Dose-Dependent Intestinal Absorption and Significant Intestinal Excretion (Exsorption) of the β-Blocker Pafenolol in the Rat

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The elimination of [^{3}H]pafenolol and metabolites was investigated in fasted and fed rats. Separate groups received intravenous doses (0.3 and 3.0 μmol/kg) and oral doses (1 and 25 μmol/kg). After iv administration of pafenolol, the excretion of unchanged drug into urine and feces was about 50 and 25–30% of the given dose, respectively. The predominating mechanism for the excretion of pafenolol into feces was intestinal excretion (exsorption) directly from blood into gut lumen, since only about 3% of a given iv dose was recovered as pafenolol in the bile. When the oral dose was raised from 1 to 25 μmol/kg, the mean (±SD) bioavailability, calculated from urine data, increased from 14 ± 9 to 30 ±11% ($P < 0.05$) in the starved rats and from 14 ± 3 to 16 ± 3% in the fed animals. In parallel, the fraction absorbed from the gut (f_a) increased from 19 ± 9 to 31 ± 10% in the starved rats and from 16 ± 4 to 19 ± 5% in the fed animals, respectively. This indicates that the low bioavailability is due primarily to poor intestinal uptake.

KEY WORDS: pharmacokinetics; double peaks; dose-dependent absorption; intestinal excretion; exsorption.

INTRODUCTION

Pafenolol, (±)-*N*-isopropyl-N^1-2-[-4-(2-hydroxy-3-isopropyl-aminopropoxy)-phenyl]ethylurea (Fig. 1), is a highly selective β_1-adrenoceptor antagonist (1,2). The drug is a weak base with a pK_a of 9.7 and the solubility of the base in water is 1 mg/mL. Pafenolol has intermediate lipophilic properties (K_D = 0.3, *n*-octanol-phosphate buffer at pH 7.4 and 25°C) in comparison with other β-adrenoceptor antagonists (3,4). Following oral administration of a pafenolol solution (150 mL) to fasted subjects, a first peak in the blood concentration–time profile is usually achieved during the first hour and a second, more pronounced, peak appears 3–4 hr postdose (3,4). More than 95% of the available dose is absorbed during this second phase. The absolute systemic bioavailability in man is about 25% for an oral 25-mg dose and 45% when the dose is increased to 100 mg. The presence of food in the gastrointestinal tract reduces the bioavailability by 40% and the second peak becomes less apparent (5). The low bioavailability in man is due primarily to poor intestinal uptake. Following intravenous administration 50% of the given amount is excreted in urine and approximately 25% in feces as unchanged drug. In urine 10% is recovered as metabolites (3,4). The half-life is 3.5 hr following intravenous administration and 6 hr when the drug is given as an oral solution, probably a result of a prolonged absorption from the ileocolonic region (3,4,6).

The pharmacokinetics of pafenolol in rat have been shown to be similar to that in man and therefore the rat is a suitable model for mechanistic studies of the intestinal absorption of pafenolol (7). Thus, the oral bioavailability of a solution is dose dependent in the rat and the blood concentration–time profile usually has two peaks. More than 90% of the absorption of the available dose is associated with the second peak which appears about 4 hr after dosing in both starved and fed animals. The bioavailability increases significantly, from 15 to 27% in the starved and from 9.1 to 21% in the fed rats, when the oral dose is raised from 1 to 25 μmol/kg. Food lowers the degree of bioavailability. Total clearance is constant for intravenous doses between 0.3 and 3.0 μmol/kg. Like in man, the oral dose exhibits absorption rate-limited kinetics. The terminal half-life is approximately 2 hr after iv administration and 3 hr following an oral dose (7).

In this study we have quantitatively evaluated major routes of pafenolol elimination in the rat after intravenous and oral administration and investigated the mechanism(s) for the incomplete and discontinuous intestinal absorption.

MATERIALS AND METHODS

Drugs and Chemicals. Tritium-labeled pafenolol (19.0 MBq/μmol) was used (Fig. 1). The radiochemical purity, determined by HPLC and on-line detection by a Berthold detector, was more than 97%. The specific radioactivity was determined by HPLC, UV detection, and scintillation counting. All other chemicals used were of analytical grade.

Animals. Male albino Sprague–Dawley rats (ALAB, Sollentuna, Sweden), weighing 220–270 g, were used in the study. The rats were deprived of food at least 12 hr before drug administration and food was provided 7 hr after the drug administration. Tap water was provided freely. During the fasted period the rats were kept in cages with wide screen bottoms to prevent coprophagy.

Mass Balances. The intravenous (iv) doses were 0.3 and 3.0 μmol/kg, and the oral doses 1.0 and 25 μmol/kg. Intravenous and oral dosings were performed by bolus injection through a Silastic catheter (o.d., 0.95 mm) placed in the jugular vein and by intragastric intubation, respectively. The volume of the administered solution was 0.5–0.7 mL. The iv catheter was inserted into the jugular vein and passed under the skin and exteriorized at the back of the neck during ether anesthesia the day before the experiment. The rats who received the oral doses were also exposed to ether anesthesia for about 15 min the day before the experiment to mimic the pretreatment procedure of the iv experiment. Each dose was administered as a saline solution of about 20°C and the radioactivity was about 40 μCi. Each dose was given to separate groups of five unfed and fed rats. The animals were individually housed in metabolic cages. Urine and feces were collected quantitatively for 0–6, 6–12, 12–24, 24–48, and 48–72 hr. At the end of each sampling interval the cages were rinsed carefully with water, which was accounted for urine and stored in separate bottles.

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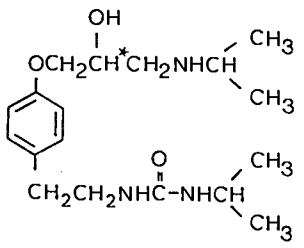

pafenolol (H 138/03)

Fig. 1. Structural formula of pafenolol; the star indicates the position of ^{3}H-labeling.

Biliary Excretion. A Silastic catheter (o.d., 0.95 mm) was inserted into the jugular vein for drug administration, and a polyethylene catheter (PE-50; o.d., 0.96 mm) was introduced into the carotid artery for blood sampling. The bile duct was cannulated with a polyethylene catheter (PE-10) and another polyethylene catheter (PE-50) was inserted in the duodenum approximately 5 mm proximal to the papilla of Vater. The catheters were passed under the skin and exteriorized at the back of the neck, where the biliary and the duodenal catheters were connected to allow for enterohepatic recirculation of bile during the postoperative period. Seven unfed rats received an iv bolus dose of 3.0 μmol/kg of ^{3}H-labeled pafenolol of about 70 μCi per dose. Blood samples were drawn from the heparinized catheter in the carotid artery after 2, 5, 10, 15, 30, 60, 90, 110, 200, 290, 400, and 540 min. The weight of the blood samples varied between 0.075 and 0.300 g. Maximally 2 mL blood was taken from each animal. The bile was collected quantitatively on ice for 0–20, 20–40, 40–80, 80–140, 140–260, and 260–540 min. All samples were stored at −20°C until analyzed.

Analytical Methods. Bile and urine samples (0.1–1.0 mL) were weighed and diluted to 1 mL with water prior to radioactivity measurements. Feces samples were weighed and homogenized in an Ultra Turrax for 5 min after the addition of water equal to four times the amount of feces. Aliquots of the homogenate (0.1–0.2 g) were treated at 80°C for 30 min with a mixture of 0.2 mL of conc. hydrogen peroxide and 0.2 mL of 70% perchloric acid. To all samples 10 mL of scintillation fluid was added and the radioactivity was measured by liquid scintillation counting in a Packard Tri-Carb B 2450.

Pafenolol in blood, urine, feces, and bile was assayed by a straight-phase liquid chromatographic method with UV detection and liquid scintillation counting of collected fractions of the effluent containing unchanged pafenolol (7). Unlabeled pafenolol was added in excess (150 nmol) as internal standard to each sample. The weights of the samples were between 0.1 and 0.5 g and they were diluted 10–1000 times prior to analysis.

Pharmacokinetic Evaluation. The oral bioavailability (F) was calculated from the dose-adjusted ratio of the cumulatively excreted amounts of parent drug in urine after the oral and iv doses. The mean dose-adjusted recovery of all iv doses was used as a reference since neither dose nor feeding affected the elimination of pafenolol. Assuming that metabolites potentially formed in the intestinal lumen did not enter the systemic circulation, the fraction of the oral dose absorbed from the gastrointestinal tract (f_a) was obtained from the following ratio:

$$f_a = \frac{\text{total radioactivity in urine after po dose} * \text{dose iv}}{\text{total radioactivity in urine after iv dose} * \text{dose po}} \quad (1)$$

The mean dose-adjusted amount of total radioactivity in urine after all iv doses was used as a reference. The degree of first-pass effect in the gut wall and the liver (E) of the fraction of pafenolol dose that was absorbed was calculated according to

$$E = 1 - F/f_a \quad (2)$$

The fraction of the given dose that was metabolized (f_m) was calculated as Eq. (3):

$$f_m = f_{tot} - f_{unch} \quad (3)$$

where f_{tot} is the recovered fraction of total radioactivity in urine and feces and f_{unch} the corresponding fraction of pafenolol. The fraction of the absorbed oral dose metabolized systematically (f_{ms}), i.e., when the drug has passed the gut, liver, and lung, was calculated from Eq. (4):

$$f_{m_s} = \frac{f_m}{f_a} - E \quad (4)$$

The blood concentration–time data of pafenolol following the iv bolus dose were fitted to bi- and triexponential functions. Nonlinear regression analysis was performed using PCNONLIN (8). Since the relative error of the HPLC assay method was somewhat larger at the low concentrations (7), the weighting factor $1/C_{calc}$ was used for the curve-fitting analysis. C_{calc} was the calculated concentration by PCNONLIN. Discrimination between models was based on the standard goodness-of-fit criteria such as visual inspection, trends in residuals between observed and calculated concentrations, standard error of the parameter estimates, and weighted sum of squares (F test).

Data are presented as mean ± SD. Significance tests between the doses were performed by one-way analysis of variance (ANOVA) followed by Scheffe's contrast test.

RESULTS

Mass Balance. The mean accumulated total recovery of radioactivity in urine and feces after all intravenous doses was 92 ± 5% of the given dose. The average excretion of unchanged pafenolol in urine and feces based on the same doses was 50 ± 6 and 24 ± 4%, respectively (Table I). The amount of metabolites excreted in urine and feces was 13 ± 4 and 4.9 ± 1.8% of the given dose, respectively (Tables I and II). After the iv dose, approximately 90% of the recovery of pafenolol in urine was excreted during the first 6 hr, while following the oral dose the greatest fraction (approximately 25%) was excreted between 6 and 12 hr (Fig. 2).

After the oral doses, the mean recovery of the accumulated radioactivity in urine and feces was 94 ± 5%, with the major part 81 ± 7% in feces. When the dose was raised from 1 to 25 μmol/kg, the mean bioavailability increased from 14 ± 9 to 30 ± 11% ($P < 0.05$) in the unfed rats and from 14 ±

Table I. Mean Recoveries (±SD) of Total Radioactivity and Pafenolol in Feces and Urine in the Rat (% of Dose) over a Collection Period of 72 hr

		Urine		Feces		Fraction absorbed	Bioavailability
	n	Total radioactivity	Pafenolol	Total radioactivity	Pafenolol	(f_a)	F
0.3 iv stv*	5	58 ± 4.1	47 ± 3.1	30 ± 3.3	26 ± 1.9	—	—
0.3 iv ustv*	5	61 ± 3.7	53 ± 3.4	31 ± 2.5	25 ± 4.1	—	—
3.0 iv stv	5	69 ± 3.7	47 ± 3.9	26 ± 4.9	21 ± 4.1	—	—
3.0 iv ustv	5	62 ± 11.6	53 ± 10.1	30 ± 5.8	26 ± 4.0	—	—
1.0 po stv	4	12 ± 5.7	6.9 ± 4.3[a,*]	78 ± 11.3	74 ± 11.7	19 ± 9.2	14 ± 8.5[a]
1.0 po ustv	5	10 ± 2.5	6.8 ± 1.4	81 ± 6.0	76 ± 5.1	16 ± 4.0	14 ± 2.9
25 po stv	5	20 ± 6.2	15 ± 5.5[a,b]	81 ± 6.6	77 ± 5.4	31 ± 10.0	30 ± 11.0[a,b]
25 po ustv	5	12 ± 3.2	8.1 ± 1.8[b]	83 ± 5.4	79 ± 4.8	19 ± 5.1	16 ± 3.5[b]

* Stv, starved rats; ustv, unstarved rats. Groups with the same number in the exponent are significantly different: (a, b) $P < 0.05$.

3 to 16 ± 3% in the fed animals. In parallel, the fraction of the absorbed dose (f_a) increased from 19 ± 9 to 31 ± 10% in the unfed rats and from 16 ± 4 to 19 ± 5% in the fed animals, respectively. The bioavailability of pafenolol was significantly lower for the high oral dose in the fed rats compared to the unfed rats (Table I).

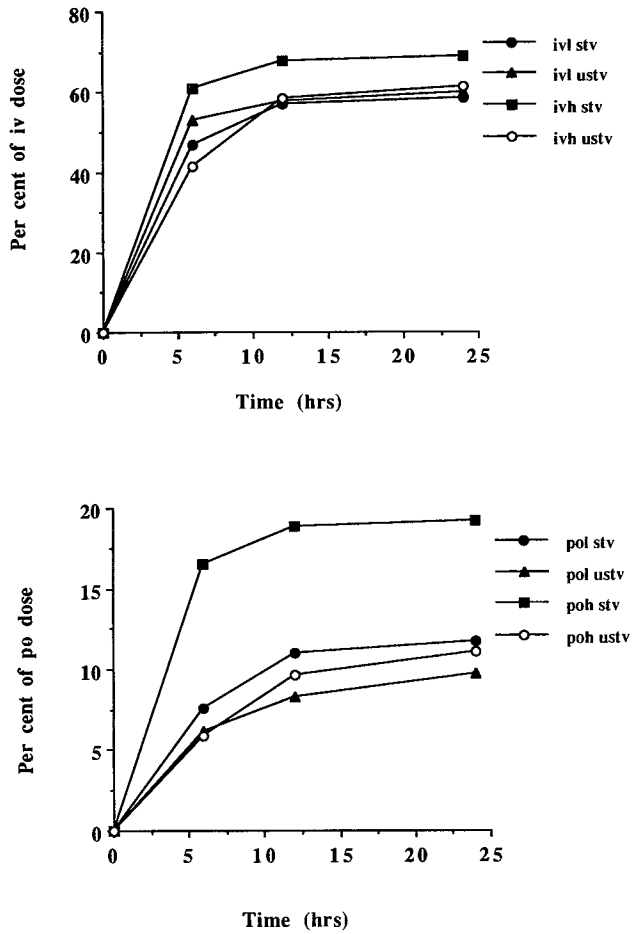

Fig. 2. Mean (±SD) cumulative urinary excretion of total radioactivity after iv (upper graph, ivl = 0.3 and ivh = 3.0 μmol/kg) and oral (lower graph) administration of 1.0 μmol/kg (pol) and 25 μmol/kg (poh) doses of pafenolol to starved (stv) and unstarved (ustv) rats (n = 5).

The degree of metabolism of the systemically available oral dose (f_{m_s}) and the first-pass extraction values of pafenolol in the gut and liver (E) following the various oral doses are presented in Table II. Increasing the oral dose from 1.0 to 25 μmol/kg in the unfed animals significantly decreased the first-pass extraction (E), from 31 ± 12 to about 5.0 ± 6% ($P < 0.05$). No saturation in first-pass effect was observed after the corresponding dose escalation in fed rats (Table II).

Excretion into Bile. The pharmacokinetic parameters of pafenolol in bile duct cannulated rats are presented in Table III. The coefficient of variation of the individual parameter estimates from PCNONLIN was less than 1%, which was considerably lower than the coefficient of variation of the pharmacokinetic parameters between the animals (10–20%).

Following the iv dose the fractions of total radioactivity and pafenolol excreted into the intestine via the bile duct were 4.6 ± 3 and 2.8 ± 1%, respectively (Fig. 3). A stable bile flow of 17 ± 4 μL/min was recorded during these experiments, which was in agreement with previous reports (9).

DISCUSSION

In a previous study it was found that the total clearance of pafenolol is approximately 50 mL/min/kg and linear in the dose range 0.3–3.0 μmol/kg (7). As renal excretion of unchanged drug accounts for about 50% of the total elimination, the renal clearance is about 25 mL/min/kg, which suggests that both glomerular filtration and tubular secretion are involved in the renal elimination (10,11). The second most important route is elimination into feces, which accounts for approximately 25–30% after an iv dose. There are two mechanisms behind this elimination route, namely, biliary secretion and excretion directly from the blood into the intestinal lumen (exsorption). The accumulated amount of unchanged pafenolol in bile is about 3% of an iv dose. As the bile flow was not significantly affected by the surgery (9), this means that the predominating mechanism for the excretion into the intestinal lumen is a direct transport of pafenolol from the

Table II. Mean Values (±SD) of Excreted Pafenolol Metabolites, First-Pass Extraction E, and Metabolism of Systemically Available Drug (f_{m_s}) Following iv and Oral Administration of Pafenolol to Starved (stv) and Unstarved (ustv) Rats over a Collection Period of 48 hr (n = 5)

Dose (μmol/kg)	% of dose			% of absorbed dose[a]				
	Urine (1)	Feces (2)	Total (3)	Urine	Feces	Total	E	f_{m_s}[b]
0.3 iv stv	12 ± 2.2	4.7 ± 1.8	16 ± 1.2	a	b	c	—[c]	16 ± 1.2
0.3 iv ustv	8.1 ± 2.0	6.3 ± 2.5	15 ± 3.4	a	b	c	—[c]	15 ± 3.4
3.0 iv stv	22 ± 3.1	4.4 ± 1.4	27 ± 3.4	a	b	c	—[c]	27 ± 3.4
3.0 iv ustv	8.7 ± 6.3	4.3 ± 1.9	13 ± 5.7	a	b	c	—[c]	13 ± 5.7
1.0 po stv	5.0 ± 1.5	3.9 ± 2.1	8.9 ± 2.9	28 ± 5.9	23 ± 17	52 ± 22	31 ± 12*	21 ± 14
1.0 po ustv	3.2 ± 1.3	4.3 ± 2.4	7.8 ± 2.9	20 ± 4.6	28 ± 15	48 ± 15	14 ± 9.0	34 ± 16
25 po stv	4.4 ± 1.0	4.0 ± 4.0	8.8 ± 4.3	15 ± 3.3	16 ± 15	31 ± 18	5.0 ± 5.8*	25 ± 14
25 po ustv	3.7 ± 2.0	3.8 ± 2.4	7.5 ± 3.2	19 ± 6.2	21 ± 13	40 ± 13	14 ± 10	27 ± 16

[a] (a) Values identical to those in column 1; (b) values identical to those in column 2; (c) values identical to those in column 3.
[b] Percentage of the available dose metabolized is calculated according to Eq. (3), but presystemic metabolism is not included.
[c] First-pass extraction in the lung is assumed to be 0.
* $P < 0.05$.

blood across the intestinal wall, accounting for approximately 20% of the total elimination. The same excretion mechanism may account for the approximately 30% recovery in feces of intravenously administered pafenolol in man (4). Intestinal excretion (exsorption) has been demonstrated for quartenary ammonium compounds, cardiac glycosides, and strongly acidic drugs as well as for weak bases such as acebutolol, procainamide, and theophylline (12–17). The low degree of biliary excretion of pafenolol and metabolites also excludes enterohepatic circulation as a cause of the double peaks in the blood concentration–time profile seen after oral dosing to rats and humans (3–5,7).

Metabolism is the third elimination process and accounts for 18% of the total elimination after iv administration. The ratio between the accumulated amount of metabolites in urine and that in feces is approximately 3.0, which means that the renal route is the most important elimination pathway for systemically formed metabolites. The ratio between pafenolol and the metabolites in feces indicates that pafenolol is excreted to a greater extent into the intestinal lumen than the metabolites. The degree of metabolism of the systemically available oral dose (f_{m_s}) is estimated as approximately 26% according to Eq. (4) (Table II). There seems to be no decrease in this metabolism when the higher oral dose is given. On the other hand, the small and existing first-pass extraction decreased when the high oral dose was given to starved rats, probably due to saturation of the enzymes located in the gut wall and/or liver.

A higher recovery of metabolites in feces after oral administration accounts for the finding that the systemic metabolism of the available oral dose was 26%, compared to 18% after iv administration. The recovery of metabolites in feces is five times greater after po than iv administration, probably because the iv dose does not have the same access to enzymes and/or microflora in the gut lumen. These presystemically formed metabolites never reached the systemic circulation and therefore they were not included in the calculations of first-pass effect (E) in the gut/liver. Possible explanations why these metabolites did not enter the systemic circulation are metabolism in the intestinal lumen/enterocyte to hydrophilic nonabsorbable metabolites and avid hepatic extraction followed by biliary excretion. However, the latter seems less likely, since biliary excretion is also low following oral administration.

Table III. Disposition Data Following an Intravenous Dose of 3 μmol/kg of Pafenolol to Rats with a Cannulated Bile Duct for Concomitant Bile Sampling

Rat No.	Weight (g)	V_{ss} (L/kg)	Cl (mL/min/kg)	$t_{1/2}$ (hr)	AUC/dose (min/L)
1	271	9	40	3	91.7
2	267	9	51	2	73.6
3	263	6	38	2	101
4	270	10	42	3	88
5	266	10	41	3	91.5
6	171	8	41	2	143
7	220	7	41	2	119
Mean	247	8	42	2	113
SD	38	2	4	0	24

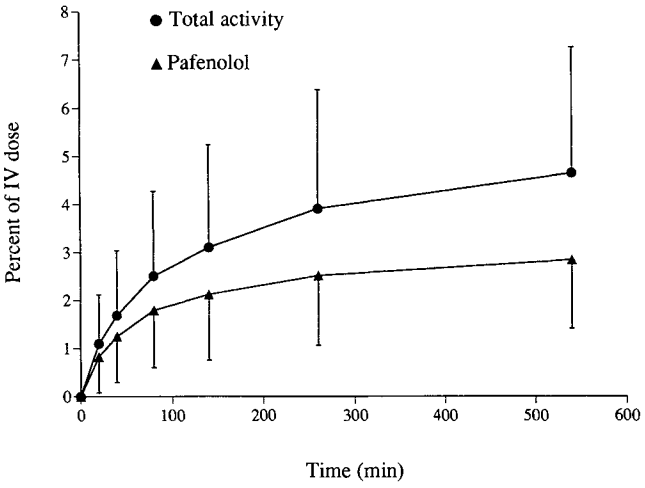

Fig. 3. Mean (±SD) cumulative biliary excretion of total radioactivity and pafenolol after an iv dose of 3.0 μmol/kg to starved rats (n = 7).

The low and dose-dependent bioavailability in this excretion study confirmed previous results based on blood concentration data (7). Incomplete gastrointestinal uptake seems to be the major cause of the low bioavailability, as on average, less than 10% of the oral dose was recovered as metabolites in urine and feces, excluding presystemic elimination as a predominant cause of the low bioavailability. Moreover, at least 75% of the oral dose was recovered in unchanged form in feces, and of that, maximally 4–10% can be attributed to intestinal exsorption and biliary excretion according to intravenous data. This means that the main reason for the dose-dependent bioavailability seems to be an increase in the fraction of the oral dose absorbed (f_a), accounting for about 75% of the doubling of the systemically available dose, while the remaining 25% is due to decreased presystemic metabolism

In conclusion, this study shows that the low oral bioavailability of pafenolol results from incomplete intestinal absorption. The dose-dependent increase in the bioavailability after the high oral dose was due primarily to increased intestinal uptake. The biliary excretion is low, confirming that enterohepatic circulation can be excluded as a possible mechanism for the double peaks observed in the oral blood concentration–time profile. Intestinal excretion is the second most important elimination route of pafenolol, next to renal excretion. Furthermore, it was shown that pafenolol is eliminated by similar routes in rat and man (3–5).

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