Rectal Bioavailability of Lidocaine in Rats: Absence of Significant First-Pass Elimination

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Abstract □ Drugs administered rectally generally are considered to enter the systemic circulation without passing first through the liver since the lower hemorrhoidal veins do not drain into the portal system. To test this hypothesis, the systemic availability of the high clearance drug lidocaine was investigated in rats following oral (20 mg) and rectal (20 mg) administration to six rats and intraarterial (5 mg) administration to another six rats. Whole blood concentrations of lidocaine were determined by capillary GLC with nitrogen detection. Systemic availability was evaluated by two methods. For the rectal route, the results were 105.6 ± 43.3 and 83.1 ± 22.3% compared to those for intraarterial administration; for the oral route, these values were 7.7 ± 2.3 and 7.1 ± 2.3%. These results clearly indicate a significant bypass of the liver following rectal administration of lidocaine. Mean elimination half-lives following oral (54 ± 9 min) and rectal (79 ± 36 min) administration were not significantly different; however, rectal elimination half-lives sometimes were slightly prolonged. The mean peak concentration times of 11.5 ± 7.5 (oral) and 15.6 ± 10.6 (rectal) min were not significantly different whereas the mean peak concentrations were significantly different ($p < 0.01$) [0.92 ± 0.49 (oral) and 8.71 ± 3.30 (rectal) $\mu g/ml$]. The mean elimination half-life following intraarterial administration (33 ± 3 min) was significantly shorter than both the mean oral and rectal half-lives, and the calculated total blood clearance of lidocaine had an average value of 36 ± 9 ml/min. The results show that it is possible to bypass the liver, at least partially, when giving a high clearance drug rectally to rats. For lidocaine, this bypass is almost complete.

Keyphrases □ Lidocaine—pharmacokinetics following rectal, oral, and intraarterial administration, rats □ Pharmacokinetics—lidocaine following rectal, oral, and intraarterial administration, rats □ First-pass effect—lidocaine following rectal and oral administration, rats □ Bioavailability—lidocaine following rectal, oral, and intraarterial administration, rats

The drug administration route can affect bioavailability markedly. High clearance drugs in particular show substantially decreased bioavailability following oral administration, caused by liver and/or gut wall metabolism. This phenomenon is called the first-pass effect, and it has been demonstrated in several animal species and in humans. Such drugs include lidocaine (1–3), propranolol (4, 5), meperidine (6), salicylamide (7), and nitroglycerin (8, 9).

It has often been speculated that drugs given rectally to humans enter into the general circulation without passing first through the liver (10), but sufficient data are lacking to support this hypothesis. However, the rectal bioavailability of lidocaine (aqueous solution) in humans recently was shown to be about twice as high as the oral bioavailability, indicating a difference in the first-pass effect between the oral and rectal routes (11).

To determine if a similar difference occurs in rats, the systemic availability of lidocaine was studied following oral, rectal, and intraarterial administration. Lidocaine was chosen as the model substrate because it undergoes a substantial first-pass effect on oral and portal administration in humans (1, 2), dogs (3), and monkeys (1) and in rat liver perfusions (12–14).

EXPERIMENTAL

Animals and Sampling Techniques—Male Wistar rats, 200–250 g, were used. Before each experiment, the animals were starved overnight with free access to water. During that period, the animals were kept in a metabolic cage to prevent them from eating their own feces or sawdust.

In the 7-day period between two experiments with one rat, the body weight of the animals generally increased 5–10%.

A cannula[1] (polyvinyl chloride; 50 cm long × 0.5 mm i.d. × 1.0 mm o.d.) filled with heparinized saline[2] (200 IU/ml) was inserted between 9 and 10 am into the right vena jugularis externa ~40 mm from the midpoint of the vena jugularis externa, the vena jugularis anterior, and the acromiodeltoid and cephalic vein under light ether anesthesia. In this way, the end of the cannula was close to the right atrium. To avoid destruction by the animal, the cannula was pulled subcutaneously, emerging on the nape of the neck. The animals then were placed in restraining cages constructed to allow free movement and withdrawal of blood samples without touching the animals.

Each rat received lidocaine orally and rectally with an interval of 1 week. The oral and rectal administrations were given to the same animal. Because no attempt was made to keep the cannula open, the left vena jugularis externa was cannulated after 1 week.

Blood samples were taken at 0, 3, 6, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 min following intraarterial and rectal administration and at 3, 6, 10, 15, 20, 30, 45, 60, 75, 90, and 120 min following oral administration. No blood samples were taken during the infusion.

Blood samples, 0.15 ml, were taken with a 1-ml disposable syringe[3] (polypropylene) after discarding the contents of the cannula (±0.10 ml) together with the mixed blood–heparinized saline (total 0.15 ml). After sampling, the cannula was filled with heparinized saline (0.10 ml). The samples were stored in closed heparinized polyethylene containers in a refrigerator at 4° and were assayed the next day.

A check confirmed that no measurable adsorption of lidocaine occurred in the concentration range of 0.1–10.0 μg of lidocaine/ml of blood at the polyvinyl chloride cannula or at the polyethylene containers.

Treatments—Lidocaine was administered intraarterially by introducing a cannula (polyvinyl chloride; 50 cm long × 0.5 mm i.d. × 1.0 mm o.d.) about 1 cm into the left common carotid artery in the caudal direction. To avoid destruction of the cannula by the animal, the cannula was pulled subcutaneously, emerging on the nape of the neck. Lidocaine[4], 5.0 mg in saline solution (0.1 ml), was infused over 2 min by an infusion pump[5] and was followed immediately by a saline infusion (0.2 ml) for 4 min.

Lidocaine was administered orally (20 mg) as a lidocaine[4] solution (0.4 ml) by introduction into the stomach using a stomach tube. It was administered rectally (20 mg) as a lidocaine[4] solution (0.4 ml) through a septum using a syringe with a sharp needle. To prevent expulsion of the solution, the end of the rectum was closed by introduction of the septum. This septum was the tip of the plunger of a 2.5-ml disposable syringe[6] (sterile polypropylene). The septum was kept in place by a ligature with a thread that was introduced subcutaneously around the anus.

Assay of Lidocaine in Plasma—To 0.1 ml of whole blood were added 1.0 ml of distilled water and 50 μl of ethanol containing 0.50 μg of N-methylhexobarbital as the internal standard. The mixture was extracted twice with 3 ml of pentane on a whirl mixer for 10 sec. After centrifugation for 3 min at 2500×g, the upper organic layers were transferred to a conical

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[1] Talas, Ommen, The Netherlands.
[2] Tromboliquine, Organon, Oss, The Netherlands.
[3] BDH, Poole, England.
[4] Lidocaine hydrochloride, Astra, The Netherlands.
[5] Unita I, type 871022, Braun.
[6] H802S, BDH, Poole, England.

Table I—Elimination Half-Lives and *AUC* Values of Lidocaine[a] following Oral and Rectal Administration (20 mg) to the Same Rat

Rat	Elimination Half-Life, min		*AUC*, μg min/ml[b]		*AUC*, μg min/ml[c]	
	Oral	Rectal	Oral	Rectal	Oral	Rectal
1	45	70	42	551	39	507
2	45	60	58	405	55	363
3	65	65	26	631	23	551
4	55	140	61	706	56	442
5	50	100	48	1056	46	697
6	65	38	34	352	31	351
Mean	54	79	45	617	42	485
SD	9	36	14	253	13	130

[a] Based on whole blood concentrations. [b] Determined according to Method I. [c] Determined according to Method II.

evaporation tube. The solvent was evaporated on a water bath (40°) under a stream of dry nitrogen, and the residue was dissolved in 100 μl of ethanol.

Two microliters of this solution was brought onto the needle of a GLC solid injection system, similar to that used previously for the determination of underivatized nitrazepam in plasma (15). After evaporation of the ethanol, the needle was injected into the injection port of the gas–liquid chromatograph[7] equipped with a dual nitrogen–phosphorus detector[8]. The temperatures were 160° (column), 250° (injection port), and 300° (detector). A 10-m × 0.40-mm i.d. capillary SCOT column[9] was used. The support layer consisted of silanized, fumed silica[10] (particle size of <10 μm) coated with a stationary phase[11].

Linear calibration curves were obtained between 0.10 and 10.0 μg of lidocaine/ml of blood. The sensitivity limit of this method is ~50 ng of lidocaine/ml of blood.

Calculations and Pharmacokinetic Analysis—The postinfusion whole blood concentrations of lidocaine were fitted according to two-compartment kinetics (16). Clearance values were determined by dividing the given dose by the integrated total area under the concentration curves. In the oral and rectal experiments, the elimination rate constant, k_{el}, was obtained by regression analysis of log plasma concentration *versus* time, generally beginning 30 min after dosing. Elimination half-lives, $t_{1/2el}$, subsequently were calculated from:

$$t_{1/2el} = 0.69/k_{el} \qquad (Eq. 1)$$

The bioavailability, *F*, of the oral and rectal doses compared to the intraarterial dose was calculated as the ratio of the corresponding areas under the experimental curves (obtained by the trapezoidal rule) corrected for the undetermined area. The area beyond the last sampling point was obtained by two methods (17): (*a*) extrapolating the apparent exponential concentration decay phase of the individual experimental oral and rectal curves to infinite time (Method I); and (*b*) dividing the last experimentally determined concentration by the mean elimination rate constant after intraarterial infusion (Method II).
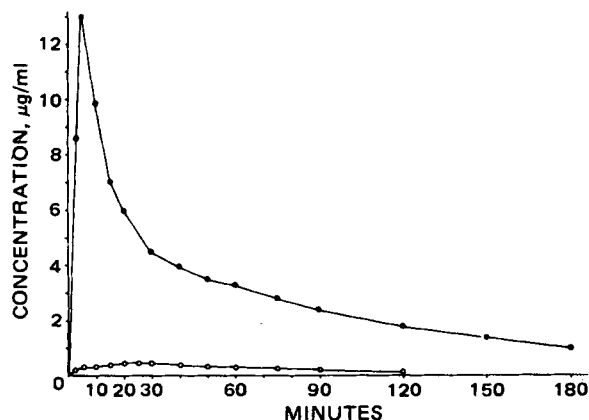

Figure 1—*Whole blood concentrations of lidocaine on a linear scale following 20-mg oral (O) and rectal (●) administration to Rat 1.*

[7] Hewlett-Packard model 5710.
[8] Hewlett-Packard model 18789A.
[9] Duran 50 glass.
[10] Tullanox, Cabot Corp., Boston, Mass.
[11] Carbowax 20M-KOH.

Corrections also were made for differences in the given dose by:

$$F = \frac{D_{ia}AUC_x}{D_x AUC_{ia}} \qquad (Eq. 2)$$

where D_{ia} and D_x are the intraarterial and the oral or rectal dose, respectively, and AUC_{ia} and AUC_x are the intraarterial and the oral or rectal areas under the curve, respectively. The oral and rectal parameters were determined for each animal and compared to the mean intraarterial value, and statistical differences were tested by a paired *t* test. When differences between the two groups of animals (intraarterial and rectal or oral) were tested, a nonpaired *t* test was used.

RESULTS

Figures 1 and 2 show the whole blood lidocaine concentration–time curves for a representative rat following oral and rectal administration. There was a remarkable difference in the concentration peaks. Table I gives the experimentally determined areas under the curve after oral and rectal administration. The AUC_{rect}/AUC_{or} ratios calculated by Methods I and II are given in Table II, indicating that the mean rectal systemic availability was 14.7- (Method I) and 13.0- (Method II) fold higher than the mean oral systemic availability.

A substantial amount of the dose absorbed rectally bypassed the liver and entered directly into the systemic circulation. Although substantial intraindividual differences were noted among the elimination half-lives of lidocaine on oral and rectal administration (Table I), the respective mean values of 54 and 79 min were statistically significantly different (paired *t* test, $p > 0.10$). Rats 4 and 5 in particular had rectal elimination half-lives that were prolonged compared to the oral administration ones. It is possible that the absorption phase extends partially into the elimination phase.

The peak concentration times, t_{max}, and peak concentrations, C_{max}, were determined with respect to the absorption rate (Table III). The mean t_{max} was 11.5 min orally and 15.6 min rectally ($p > 0.10$). However, the large difference in the mean C_{max} values of 0.92 and 8.71 μg/ml orally and rectally, respectively ($p < 0.01$), reflects the enormously increased *AUC* following rectal administration.

Following intraarterial administration of lidocaine to a second series of rats, the blood concentration–time curves exhibited two distinct phases (Fig. 3) and could be fitted to two-compartment kinetics (16). Table IV shows the data obtained following intraarterial infusion of lidocaine to
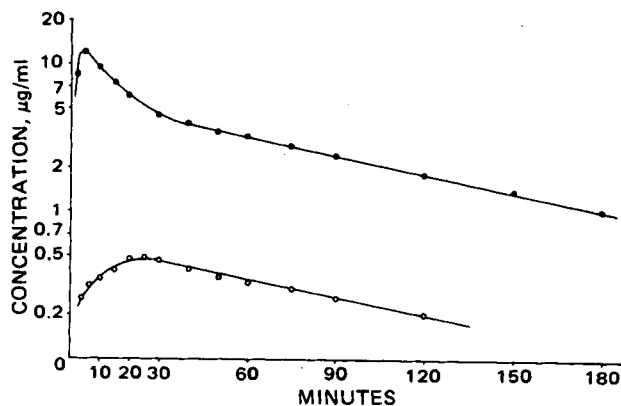

Figure 2—*Whole blood concentrations of lidocaine on a semilog scale following 20-mg oral (O) and rectal (●) administration to Rat 1.*

Table II—AUC Ratios (Rectal/Oral) Calculated According to Methods I and II

Rat	AUC_{rect}/AUC_{or} Method I	AUC_{rect}/AUC_{or} Method II	Method I/Method II
1	13.1	13.0	1.00
2	7.0	6.6	1.06
3	24.3	24.0	1.01
4	11.6	7.9	1.47
5	22.0	15.2	1.45
6	10.4	11.3	0.92
Mean	14.7	13.0	1.15
SD	6.9	6.3	0.24

Table III—Peak Concentration Times [a] (t_{max}) and Peak Concentrations [a] (C_{max}) following Oral and Rectal Administration (20 mg) of Lidocaine to the Same Rat

Rat	t_{max}, min Oral	t_{max}, min Rectal	C_{max}, µg/ml Oral	C_{max}, µg/ml Rectal
1	10	30	0.45	6.08
2	5	10	1.75	5.90
3	25	5	0.50	12.34
4	6	21	0.95	5.51
5	15	20	1.16	12.55
6	8	5	0.70	9.87
Mean	11.5	15.6	0.92[b]	8.71[b]
SD	7.5	10.6	0.49	3.30

[a] Based on whole blood concentrations. [b] $p < 0.01$.

Table IV—Pharmacokinetic Parameters of Lidocaine following Intraarterial Infusion Based on Whole Blood Concentrations

Rat	$t_{1/2\beta}$, min[a]	AUC, µg min/ml	Clearance, ml/min
A	32	111	45
B	30	119	42
C	35	156	32
D	36	184	27
E	33	194	26
F	31	113	44
Mean	33	146	36
SD	3	37	9

[a] The value $t_{1/2\beta}$ is the half-life of the β-phase.

Table V—Systemic Availability (F) of Lidocaine following Oral and Rectal Administration to the Same Rat Calculated According to Methods I and II as the Ratio of the Rectal or Oral Value to the Mean Intraarterial Systemic Availability [a]

Rat	F, % Method I Oral	F, % Method I Rectal	F, % Method II Oral	F, % Method II Rectal
1	7.2	94.4	6.7	86.8
2	9.9	69.3	9.4	62.2
3	4.5	108.0	3.9	94.4
4	10.6	120.9	9.6	75.7
5	8.2	180.8	7.9	119.4
6	5.8	60.3	5.3	60.1
Mean	7.7	105.6	7.1	83.1
SD	2.3	43.3	2.3	22.3

[a] Corrections were made for differences in the administered dose.

these rats. The mean elimination half-life was significantly shorter (33 min) than the mean oral and rectal half-lives ($p < 0.001$ and $p < 0.010$, respectively). The total blood clearance of lidocaine calculated by dose/ AUC_{ia} had an average value of 36 ml/min (Table IV).

The absolute oral and rectal bioavailability values of lidocaine were calculated for each rat by dividing the corrected individual AUC_{or} or AUC_{rect} by the mean AUC_{ia}. These values varied from 60.3 to 180.8% (Method I) and from 60.1 to 119.4% (Method II), with an average of 105.6 and 83.1%, respectively, for the rectal route, and from 4.5 to 10.6% (Method I) and from 3.9 to 9.6% (Method II), with an average of 7.7 and 7.1%, respectively, for the oral route (Table V).
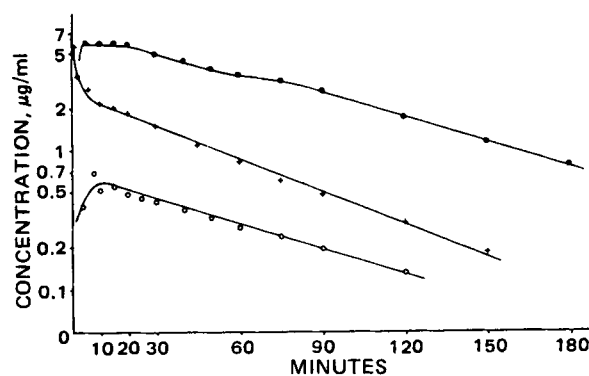
Figure 3—*Mean whole blood concentrations of lidocaine on a semilog scale following oral (O, 20 mg) and rectal (●, 20 mg) administration to Rats 1–6 and intraarterial (+, 5 mg/2 min) administration to Rats A–F.*

DISCUSSION

The experimental results demonstrate that the bioavailability of lidocaine following rectal administration to the rat is far greater than that following oral administration. This result strongly supports the hypothesis that rectal administration can result in a bypass of the liver. For a high clearance drug such as lidocaine, this bypass means increased systemic availability. As derived from the ratio of AUC_{rect} to AUC_{ia} (Table V), the mean bypass of the liver according to Methods I and II was roughly 100 and 80%, respectively, although substantial variations were observed. In addition, Table V shows that calculation of the systemic availability following rectal administration according to Methods I and II results in different mean values, which are due mainly to variations in the data of Rats 4 and 5. This difference also can be observed in Table I, where the oral and rectal AUC are calculated according to Methods I and II. The ratio of I to II in Table II shows that only the data of Rats 4 and 5 changed. Both data sets are given since there is no reason to prefer one method to the other (17).

If the liver is not bypassed before a high clearance drug reaches the systemic circulation, the result is extensive drug loss caused by hepatic first-pass metabolism, indicated by the present oral results with lidocaine. In general, differences in the extent of absorption might explain the observed differences in systemic availability. However, lidocaine was administered orally and rectally in an aqueous solution, which probably gives the least chance of pharmaceutical bioavailability problems. The results of this study do not permit definite conclusions about the extent of absorption. To assess the exact amount of lidocaine absorbed following a certain administration route, experiments with radiolabeled drug are indispensable. However, if rectal absorption is not complete whereas oral absorption is, the difference between oral and rectal availability will be even more in favor of the avoidance of first-pass metabolism by the rectal route.

Some pharmacokinetic factors also should be considered. Lennard et al. (12) indicated that with low doses of lidocaine, which resulted in initial blood concentrations of ~2 µg/ml, the drug was extracted almost completely by the perfused rat liver (>97%). Similarly, Nyberg et al. (13) showed that extraction was ~100% in the perfused rat liver at an initial concentration of 10 µg/ml. Shand et al. (14) determined, in the same system, an extraction ratio of 0.95 during constant infusion of lidocaine into the perfusion reservoir at concentrations entering the liver of 5–10 µg/ml. Linear kinetics were observed in all of these cases. One might infer from the shape of the single rectal concentration curve that nonlinear kinetics are involved, but no definite conclusions may be drawn concerning saturation phenomena due to limited data (only Rats 4 and 5 showed this curve shape) (12). Other factors also may be involved; one example is of hemodynamic origin, i.e., a reduced blood flow through the liver results in a lower clearance. In addition, high lidocaine concentrations can cause bradycardia and cardiac depression (18). Finally, it is difficult to distinguish between the experimental situation where the absorption phase extends into the elimination phase and saturation kinetics. In both situations, the experimental curves may look much the same.

The lidocaine clearance value of 36 ml/min (115 ml/min/kg) following intraarterial administration is substantially higher than that reported for liver blood flow (19–23). Following intraarterial administration, ~20% of the cardiac output flows directly through the liver; therefore, with

reference to the venous blood sampling site, this flow will result in a first-pass effect and the actual systemic clearance will be overestimated (24). Even after correcting for this effect by assuming a hepatic extraction of 0.97 (12), the mean systemic clearance of 28.8 ml/min still is greater than the normal liver blood flow. This result could indicate extrahepatic elimination in the rat or an acute hemodynamic effect of lidocaine on its own disposition as a result of an increase in liver blood flow. Such an increase in flow was observed in humans following steady-state intravenous infusion (25).

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Use of Molecular Negentropy to Encode Structure Governing Biological Activity

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Abstract □ A drug molecule is considered to be an information source with an information content available to receptive tissue. In nonspecific interactions, much of the information content has quality as judged by the receptor. Quantitation of the information content using Shannon's equation gives the molecular negentropy. This index is shown to rank molecules according to symmetry and to encode structural characteristics influencing physical properties and biological activity in certain cases.

Keyphrases □ Structure–activity relationships—quantitation of molecular information content by negentropy calculations, correlation between biological activity and molecular structure □ Negentropy—mathematical analysis of correlation between biological activity and molecular structure, molecular information content available to receptor molecule □ Drug–receptor interaction—structure–activity relationships, negentropy of molecules, mathematical analysis of molecular structure and biological potency

A drug molecule may be regarded as a message containing information in the form of electron probability fields distributed in space around a framework of atomic nuclei. Therefore, drug–receptor interaction may be viewed as a presentation of the message, with its information content, to a receiver. Some information in the message may be interpretable by the receiver or receptor, leading to the beginning of events culminating in a biological response.

It follows that the efficacy of a drug depends on the information content and its quality as judged by the receptor. The quality of the information content in the drug molecule depends on the ability of the receptor to interpret the fields and to translate the interactions into a significant change in the receptor and its adjacent structures.

BACKGROUND

Under some circumstances, most if not all of the information content of a drug molecule has quality; that is, a receptor may be capable of interpreting the entire message presented by the drug. These circumstances are commonly referred to as nonspecific actions. In this category are molecules which, by virtue of the mere presence of atoms and bonds, are capable of eliciting a biological response. There usually is a rough correlation between size, expressed as the number of atoms, and the potency. However, various isomers frequently have different potencies. For example, in *in vitro* studies, there often is a decline in activity for the isomer series butanol > isobutanol > *tert*-butanol. Several physicochemical correlates have been presented to explain this trend, but all point to bulk phase phenomena, not to events occurring at the molecular level between the drug and the receptor.

If the information content of a nonspecific-acting molecule is of considerable importance to the potency, then quantitation of this characteristic would be a productive approach in analyzing the structure–activity relationships and the molecular level mechanism.

The information content of a message, whether it is a molecule, a book, or communication network, can be quantitated through information theory (1), particularly by use of the equation developed by Shannon and Weaver (2). This equation has its roots in the probabilities of choice among items classified into sets of equivalent items. A specific example using the propane molecule illustrates the assignment of equivalent atoms