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Research Article

Pharmacokinetics of a Single Intravenous and Oral Dose of Pafenolol—a Beta$_1$-Adrenoceptor Antagonist with Atypical Absorption and Disposition Properties—in Man

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The pharmacokinetics of pafenolol were studied in eight young healthy individuals. The doses were 10 mg iv and 40 mg orally. Each dose was labeled with 100 μCi [^{3}H]pafenolol. The plasma concentration–time curve of the oral dose exhibited dual maxima. The second peak was about four times higher than the first one. Maximum concentrations were attained after 0.9 ± 0.2 and 3.7 ± 0.6 hr. The mean bioavailability (F) of the oral dose was 27.5 ± 15.5%. The reduction in F was due mainly to incomplete gastrointestinal absorption. The drug was rapidly distributed to extravascular sites; $t_{1/2\lambda 1}$ was 6.6 ± 1.8 min. The volumes of distribution were V_c = 0.22 ± 0.08 liter/kg, V_{ss} = 0.94 ± 0.17 liter/kg, and V_z = 1.1 ± 0.16 liters/kg. The iv dose of pafenolol was excreted in unchanged form in the urine to 55.6 ± 5.1% of the given dose and in the feces to 23.8 ± 5.7% within 72 hr. The corresponding recoveries of the oral dose were 15.8 ± 5.9 and 67.0 ± 10.2%, respectively. About 10% of both doses was recovered as metabolites in the excreta. Approximately 6% of the oral dose was metabolized to nonabsorbable compounds in the intestine. The mean total plasma clearance was 294 ± 57 ml/min, of which renal clearance, metabolic clearance, and gastrointestinal and/or biliary clearance were responsible for 165 ± 31, 31 ± 15, and 95 ± 32 ml/min, respectively. The half-life of the terminal phase determined from plasma levels up to 24 hr after dosing was 3.1 ± 0.3 hr for the iv dose and 6.7 ± 0.7 hr for the oral dose.

KEY WORDS: gastrointestinal absorption; site specific; beta-blocker; intestinal metabolism; pafenolol.

INTRODUCTION

Pafenonol (±)-*N*-isopropyl-*N'*-2-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]-ethylurea (Fig. 1) is a highly selective beta$_1$-adrenoceptor antagonist (1,2) devoid of intrinsic sympathomimetic and membrane stabilizing activity (1,3). Pafenolol has intermediate lipophilic properties in comparison with other beta-adrenoceptor antagonists. The partition coefficient between *N*-octanol/water in phosphate buffer, pH 7.4 and 25°C, is 0.3. In animals, pafenolol is two to three times more potent than metoprolol in reducing exercise tachycardia (1) and has a considerably longer duration of action than metoprolol (3). The drug effectively lowers the blood pressure in man with daily doses between 25 and 100 mg (4–9).

The objective of this study was to evaluate the absorption and disposition characteristics of pafenolol after administration of a pharmacologically active intravenous and oral dose to young healthy male subjects.

MATERIALS AND METHODS

Study Design

Eight healthy males were recruited for the study. The mean age was 24.4 years (range, 23 to 26 years) and the mean weight was 73.5 kg (range, 65 to 81 kg). All individuals had normal electrocardiograms, blood biochemistry, and hematological test values. The subjects were informed both verbally and in writing about the experimental procedure and the purpose of the study and their written consent was obtained before the study was started. The protocol was approved by the Drug Department of the Swedish National Board of Health and Welfare, the Ethics Committee of the Medical Faculty of the University of Göteborg, and the Isotope Committee of the Sahlgren's Hospital, Göteborg.

The subjects were randomly given 10 mg of pafenolol iv or 40 mg orally. Each dose contained 100 μCi (3.7 MBq) of [^{3}H]pafenolol with a specific radioactivity of 0.78 mCi/mg and held a radiochemical purity of 97.4%. The iv dose was given by constant infusion of 1 mg per min during 10 min. The oral dose was given as a slightly acidic water solution, pH 4.0. The doses were administered after an overnight fast of at least 10 hr. Standardized lunch and dinner were served

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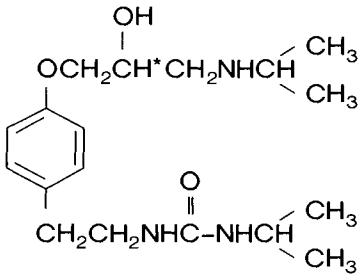

Fig. 1. Chemical structure of pafenolol. The asterisk marks the position of the labeling.

after 3 and 8.5 hr, respectively. The interval between the two experiments was at least 1 week and the whole study was completed within 2 months.

Blood samples (8 ml) were drawn from an antecubital vein after 1, 5, 10, 20, 35, 50, 75, and 100 min and 2.5, 4, 6, 8, 10, 12, and 24 hr for the iv dose and 20, 40, 60, and 90 min and 2, 2.5, 4, 6, 8, 10, 12, and 24 hr for the oral dose. During the first 12 hr an indwelling Venoject catheter was used. The catheter was kept open with a heparin lock. The last two blood samples, 24 and 30 hr after the administration, were drawn by separate vein punctures. The blood was cooled to room temperature and the plasma was separated by centrifugation. The plasma was stored at −20°C until analyzed.

Urine was collected quantitatively at selected intervals for 72 hr. The urine portions were weighed and appropriate volumes were transferred to 100-ml plastic bottles, which were stored at −20°C until analyzed.

Feces were collected quantitatively in three daily portions, which were stored at −20°C.

Determination of Unchanged Pafenolol in the Plasma and Urine

The concentration of pafenolol in plasma and urine was determined gas chromatographically with electron capture detection after extraction with methylene chloride–hexane (1 + 1) and derivatization with pentafluoropionic anhydride. Pafenolol and internal standard, the propylurea analogue of pafenolol, were chromatographed as diacylcarbodimide derivatives using a Varian 3700 gas chromatograph equipped with a glass column (2.5 m, 2-mm i.d.) packed with 3% OV-17 on 100- to 120-mesh Gas Chrom Q. The injection block temperature was 350°C, and the oven temperature 205°C. Minimum determinal concentration with relative SD < 15% was 15 nmol/liter.

Determination of Unchanged Pafenolol in Feces

The concentration of pafenolol in feces was determined by straight phase liquid chromatography (LC) combined with liquid scintillation counting. The LC system consisted of an Altex pump, a Rheodyne injection valve fitted with a 250-μl sample loop, and an LC spectrophotometer, Lambda-Max 480. The samples were chromatographed at ambient temperature on a 150-mm × 4.5-mm-i.d. column with Lichrosorb SI 60 5-μm packing applied with a balanced density slurry techniques. The mobile phase consisted of 17% ammoniacalic methanol (8% NH_3) in methylene chloride. The UV absorption was recorded at 280 nm.

The feces samples were thawed immediately before analysis, diluted with equal amounts of water, and homogenized in a Colworth Stomacher 3500 (Seward and Company, Ltd., London, UK) for 5 min. Unlabeled pafenolol was added to 0.4–1.0 g of the feces homogenate and the homogenate was extracted with 1.0 ml of methylene chloride at pH >11. After centrifugation, 200 μl of the organic phase was injected onto the column. The fraction corresponding to the UV peak of unlabeled pafenolol was collected in scintillation vials and the radioactivity was determined by liquid scintillation counting in a Searle Mark III spectrometer after the addition of 10 ml of scintillation cocktail, Insta-Gel. The quenching was corrected by external standardization. The background was determined by collecting 0.5-min fractions before and after the peak. The recovery of the extraction procedure was determined from added amounts of unlabeled pafenolol.

Determination of Total Radioactivity in Plasma, Urine, and Feces

Plasma, 0.5 to 1.0 ml, and urine, 0.5 to 1.0 g, were diluted to 1.0 ml with water. The total radioactivity was determined by liquid scintillation counting after the addition of 10 ml of scintillation cocktail to the diluted plasma and urine samples.

Feces homogenate, 0.1 to 0.2 g, was treated at 80°C for 30 min with a mixture of 0.2 ml of concentrated hydrogen peroxide and 0.2 mg of concentrated perchloric acid. After cooling to room temperature, 10 ml of scintillation cocktail was added and the radioactivity was determined by liquid scintillation counting.

Calculations

The pharmacokinetic characteristics of pafenolol were evaluated by means of the equations of a two-compartment model and by noncompartmental methods. Curve fitting to the biexponential postinfusion plasma concentration–time curve of the iv dose was performed by the NONLIN program (10) on a Digital VAX 11 computer. The data were weighted by their reciprocals and the goodness of fit was evaluated by the sum of squared deviations and the Akaike value.

Total plasma clearance (CL) was calculated as

$$CL = \frac{dose_{iv}}{AUC_{iv}}$$

where AUC_{iv} is the integrated area of the computer derived equation for the plasma concentration–time curve of the corresponding dose given as a bolus (11). Renal clearance, CL_R, and metabolic clearance, CL_M, were derived from the relationships

$$CL_R = \frac{A_e}{dose_{iv}} \cdot CL$$

and

$$CL_M = \frac{A_m}{dose_{iv}} \cdot CL$$

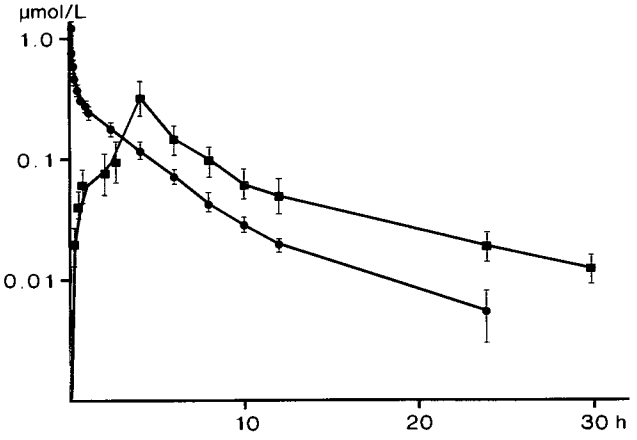

Fig. 2. Mean plasma concentration of pafenolol after administration of 10 mg intravenously (●) and 40 mg orally (■) to eight healthy subjects. The bars indicate SE.

where A_e is the amount of pafenolol recovered in the urine at infinite time and A_m the corresponding recovery of metabolites in urine plus feces.

A third clearance term, CL_{rest}, was calculated as

$$CL_{rest} = CL - CL_R - CL_M$$

CL_{rest} was assumed mainly to represent biliary and/or gastrointestinal clearance.

The volume of distribution at steady state (V_{ss}) was determined by the equation

$$V_{ss} = \frac{dose_{iv} \cdot AUMC}{AUC_{iv}^2} - \frac{dose_{iv} \cdot T}{2 \cdot AUC_{iv}}$$

where T is the infusion time and AUMC the area under the first moment curve from time zero to infinity derived by

$$AUMC = \int_0^t t\, C_t\, dt + \frac{t^* \cdot C_t^*}{\lambda_2} + \frac{C_t^*}{\lambda_2^2}$$

where t is the time between time 0 and the time for the last blood sample, t^* the time of the last blood sample, C_t^* the concentration of pafenolol in this sample, and λ_2 the rate constant of the terminal phase of the plasma concentration–time curve.

The bioavailability of the oral dose (F) was determined by the equation

$$F = \frac{AUC_{oral} \cdot dose_{iv}}{AUC_{iv} \cdot dose_{oral}} \quad \text{and} \quad F = \frac{X_{u_{oral}} \cdot dose_{iv}}{dose_{oral} \cdot X_{u_{iv}}}$$

where X_u is the amount of drug excreted in the urine during 72 hr.

AUC_{oral} was determined by the use of the linear and, after 6 hr, the log-linear trapezoidal rule and extrapolation to infinity by the term C_t^*/λ_2.

The half-life of pafenolol after oral administration was determined from the individual regression lines of log plasma concentration vs time in the 8- to 24-hr interval.

Statistics

The Wilcoxon matched-pairs signed-ranks test was used for statistical evaluation of differences between the terminal half-life of the iv and that of the oral dose. Statistical significance was assumed for $P < 0.05$.

RESULTS

The mean plasma concentration–time curves of the intravenous and oral dose are shown in Fig. 2. The absorption characteristics of the oral dose of pafenolol are listed in Table I. In all individuals, except No 7, double-peaked plasma profiles were observed. Figure 3 shows a representative time course of the plasma levels after oral administration. The first peak was usually seen within the first hour after administration and the second peak was attained 2.5 to 4 hr after dosing. The second peak was, on average, four times higher than the first one (Table I). The mean fraction of the oral dose available systemically was 27.5 ± 15.5% based on plasma concentration data and 28.6 ± 9.4% calculated from the excretion of unchanged drug in the urine.

The plasma concentration–time curve of intravenously administered pafenolol was adequately described by the equation of a two-compartment model. Various parameters associated with the disposition of pafenolol are given in Table II. The mean half-life of the distribution phase ($t_{1/2\lambda 1}$) was

Table I. Individual and Mean Absorption Characteristics and Half-Life of Pafenolol Derived from the Oral Dose of 40 mg in Solution

Subject No.	t_{1max} (hr)	t_{2max} (hr)	C_{1max} (nmol/L)	C_{2max} (nmol/L)	F_{plasma} (%)	F_{urine} (%)	$t_{1/2}$ (hr)
1	1.0	4.0	93	265	39.3	37.5	6.8
2	0.67	4.0	86	503	59.6	40.3	7.2
3	1.0	4.0	58	271	27.6	38.3	6.4
4	1.0	4.0	81	226	23.2	23.0	7.4
5	1.0	4.0	66	302	23.4	30.5	5.8
6	0.67	3.25	30	82	11.2	16.8	5.7
7	1.5	[a]	177	[a]	21.6	25.4	7.3
8	1.0	2.5	33	78	14.4	17.3	6.8
Mean	0.91[b]	3.7	64[b]	247	27.5	28.6	6.7
SD	0.16	0.6	25	145	15.5	9.4	0.7

[a] One peak only.
[b] Value from subject 7 not included in the calculation of the mean.

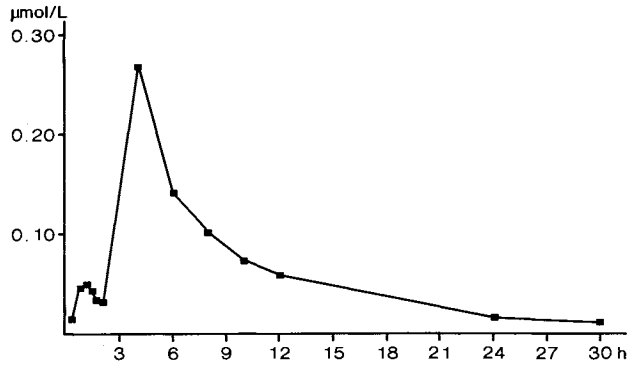

Fig. 3. Plasma concentration of pafenolol after oral administration of 40 mg of the drug, subject 3.

6.5 min (range, 4.1 to 8.7 min) and the drug was initially distributed in a mean body space (V_c) of 0.22 liter · kg^{-1} (range, 0.13 to 0.36 liter · kg^{-1}).

A major fraction of both the iv and the oral dose was recovered as unchanged pafenolol in the urine and feces over a 72-hr period (Table III). The accumulated recovery of radioactivity over this period was more than 90% of the given dose for both the iv and the oral route of administration.

The individual and mean total plasma clearance values of pafenolol determined from the iv dose are shown in Table II. The renal clearance was, on average, 56% of the total plasma clearance and the metabolic clearance constituted approximately 10% of the total clearance. The clearance by the remaining elimination process(es), gastrointestinal and/or biliary clearance, corresponded to approximately one third of total clearance.

The terminal half-life was different for the iv and the oral dose. Nonlinear regression analysis of the plasma concentration–time data of the iv dose yielded a mean $t_{1/2}$ of 3.1 ± 0.3 hr (Table II). Linear regression analysis of log plasma concentration vs time in the terminal phase following oral dosing yielded a mean half-life of the terminal phase of 6.7 ± 0.7 hr ($P < 0.005$) (Table I).

DISCUSSION

The results of this study indicate that pafenolol is a drug with atypical absorption properties. The mean bioavailability of an oral solution of 40 mg is approximately 30% with a fivefold intersubject variation. Incomplete gastrointestinal uptake seems to be the major cause of the reduced 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 reduced bioavailability. In addition 67% of the oral dose was recovered unchanged in the stool. Based on intravenous data approximately 1/10 of this amount was due to biliary secretion or secretion of unchanged drug across the gastrointestinal epithelium (exsorption) of drug reaching the systemic circulation (Table III), while 60% was not absorbed from the intestines.

The atypical plasma concentration–time profile with two peak concentrations at a distance of approximately 3 hr apart may also result from poor absorption of pafenolol. The ratio between the peaks and the time interval between them are consistent with a minor fraction of the dose being absorbed in the upper region of the small intestine, followed by cessation, or in some subjects a substantial reduction, of the absorption until the drug reaches the ileocecal region (12), where the major amount of pafenolol seems to be absorbed. The rapid increase and decline of the plasma concentration during the second absorption phase indicate that the absorption during this period is quite rapid and that the region of absorption is relatively narrow.

Similar results with double peaks, which cannot be attributed to enterohepatic recycling as a corresponding time pattern was not observed for the intravenous dose, have been reported for penicillamine (13) cimetidine (14) veralipride (15), and cyclosporin A (16). For the latter, influence of food was assumed to cause the double peaks, while for the other three drugs two different absorption sites were postulated as an explanation for their atypical time profiles in the plasma.

The approximately twofold longer terminal half-life of pafenolol when given orally compared with intravenous administration indicates that the absorption proceeds down the colon but at a much lower rate than in the region of optimal absorption.

The rate and volumes of distribution were similar to those reported for the more polar betablockers sotalol and nadolol (17). No attempt was made to determine the degree of protein binding in the present study. Preliminary data

Table II. Individual and Mean Disposition Characteristics of Pafenolol Derived from the iv Dose of 10 mg

Subject No.	V_{ss} (L/kg)	V_z (L/kg)	$t_{1/2\lambda 1}$ (min)	$t_{1/2}$ (hr)	CL (ml/min)	CL_R (ml/min)	CL_M (ml/min)	CL_{rest} (ml/min)
1	0.86	1.0	5.0	2.7	309	172	41	96
2	0.92	1.1	5.7	3.0	315	212	22	81
3	1.0	1.1	4.6	3.1	290	136	[a]	[a]
4	0.78	1.1	8.0	3.4	242	147	19	76
5	0.80	0.92	7.7	3.5	239	141	23	75
6	1.2	1.4	8.7	3.2	385	204	22	159
7	0.78	0.90	4.1	3.0	223	132	27	64
8	1.2	1.2	8.1	3.1	351	179	61	111
Mean	0.98	1.1	6.5	3.1	294	165	31	95
SD	0.17	0.16	1.8	0.3	57	31	15	32

[a] Incomplete fecal recovery.

Table III. Excretion of [^{3}H]Pafenolol and Metabolites in Urine and Feces over a Time Period of 72 hr Following iv and Oral Administration of 10 and 40 mg of [^{3}H]Pafenolol, Respectively[a]

	% of dose					
	iv		Oral		Oral calc	
Substance	Urine	Feces	Urine	Feces	Urine	Feces
Pafenolol	55.6 ± 5.1	23.8 ± 5.7	15.8 ± 5.9	67.0 ± 5.9	15.3	6.5
Metabolites	5.9 ± 3.4	4.8 ± 2.0	1.9 ± 1.1	7.2 ± 4.0	1.7	1.3

[a] The columns labeled "oral calc" represent calculated excretion data of the systemically available oral dose assuming that the elimination of this dose was identical to the iv dose.

from a separate study indicate, however, that the binding to plasma proteins is negligible.

According to recovery data, systemically available pafenolol is eliminated by three separate processes of which renal excretion accounts for the main part, approximately 55%, in man. The second most important route of pafenolol elimination is excretion into the gastrointestinal tract, which accounts for about one-third of the elimination of pafenolol according to intravenous data. This process is probably mediated by biliary secretion and/or secretion of unchanged drug across the gastrointestinal epithelium (exsorption). Secretion of unchanged drug from the mesenteric capillary blood into the intestinal lumen has been found to contribute significantly to the elimination of acebutolol—another beta$_1$-adrenoceptor antagonist—in the dog (18), and recently exsorption of theophylline was reported to be more than 50 times greater than its biliary secretion in the rat (19).

Biotransformation, the third mechanism of pafenolol elimination, accounts only for about 10% of the total body clearance of this particular drug. However, following oral dosing the recovery of metabolites in the feces was about five times greater than that calculated from the systemically available dose (Table III). The good agreement between found and calculated recoveries of unchanged drug and metabolites in the urine shows that the excess of metabolites in the feces was not due to more extensive metabolism of the systemically available oral dose than following intravenous administration. It also indicates that first-pass metabolism by the liver was probably not the cause of the increased amount of metabolites in the feces as this would likely have led to an increase in the urinary excretion of metabolites. Metabolism in the intestinal lumen or in the mucosa to nonabsorbable metabolites, possibly conjugates, could, however, result in the increased amount of pafenolol metabolites in the feces after oral dosing. Alternatively, metabolites formed in the intestine are efficiently extracted by the liver and secreted by the bile without reaching the systemic circulation.

In conclusion, this study has shown that pafenolol is a drug with unique absorption properties. The mean bioavailability for an oral 40-mg dose is only about 28% because of incomplete absorption. The major fraction of the dose is absorbed in distal ileum. Its distribution characteristics are similar to those of much more polar beta-adrenoceptor antagonists. The elimination is mediated by three processes namely, renal excretion, biliary and/or intestinal secretion, and metabolism, in descending order. Total-body clearance is about 300 ml/min. A small fraction of an oral dose is probably metabolised already in the intestine. These metabolites do not seem to enter the systemic circulation.

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