Regional Gastrointestinal Absorption of the Beta-Blocker Pafenolol in the Rat and Intestinal Transit Rate Determined by Movement of ^{14}C-Polyethylene Glycol (PEG) 4000

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The gastrointestinal absorption characteristics of pafenolol following oral administration as a solution in man and rat has previously been found to be a double-peak phenomenon and exhibited dose-dependent bioavailability, despite negligible presystemic metabolism. In both man and rat the first peak appeared approximately 0.5–1 hr postdose and the second, more pronounced peak 3–4 hr postdose. In rat more than 90% of the available dose was absorbed during the second peak. In the present study we investigated the absorption of a solution of pafenolol in rats after intrajejunal and intraileal administration. The resulting blood concentration–time profile of pafenolol exhibited one peak only; the extent of absorption was similar to that observed when the same dose was given orally. The small intestinal transit time of the ^{14}C-PEG 4000 solution was found to be more than 3 hr. The transit rate was higher in the proximal part of the small intestine compared to the more distal part, where the transit of the solution was staggered. In conclusion, the results of the intestinal transit time investigation and the administrations of pafenolol at different levels of the alimentary tract indicate that pafenolol is a drug with a specific absorption site located in the ileocolonic region.

KEY WORDS: pharmacokinetics; oral absorption; intestinal permeability; bioavailability; double-peaks; dose dependency.

INTRODUCTION

Pafenolol is a highly selective β_1-adrenoceptor antagonist (1,2) that exhibits unusual absorption properties in man and rat. In both species a first peak in the blood concentration–time profile is usually observed during the first hour and a second, more pronounced peak appears 3–4 hr after oral administration. More than 90% of the available dose is absorbed during this second peak. Furthermore, the oral bioavailability in man and rat increases with increasing pafenolol doses (3–7). When pafenolol was given as a solution (150 ml) to fasted volunteers, the bioavailability increased from 25 to 45% when the oral dose was increased from 25 to 100 mg (3,4). Similarly the oral bioavailability increased from 15 to 30% in the rat when the oral dose was increased from 1.0 to 25 μmol/kg (given as a solution of 0.7 ml) (5). Because of the close resemblances of the pharmacokinetics of pafenolol in man and rat, the rat has been considered a suitable model for further investigation of the mechanisms underlying the absorption of pafenolol from the gastrointestinal tract (5–7).

In rat studies carried out by us previously, the main cause of the dose-dependent bioavailability was found to be a nonlinear increase in the gastrointestinal uptake. In addition, we have demonstrated that saturation of metabolic enzymes in the gut wall has a minor contributory effect to the dose-dependent bioavailability and that the first-pass effect of the liver is negligible (5–7). Systemically available pafenolol was shown to be eliminated in the rat mainly by renal and intestinal excretion (exsorption) of unchanged drug. These processes accounted for 50 and 25% of the total clearance, respectively. The remaining part of the total clearance, approximately 25%, was due to metabolism (6,7).

Our main objectives in the present study were to investigate the absorption of pafenolol in rats after intrajejunal and intraileal administration and to study the intestinal transit rate of a ^{14}C-PEG 4000 saline solution after duodenal administration. In addition, the pharmacokinetics of pafenolol given as a solution into the peritoneum were explored and the potential influence of peritoneal surgery on the disposition of intravenously administered pafenolol was studied in one group of rats.

MATERIALS AND METHODS

Drugs and Chemicals

Specifically tritium-labeled pafenolol (19.0 MBq/μmol) was used. The radiochemical purity, determined by HPLC and on-line detection with a radioactivity detector (Berthold Wildbad, Germany), was higher than 97%. The radioactive substance was stored as a base in a 99.5% ethanol solution at −20°C. The doses were prepared by evaporating the ethanol under nitrogen, dissolving the residue in saline, then adjusting the pH to 5.0 with 0.1 *M* HCl. Unlabeled pafenolol (MW 337.5) was added to achieve the required dose. The pH was raised to 6.8–7.0 with 0.1 *M* NaOH. The specific radioactivity of each dose was determined by HPLC with UV detection, followed by scintillation counting of collected fractions.

In the investigation of the transit rate in the small intestine, a saline solution (pH 7.4) containing 1 g/L of PEG 4000 was given intraduodenally through a catheter. Radiolabeled polyethylene glycol (^{14}C-PEG 4000), with a purity of 97% (Amersham Laboratories, Buckinghamshire, England), was added in appropriate amounts to achieve a total radioactive dose of approximately 0.01 MBq. All other chemicals used in this study were of analytical grade.

Animals

Male Sprague–Dawley rats (ALAB, Sollentuna, Sweden), weighing 220–270 g, were used in the study. The rats were housed under standard conditions in the animal unit at the Biomedical Center, Uppsala University. The room temperature was 22.2 ± 1.0°C, the humidity 55 ± 5%, and a 12-hr light–dark cycle was employed (6 AM to 6 PM, light

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period). All rats in the present study were deprived of food for at least 12 hr before drug administration. Food was provided 7 hr after drug administration. Tap water was freely available. During the period when food was withheld the rats were kept in cages with wide-screen bottoms to prevent coprophagy. The intravascular, intraperitoneal, and intraintestinal catheters needed in the experiments were inserted under anesthesia the day before the experiment. The animals were anesthetized by intraperitoneal injections of Xylazine (15 mg/kg) and ketamine (85 mg/kg). The iv dose was given via the vena jugularis, and the ip doses through a catheter placed in the peritoneum and attached to the abdominal wall. The rats receiving the iv dose were also exposed to the same peritoneum surgery. The intraintestinal doses were given in two regions of the small intestine, located 55 (intrajejunal) and 30 cm (intraileal) from the cecum, respectively. A small incision was made in the intestine and the catheter was carefully placed into the lumen and attached with a thread (sterile surgical suture, 6-0 silk, Davis-Geck). The catheters were passed under the skin and exteriorized at the back of the neck. All the catheters used for drug administration and blood sampling were polyethylene catheters (PE-50; o.d., 0.965 mm). The rats were not restrained or anesthetized at any time during the experiments.

Study Design

Absorption and Disposition. Pafenolol was administered intravenously, intraperitoneally and intraintestinally as a solution to four groups of five rats. The iv dose was 3.0 μmol/kg (1.9 MBq) and the ip doses were 1.0 and 25 μmol/kg (3.0 MBq). The total volume given iv and ip was 0.4 and 0.7 ml, respectively. The intraintestinal doses were the same, 25 μmol/kg (5.2 MBq), and the total volume administered was 0.7 ml. The doses were administered as bolus injections and the catheters were rinsed with saline. Blood samples were withdrawn from a heparinized catheter placed in the arteria carotis at 2, 4, 6, 10, 15, 30, 60, 120, 240, 420, and 540 min after the iv dose, 2, 5, 10, 15, 30, 60, 90, 120, 180, 360, and 600 min after the ip doses, and 10, 20, 50, 90, 120, 150, 190, 240, 300, 420, and 600 min following intraintestinal administration. The total volume of blood taken from each animal was 2 ml and varied between 75 and 250 μl. After each sample the catheter was rinsed with 0.3 ml saline. All blood samples were stored at −20°C until analysis.

Transit Rate. In the small intestinal transit rate experiments 0.5 ml of an isotonic ^{14}C-PEG 4000 saline solution (pH 7.4) was administered via a catheter placed in duodenum. Two groups of seven rats each received the ^{14}C-PEG 4000 saline solution. The first group was decapitated 90 min after administration and the second group 190 min after dosing. The small intestine, cecum, and colon were excised very carefully over a 2-min period to carry out the procedure. No postmortem contractions were observed. The whole intestine was carefully stretched and divided into segments by tying off with a thread to prevent further spreading of the solution. The small intestine was cut into seven parts of 15 cm each, the cecum was taken as a separate part, and the colon was divided into two segments. To avoid spillage double knots were made at each incision. All samples were stored at −20°C until analyzed.

Measurements of Pafenolol in Blood. Pafenolol was assayed in blood by a normal-phase HPLC method with UV detection and liquid scintillation counting of collected fractions containing unchanged pafenolol. The analytical procedure has been described earlier (5,8). The reproducibility, expressed as the coefficient of variation of repeated determinations of standards (10 samples), was 3 and 6% for the highest (5000 dpm) and lowest (120 dpm) radioactivity injected, respectively. The minimum limit of determinable radioactivity value used was 120 dpm, which was three times the background radiation level.

Determinations of ^{14}C-PEG 4000 in the Intestinal Segments. Approximately 15–20 ml of water was added to the different intestinal segments. These were then homogenized in an Ultra Turrax for 5 min. Weighed samples (0.1–0.2 g) of the homogenate were added to 10 ml of Beckman Ready Safe scintillation fluids and total radioactivity was determined by liquid scintillation counting (Beckman Instruments Model 244).

Data Analysis. Bi- and triexpontential functions were fitted to the blood concentration–time data of pafenolol following an iv bolus dose. Nonlinear regression analysis was performed by PCNONLIN (9). Since the relative error of the HPLC assay method was somewhat larger in the lower concentration range, the weighting factor $1/C_{calc}$ was employed, where C_{calc} was the model-predicted concentration. 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). Systemic clearance, Cl, was determined from individual blood concentrations of pafenolol following iv administration according to Eq. (1):

$$Cl = \frac{Dose}{AUC_{iv}} \quad (1)$$

The volume of distribution at steady state, V_{ss}, was determined by Eq. (2)

$$V_{ss} = \frac{Dose \cdot AUMC_{iv}}{(AUC_{iv})^2} \quad (2)$$

where AUC_{iv} and $AUMC_{iv}$ are calculated from the fitted intercepts and rate constants of the function giving the best description of the observed data.

The area under the concentration-versus-time curve

Table I. Individual and Mean Disposition of Pafenolol Parameters Following a Single iv Dose of 3 μmol/kg to Rats Exposed to Surgery in the Peritoneum

Rat no.	V_{ss} (L/kg)	Cl (ml/min/kg)	AUC/dose (min/L)	$t_{1/2}$ (hr)
1	4.4	48.9	81.3	1.7
2	4.4	49.4	80.0	1.6
3	4.9	47.3	85.0	1.8
4	5.2	42.4	92.9	2.1
5	4.9	46.0	86.7	1.9
Mean	4.8	46.8	85.2	1.8
SD	0.4	2.8	5.1	0.2

(AUC) for each individual rat receiving an extravascular dose was calculated using a combination of the linear and the logarithmic trapezoidal rule up to the last time point. The area to infinite time beyond the last sample (residual area) was estimated by dividing the predicted blood concentration at the last time point by the terminal rate constant. The half-life was determined by linear regression analysis of the logarithm concentration vs time for three to five of the last blood samples.

The bioavailability of the extravascular doses (F) was determined from the ratio of the dose-adjusted AUCs of the extravascular doses to the iv dose. In the bioavailability calculations, the mean of the dose-adjusted AUCs for all individual rats receiving an iv dose was used as reference, since this area has been shown to be independent of the dose in the dose range studied (5–7).

The mean values of the disposition parameters characterized by the three-compartment model describing the blood concentration–time curve of the iv dose were used to deconvolute the absorption profile of the extravascular doses in the individual rats to obtain an estimate of bioavailability (F_{deconv}), according to the method of Iga *et al.* (10). The time to absorb 50% ($T_{50\%}$) and 90% ($T_{90\%}$) of the available dose was estimated by linear interpolation between the calculated data points.

The data in this study are presented as mean values and ±SD unless otherwise stated. Student's unpaired t test was used for statistical testing.

RESULTS

The individual blood concentration–time profiles of pafenolol after intravenous administration of 3.0 μmol/kg were better described by a triexponential disposition model than by a biexponential model. The coefficient of variation of the individual parameter estimates was less than 1%, which implies that the experimental variability was low. The coefficient of variation of the pharmacokinetic parameters between the animals was approximately 10%. The individual and mean values of the volume of distribution (V_{ss}), systemic blood clearance (Cl), and terminal half-life are given in Table 1.

The blood concentration–time profiles of pafenolol in the individual rats following intraintestinal administration at 55 or 30 cm from the cecum (sites 1 and 2) are shown in Figs. 1 and 2, respectively. All curves exhibited only one peak. The median time to reach the peak was 50 min in both groups of rats. The interindividual variation in the systemic availability was extensive when pafenolol was administered in the two regions of the small intestine. The bioavailability was approximately the same at the two sites of administration. The median values of F_{AUC} were 24.9% (range, 12.6–51.0%) for site 1 and 21.7% (range, 10.6–82.7%) for site 2. The median residual areas were 6.2% (range, 1.8–10.8%) and 13.6% (range, 1.9–26.8%), respectively. The estimation of bioavailability using the deconvolution method (F_{deconv}) showed good agreement for all animals in both groups compared to F_{AUC}. The corresponding mean half-lives for the two administration sites were 3.2 ± 1.0 and 2.4 ± 0.5 hr, respectively (Tables II and III).

The distribution of radioactivity in the different intestinal segments 90 and 190 min after duodenal administration of a saline solution containing ^{14}C-PEG 4000 is displayed in Figs. 3 and 4. The recovery of the given radioactivity dose was greater than 95%. After 90 min on average 85–90% of the recovered radioactivity was located in segments 5, 6, 7, which correspond mainly to ileum (Fig. 3). As indicated in Fig. 4, the solution has just started to enter the large intestine 190 min after intraduodenal administration. About 65% of the radioactivity was still left in the more distal part of the ileum (segments 6 and 7) and between 15 and 20% was found in the cecum and proximal colon (segments 8 and 9).

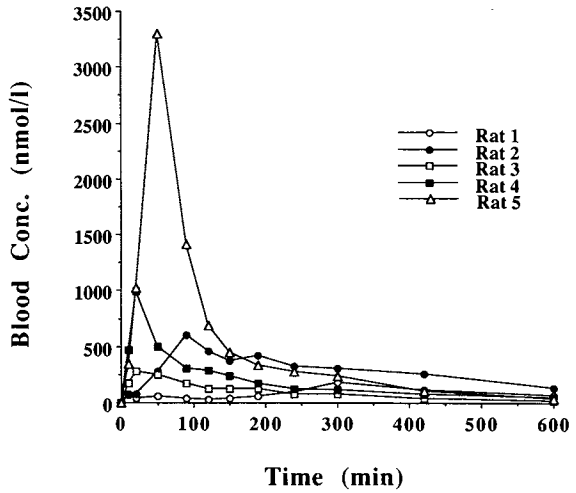

Fig. 1. Individual blood concentration–time curves of pafenolol following intrajejunal administration (55 cm from cecum) of 25 μmol/kg to five starved rats.

The absorption of pafenolol from peritoneum was very rapid as illustrated in the individual blood concentration–time profiles (Fig. 5). The time to achieve maximum blood concentration (t_{max}) was approximately 5 min. The mean values of $T_{50\%}$ and $T_{90\%}$ after the low ip dose were 7.0 ± 0.5 and 26 ± 3.2 min, respectively. The same parameters following the high ip dose were 7.0 ± 2.9 and 25 ± 15 min, respectively. Bioavailability was complete in both groups.

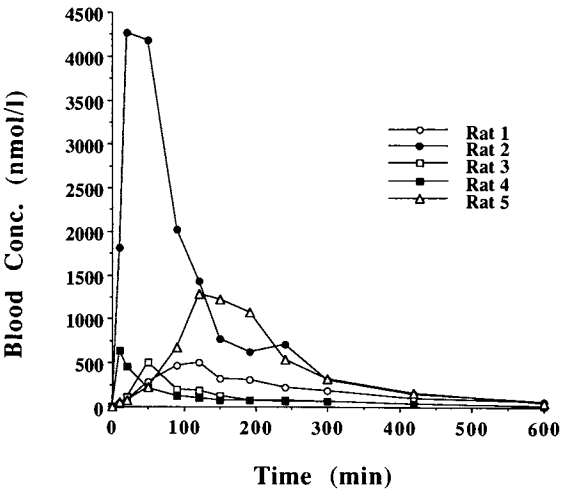

Fig. 2. Individual blood concentration–time curves of pafenolol following intraileal administration (30 cm from cecum) of 25 μmol/kg to five starved rats.

Table II. Individual and Mean Absorption Characteristics and Half-Lives of Pafenolol in the Rat Following Administration of 25 μmol/kg Through a Catheter Placed 55 cm from the Cecum

Rat no.	C_{max} (nM)	t_{max} (min)	AUC/dose (min/L)	F_{AUC} (%)	F_{deconv} (%)	$T_{50\%}$ (min)	$T_{90\%}$ (min)	$t_{1/2}$ (hr)
1	206	300	10.7	12.6	11.5	280	500	3.6
2	700	90	34.4	40.4	36.0	150	425	4.0
3	300	20	16.2	19.0	13.0	48	263	2.3
4	1217	20	21.2	24.9	21.0	35	356	4.1
5	3667	50	43.4	51.0	58.6	35	67	1.8
Mean	1218	96	25.2	29.6	28.0	110	322	3.2
SD	1425	118	13.4	15.8	19.6	107	167	1.0
Median	700	50	21.2	24.9	21.0	48	356	3.6

However, after the high ip dose a discrepancy between the two methods of calculation was noted; the AUC method and the deconvolution method resulted in mean values of 107 ± 16.4 and 89.0 ± 11.0% ($P < 0.05$) for F, respectively. The residual area was less than 3% in all rats. The half-life was 2.0 ± 0.3 and 1.8 ± 0.2 hr after the low and high ip doses, respectively (Table IV).

DISCUSSION

A previous study of different intravenous doses of pafenolol has shown that pafenolol is rapidly and extensively distributed to extravascular sites. Estimated V_{ss} was approximately 5.5 L/kg (5). In the same study the average Cl was about 50 ml/min/kg and was linear in the blood concentration range 1–2000 nmol/L. In the present study on rats exposed to peritoneal surgery, estimates of V_{ss} and Cl were similar to the previous results, indicating that this type of surgery has no affect on the disposition of pafenolol.

Pafenolol is a beta-blocker with unusual intestinal absorption properties in both rat and man. One interesting characteristic is the reproducible appearance of two peaks in the blood concentration–time profile following oral administration (3–5). The double-peak phenomenon has previously been observed for several orally administered drugs, such as cimetidine, L-dopa, morphine, penicillamine veralipride, and others (13–17). There are several potential explanations for this observation such as enterohepatic circulation (EHC), interruption of gastric emptying, pH-dependent solubility, and different permeabilities in various regions of the gastrointestinal tract. In an earlier study we have shown that only about 4% of an iv dose is excreted into the bile as pafenolol and metabolites, which excludes EHC as a possible mechanism for the double peaks (7). An alternative hypothesis for the double peaks, namely, a biphasic pattern of gastric emptying due to the cyclic fluctuations in the gastrointestinal motility of the empty stomach (13,14), was considered less likely for pafenolol, since the second peak appeared consistently at 4 hr postdose. A third explanation, pH-dependent solubility, seems less plausible since the intestinal absorption is dose dependent. Finally, the distinct peaks in the oral blood concentration–time curves have been attributed to absorption at two well-separated sites in the gut. The existence of specific absorption sites ("absorption windows") in the gastrointestinal tract confined to the upper part of the small intestine and to the distal part, or the cecum and/or proximal colon, has been proposed previously to lead to the discontinuous absorption of pafenolol (5). In the present study we showed that the small intestinal transit time for a solution was approximately 90 min down to the proximal ileum. In this region the absorption of pafenolol seems to be low (5). After an additional 100 min, i.e. when the major fraction of an oral pafenolol dose has been absorbed from a solution, the majority of the solution was still left in the distal ileum, and only about 20% had entered the cecum and colon. These results support our earlier hypothesis that distal ileum is the major site for absorption of pafenolol after oral administration. The results further show that the ileocolonic transit rate seems to be very low, especially compared to the transit rate measured in the upper part of the small intestine, which agrees with previous results (18–21).

The interindividual variability in rate and extent of absorption when pafenolol was administered in the jejunal (site 1) and ileal (site 2) regions of the small intestine was greater

Table III. Individual and Mean Absorption Characteristics and Half-Lives of Pafenolol in the Rat Following Administration of 25 μmol/kg Through a Catheter Placed 30 cm from the Cecum

Rat no.	C_{max} (nM)	t_{max} (min)	AUC/dose (min/L)	F_{AUC} (%)	F_{deconv} (%)	$T_{50\%}$ (min)	$T_{90\%}$ (min)	$t_{1/2}$ (hr)
1	574	120	18.5	21.7	21.5	90	250	3.0
2	4996	20	74.7	87.7	96.0	28	69	1.9
3	556	50	9.1	10.7	9.6	38	136	2.9
4	780	10	9.0	10.6	9.0	13	300	2.4
5	1430	120	47.1	47.1	48.3	113	175	2.0
Mean	1667	64	30.3	35.6	36.9	56	186	2.4
SD	1894	53	27.9	32.7	36.7	43	91	0.5
Median	780	50	18.5	21.7	21.5	38	176	2.4

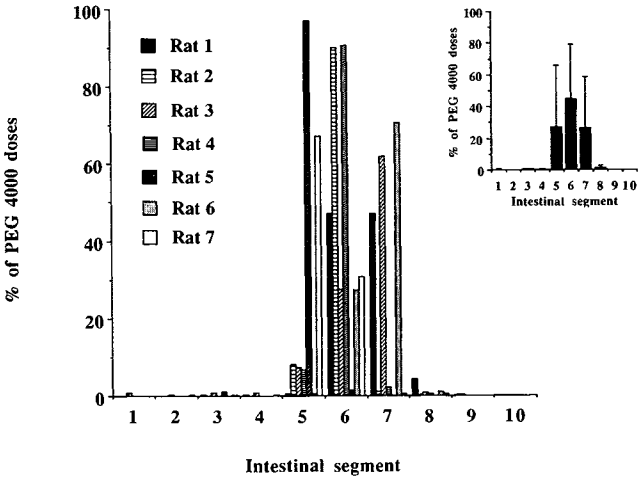

Fig. 3. The individual distribution of radioactivity in the different intestinal segments 90 min after intraduodenal administration of an isotonic saline solution containing ^{14}C-PEG 4000 to one group of seven rats. Segments 1–7 represent the small intestine, and segments 8–10 the colon. The inset shows the mean values (±SD).

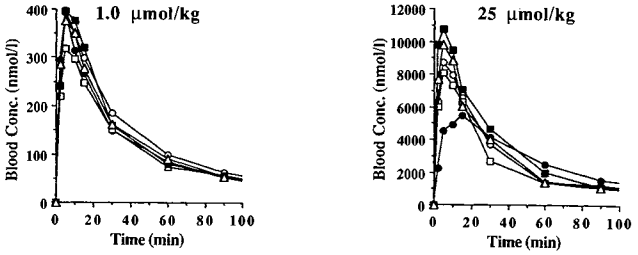

Fig. 5. Individual blood concentration–time curves of pafenolol during the first 100 min following intraperitoneal administration of 1.0 and 25 μmol/kg to two groups of five rats.

than previously found after oral administration of the same dose. Median bioavailability (F) was about 22–25%, which is slightly less (F = 30%) than that after oral administration of the same dose (5–7). The slight reduction in the bioavailability following intrajejunal and intraileal administration and the observation that the blood concentration–time profiles contain only one peak lend further support to our earlier conclusion that the absorption of pafenolol takes place mainly in the ileocolonic region. The greater variation in the absorption of pafenolol after jejunal and ileal administration than after oral gavage could be explained by a substantially lower permeability in the proximal colon than in ileum. Then a prolonged residence time in the ileum would result in a higher bioavailability due to the longer time for absorption. However, this hypothesis seems less likely, as the rats with the highest values of F did not show any pronounced prolonged absorption. Another, and perhaps more plausible, explanation for the erratic absorption is variations in the condition in the intestinal lumen affecting the absorption conditions.

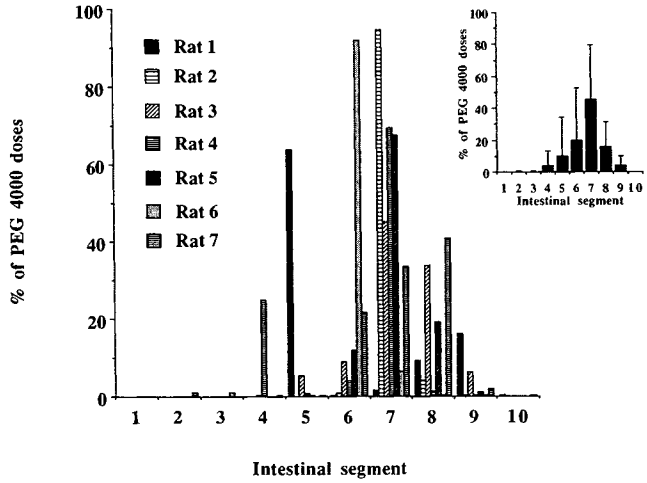

Fig. 4. The individual distribution of radioactivity in the different intestinal segments 190 min after intraduodenal administration of an isotonic saline solution containing ^{14}C-PEG 4000 to one group of seven rats. Segments 1–7 represent the small intestine, and segments 8–10 the colon. The inset shows the mean values (±SD).

The half-life of pafenolol has previously been shown to be about 1 hr longer after oral than after iv administration (5). The half-life was also longer following intraintestinal administration than after the iv and the ip administrations in this study. This might be a consequence of absorption rate-limited kinetics (flip-flop), probably mediated by low permeability over the epithelium of the cecum/colon. Another possibility is a slow release rate of the drug from a hypothetical complex between pafenolol and luminal constituents.

There are several plausible explanations why pafenolol is absorbed primarily (more than 90%) in the ileocolonic region. One is a pH-sensitive absorption of pafenolol favored by the lower pH in colon (22,23). However, the nonlinear increase in absorption makes this explanation less likely (5–7). Another explanation could be that the intestinal excretion (exsorption) of pafenolol interacts with the absorption in the same way as has been proposed earlier for monoquarternary ammonium compounds (24). Such a secretion mechanism would be saturated at higher luminal concentrations of pafenolol. If the capacity for secretion of pafenolol is low in the ileocolonic region, this should lead to a higher intestinal uptake in this region. A third, and perhaps more plausible, explanation is the formation of a stable micellar complex between bile acids and pafenolol. Such a complex has been proposed to be the main reason for the low bioavailability of nadolol, another β-adrenoceptor blocker (25,26). This mechanism has the potential to explain the poor, dose-dependent, and biphasic gastrointestinal absorption of pafenolol.

Unlike absorption of pafenolol from different parts of the gastrointestinal tract, the absorption from peritoneum is rapid, complete, and very reproducible as shown in the present study. The mean bioavailabilities of the two ip doses, 104 and 107%, indicate complete uptake from the peritoneum and negligible hepatic extraction during first pass. This conclusion is valid provided that the rapid absorption of the ip dose did not cause saturation of the liver enzymes. This supposition is in agreement with previous findings from a urinary excretion study of pafenolol and metabolites in rats given oral and intraperitoneal doses of the drug (7). The reason the bioavailability exceeded 100% in the present study was probably minor interindividual differences in the systemic clearance between the two groups of rats used for iv and ip administration. The half-life after ip administration

Table IV. Mean Absorption Characteristics and Half-Lives of Pafenolol into Two Groups of Five Rats Each Following a Single Intraperitoneal Dose of 1.0 and 25 μmol/kg Through a Catheter Placed in the Peritoneum

Dose (μmol/kg)	C_{max} (n*M*)	t_{max} (min)	AUC/dose (min/L)	F_{AUC} (%)	F_{deconv} (%)	$T_{50\%}$ (min)	$T_{90\%}$ (min)	$t_{1/2}$ (hr)
1.0	376 ± 33.5	5 ± 0	89.4 ± 7.1	104 ± 8.3	97.7 ± 5.3	7 ± 0.5	26 ± 3.2	2.0 ± 0.3
25	9066 ± 1767	7 ± 4	91.9 ± 14.1	107 ± 16.4	89.0 ± 11	7 ± 2.9	25 ± 15	1.9 ± 0.2

was about 2 hr, which agreed very well with the half-life after iv administration in this and an earlier study (5). This indicates that the elimination of pafenolol is linear in the rat for blood concentrations up to about 8000 n*M*, which was the upper level attained for the ip dose.

In conclusion, our study demonstrates that ileocecal region of the gastrointestinal tract is the main site for the absorption of pafenolol after oral administration. The transit rate of a solution is more rapid in the upper than in the lower part of the small intestine. Absorption of pafenolol from the peritoneum is rapid and complete and presystemic elimination in the liver seems negligible.

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