Evidence for an Interaction Between the β-Blocker Pafenolol and Bile Salts in the Intestinal Lumen of the Rat Leading to Dose-Dependent Oral Absorption and Double Peaks in the Plasma Concentration–Time Profile

Hans Lennernäs[1,3] and Carl-Gunnar Regårdh[2]

Received April 29, 1992; accepted December 28, 1992

Pafenolol is a β-blocker with unusual oral absorption properties. The blood concentration–time profile exhibits two peaks, and the bioavailability is low and dose dependent because of incomplete and nonlinear intestinal uptake. We addressed the question whether the intestinal absorption of pafenolol was affected by bile depletion in the gut lumen of rats. Further, the hypothesis that variable gastric emptying accounts for double peaks in blood was tested by duodenal administration of pafenolol. Following intraduodenal administration to rats with intact bile secretion, double peaks were observed in the blood concentration–time curve. The bioavailability was 6.8 ± 0.7% for the low dose (1 μmol/kg) and increased significantly to 28 ± 10% following the high duodenal dose (25 μmol/kg). These blood concentration–time profiles exclude interrupted gastric emptying as cause of the twin peaks. In bile duct-cannulated rats the intestinal absorption of the low dose (1 μmol/kg) was still poor (F = 10.7 ± 5.5%) and the blood concentration–time profile contained two peaks. Following administration of a high duodenal dose (25 μmol/kg) to rats with an almost bile-free small intestine, the absorption rate increased and the double-peak phenomenon disappeared in five of seven rats, while the bioavailability increased significantly, to 62 ± 27%. These results suggest that the low bioavailability of pafenolol is due to a complexation between bile and pafenolol in the gut lumen, preventing intestinal uptake in the major part of the small intestine. Further, such complex formation in the intestinal lumen may be the underlying mechanism of the double peaks observed in the blood concentration–time profile.

KEY WORDS: pharmacokinetics; oral absorption; double peaks; absorption interaction; intestinal excretion; bioavailability; dose dependency.

INTRODUCTION

Pafenolol, (±)-*N*-isopropyl-N^1-2-[-4-(2-hydroxy-3-isopropylaminopropoxy)-phenyl]ethylurea, is a highly selective β_1-adrenoceptor antagonist (1,2). The drug has a pK_a of 9.7, a water solubility of 1.0 mg/mL as a base, and a partition coefficient of 0.3 for octanol–phosphate buffer (pH 7.4) at 25°C. The pharmacokinetics of pafenolol in man have been investigated in fasted volunteers who received 150 mL of a slightly acidic solution of pafenolol orally (3,4). The bioavailability increased from 25 to 47% when the oral dose was raised from 25 to 100 mg. The low bioavailability was found to be due to incomplete intestinal uptake. The plasma concentration–time curves exhibited double peaks. The first peak was usually achieved during the first hour and the second, more pronounced peak was apparent 3–4 hr after dosing. More than 90% of the available dose was absorbed during the second peak and was attributed to absorption from the ileocolonic region (5). When the solution of pafenolol was coadministered with food, the bioavailability was reduced by approximately 40%. Moreover, the second peak in the oral plasma curve disappeared and a more smooth plasma profile was observed (6).

We reported that the absorption and elimination of pafenolol in rats are similar to those in man (7–10). The systemic elimination consists of renal and intestinal excretion (exsorption) and metabolism to approximately 50, 25, and 20%, respectively (8). Thus the oral blood concentration–time profile exhibits two peaks following administration of pafenolol as a solution (0.7 mL) and more than 90% of the available oral dose is absorbed during the second peak, which appears 3–4 hr postdose (7). Further, the double-peak phenomenon of the oral blood concentration–time profile in rat was due to absorption of pafenolol from two distinct regions of the alimentary tract, i.e., the small intestine and the ileocolonic region (9). Oral bioavailability increases from 15 to 30% when the dose is increased from 1 to 25 μmol/kg (7–10). Based on excretion studies of pafenolol in rats, we have shown that the presystemic metabolism is relatively small and can therefore be ignored as an explanation for the low and dose-dependent bioavailability. Instead, a nonlinear increase in intestinal uptake seems to be the primary underlying mechanism of the dose-dependent bioavailability (8,9). Following oral administration of pafenolol to fed rats, both the intestinal uptake and the bioavailability of pafenolol are reduced (7,8).

The objective of the present study was to investigate the effects of variable gastric emptying and bile in the gut lumen on the intestinal absorption of pafenolol in rats.

MATERIALS AND METHODS

Drugs and Chemicals. Specifically labeled ^{3}H-pafenolol (19.0 MBq/μmol) was used. The radiochemical purity, determined by HPLC and flow-through monitoring by 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, followed by acidification with 0.1 *M* HCl until the pH reached 5.0. Unlabeled pafenolol (MW 337.5) was added to achieve the required dose. The pH was then raised to 6.8–7.0 with 0.1 *M* NaOH. The specific radioactivity of the different doses was determined by HPLC with UV detection followed by scintillation counting. The pafenolol doses used are shown in Table I.

Animals. Male albino Spraque–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 of the Biomedical Center, Uppsala Univer-

[1] Department of Biopharmaceutics and Pharmacokinetics, University of Uppsala, BMC, Box 580, S-751 23 Uppsala, Sweden.
[2] Pharmacokinetics and Drug Metabolism, Preclinic Research and Development, Astra Hässle AB, Mölndal, Sweden.
[3] To whom correspondence should be addressed.

0724-8741/93/0600-0879$07.00/0

Table I. Mean (±SD) of Absorption Parameters Obtained from Deconvolution of the Blood Concentration–Time Profile Following Intraduodenal (id) Administration of Pafenolol to Rats[a]

Dose (μmol/kg)	Condition	n	$T_{50\%}$ (min)	$T_{90\%}$ (min)	F_{deconv} (%)
			Intact bile flow		
1.0 id	Unfed	7	133 ± 28	300 ± 100	8.0 ± 1.1[a]
25 id	Unfed	7	160 ± 42	213 ± 56	30 ± 11[a]
			Bile duct cannulation		
1.0 id	Unfed	3	92 ± 21	256 ± 62	14 ± 5.7[b]
25 id	Unfed	7	66 ± 19	154 ± 72	69 ± 19[b]

[a] Groups with the same superscript letter are significantly different: [a] $P < 0.001$; [b] $P < 0.001$.

sity, where the room temperature was 22.2 ± 1.0°C and the humidity 55 ± 5%, under a 12-hr light–dark cycle (6 AM to 6 PM, light period). Rats were deprived of food for about 12–16 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 intraarterial, intraduodenal, and bile duct 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). Each rat had a polyethylene catheter (PE-50; o.d., 0.96 mm) inserted into the duodenum above the papilla of Vater. The same type of catheter was inserted into the carotid artery for blood sampling. In two groups of rats the bile duct was cannulated with a polyethylene catheter (PE-10). 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 each other to maintain enterohepatic recirculation of bile during the postoperative period.

Design of the Animal Experiments. Pafenolol solution was administered intraduodenally (id) to four groups of rats (Table I). The intraduodenal doses (1.0 and 25 μmol/kg) were given through the id catheter as bolus injections of 0.5–0.7 mL (including rinsing volume). The first two groups of seven rats each had an intact bile flow. In the remaining two groups of rats the bile duct was cannulated to prevent bile secretion into duodenum (Table I). In these rats the exterior connection of the bile and duodenal catheters was broken 4 hr before drug administration. The duodenal catheter was cleaned of bile and saline was infused intermittently into the duodenum to remove any bile from the small intestine prior to drug administration. The total volume of saline introduced into the duodenum was 3 mL. Since the small intestine transit time is approximately 3–4 hr (9), the luminal concentration of bile salts should be significantly reduced in the bile duct-cannulated rats by this procedure. Blood samples were withdrawn from the heparinized catheter placed in the carotid artery at 10, 20, 50, 90, 120, 150, 190, 240, 300, 420, 600, and 720 min following duodenal administration to all four groups. The rats were not restrained or anesthetized at any time during the experiments. The total volume of blood taken from each animal was 2 mL. All blood samples were stored at −20°C until analysis.

Measurements of Pafenolol in Blood. Pafenolol was assayed in blood by a normal-phase HPLC method with UV detection followed by liquid scintillation counting of the collected fractions which contained unchanged pafenolol. The analytical procedure has been described in earlier papers (10,11). Reproducibility, expressed as the coefficient of variation of repeated determinations of standards (10 samples), was 3 and 6% for the highest and lowest radioactivity concentrations, respectively. The minimum limit of determinable radioactivity value used was 120 dpm, which was three times the background radiation level.

Data Analysis. The area under the concentration-versus-time curve (AUC) for each individual rat was calculated by using the linear and the logarithmic trapezoidal rule for ascending and descending blood concentrations, respectively, up to the last time point. The area to infinite time beyond the last sample 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 log concentration vs time for the last three to five blood samples.

The bioavailability of the duodenal doses was determined from the dose-adjusted ratio of the AUC after the duodenal and iv doses (F_{AUC}). The AUCs of the iv doses were taken from two previous studies. In the rats which had an intact bile flow the iv reference for the AUC was taken from Ref. 9, and in the bile duct-cannulated rats the AUC_{iv} was taken from Ref. 8.

The blood concentration–time curves following oral and duodenal administration were subjected to deconvolution analysis (12) in order to obtain an estimate of the absorption rate. 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. In addition, the bioavailability (F_{deconv}) value was obtained.

All results are presented as mean values and standard deviations unless stated otherwise. Student's unpaired *t* test was used for significance testing between doses.

RESULTS

The individual blood concentration–time curves for pafenolol administered as a saline solution into the duodenum of animals with intact bile duct are shown in Figs. 1 and 2. The first peak was achieved during the first 30 min and the second, significantly higher peak in the blood concentration vs time profile was observed after approximately 3–3.5 hr (Table II). The ratio C_{max2}/C_{max1} was 2.0 ± 1.2 following the low duodenal dose but increased significantly, to 15 ± 12 ($P < 0.05$), after administration of the high dose. More than 90% of the systemically available dose was absorbed during the second absorption phase after both the low and the high duodenal dose. The times to absorb 50 and 90% of the available dose following administration of 1 μmol/kg were 133 ± 28 and 300 ± 100 min, respectively. The corresponding values after the high dose were 160 ± 42 and 213 ± 56 min (Table I). The mean bioavailability based on the AUC method increased from 6.8 ± 0.7% for the low dose to 28 ± 10% ($P < 0.001$) for the high duodenal dose (Table II). The mean extrapolated area for each dose level was 7.5 ± 3.4 and 1.5 ± 0.3%. The corresponding bioavailabilities calculated

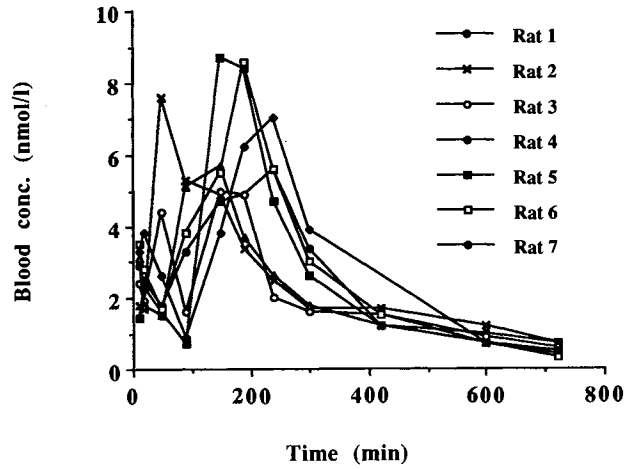

Fig. 1. Individual blood concentrations of pafenolol following duodenal administration of a solution (1.0 μmol/kg) to seven unfed rats with intact bile flow.

by deconvolution were 8.0 ± 1.1 and 30 ± 11% ($P < 0.001$), respectively (Table I). The average values for the terminal half-life in these two groups were 3.2 ± 0.8 and 1.8 ± 0.2 hr ($P < 0.01$) (Table II).

The blood concentration–time profiles following duodenal administration of the low dose to three bile duct-cannulated rats are shown in Fig. 3. The double-peak phenomenon remained after this low dose, the ratio of C_{max2}/C_{max1} was 0.6 ± 0.2, i.e., inversed compared to rats with intact bile flow. The first and the second peaks were observed at approximately 15 and 150 min, respectively. $T_{50\%}$ and $T_{90\%}$ of the available dose were 92 ± 21 and 256 ± 62 min, respectively. The average values of bioavailability estimated by the AUC method and deconvolution were 11 ± 4.6 and 14 ± 5.7%, respectively. The extrapolated area was 8.8 ± 3.5% and the mean elimination half-life was 2.8 ± 0.4 hr (Tables I and II).

Duodenal administration of the high dose of pafenolol to bile duct-cannulated rats generated a blood concentration–time profile which contained only one peak, at 83 ± 40 min, in five of seven animals (Fig. 4). The absorption rate parameters, $T_{50\%}$ and $T_{90\%}$, were 66 ± 19 and 154 ± 72 min, respectively. The bioavailability increased significantly, to 62 ± 27 and 69 ± 19%, when estimated by the AUC and deconvolution methods, respectively. The extrapolated area was 4.9 ± 2.5% and the elimination half-life was 2.6 ± 0.5 hr (Table II).

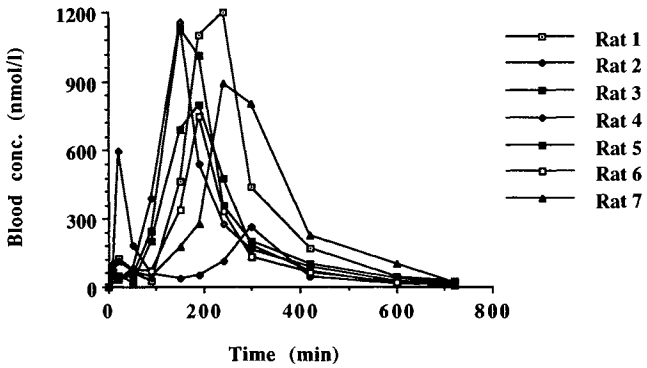

Fig. 2. Individual blood concentrations of pafenolol following duodenal administration of a solution (25 μmol/kg) to seven unfed rats with intact bile flow.

DISCUSSION

Duodenal administration of a solution of pafenolol had no effect on the double peaks in the plasma concentration–time profile. This confirms our previous hypothesis that variable gastric emptying could not explain the double-peak phenomenon (7). Instead, absorption at two distinct sites in the gastrointestinal tract, proximal and distal small intestine, has been found to be a plausible mechanism (9).

Following duodenal administration in the unfed state $T_{50\%}$ was approximately 140 min, which is 40–65 min less than after oral administration (7). The difference can be attributed to the residence time in the stomach. The time to absorb 90% of the dose was 100 min shorter following the high duodenal dose compared to the low duodenal dose. The high values for $T_{50\%}$ and $T_{90\%}$ indicate that the drug is absorbed from the distal ileum and probably from the colon as well. This is supported by data from one of our earlier studies, where about 65% of a duodenally given solution of ^{14}C-PEG 4000 solution was still left in the distal ileum and about 20% had entered the colon after 190 min (9).

The bioavailability of pafenolol following duodenal administration to rats with an intact bile flow was dose dependent. In the unfed rats the systemic availability of the low duodenal dose was significantly lower compared to the same dose given orally (7). However, for the high dose the bioavailability was similar, irrespective of the administration site. Previous studies have shown the nonlinear increase in bioavailability to be due to increased absorption from the intestine (8,10).

Following duodenal administration of the low dose of pafenolol to bile duct-cannulated rats, absorption was virtually the same as in rats with normal bile flow to the small intestine. The bioavailability was in the same range, 6–12%, and the double-peak phenomenon remained. However, after the high duodenal dose to bile duct-cannulated rats, both the rate and the extent of absorption were significantly increased. The blood concentration–time profile displayed only one peak in five of seven animals, which appeared about 80 min postdose. The absorption of the systemically available dose was completed within 150 min, i.e., when the drug was still present in the small intestine (9), and the mean bioavailability increased significantly, from approximately 30% (intact bile secretion) to about 65% (range, 30–99%). These results indicate that the presence of bile in the intestine has a significant impact on the absorption of pafenolol in the rat. When the duodenal dose of pafenolol was low there was probably enough bile left in the gut to significantly interfere with the absorption of the β_1-blocker, whereas the major fraction of the high dose was unaffected by the low intestinal content of bile. Another plausible hypothesis for the poor uptake of the low dose is the existence of an intestinal excretion mechanism that might oppose the absorption of pafenolol at low luminal concentrations (8). The low bioavailability observed in a couple of the rats given the higher dose (Nos. 6 and 7) could be due to inefficient depletion of the bile in the small intestine. The appearance of double

Table II. Mean (±SD) of Absorption Parameters and Half-Life Following Duodenal Administration of Pafenolol to Normal and Bile Duct-Cannulated Rats

Dose (μmol/kg)	n	C_{max1} (nmol/L)	C_{max2} (nmol/L)	$\frac{C_{max2}}{C_{max1}}$	t_{max1} (min)	t_{max2} (min)	AUC/dose (min/L)	F_{AUC} (%)	$t_{1/2}$ (h)
				Rats with intact bile flow					
1.0	7	3.6 ± 2.0	6.7 ± 1.8	2.0 ± 1.2[a,*]	18 ± 16	176 ± 40	5.8 ± 0.6	6.8 ± 0.7[c]	3.2 ± 0.8[b]
25	7	157 ± 219	913 ± 345	15 ± 12[a]	20 ± 14	209 ± 55	24 ± 8.5	28 ± 10[c]	1.8 ± 0.2[b]
				Bile-cannulated rats					
1.0	3	19.0 ± 7.2	10.7 ± 4.6	0.6 ± 0.2	17 ± 5.8	143 ± 50	12 ± 6.2	11 ± 5.5[d]	2.8 ± 0.4
25	7	2310 ± 1089	—	—	83 ± 40	—	69 ± 31	62 ± 27[d]	2.6 ± 0.5

* Groups with the same superscript letter are significantly different: (a) $P < 0.05$; (b) $P < 0.01$; (c, d) $P < 0.001$.

peaks in these two animals further supports the idea of incomplete bile removal. By deleting the F values in rats 6 and 7, a mean bioavailability of 73 ± 24% (F_{AUC}) and 81 ± 25% (F_{deconv}) is obtained in the bile-free rats.

Bile salts form micelles in aqueous media with themselves and with other compounds which can have different effects on intestinal absorption of drugs. Decreased absorption of nadolol, griseofulvin, ketoconazole, imipramine, and sulfaguanidine (13–17) has been explained by this interaction when studied by *in situ* intestinal perfusion. On the other hand, bile acids might lead to increased intestinal absorption of these drugs *in vivo*, by improvement of the dissolution rate of these poorly water-soluble drugs (18,19) and/or by increasing the membrane permeability (20–22). For cyclosporin the presence of bile in the intestinal lumen is crucial for intestinal absorption (23). However, the oral absorption of nadolol *in vivo* was lowered by the presence of bile acids in the lumen, possibly because of the formation of stable micellar complexes between nadolol and bile acids, with a resulting loss of thermodynamic activity (13,14,24). Complex formation between bile acids and pafenolol may also account for the low, discontinous, and dose-dependent intestinal uptake of this drug.

The rapid cessation of the absorption of pafenolol following both oral and duodenal administration is consistent with rapid micellar complexation in the proximal part of the small intestine, where the luminal concentration of bile acids is high. In the distal ileum the micelles dissociate (no uptake of intact micelles takes place) and the bile acids are actively reabsorbed (25–27), followed by enhanced intestinal absorption of pafenolol and the second and major peak in its plasma concentration. Interactions with bile acids could also account for the dose-dependent absorption of the drug. At high drug concentrations in the intestinal lumen the binding to the complex(es) might be saturated and more pafenolol is available for absorption.

Further support for the influence of bile on the absorption of pafenolol was obtained in a human study where the absorption of the drug decreased by approximately 40% when a solution of pafenolol was coadministered with breakfast. The time course of the plasma concentration–time profile was also affected in the postprandial state. Only one peak was observed and the terminal half-life was prolonged (6). Together, these observations are consistent with increased micelle complex formation due to food-stimulated biliary secretion.

In conclusion, the intestinal absorption of pafenolol is increased in the rat when the small intestine is depleted of bile. Complex formation between pafenolol and the bile acids in the intestinal lumen preventing intestinal uptake of the drug is probably the underlying mechanism for the low, dose-dependent, and variable absorption and the double peaks observed in the blood concentration–time profile of pafenolol.

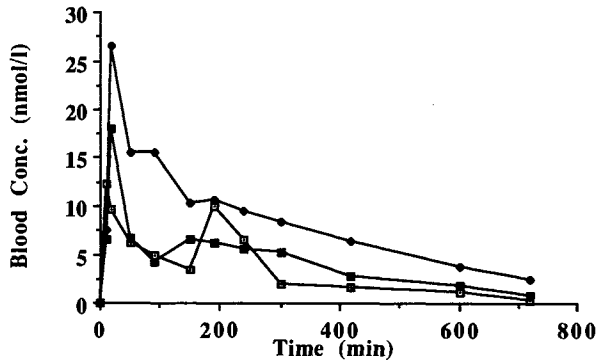

Fig. 3. Individual blood concentrations of pafenolol following duodenal administration of a solution (1.0 μmol/kg) to three unfed rats with interrupted bile flow for 4 hr before dosing.

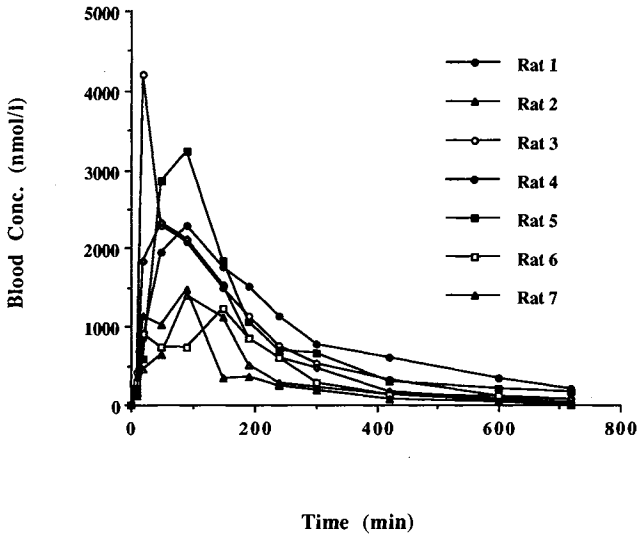

Fig. 4. Individual blood concentrations of pafenolol following duodenal administration of a solution (25 μmol/kg) to seven unfed rats with interrupted bile flow for 4 hr before dosing.

REFERENCES

1. J.-A. Björkman, L. Ek, E. Carlsson, and B. Lundgren. Pafenolol II. Cardiovascular effects in anaesthetized dogs. Abstract, XVII Joint Meeting of the Scandinavian Physiological and Pharmacological Society, Reykjavik, August 1982. *Acta Physiol. Scand. Suppl.* 508:42 (1982).
2. B. Lundgren, E. Carlsson, and L. Ek. β-Blocking potency and selectivity in in vivo and in vitro experiments. Abstract, XVII Joint Meeting of the Scandinavian Physiological and Pharmacological Society, Reykjavik, August 1982. *Acta Physiol. Scand. Suppl.* 508:44 (1982).
3. C. G. Regårdh, A. Heggelund, K. Kylberg-Hansen, and P. Lundborg. Pharmacokinetics of pafenolol after iv and oral administration of three separate doses of different strength to man. *Biopharm. Drug Disp.* 11:607–618 (1990).
4. C. G. Regårdh, P. Lundborg, M. Gabrielsson, A. Heggelund, and K. Kylberg-Hansen. Pharmacokinetics of a single intravenous and oral dose of pafenolol—a $beta_1$-adrenoceptor antagonist with atypical absorption and disposition properties in man. *Pharm. Res.* 7:1222–1227 (1990).
5. S. S. Davis, J. G. Hardy, and J. W. Fara. Transit of pharmaceutical dosage forms through the small intestine. *Gut* 27:886–892 (1986).
6. A. Heggelund, C. Jansson, P. Lundborg, and C. G. Regårdh. The effect of food on the gastrointestinal absorption of pafenolol—a preliminary study. *Hässle Report* No. 206-778:1–10 (1982).
7. H. Lennernäs and C. G. Regårdh. Pharmacokinetics of pafenolol in the rat: A suitable model for studying absorption mechanisms of a drug exhibiting unusual absorption properties in man. *Biopharm. Drug Disp.* 11:619–631 (1990).
8. H. Lennernäs and C. G. Regårdh. Dose-dependent intestinal absorption and significant intestinal excretion (exsorption) of the beta-blocker pafenolol in the rat. *Pharm. Res.* 5:727–731 (1993).
9. H. Lennernäs and C. G. Regårdh. Regional gastrointestinal absorption of the beta-blocker pafenolol in the rat and intestinal transit rate determined by movement of ^{14}C-PEG 4000. *Pharm. Res.* 1:130–135 (1993).
10. H. Lennernäs, L. Renberg, K.-J. Hoffman, and C. G. Regårdh. Presystemic elimination of pafenolol in the rat after oral and ip administration and identification of the main metabolite in both rats and humans. *Drug Metab. Disp.* 3 (1992).
11. P.-O. Lagerström and B.-A. Persson. Method for pafenolol in dog plasma. *Hässle Report* No. BA-043 (1979).
12. K. Iga, Y. Ogawa, T. Yashiki, and T. Shimamoto. Estimation of drug absorption rates using a deconvolution method with non-equal sampling times. *J. Pharmacokin. Biopharm.* 14:213–225 (1986).
13. T. Yamaguchi, T. Oida, C. Ikeda, and Y Sekine. Intestinal absorption of a β-adrenergic blocking agent nadolol. III. Nuclear magnetic resonance spectroscopic study on nadolol-sodium cholate micellar complex and intestinal absorption of nadolol derivatives in rats. *Chem. Pharm. Bull.* 34:4259–4264 (1986).
14. T. Yamaguchi, C. Ikeda, and Y Sekine. Intestinal absorption of a β-adrenergic blockingagent nadolol. I. Comparison of absorption behavior of nadolol with those of other β-blocking agents in rats. *Chem. Pharm. Bull.* 34:3362–3369 (1986).
15. T. Kimura, K.-I. Inui, and H. Sezaki. Differences in effects on drug absorption between dihydroxy and trihydroxy bile salts. *J. Pharmacobio-Dyn.* 8:578–585 (1985).
16. F. G. J. Poelma, R. Breäs, and J. J. Tukker. Intestinal absorption of drugs. III. The influence of taurocholate on the disappearance kinetics of hydrophilic and lipophilic drugs from the small intestine of the rat. *Pharm. Res.* 7:392–397 (1990).
17. F. G. J. Poelma, R. Breäs, J. J. Tukker, and D. J. A. Crommelin. Intestinal absorption of drugs. The influence of mixed micelles on the disappearance kinetics of drugs from the small intestine of the rat. *J. Pharm. Pharmacol.* 43:317–324 (1991).
18. T. R. Bates, M. Gibaldi, and J. L. Kanig. Rate of dissolution of griseofulvin and hexoestrol in bile salt solutions. *Nature* 210:1331–1333 (1966).
19. M. Gibaldi and S. Feldman. Mechanisms of surfactant effects on drug absorption. *J. Pharm. Sci.* 59:579–589 (1970).
20. S. Feldman and M. Gibaldi. Physiologic surface-active agents and drug absorption. I. Effect of sodium taurodeoxycholate on salicylate transfer across the everted rat intestine. *J. Pharm. Sci.* 58:425–428 (1969).
21. S. Miyazaki, H. Inoue, T. Yamahira, and T. Nadai. Interaction of drugs with bile components. I. Effects of bile salts on the dissolution behaviour of indomethacin and phenylbutazone. *Chem. Pharm. Bull.* 27:2468–2472 (1979).
22. M. Yonezawa. Basic studies of intestinal absorption I. Changes in the rabbit intestinal mucosa after exposure to various surfactants. *Nihon Univ. J. Med.* 19:125–141 (1977).
23. P. F. Whitington, B. H. Kehrer, S. H. Whitington, B. Shneider, and D. B. Black. The effect of biliary enteroenteostomy on the pharmacokinetics of enterally administered cyclosporine in rats. *Hepatology* 9:393–397 (1989).
24. T. Yamaguchi, C. Ikeda, and Y Sekine. Intestinal absorption of a β-adrenergic blocking agent nadolol. II. Mechanism of the inhibitory effect on the intestinal absorption of nadolol by sodium cholate in rats. *Chem. Pharm. Bull.* 34:3836–3843 (1986).
25. E. R. Schiff, N. C. Small, and J. M. Dietschy. Characterization of the kinetics of the passive and active transport mechanisms for bile acid absorption in the small intestine and colon of the rat. *J. Clin. Invest.* 51:1351–1362 (1972).
26. B. Angelin, K. Einarsson, and K. Hellström. Evidence for the absorption of bile acids in the proximal small intestine of normo- and hyperlipidaemic subjects. *Gut* 17:420–425 (1976).
27. F. D. Wilson and J. M. Dietschy. Characterization of bile acid absorption across the unstirred water layer and brush border of the rat jejunum. *J. Clin. Invest.* 51:3015–3025 (1972).