Pharmacokinetics of pindolol in humans and several animal species

The absorption, distribution, detoxification, and excretion of pindolol were investigated in mice, rats, dogs, rhesus monkeys, and humans. The absorption was very good in all species; however, the quantitative composition of the final excretion products was unique for each species. Considerable interspecies variation was also apparent with respect to excretion patterns. The pharmacokinetics of pindolol in humans was investigated in single- and multiple-dose studies. All results were in agreement with a three-compartment model. The absorption was rapid and a first-pass effect of 12% to 25% of the dose (mean 20%) was calculated. The half-lives of the excretion of radioactivity were 3.0, 1.2, and < 100 hours. The pharmacokinetic parameters obtained in normal volunteers were compared with corresponding values obtained in patients with hypertension, renal insufficiency, or liver impairment. Results in these patients were not significantly different. The bioavailability interaction was investigated with drugs often coadministered with a beta blocker. No drug-drug interaction was found with hydralazine, hydrochlorothiazide, coumarin, or aspirin. Pindolol coadministration resulted in a possible lowering of digoxin levels. The bioavailability of the tablet dosage form proposed for marketing was compared to that of a solution and found to be optimal (Am Heart J 104:357, 1982.)

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Metabolism and bioavailability studies have been carried out to support the safety and efficacy of pindolol (Visken). Studies in animals have been directed toward the validation of toxicity trials and were concerned with pharmacokinetics and detoxification (Table I). Studies in humans, in addition, have dealt with first-pass effect, steady-state conditions, pharmacokinetics in disease states, drug-drug interactions, and bioavailability. Most of the animal studies and many of the human studies were done with a radiolabeled drug. The most frequently used radiolabeled pindolol preparation contained a specific carbon-14 label in the *N*-isopropyl group (Fig. 1). This label proved to be metabolically unstable (degradation of the side chain) in some animal species. Pindolol studies in these species were repeated with ^{14}C-pindolol labeled specifically in 2-position of the indole ring system.

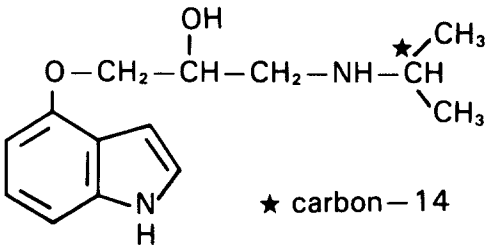

Fig. 1. *N*-Isopropyl group.

ABSORPTION AND EXCRETION

The absorption and excretion data obtained in humans and pivotal animal species are summarized in Table II. The absorption data in the rat (5 mg/kg dose) were obtained directly from animals with cannulated bile ducts. In all other species indirect estimates were obtained by comparing oral and intravenous blood concentrations and excretion patterns. In all species pindolol was well absorbed, with estimates ranging from > 80% to 100%.

Considerable interspecies variation was observed in the excretion patterns. In the dog, where side-chain degradation was a major pathway of detoxification (Table III), side-chain–labeled pindolol gave a poor recovery and thus invalid results. In all other species side-chain degradation was a minor biotransformation pathway, and the position of the carbon-14 label was of no significance. Urinary excretion accounted for > 70% of the dose in humans, dogs, and rhesus monkeys and for less in rodents. A definite relationship with the dose was observed in rats where the percentage in the urine

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Table I. Tabulation of metabolism studies

Species	Route of administration	Pharmacokinetics			Detoxification	
		Blood level	*Distribution*	*Excretion*	*Low dose*	*High dose*
	Oral		X			X
Mouse	IV		X			
	Oral	X	X	X	X	X
Rat	IV	X	X	X		
Rabbit	Oral					X
	Oral	X		X	X	
Cat	IV	X		X	X	
	Oral	X		X	X	X
Dog	IV	X	X	X		
Squirrel monkey	Oral	X		X	X	
	Oral	X		X	X	
Rhesus monkey	IV		X			
Baboon	Oral	X		X	X	
	Oral	X		X	X	
Human	IV	X		X		

Table II. Pindolol—absorption and excretion

Species / *Dose (mg/kg)*	*Human* 0.07-0.14	*Mouse* 124	*Rat* 5	*Rat* 150	*Dog* 2.5	*Dog* 2.5*	*Monkey* 0.3
% Dose in urine	81.4	40.6	28.9	54.5	47.5	71.9	81.6
% Dose in feces	8.2	39.5	62.5	32.2	14.4	26.7	11.0
% Dose in bile	—	—	44.0	—	—	—	—
Total recovery	89.6	89.8	91.4	86.7	61.9	98.6	92.6
Minimum absorption (%)	83	80	73	70	85	85	85
Probable absorption (%)	100	80	90	90	100	100	100

*Pindolol labeled with ^{14}C in the indole ring.

was increased at a higher dose, in parallel with the percentage of unchanged drug excreted. Total recovery was over 86% in all species.

METABOLIC PATHWAYS

The metabolic pathways of pindolol are illustrated in Fig. 2. Simple conjugation of the existing side-chain hydroxyl group with glucuronic acid yields the diastereoisomers Ia and Ib (*d* or *l* pindolol with D-glucuronic acid). The previously mentioned degradation of the side chain gives rise to the primary products IX (hydroxy acid) and isopropylamine. The other metabolites are derivatives of ring-hydroxylated intermediates. Oxidation in 2-position leads to the oxindol IV, oxidation, and conjugation in 3-position to the indoxyl sulfate V. The latter, by oxidative dimerization, can give rise to the blue pigment VIII, which is found in trace quantities in all animal species at high doses. It is not found in humans. Through oxidation in positions 2 and 3, followed by loss of a 1-carbon fragment, the anthranilic acid VII is obtained. Metabolites II and VI constitute the glucuronic acid and sulfuric acid conjugates of 5-hydroxy pindolol, respectively. Likewise, metabolites III and X are the corresponding conjugates of 6-hydroxy pindolol. Hydroxylation in the 7-position was not observed.

Quantitative metabolite patterns in urine are shown in Table III. Again, considerable interspecies variation is apparent. In man 35% of the dose was excreted as unchanged drug and all the metabolic pathways depicted in Fig. 2, except III → VIII, were active, none of them constituting a distinct major pathway. The results in the mouse show that, together with a small amount of unchanged drug, all known metabolites were present in small percentages. In the rat, 3-hydroxylation and the subsequent loss of the 2-carbon (→VII) was the major pathway of detoxification; conjugation of the side-chain hydroxyl group (Ia and Ib) was not observed. In the dog, degradation of the side chain was the major biodegradation pathway, giving rise to IX and 1 and

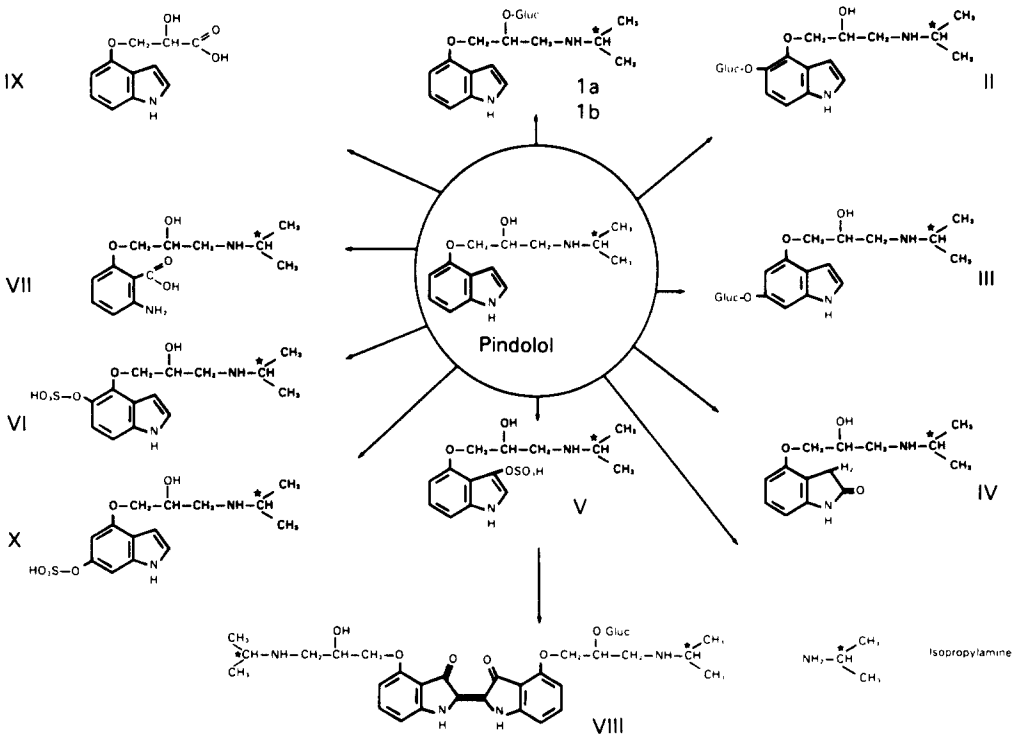

Fig. 2. Biotransformation pathways of pindolol.

Table III. Pindolol—characterization and quantitation of the urinary metabolites

Metabolite		% of dose						
		1,2 Human 0.64 mg/kg	*2 Mouse* 124 mg/kg	*2 Rat* 30 mg/kg	*2 Dog* 2.5 mg/kg	*3 Dog* 2.5 mg/kg	*2 Rhesus monkey* 0.4 mg/kg	*3 Rhesus monkey* 2.5 mg/kg
Designation	*No.*							
[14]C-activity	IA	74.3	39.9	70.5	43.8	71.2	74.0	79.0
Pindolol	IB	35.0	4.3	12.5	0.6	1.9	0.7	2.2
(+)Pindolol glucuronide	II	1.1	0.8	—	2.5	3.5	28.8	32.7
(−)Pindolol glucuronide		2.7	0.3	—	3.2	6.5	19.0	27.1
5-OH glucuronide	III	2.1			3.3	7.9	—	—
	IV		4.5	5.6			—	
6-OH glucuronide		1.3	5.2		—	—	—	—
Pindolol oxindole	V	2.5	4.6	7.2				
	VI				4.8	5.7	1.7	—
3-OH sulfate	VII	1.1	5.7	12.4			12.4	
5-OH sulfate		9.4	0.2	5.1	1.3	2.9	—	2.4
Pindolol anthranilic acid	IX	3.4	0.5	10.3	4.5			3.8
	X					18.0	ND	—
Hydroxy acid	1	ND	ND	ND	ND		0.9	
6-OH sulfate		2.4	4.2	0.9	2.0	3.4	2.1	3.2
Isopropylamine		7.1	3.2	5.1	13.0	ND	65.6	—
Total metabolites identified		68.1	33.5	59.1	35.2	49.8	8.4	ND
Not identified		6.2	5.4	11.4	8.6	21.4		71.4
								7.6

[1]Fifteen milligrams three times a day for 3 days; 0- to 192-hour collection.
[2]Side-chain-labeled [14]C-pindolol.
[3]Ring-labeled [14]C-pindolol.

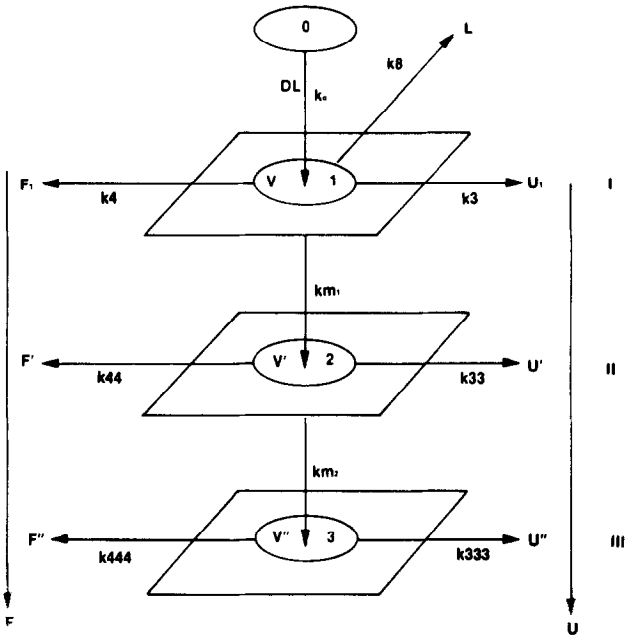

Fig. 3. Pindolol. Compartmental model representing the pharmacokinetics in humans.

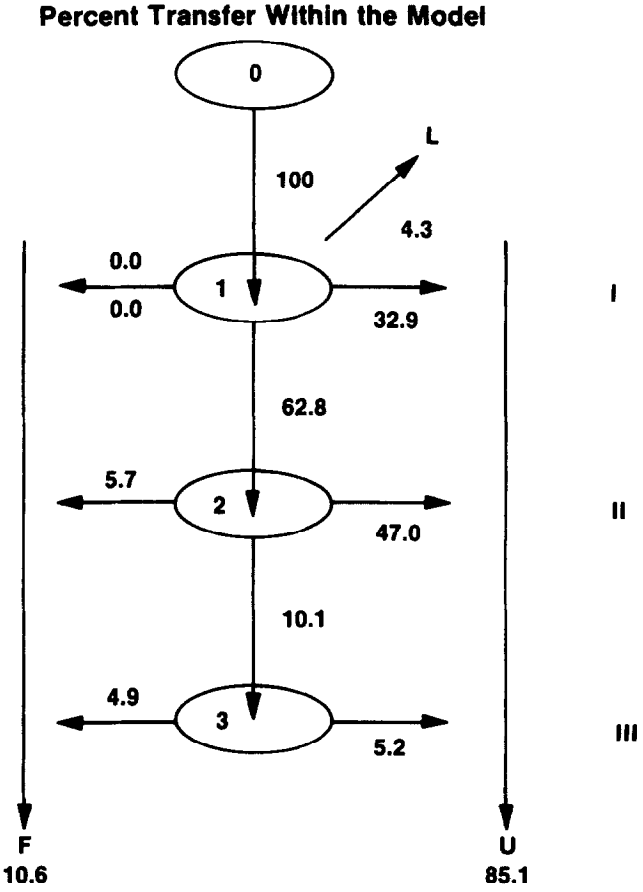

Fig. 4. Pindolol pharmacokinetics in humans.

possibly to metabolites otherwise not encountered. The 6-hydroxy pindolol was only present in the form of its sulfate. The major pathway of detoxification in the rhesus monkey was conjugation of the existing hydroxyl group. The glucuronates of 5-hydroxy pindolol and 6-hydroxy pindolol were absent, as were the oxindol metabolite IV and the anthranilic acid metabolite VII. In all species, with the exception of the dog, 80% to 90% of the drug-derived excretion products were identified and quantitated.

From the results, it can be concluded that the same biotransformation pathways are active in all species. There were quantitative differences in the relative amounts of metabolites excreted, and not all metabolites were excreted by each species. However, each of the metabolites found in humans was also found in at least three of the animal species. Also, the exposure to unchanged drug and metabolites at nontoxic dose levels was a multiple of that in humans at therapeutic dose levels. Thus, the safety of pindolol and all of its metabolites was indirectly assured by the results of the toxicity studies.

PHARMACOKINETICS IN HUMANS

The pharmacokinetics of ^{14}C-labeled pindolol were investigated in two studies. In a single-dose study, 5 and 10 mg were administered orally and 0.4 mg intravenously to small groups of human volunteers. In a multiple-dose study, nine consecutive 15 mg doses were given in 8-hour intervals to five volunteers. In both studies, blood, urine, and feces were collected and analyzed for radioactivity and unchanged drug. The data from both studies were then analyzed and interpreted with the help of a compartmental model. The model had to fulfill the following requirements—absorption had to be quantitative and to start after a short lag time, the elimination of unchanged drug had to be monophasic, and two groups of metabolites, one disappearing relatively fast and the second one relatively slowly, had to be excreted into urine and feces simultaneously. A model fulfilling these conditions is shown in Fig 3: 100% of the drug was assumed to be in compartment 0 at time 0. After a delay, (DL) absorption started and 100% of the drug appeared in compartment 1. The drug was then either excreted unchanged or metabolized (km_1). Since the liver was included in compartment 1, any first-pass metabolism would be included in step km_1. The model allowed for two types of metabolites formed consecutively, type I and type II, both excreted simultaneously into urine and feces. Unchanged

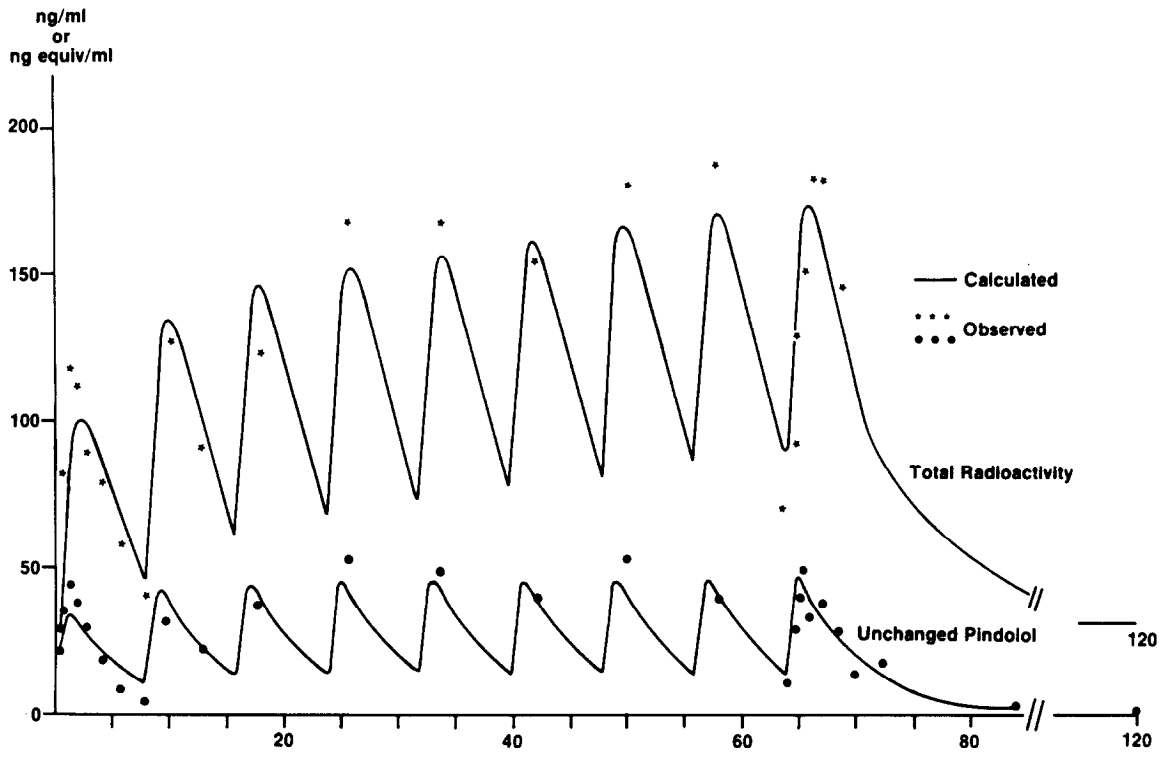

Fig. 5. Blood levels of total radioactivity and unchanged pindolol during and following multiple oral doses (15 mg three times a day for 3 days) of ^{14}C-pindolol in humans. (Comparison of calculated curves with observed points.)

drug type I and type II metabolites were given their own distribution volumes allowing for independent distribution at all levels. The model also makes allowance for a loss to compensate for less than 100% recovery.

The data were subjected to simultaneous curve fitting using the equations underlying the model, and a perfect fit with a correlation of 1.00 was obtained. From the numerical equations the amounts transported along each arrow between time zero and infinity were calculated. The values obtained are shown in Fig. 4. The 100% absorption was part of the model. There is a loss of 4.3% postulated, which is most likely due to incomplete sample collection. A total of 32.7% of the dose is projected to be excreted unchanged, all of it in the urine. Type I metabolites in urine and feces comprise 51.7% of the dose, mostly in urine, and type II metabolites 10.1%, again mostly in the urine. The nature of these metabolites was also investigated. It was found that all known human metabolites (Fig. 2) were excreted as type I metabolites. Type II metabolites comprised "diffuse radioactivity." They most likely arose when the carbon-14–labeled isopropyl group was separated from the rest of the molecule and entered the intermediary metabolism as a radioactive 3-carbon fragment. As a matter of fact it can be inferred from Table III that side-chain degradation accounted for about 10% of the dose in humans (formation of isopropylamine).

The pharmacokinetic parameters of pindolol in humans are shown in Table IV. The mean values and/or ranges were drawn from all published and internal studies and represent work done all over the civilized world. The absorption process was found to be formulation dependent, with solutions showing the shortest delay time, absorption half-life, and time to peak. Tablets showed intermediate values, and capsules were slowest. The first-pass effect, determined directly or calculated from the available data, was 19% of the dose. The peak height in the dose range of 2.5 to 20 mg showed a mean value of 4.5 ng/ml/mg. The elimination half-lives were 3.0 hours for pindolol, 1.4 hours for metabolites, and ~ 100 hours for the "diffuse radioactivity." For all parameters, the agreement between investigators and studies is remarkable. It can be calculated and it was shown in the multiple-dose study (Fig. 5) that steady state for pindolol and metabolites is attained on the second day of dosing, with the plasma

Table IV. Pindolol—pharmacokinetic parameters in humans

Parameter definition	*Mean value*	*n*	*Range*
Absorption delay	*	8	6-20 min
Half-life of absorption	*	12	4-30 min
First-pass effect	19%	15	10-25%
Time to peak	*	19	0.6-3 hr
Peak height/mg dose	4.5 ng/ml	20	2.9-6.6 ng/ml
Half-lives of elimination			
Pindolol	3.0 hr	22	1.7-3.8 hr
Metabolites (I)	1.4 hr	2	0.6-2.2 hr
Residue (II)	~ 100 hr	2	60-130 hr

*Formulation dependent.

Table V. Interaction studies with pindolol

Concomitant administration	*Effect of bioavailability of*	
	Pindolol	*Other compound*
Food	None	—
Hydralazine	None	None
Hydrochlorothiazide	None	None
Digoxin	—	↓
Aspirin	None	—
Coumarin	—	None

concentration only slightly higher than after a single dose while total radioactivity increases, since it represents, in part, the fate of the separated isopropyl group.

The parameters in Table IV were determined in healthy subjects. Since it was possible or even likely that the same parameters would be different in severe disease states, comparative studies were undertaken. The changes in the elimination half-life of pindolol as a representative parameter are shown in Fig. 6. In three studies in patients with partial to total renal insufficiencies, it was found that the elimination half-life was generally higher by a factor of 1.5. The same was true in one study in patients with pronounced liver impairment. This increase was relatively small. Under normal conditions about 35% of the drug is excreted unchanged by the kidneys and 65% is metabolized by the liver. It can be assumed, therefore, that the smallness of the increase is due to compensation of one elimination pathway by the other in cases of severe impairment. Hypertension in the absence of renal insufficiency did not have a significant influence on the pharmacokinetic parameters of pindolol.

BIOAVAILABILITY

The bioavailability studies consisted of one study to define the dose-bioavailability relationship, one

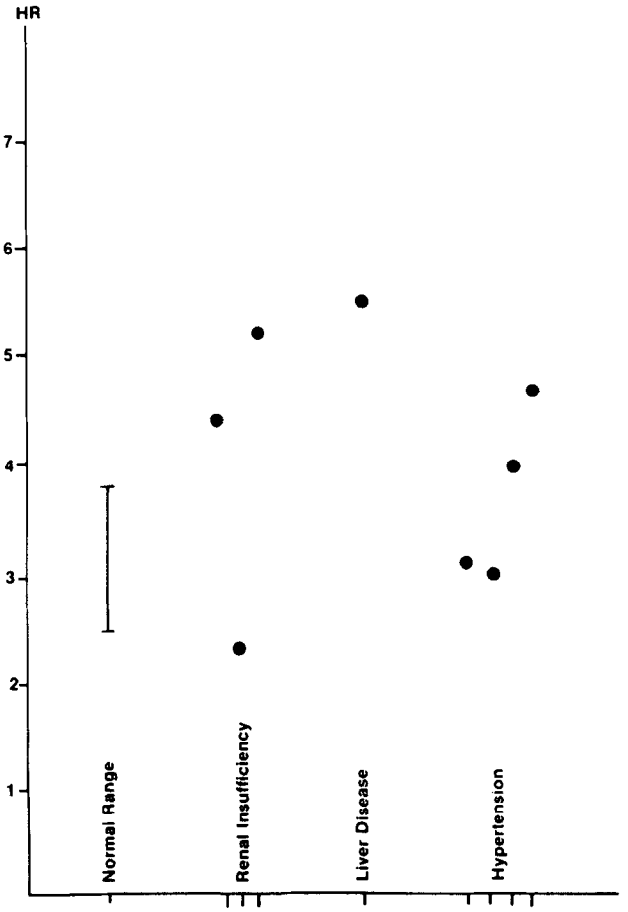

Fig. 6. Elimination half-life for pindolol in disease states.

study to assess the bioavailability of a service form (capsule) and the tablet proposed for marketing, and several studies investigating the influence of concomitant administration of food or drugs on the bioavailability of pindolol or, vice versa, the influence of pindolol on coadministered drugs.

The dose-bioavailability relationship was investigated by administering a solution of pindolol at three dose levels, 5, 10, and 20 mg, to a panel of healthy volunteers in a crossover design study. The plasma levels obtained are shown in Fig. 7. When plotting either "peak height" or "area under the plasma concentration/time curve" vs. dose, a perfectly straight line dissecting the origin is obtained. Thus a linear relationship was shown between bioavailability and dose in the range of 0 to 20 mg. "Time to peak" was the same for all dose levels.

The bioavailability of the dosage forms was investigated at a dose level of 20 mg by administering a capsule service form, the tablet proposed for marketing, and a reference solution to a panel of healthy volunteers in a crossover-design study. The results in Fig. 8 show that the tablet proposed for marketing

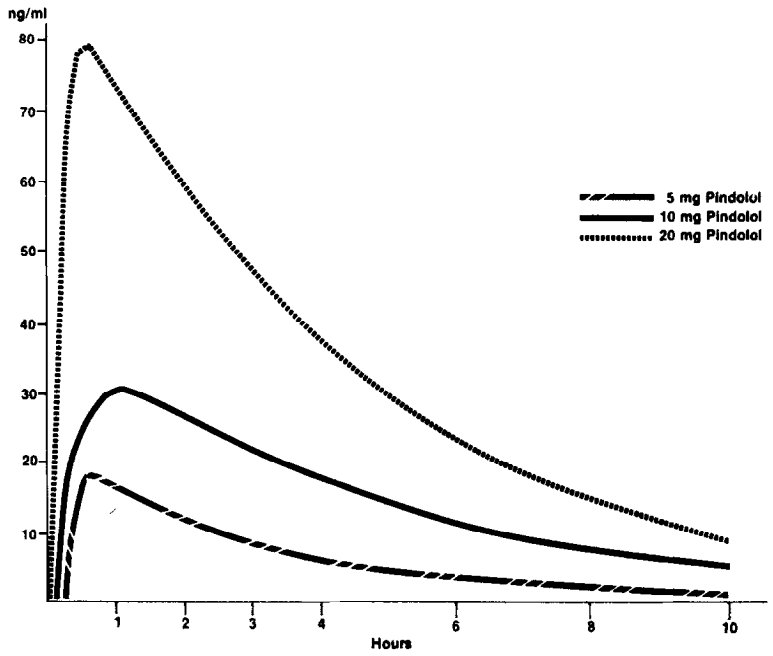

Fig. 7. Mean plasma concentration of pindolol after single oral doses in human volunteers.

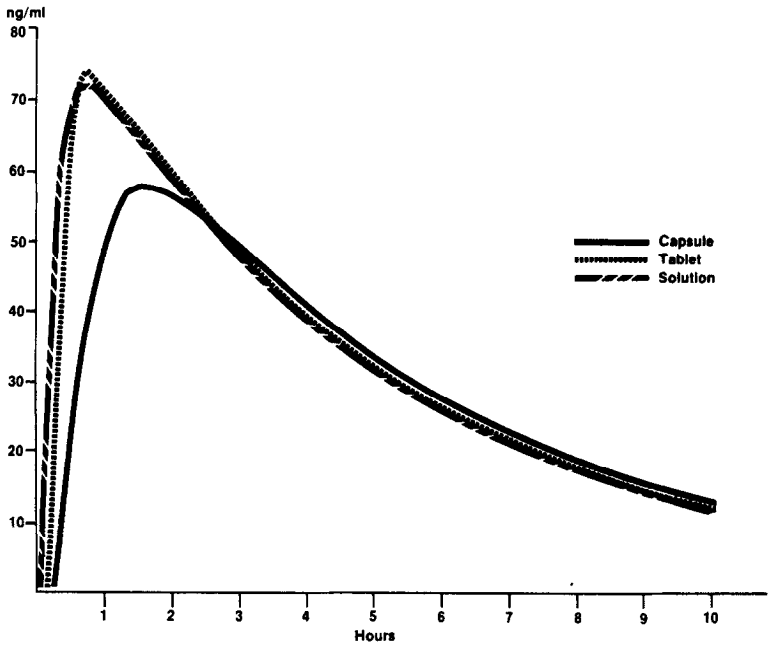

Fig. 8. Mean plasma concentration of pindolol after single oral doses in human volunteers.

is bioequivalent to the solution and, therefore, represents an optimal formulation. The capsule formulation was also found to be equivalent to the solution with respect to "area under the curve." However, all the absorption parameters including peak height were different (slower absorption), a result that is characteristic for a hard gelatin capsule formulation.

The interaction between pindolol on one side and food, hydralazine, or hydrochlorothiazide on the other side was investigated in single-dose, crossover studies in healthy volunteers. The influence of aspirin coadministration was investigated in a multiple-dose study in healthy volunteers, and the influence of pindolol on digoxin and coumarin bioavailability was studied in patients stabilized on the drug.

The results of the interaction studies are summarized in Table V. It was found that neither the presence of food nor the coadministration of hydralazine, hydrochlorothiazide, or aspirin had any influence on the bioavailability of pindolol. Vice versa, the coadministration of pindolol did not change the bioavailability of hydralazine, hydrochlorothiazide, or coumarin. There was a statistically significant drop in digoxin plasma concentrations to values at the lower end of the therapeutic range.

Pharmacokinetic comparison of pindolol with other beta-adrenoceptor–blocking agents

Many beta-adrenoceptor–blocking agents are well studied today. They differ from one another not only in their pharmacologic profiles (cardioselectivity, intrinsic sympathomimetic activity, membrane-stabilizing activity) but also in their metabolic and pharmacokinetic profiles. The profiles of the following 10 beta blockers have been compared: acebutolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, and timolol. Differences in the aromatic ring structure lead to differences in lipophilic characteristics. They in turn influence the pharmacokinetic parameters such as hepatic extraction ratio, protein binding, volume of distribution, and the ratio of renal versus hepatic clearance. Incomplete oral bioavailabilities are reported both for the lipophilic drugs (e.g., labetalol, oxprenolol, and propranolol) due to extensive first-pass metabolism and for the more hydrophilic drugs (e.g., atenolol, acebutalol, and nadolol) due to medium or low absorption. Low bioavailabilities (as in the case of propranolol) are the source of large biologic variations, nonlinearities, or increased plasma levels with food, with age, in nonsmokers, or in disease states (e.g., hypothermia and renal, hepatic, celiac, Crohn's, or inflammatory disease). The pharmacokinetic comparison in this series of beta blockers reveals that pindolol with its medium lipophilicity has some important advantages. A low daily dosage is possible because of the high bioavailability, the low first-pass effect, the moderate metabolism, and the potency of this drug. Due to the low first-pass effect and the low daily dosage there are no saturation effects, and a good dose linearity is observed. This, combined with moderate metabolism and low protein binding, results in small variability and a good predictability in plasma levels and drug effects. Due to the balanced renal and hepatic clearance, no relevant drug accumulation has to be expected in patients with liver or kidney impairment. (Am Heart J 104:364, 1982.)

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In this paper the pharmacokinetic properties of pindolol (Visken) are compared with the pharmacokinetics of the 10 most frequently studied beta-adrenoceptor–blocking agents. Such a comparison is valuable and necessary for three reasons. First, much is known and published about the pharmacokinetics and metabolism of the beta blockers; compared to other drug groups their pharmacokinetics have been the most extensively studied. Second, beta-blocking drugs are used in chronic treatment; therefore, the question of their long-term efficacy and safety is of paramount concern. The predictability from dose to plasma levels to effects, both therapeutic and adverse, is vital. And third, the pharmacokinetics of the beta blockers are relevant because definite relationships between plasma concentrations and effects exist; for example, in exercise-induced tachycardia or in antihypertensive parameters.

The chemical structures of the 10 beta blockers discussed here are shown in Fig. 1. They are all chemically and structurally similar, with an aromatic ring system as the center of the molecule. Acebutolol, atenolol, metoprolol, oxprenolol, pindolol, and propranolol all have an isopropylaminopropoxy side chain. The side chain is slightly different for labetalol and sotalol; nadolol and timolol both have an isobutyl instead of an isopropylaminopropoxy side chain. However, the major chemical differences are

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