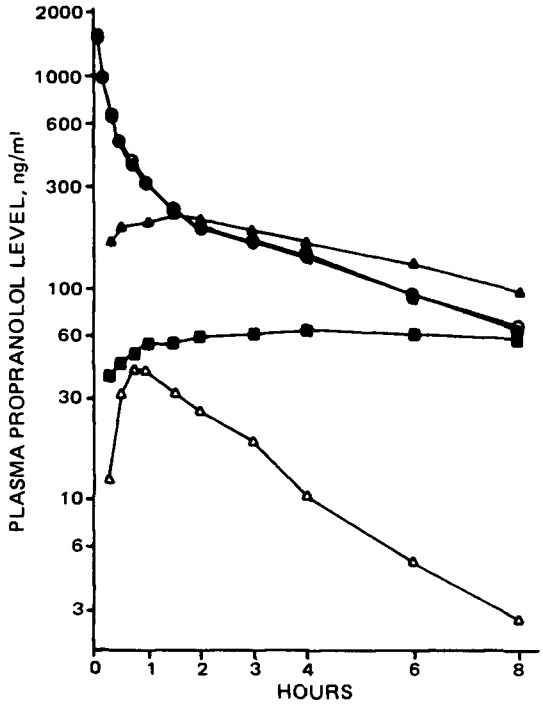

Figure 4—*Mean blood levels of propranolol in dogs* (n = *3*). *Key:* ○, *intravenous;* △, *oral;* ●, *nasal solution;* ▲, *nasal SR-D; and* ■, *nasal SR-E.*

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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