(19). Furthermore, the photoproduct, cholesterol-5α,6α-epoxide, is suspected of inducing skin cancers (20), and 7-dehydrocholesterol rearranges in the skin under photoirradiation to vitamin-D_3 which effects calcium stasis (21). Thus, our results on the irreversible binding of the commonly used progestogen, norethisterone, to plasma proteins may be important in the further delineation of side-effects of oral contraceptives.

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Site Specific Rectal Drug Administration in Man with an Osmotic System: Influence on "First-Pass" Elimination of Lidocaine

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Abstract: Lidocaine was administered to healthy volunteers at different sites in the rectum. Unchanged drug and monoethylglycinexylidide (MEGX) concentrations were measured in plasma with a newly developed gas chromatographic method. Lidocaine was given rectally by means of an osmotic system (Osmet®) which delivered 25 mg/h at zero-order rate. In a pilot experiment in two subjects it was shown that lidocaine administration close to the anus for 5 h resulted in higher lidocaine plasma levels as compared to administration at 15 cm from the anus. Six other subjects participated in three separate experiments, in which lidocaine was administered rectally close to the anus and at 7.5 and 15 cm from the anus. A zero-order infusion plasma level profile was found for both the parent compound and its metabolite. The MEGX/lidocaine plasma concentration ratio was calculated for all experiments. After administration most proximal to the anus the mean metabolite/parent drug concentration ratio was significantly less than that obtained after administration at 15 cm from the anus, whereas at approximately 7.5 cm from the anus the values were in-between. Comparison of the AUC lidocaine/AUC MEGX ratios gave similar results; the highest value, 3.2 ± 1.3 (mean ± S. D.), was found after administration close to the anus, while at 15 cm from the anus the ratio was 1.6 ± 0.3 ($p < 0.01$). The terminal elimination half-lives of lidocaine and MEGX did not differ for the three sites of administration, and the mean values were 110 and 180 min respectively. The results of this study demonstrate that the site of drug administration in the human rectum determines the degree of hepatic "first-pass" elimination of high-clearance drugs. Maximal avoidance of presystemic elimination is achieved when administration takes place close to the anus.

Lidocaine is subject to extensive hepatic "first-pass" elimination when given orally, which gives rise to low and variable systemic availability (1, 2). A more appropriate route for high-clearance drugs like lidocaine, propranolol, some narcotic analgesics and nitroglycerin, should be non-hepatic and non-invasive. Rectal, dermal and buccal routes of drug administration have been suggested as alternatives (3, 4, 5). We have been particularly interested in the rectal route, because it has been recently shown in man that it is in principle possible, at least partly, to bypass the liver. When lidocaine was administered rectally as an enema, the systemic availability was doubled as compared to oral administration to the same subjects (6). In rats complete avoidance of hepatic "first-pass" elimination was found rectally with propranolol and lidocaine (7, 8). The partial avoidance of hepatic presystemic elimination in man can be explained by the venous drainage of the rectum (9). The lower and probably also the middle rectal hemorrhoidal veins pass the absorbed drug directly into the inferior vena cava. More upwards in the rectum the drug passes into the upper hemorrhoidal vein which is connected to the

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portal system. Therefore, a drug administered and absorbed in the distal rectum should be subject to hepatic "first-pass" elimination, whereas in the lower proximal part of the rectum avoidance of presystemic elimination should occur. In the present investigation this hypothesis was tested by administering the high-clearance drug lidocaine at specific sites in the rectum and measuring the parent drug and its primary metabolite MEGX in the general circulation. Similar studies were recently performed in rats with lidocaine and propranolol (10, 11), and it was found that the degree of avoidance of "first-pass" elimination was indeed highly dependent on the site of drug administration in the rectum. When the drug was administered in the lower part, close to the anus, avoidance of presystemic elimination was maximal. In the present study in man, an osmotic delivery system for zero-order and site-specific rectal drug administration were used. This system has recently been shown to produce zero-order drug release with the low-clearance drugs antipyrine and theophylline, resulting in plasma concentration time profiles comparable to those obtained following i.v. infusion (12, 13).

Materials and Methods

Subjects and drug administration

Eight healthy male volunteers, aged 22–34 years, body weights 60–82 kg, participated: two in the pilot study and six in the experimental study. All gave their written informed consent. In the pilot study an osmotic system with lidocaine was applied in the lowest part of the rectum for the first 5 h and subsequently it was pushed upwards to approximately 15 cm from the anus and left there for another 5 h. During the experiment and for 4 h afterwards a blood sample was taken every 30 min from a cannula in a forearm vein. In the second study all subjects participated three times and received lidocaine rectally in an osmotic system for 8 h in each experiment. The protocol of the study had been reviewed by the Committee for Medical Ethics of the University Hospital and the Faculty of Medicine of the University of Leiden. The experiments were carried out in a random cross-over way with a period of at least one week in between the three experiments. Lidocaine was administered close to the anus and at approximately 7.5 and 15 cm from the anus. Blood samples were taken from a cannula in a forearm vein just before insertion of the osmotic system and at 1, 2, 3, 4, 5, 6, 7, 8, 8.5, 9, 10, 11 and 12 h. The osmotic systems were inserted into the rectum at 9.00 a.m., if possible after defecation. If the subjects had to empty their bowel during the 10 or 8 h of lidocaine administration, the system (to which a thread was attached) was pulled out of the rectum just prior to defecation and inserted again afterwards. There were no restrictions for the volunteers with regard to food, drinking coffee or tea and exercise during the experiments.

Plasma samples were obtained by centrifuging the heparinized blood samples immediately after withdrawal and were stored at −20 °C until assayed.

Osmotic delivery system and in vitro release

The osmotic delivery system (Osmet®) operates according to a principle described by Theeuwes (14) and was kindly supplied by ALZA Corporation, Palo Alto, California, USA. The system had a diameter of 13 mm and a length of 43 mm, a nominal pumping rate of 65 µl/h and a filling volume of approximately 2.25 ml. The systems were filled with an aqueous solution of lidocaine HCl (Brocacef, Maarssen, The Netherlands) containing 475 mg/ml. To avoid loss by diffusion a polyethylene tubing flow moderator (length 35 mm, o.d. 1.2 mm, i.d. 0.8 mm) was inserted into the reservoir. The *in vitro* release rate of lidocaine from the osmotic device was determined in 250 ml isotonic saline at 37 °C. The lidocaine concentrations were measured spectrophotometrically (λ = 263 nm). The nominal release rate of lidocaine HCl was 25 mg/h (calculated as the base). To ensure a zero-order release at the moment of rectal insertion, the systems were preincubated before application *in vivo* in distilled water at 37 °C for 8 h. To the osmotic devices which were applied at 7.5 and 15 cm from the anus a flexible teflon rod with an o.d. of 3 mm was attached to the systems to place and keep them at the desired site in the rectum.

No feelings of discomfort were reported by the subjects during the experiments.

Assay of lidocaine and MEGX

A newly developed gas chromatographic method was used to measure lidocaine and MEGX in plasma simultaneously. To 1.00 ml plasma, 0.4 µg etidocaine as internal standard, 100 µl buffer pH 9 and 100 µl acetaldehyde 5 % in water were added. After mixing and waiting for approximately 30 min, 100 µl acetaldehyde solution was added again and the mixture was extracted with 5.0 ml pentane/dichloromethane 1/1 (volume parts). After centrifugation the upper organic layer was transferred to a conical evaporation tube. The solvent was evaporated to dryness at 40 °C under reduced pressure in a Buchler Vortex Evaporator. The residue was dissolved in 100 µl 2 % acetaldehyde in ethanol. An aliquot of 1 to 2 µl was injected into the GC (Hewlett-Packard 5711) with a N/P selective detector and a solid injection system (15). The column, length 5 m and diameter 0.40 mm, was of the capillary SCOT type with Carbowax 20 M as the stationary phase on Tullanox as support layer; the oven temperature was 175 °C, the injection port and detector temperatures were 250 and 300 °C, respectively, while helium was used as carrier gas. Linear calibration curves were obtained from 2–500 ng/ml plasma for both lidocaine and MEGX. In this assay procedure lidocaine is measured unchanged, but MEGX as a cyclic condensation product between the metabolite and acetaldehyde, because unchanged MEGX has a very poor chromatographic behaviour. MEGX reacts in plasma quantitatively with acetaldehyde to the cyclization product in alkaline solutions within approximately 30 min (16). It has been suggested that this product is also formed *in vivo* (17, 18), but when plasma samples after lidocaine administration were analyzed within 1 h without adding acetaldehyde, no measurable concentrations of the cyclization product were found (less than 0.5 ng/ml calculated as MEGX). However, when the sample is stored, the cyclization product is formed in significant amounts even at −20 °C because acetaldehyde is formed in plasma on standing. Therefore, quantitative conversion of MEGX into the cyclic condensation product avoids artifacts that may interfer with the assay following sample storage.

Calculations

The dose administered rectally with the osmotic system was calculated from the difference between the total amount of lidocaine put into the osmotic device, the amount which was released *in vitro* during preincubation and the amount left after rectal application. The latter amount was determined spec-

trophotometrically after destruction and rinsing the reservoir of the system with water.

The elimination half-lives were determined by least-square regression analysis of the log-linear terminal parts of the plasma concentration time curves. Total areas under the curve (AUC) for lidocaine and MEGX were calculated by the linear trapezoidal rule from t = 0 to the maximum concentration and after that with the logarithmic trapezoidal rule to infinity (19). The area beyond the last measured concentrations was determined by dividing concentration by the plasma elimination rate constant. Statistical differences were assumed to be significant when $p < 0.01$ (two-sided), calculated with Student's t-test.

Results

Figure 1 shows the *in vitro* release of lidocaine from the osmotic delivery system. After approximately 6 h the release of lidocaine has a constant rate of 24.7 ± 0.7 mg/h (mean ± S.D.; n = 3). Since application *in vivo* occurred after preincubation of the systems for 8 h, the zero-order release rate is effective immediately after rectal insertion.

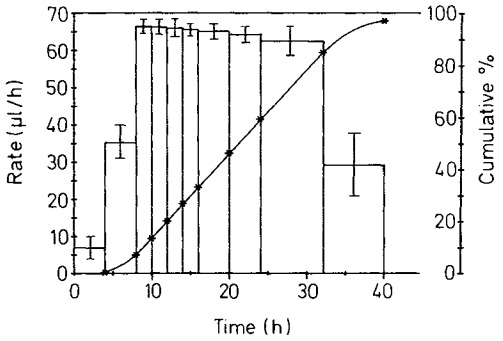

Fig. 1 The *in vitro* release of lidocaine from the osmotic delivery system in cumulative amount as percentage of dose (✳) and in absolute release rates (bars with S.D.) plotted versus time (mean; n = 3).

The administered dose of lidocaine *in vivo* was entirely in accordance with predictions based on the *in vitro* results: 246 and 261 mg for the pilot experiment and 198 ± 10 mg (mean ± S.D.) for the actual study. In one experiment (subject no. 3) the lidocaine dose was considerably less, because the osmotic system placed in a proximal location was retained in the rectum only for 2.5 h.

In Figure 2 the plasma concentration time curves of lidocaine and MEGX are shown for both subjects in the pilot study. The osmotic device was kept low in the rectum for 5 h during which period the lidocaine concentrations were high relative to the MEGX concentrations. From 5 to 10 h, the system was placed approximately 15 cm from the anus, and the ratio lidocaine/MEGX decreased considerably. These preliminary results suggest that drug delivery close to the anus produced higher lidocaine concentrations than drug delivery in the distal rectum; hence, there was sufficient reason to proceed with a more extensive study on the effect of the site of rectal drug administration on systemic availability.

In the subsequent experiments the design was such that drug delivery at different sites took place on different occasions.

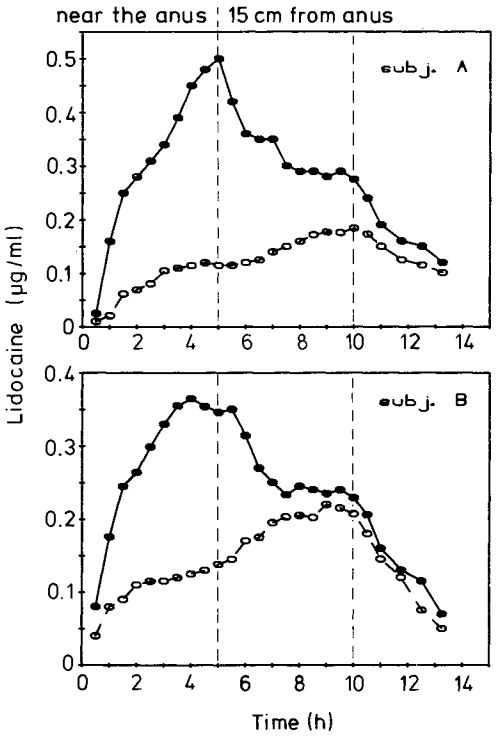

Fig. 2 Plasma concentration versus time curves of lidocaine (•) and MEGX (o) after rectal lidocaine administration close to the anus followed by administration at 15 cm from the anus in two individuals.

Figure 3 gives the mean lidocaine concentrations following administration at the three different sites in the rectum. The highest concentrations were obtained after administration close to the anus and the lowest at 15 cm from the anus (significantly different; $p < 0.01$). The concentrations after lidocaine administration at 7.5 cm were in between those in the upper and lower part of the rectum. The almost parallel curves for lidocaine and MEGX during 8 h drug administration close to the anus and at 15 cm from the anus in subject 1 are shown in Figure 4. The maximal lidocaine concentrations were 0.325 and 0.178 µg/ml after administration close to the anus and at 15 cm from the anus, respectively. The maximal MEGX concentration was higher (0.100 µg/ml) after administration in the

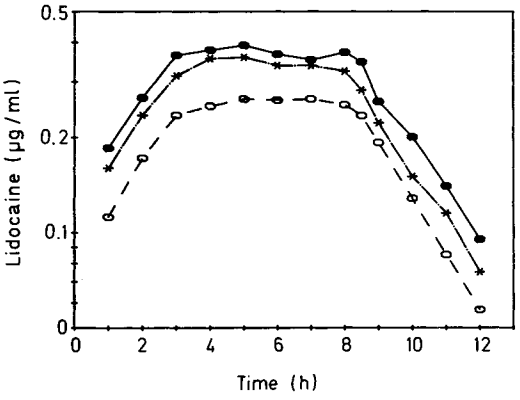

Fig. 3 Mean plasma concentration versus time curves after rectal lidocaine administration close to the anus (•), at 7.5 (✳) and at 15 cm from the anus (o); n = 6 in each experiment.

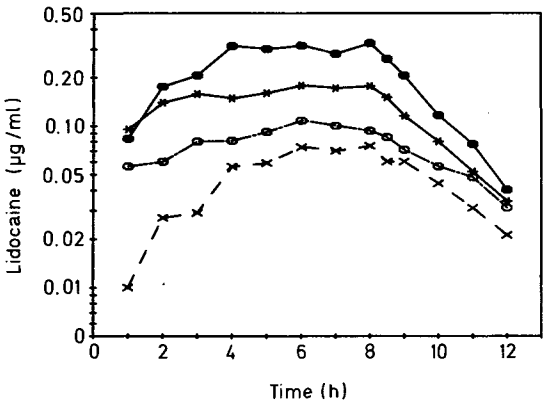

Fig. 4 Plasma concentration versus time curves of lidocaine and MEGX after rectal lidocaine administration close to the anus and after administration at 15 cm from the anus to subject 1.

	0 cm	15 cm
lidocaine	•	✳
MEGX	×	○

upper part of the rectum compared to close to the anus (0.075 µg/ml). The ratio of the lidocaine to MEGX concentrations in subject 1 after 8 h was 4.5, 2.4 and 1.9 following lidocaine administration close to the anus, at 7.5 and at 15 cm from the anus, respectively. These respective values varied in all subjects from 1.8–5.0 (mean 3.4, significantly different; $p < 0.01$), 1.7–3.1 (mean 2.2), and 1.3–2.7 (mean 1.9, significantly different; $p < 0.01$). Table I gives the terminal elimination half-lives and AUC's for lidocaine and MEGX for the three rectal experiments in all subjects. The mean elimination half-life for lidocaine was 110 min and for MEGX 180 min. Although considerable inter- and intraindividual differences in the half-lives of lidocaine and MEGX were found, they were not significantly different for the three sites of drug administration. For the evaluation of the degree of hepatic "first-pass" elimination the ratio of MEGX and lidocaine concentrations may be used as a sensitive indicator, because MEGX is a primary "first-pass" metabolite of lidocaine in man (20). In Figure 5 these values obtained at the different sites in the rectum are plotted against time for all subjects. The highest metabolite/parent drug ratios were found when administration took place approximately 15 cm from the anus, the lowest close to the anus, while the 7.5 cm values were in-between. Dividing the AUC of lidocaine by the AUC of MEGX, the highest values 1.9–5.3 (mean 3.2, significantly different; $p < 0.01$) were found close to the anus, the lowest 1.1–1.9 (mean 1.6, significantly different; $p < 0.01$) 15 cm from the anus. As is shown in Table II large interindividual differences were found, but the values obtained in the middle part of the rectum, 1.5–2.7 (mean 2.1), were always in-between those resulting from administration close to the anus and in the upper part of the rectum.

Table II. AUC ratios of lidocaine over metabolite MEGX following rectal administration at three different sites.

Subject	AUC lidocaine/AUC MEGX 0 cm	7.5 cm	15 cm
1	4.2	2.7	1.6
2	2.1	2.1	1.8
3	5.3	2.3	1.9
4	3.1	2.1	1.8
5	1.9	1.5	1.1
6	2.4	2.0	1.6
Mean ± S.D.	3.2 ± 1.3	2.1 ± 0.4	1.6 ± 0.3

Table I. Elimination half-lives and AUC (area under the plasma concentration time curve) following rectal administration of lidocaine at three different sites.

Subject	Dose mg.	Site of administration	Elimination half-life (min) Lidocaine	MEGX	Area under the curve (µg min/ml) Lidocaine	MEGX
1	195	0.0 cm	80	139	153	37
	200	7.5 cm	112 (98)	139 (144)	177	65
	204	15.0 cm	103	154	92	58
2	184	0.0 cm	76	151	121	56
	203	7.5 cm	104 (89)	163 (149)	143	69
	191	15.0 cm	88	134	128	71
3	62*	0.0 cm*	127	169	112	21
	204	7.5 cm	103 (117)	208 (194)	176	77
	211	15.0 cm	120	204	172	89
4	186	0.0 cm	126	225	244	79
	192	7.5 cm	146 (130)	211 (217)	226	110
	188	15.0 cm	118	214	199	111
5	209	0.0 cm	96	200	272	141
	211	7.5 cm	131 (109)	186 (194)	219	149
	199	15.0 cm	101	197	167	152
6	189	0.0 cm	109	161	310	130
	209	7.5 cm	124 (118)	202 (181)	245	121
	197	15.0 cm	121	181	230	142
	mean ± S.D.		110 ± 18	180 ± 29		

* Lidocaine was administered over 2.5 instead of 8 h.
Numbers in parentheses represent the mean elimination half-life for the three sites of drug administration in one subject.

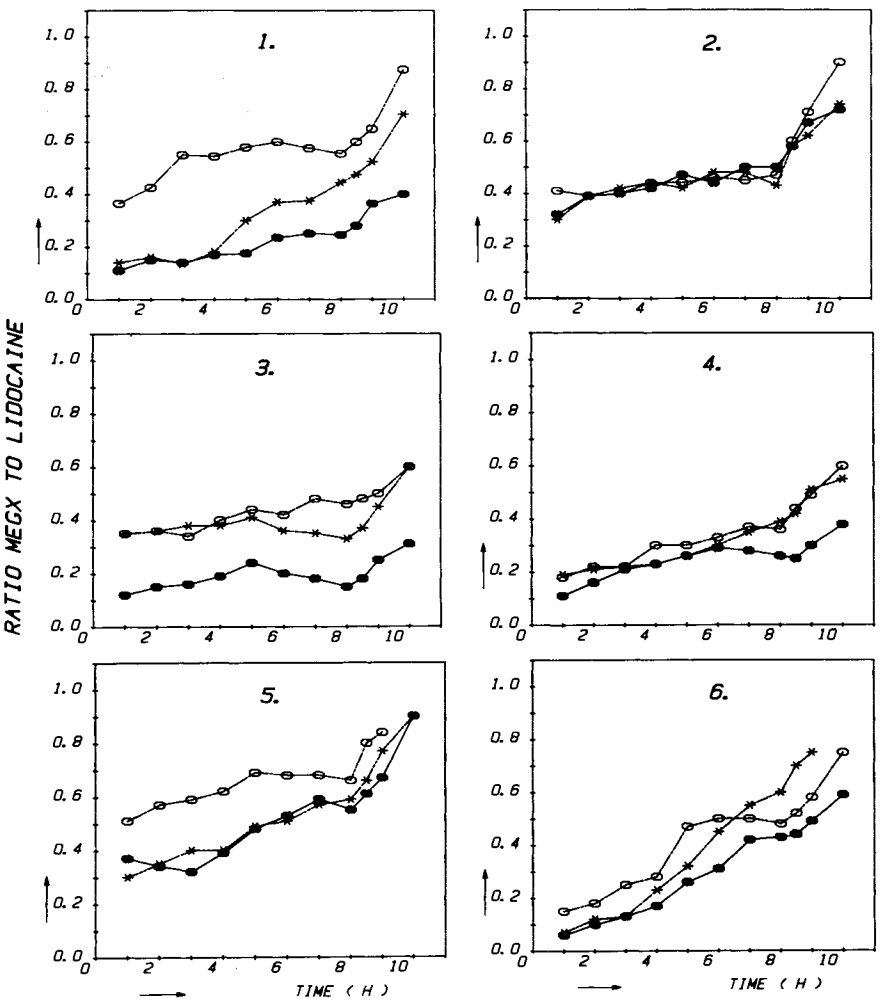

Fig. 5 MEGX to lidocaine concentration ratio versus time curves after rectal lidocaine administration close to the anus (•), at 7.5 (✳) and at 15 cm from the anus (o) in all individuals studied.

Discussion

Site-specific rectal administration of lidocaine and propranolol in rats has shown that the avoidance of presystemic elimination is very much dependent on the site of drug administration (10, 11).

In the present study this phenomenon was investigated in human subjects with the high-clearance compound lidocaine by measuring the systemic availability and the metabolite formation. An osmotic system was used for drug administration, because it allows both site-specific and zero-order drug delivery.

The results of the pilot study, visualized in Figure 2, clearly show that a decreasing amount of lidocaine enters the general circulation when the drug is administered further away from the anus. This indicates that a more pronounced hepatic "first-pass" effect occurs. In the complete experimental study lidocaine was administered at three different sites in the rectum on separate occasions in the same subjects to permit quantitative evaluations. In a previous study it was shown that the systemic availability of rectally administered lidocaine is quite reproducible in the same subject (6). The plasma concentration time profiles of both lidocaine and MEGX (Fig. 3 and 4) indicate an almost perfect zero-order input-rate into the body during the 8 h of lidocaine administration, which is quite comparable to the zero-order release rate in vitro (Fig. 1). Based on the theory of the well-stirred model for hepatic clearance (21, 22) it has been shown that when drug and metabolite are exclusively eliminated by the liver, the AUC for the metabolite is independent of route of administration and clearance of drug or metabolite. In the perfused rat liver preparation that model could adequately explain lidocaine and MEGX data (23). Evidence suggesting that the well-stirred model also applies to man has been given for nortriptyline and its hydroxy-metabolite (24) and recently for lidocaine and MEGX (20). In the latter study the dose-normalized AUC for MEGX had about the same value after oral and i.v. administration to the same subject. Similarly, in the present investigation the AUC's of MEGX for the three experiments in one subject were reasonably constant, but in most cases the AUC of MEGX was lower after administration close to the anus than more distal in the rectum. Assuming that the well-stirred model is valid for lidocaine administered rectally in man, the AUC lidocaine/AUC MEGX ratio (Table II) can be used to determine the extent of hepatic "first-pass" elimination as determined by the site of drug administration in the rectum, without knowing the dose and the amount absorbed. The same is true with regard to the MEGX/lidocaine concentration ratio at 7–8 h, when a steady-state situation is achieved (Fig. 5). The lidocaine/MEGX AUC ratio was higher close to the anus than

at 7.5 and at 15 cm from the anus. The lowest ratios were found after lidocaine administration at 15 cm from the anus. Hence it can be concluded that the degree of "first-pass" elimination of lidocaine is most pronounced in the distal part of the rectum, slightly lower at approximately 7.5 cm from the anus, and lowest close to the anus. Since the degree of absorption is not known, no conclusions can be drawn as to the absolute degree of avoidance of hepatic "first-pass" elimination. However, there is no reason to believe that the degree of absorption differed at the various sites in the rectum. The intent of the experiments was to investigate the influence of the site of drug administration in the rectum on systemic availability of high-clearance drugs in terms of a rank order for the three sites.

The MEGX/lidocaine concentration ratio (Fig. 5) increased in all cases after 8 h when lidocaine administration was stopped, because elimination half-lives for MEGX are longer than for lidocaine. The mean lidocaine elimination half-life of 110 min is in good agreement with the data reported for i.v., oral and rectal administration (6, 25, 26). MEGX elimination half-life data as reported in the literature range from 120-275 min (27, 28) and are quite comparable with the present values.

The reason for the large interindividual differences in the MEGX/lidocaine concentration ratios for the three experiments is probably due to the existence of extensive anastomoses between the lower and upper hemorrhoidal veins. This means that there is no clearcut site-related differentiation between systemic and portal direction, with considerable variability occurring from one individual to the other. In subject 2, for example, there was hardly any difference between the three rectal sites, whereas the differences in subjects 1 and 3 were considerable. Despite this variability, in all six subjects the lowest metabolite to parent drug concentration ratios were found after drug administration close to the anus. With the use of a rate-controlled dosage form this study demonstrates that the site of drug administration in the human rectum is an important factor that determines the degree of presystemic elimination. Maximal avoidance of first-pass elimination is achieved when drug administration takes place as close as possible to the anus.

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