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FIRST-PASS ELIMINATION OF LIDOCAINE IN THE RABBIT AFTER PERORAL AND RECTAL ROUTE OF ADMINISTRATION

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ABSTRACT

Lidocaine shows pronounced first-pass metabolism upon peroral administration in man (about 30 per cent peroral bioavailability). Since the rectal bioavailability is about 65 per cent in man it is assumed that some drug is directly absorbed into systemic circulation by-passing the liver. In rats peroral bioavailability is about 8 per cent whereas rectal bioavailability is about 100 per cent. This indicates that the rat is not a suitable model to study rectal lidocaine dosage forms. The purpose of this study was to investigate lidocaine disposition and bioavailability in rabbits after peroral and rectal administration. The peroral bioavailability in rabbits was found to be about 6 per cent and the rectal bioavailability is about 33 per cent. The results indicate that the rabbit is a suitable model for the study of systemic absorption of rectal lidocaine dosage forms.

KEY WORDS Lidocaine kinetics Peroral Rectal First-pass elimination

INTRODUCTION

First-pass elimination is a widely observed phenomenon for drugs metabolized during their residence at their site of administration, and during transfer to the systemic circulation. The major but not exclusive site of first-pass metabolism is the liver. Hence, first-pass elimination is of particular importance for drugs which are predominantly metabolized by the liver, and which are administered at sites from where venous drainage occurs either completely via the portal system, for example after peroral administration, or largely via the portal system, such as after deep rectal and intraperitoneal administration. As a consequence, bioavailability, characterized by the ratio of the areas under the concentration–time curves after extravascular and intravascular administration for identical or corrected dose sizes, can be assumed to be small for such drugs.

Lidocaine is most widely used by the intravenous route for treatment of ventricular arrhythmias, particularly when associated with acute myocardial

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infarction. The therapeutic range is usually assumed to be between 1·5 and 5 μg ml^{-1},[1] although some patients may need up to 8 μg ml^{-1},[1] while other patients may already experience adverse effects at concentrations at even 3 μg ml^{-1}.[2] Since there is a well-established relationship between drug concentration and antiarrhythmic activity, attempts have been made to utilize routes other than the intravenous to achieve desired blood levels. Early reports on lidocaine levels in man after peroral administration differed widely.[3,4] Boyes *et al.*[5] found in man (n = 5) a bioavailability of 34·8 per cent (range: 21·1–46·2) after 250 to 500 mg lidocaine given perorally as tablets. To test the hypothesis that first-pass metabolism is at least in part avoided when a drug is given rectally, since part of the rectal drainage is directly into the vena cava, de Boer *et al.*[6] administered lidocaine to six volunteers intravenously, perorally (gelatin capsules), and rectally (aqueous solution) in a crossover design. Corrected for dose size differences, the peroral bioavailability was 31 ± 11 per cent (S.D.) and the rectal bioavailability was 63 ± 23 per cent (S.D.).[6] In a follow-up study[7] in the same six subjects the mean peroral bioavailability was 27 per cent and the rectal bioavailability 67 per cent indicating good agreement between the individual data of the two studies.

Upon peroral administration of lidocaine (aqueous solution) to six beagle dogs the bioavailability was 78 per cent (range: 61–100),[8] suggesting that lidocaine first-pass elimination is less pronounced in canines than in man. de Boer *et al.*[9] studied also peroral and rectal bioavailability of lidocaine in rats which was found to be 7·7 per cent (range 4·5–10·6) and 105·6 per cent (range 60·3–180·8), respectively. In comparison to human findings the peroral bioavailability is much more reduced in rats whereas the absence of first-pass metabolism upon rectal administration, and hence complete bioavailability, suggests systemic uptake of lidocaine from the rat's rectum.

The purpose of this study was to investigate lidocaine disposition and bioavailability in rabbits after peroral and rectal administration, and to evaluate the rabbit as an appropriate model for the study of rectal absorption of drugs.

METHODS

Drug administration and sampling

Six male, white, New Zealand rabbits were randomly administered three lidocaine treatments in a crossover manner. The three treatments were a peroral solution 10 mg kg^{-1}, lidocaine HCl 4 per cent solution (Inenex, Gibraco Division, The Derter Corporation, Chagrin Falls, Ohio 44022, Lot no. 2048223), a rectal gel 10 mg kg^{-1}, and an intravenous injection 5 mg kg^{-1} (lidocaine HCl 1 per cent solution (Astra, Worcester, Mass. 01606, Lot no. 1072676)). A minimum washout period of one week was maintained between the randomized treatments. The rectal gel was prepared in our laboratory by

warming 2·0 g of water, adding 0·5 g of methocel (Methocel 90 HG, Dow Chemical Company, Midland, Michigan 48640, Lot no MM021716K), allowing the mixture to cool, and adding 7·5 g of lidocaine 4 per cent solution. A 35 mg kg^{-1} intramuscular dose of pentobarbital (Nembutal® sodium solution, Abbott Laboratories, North Chicago, Illinois 60064) was given in all treatments to initiate anaesthesia, which was maintained by small doses as required via an ear vein catheter. Blood samples of 3 ml were taken by cardiac puncture at 0, 3, 5, 10, 15, and 30 minutes, 1, 1·5, 2, 3, 4, and 6 hours. Blood samples were centrifuged, and the serum was removed and frozen until analysis.

Drug analysis

Lidocaine concentrations were determined by using a modification of the method of Mather and Tucker.[10] One millilitre of serum was placed into a 15 ml conical tube. One hundred microlitres of mepivacaine internal standard (10 μg ml^{-1}), 5 ml of diethyl ether, and 100 μl of 1 N NaOH were added in that order and the contents were vortexed for 30 seconds. The tube was then centrifuged at 1000 × g for 5 minutes. The ether was separated and placed into a clean 15 ml conical tube. A 400 μl sample of 1 N HCl was introduced and the tube was vortexed for 30 seconds. Following centrifugation at 1000 × g for 5 minutes, the ether was discarded and 1·5 ml of fresh ether were introduced. A 500 μl of 1 N NaOH was introduced and the tube was vortexed for 30 seconds. Following centrifugation at 1000 × g for 5 minutes the ether layer was removed and evaporated to dryness in a 2 ml auto-sampler vial. A 300 μl sample of reagent grade acetone was added and 1–3 μl of the resulting solution was analysed. Analysis was accomplished using a Hewlett Packard model 5840A gas chromatograph equipped with a 2 metre 1·8 mm i.d. 3 per cent OV-17 on Gas-Chrom Q 100/120 mesh column and a nitrogen/phosphorus detector.

Instrument gas flows were as follows: helium carrier gas 30 ml min^{-1}, hydrogen 3 ml min^{-1}, compressed air 100 ml min^{-1}. Equipment conditions were as follows: column temperature 210°, injector temperature 250°, and detector temperature 290°. Retention times were 2·19 minutes for lidocaine and 4·57 minutes for the mepivacaine internal standard. The area ratios were compared with those for a standard curve which was run daily. The standard curve consisted of a minimum of 10 points over two orders of magnitude. The coefficient of variation within days was 5·4 + 1·0 per cent at 0·1 μg ml^{-1}. The coefficient of variation of the assay varies from 8·6 per cent at 0·010 μg ml^{-1} to 2·7 per cent at 10·0 μg ml^{-1}. Recoveries were constant over the entire assay range at 97 + 2·2 per cent. The limit of detection of the assay as described was 0·010 μg ml^{-1}. However, if the sample was reconstituted with 30 rather than 300 μg of acetone following the ether evaporation step the minimum level of detection was correspondingly reduced to 0·001 μg ml^{-1}. The coefficient of variation at this level was 11·6 per cent.

Pharmacokinetic analysis

The concentration–time data obtained from the three routes of administration were analysed in two ways:

1. By curve-fitting using standard linear regression analysis procedures and standard pharmacokinetic equations (RESID program developed in our laboratories).
2. By compartment model impendent analysis using the area under the concentration–time curve from zero to the time of last-blood sample as determined by the trapezoidal rule, and determination of the remaining area according to the rule of corresponding areas. For this procedure the terminal rate constant obtained from the curve-fitting was used (AUC-RPP program developed in our laboratories).

Both programs generate also the area under the moment-curve and calculate the mean residence time.

The fraction of drug absorbed, or absolute bioavailability, F, was calculated following:

$$F = \frac{AUC_{extravascular} \cdot \dfrac{D}{(BW \cdot \beta)_{intravascular}}}{AUC_{intravascular} \cdot \dfrac{D}{(BW \cdot \beta)_{extravascular}}} \quad (1)$$

where AUC is the total area under the concentration–time curve, D is the dose size, BW is the body weight, and β is the terminal disposition rate constant.

The fraction of drug by-passing the liver following rectal administration was determined by equation (2):

$$F_{liver\ by\text{-}pass} = \frac{F_{rect} - F_{po}}{1 - F_{po}} \quad (2)$$

RESULTS

Figures 1, 2, and 3 show the serum concentration–time curves of lidocaine for the three routes of administration. Despite the fact that the peroral and rectal doses were twice the intravenous dose, the serum concentration–time curves were much lower than after i.v.; the rectal curve was always between the i.v. and the p.o. curves. The mean values for the pharmacokinetic parameters obtained by the curve-fitting procedure are listed in Table 1.

All six rabbits completed the intravenous and the rectal treatment; however, only four rabbits completed the peroral experiment. Whereas the

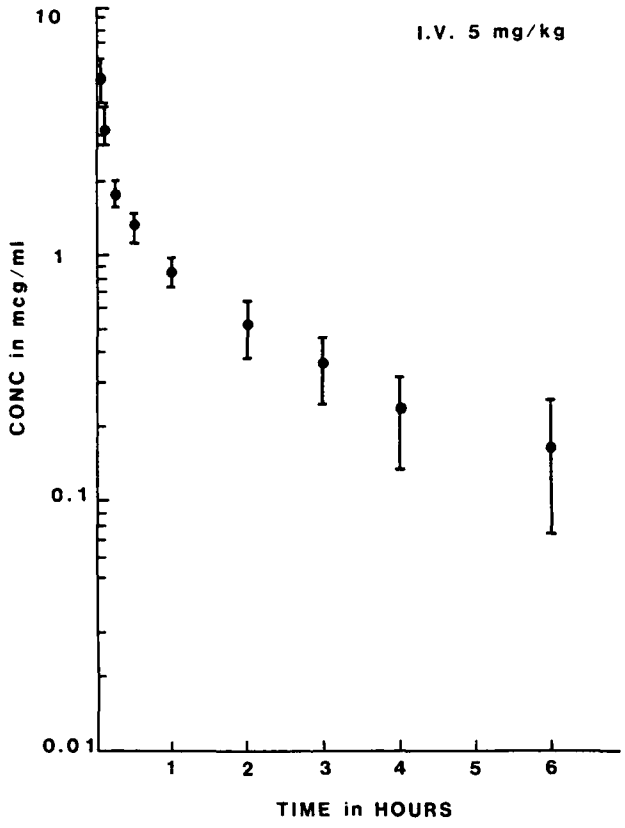

Figure 1. Mean serum (S.E.M.) concentration–time profile of lidocaine after i.v. administration in rabbits

concentration–time profiles for all six subjects after intravenous administration were best described by a biexponential decay, i.e. by the classical two-compartment model, only one out of four data sets after peroral administration was best fitted to a two-compartment model. After rectal administration four out of six data sets were best described by a two-compartment model.

The principle pharmacokinetic parameters, β, $t_{1/2}$ (elimination half-life), V_β (apparent volume of distribution), and Cl_{tot} (total clearance), were practically identical for all three routes. The rate of absorption, k_a, seems to be faster perorally than rectally. The peroral bioavailability, F, is 5·7 per cent (range 3·17 to 8·88 per cent) and the rectal bioavailability is 32 per cent (range 11·4 to 56·1 per cent).

The pharmacokinetic parameters calculated by the compartment-model independent analysis are listed in Table 2. By comparing Tables 1 and 2 it is

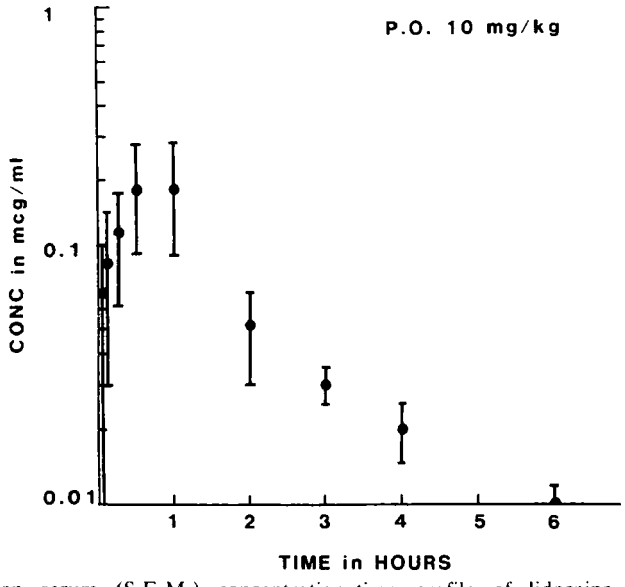

Figure 2. Mean serum (S.E.M.) concentration–time profile of lidocaine after peroral administration in rabbits

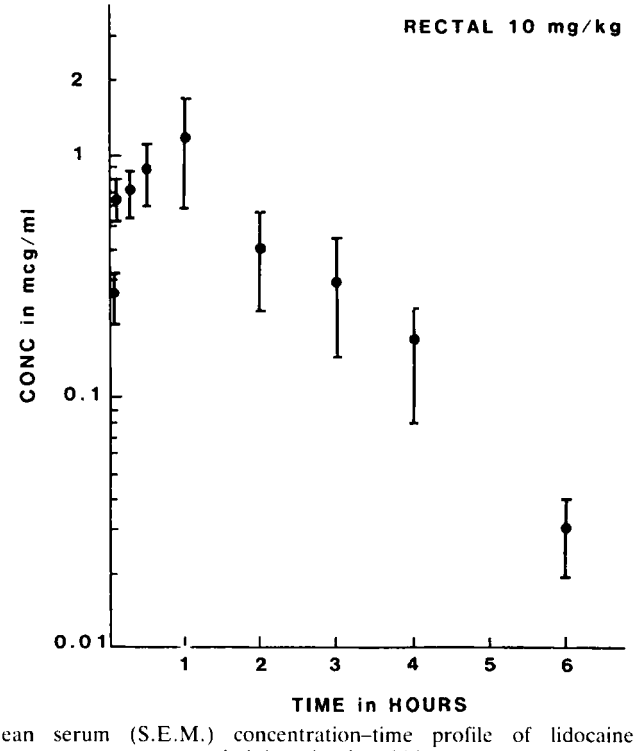

Figure 3. Mean serum (S.E.M.) concentration–time profile of lidocaine after rectal administration in rabbits

Table 1. Pharmacokinetic parameters (mean ± S.E.M.) of lidocaine after intravenous, peroral, and rectal administration. Evaluation by curve-fitting (RESID program)

Parameter	Intravenous	Peroral	Rectal
Dose (mg)	14·3 ± 1·25	28·9 ± 2·46	28·8 ± 1·89
BW (kg)	2·9 ± 0·19	2·9 ± 0·25	2·9 ± 0·19
β (h^{-1})	0·40 ± 0·06	0·47 ± 0·06	0·41 ± 0·04
α (h^{-1})	5·57 ± 0·74	–	2·91 ± 0·23
k_a (h^{-1})	–	8·77 ± 1·76	5·34 ± 1·14
$t_{1/2}$ (h)	1·95 ± 0·30	1·56 ± 0·28	1·78 ± 0·22
$t_{1/2\alpha}$ (h)	0·18 ± 0·04	–	0·25 ± 0·03
$t_{1/2a}$ (h)	–	0·095 ± 0·06	1·22 ± 1·05
k_{12} (h^{-1})	3·14 ± 1·36	–	0·97 ± 0·17
k_{21} (h^{-1})	1·33 ± 0·24	–	0·86 ± 0·09
k_{13} (h^{-1})	1·49 ± 0·28	–	2·63 ± 0·97
V_c (L kg^{-1})	1·17 ± 0·25	–	2·02 ± 1·09
V_{ss} (L kg^{-1})	3·02 ± 0·39	–	3·49 ± 0·55
V_β (L kg^{-1})	4·06 ± 0·63	3·64 ± 0·64	4·08 ± 0·64
AUC ($\mu g\ ml^{-1} \cdot h$)	3·77 ± 0·98	0·34 ± 0·05	2·73 ± 1·08
Cl_{tot} ($ml\ min^{-1}\ kg^{-1}$)	25·97 ± 3·87	28·79 ± 6·94	27·88 ± 4·94
MRT (h)	2·18 ± 0·44	2·28 ± 0·45	1·54 ± 0·39
F	1	0·057 ± 0·013	0·32 ± 0·07

apparent that the curve-fitting procedure by compartmental model analysis is appropriate because the values generated are essentially the same as those obtained from the compartment model independent analysis. The absolute bioavailability after peroral administration is 6 per cent (range 2·9 to 10·7 per cent) and 34 per cent (range 11·5 to 60·6 per cent) after rectal dosing.

Table 2. Pharmacokinetic parameters (mean ± S.E.M.) of lidocaine after intravenous, peroral, and rectal administration. Evaluation by compartment model independent analysis (AUC-RPP program)

Parameter	Intravenous	Peroral	Rectal
β (h^{-1})	0·40 ± 0·06	0·47 ± 0·06	0·41 ± 0·04
$t_{1/2}$ (h)	1·95 ± 0·30	1·56 ± 0·28	1·78 ± 0·22
V_β (L kg^{-1})	3·84 ± 0·58	3·37 ± 0·46	3·84 ± 0·58
AUC ($\mu g\ ml^{-1} \cdot h$)	3·93 ± 0·97	0·37 ± 0·06	2·73 ± 1·07
Cl_{tot} ($ml\ min^{-1}\ kg^{-1}$)	24·59 ± 3·69	26·38 ± 4·91	26·24 ± 4·58
MRT (h)	–	1·38 ± 0·47	1·62 ± 0·32
C_{max} ($\mu g\ ml^{-1}$)	7·09 ± 0·77	0·19 ± 0·07	1·43 ± 0·44
t_{max} (h)	0	1·44 ± 0·58	0·65 ± 0·12
F	1·0	0·06 ± 0·017	0·34 ± 0·08

DISCUSSION

Our investigation was undertaken to see whether the rabbit is an acceptable model in studying rectal dosage forms for possible use for therapeutic treatment with lidocaine. In man the absolute bioavailability upon peroral and rectal administration is 31 per cent and 63 per cent, respectively.[6] The rat shows perorally a bioavailability of only 7·7 per cent, but the drug is completely absorbed following rectal administration.[9] The absence of first-pass elimination following rectal administration for lidocaine disqualifies the rat as model. The rabbit, as demonstrated in this study, also has a low peroral bioavailability of 6 per cent, comparable with that in the rat, but also shows rectal first-pass metabolism resulting in a bioavailability of 34 per cent.

Apparently rectal absorption of drug in the rabbit is similar to that in man in that rectal drainage is partly to the portal vein and partly directly into the vena cava. Hence, the total quantity of drug rectally administered which reaches systemic circulation, Q_{rect}, consists of a quantity which enters portally, Q_{port}, and a quantity which by-passes the liver, $Q_{liver\ by\text{-}pass}$:

$$Q_{rect} = Q_{port} + Q_{liver\ by\text{-}pass} \tag{3}$$

For a drug which is perorally administered and completely absorbed, Q_{port} can be calculated from the dose given, D, and the extraction ratio, E, which is 1 minus peroral bioavailability:

$$Q_{port} = D(1 - E) \tag{4}$$

Assuming complete absorption upon rectal administration, with partial absorption by-passing the liver, Q_{port} becomes:

$$Q_{port} = (D - Q_{liver\ by\text{-}pass}) - E\,(D - Q_{liver\ by\text{-}pass}) \tag{5}$$

Substituting equation (5) into equation (3) results in:

$$Q_{rect} = D(1 - E) + EQ_{liver\ by\text{-}pass} \tag{6}$$

Since Q_{rect} is DF_{rect} and $Q_{liver\ by\text{-}pass}$ is $DF_{liver\ by\text{-}pass}$, the fraction rectally absorbed, F_{rect}, is:

$$F_{rect} = [1 - (1 - F_{po})] + [(1 - F_{po})F_{liver\ by\text{-}pass}] \tag{7}$$

which solved for $F_{liver\ by\text{-}pass}$ results in equation (2):[6]

$$F_{liver\ by\text{-}pass} = \frac{F_{rect} - F_{po}}{1 - F_{po}}$$

Applying equation (2) to the mean values for F_{po} and F_{rect} a value of 29·7 per cent (range 5 to 50 per cent) is obtained for $F_{liver\ by\text{-}pass}$, indicating that about 30 per cent of the rectally administered dose by-passed the liver after rectal absorption. In man this value is 57 per cent (range 20–100 per cent). Wide interindividual variations were found in both man and rabbit.

The peroral bioavailability, F_{po}, can be predicted from clearance data and an assumed constant liver blood flow. The liver blood flow, LBF, in the rabbit has been reported to be 122 ml min^{-1}.[11] The ratio of blood/plasma drug concentrations, C_b/C_p, depends on the affinity of drug for blood cells and plasma proteins. This ratio is assumed to be 0·67. The whole blood clearance, Cl_b is then:

$$Cl_b = Cl_{tot}/(C_b/C_p) \tag{8}$$

where Cl_{tot} is the plasma clearance.

The hepatic blood clearance, Cl_{hb} depends on the whole blood clearance and the fraction eliminated in urine, F_e:

$$Cl_{hb} = Cl_b\ (1 - F_e) \tag{9}$$

Since lidocaine is practically completely metabolized $Cl_{hb} \approx Cl_b$.

$$F_{po} = 1 - \frac{Cl_{hb}}{LBF} \tag{10}$$

Equation (10) applied to the mean data of Cl_{hb} calculated from Cl_{tot} after i.v. administration results in a predicted F_{po} of 6·3 per cent, which is in good agreement with the experimentally determined 6 per cent.

The present study demonstrates that bioavailability of lidocaine is much higher after rectal administration than after peroral dosing. This is similar to the findings in man, indicating that absorption from the rectum is partly via the portal route and partly via direct systemic delivery.

The results indicate that the rabbit is a more appropriate model for studies involving the rectal route of administration than the rat.

REFERENCES

1. N. L. Benowitz and W. Meister, *Clin. Pharmacokin.*, **3**, 177 (1978).
2. N. L. Benowitz, in *Cardiovascular Drug Therapy*, K. L. Melmon (Ed), Davis Co., Philadelphia, 1974, pp. 77–101.
3. A. J. Eisinger and M. D. Hellier, *Lancet*, **2**, 1303 (1969).
4. P. I. Parkinson, L. Margolin and D. S. P. Dickinson, *Brit. Med. J.*, **2**, 29–30 (1970).
5. R. N. Boyes, D. B. Scott, P. J. Jebson, M. J. Godman and D. G. Julian, *Clin. Pharmacol. Ther.*, **12**, 105 (1971).

6. A. G. de Boer, D. D. Breimer, M. D. Mattie, J. Pronk and J. M. Gubbens-Stibbe, *Clin. Pharmacol. Ther.*, **26**, 701 (1979).
7. A. G. de Boer and D. D. Breimer, in *Drug Absorption*, L. F. Prescott and W. S. Nimmo (Eds), Adis Press, Sydney, 1979, pp. 61–72.
8. R. N. Boyes, H. J. Adams and B. R. Duce, *J. Pharmacol. Exptl. Ther.*, **174**, 1 (1970).
9. A. G. de Boer, D. D. Breimer, J. Pronk and J. M. Gubbens-Stibbe, *J. Pharm. Sci.*, **69**, 804 (1980).
10. L. E. Mather and G. T. Tucker, *J. Pharm. Sci.*, **63**, 306 (1974).
11. H. Boxenbaum, *J. Pharmacokin. Biopharm.*, **8**, 165 (1980).