DISPOSITION KINETICS OF LIDOCAINE IN NORMAL SUBJECTS*

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Introduction

The use of intravenous (i.v.) lidocaine for the control of ventricular arrhthmias has made it necessary to learn more about the disposition kinetics of this drug, and from such information to establish effective and safe dosage regimens. The clinical observation of rapid onset but short duration of response (10–20 minutes) after a 50-mg or 100-mg bolus of lidocaine, together with the prompt termination of antiarrhythmic effects after discontinuing a prolonged i.v. infusion, has led to the assumption that lidocaine is readily eliminated from man.[1] The concentration of plasma or blood lidocaine determined up to one hour after an i.v. bolus declines with a half-life of 10–20 minutes.[2] Gianelly and associates[3] found that patients with coronary heart disease who are given a constant i.v. infusion without an initial bolus achieved plateau concentrations in plasma within 30–60 minutes. This observation also suggested a half-life of between 10 and 20 minutes for the drug. These collective data from blood concentrations of lidocaine tend to confirm the observations made in therapeutic settings. Beckett and co-workers, however, reported that the half-life was 1.6–1.8 hours in normal subjects.[4] These investigators based their conclusion on the rate of urinary excretion of the unchanged drug while the urine was acidic. Only 4.1–7.2% of the unchanged drug was excreted in the urine. Excretion of lidocaine is influenced by urinary pH.[5] Beckett and colleagues[4] also proposed that deethylation of lidocaine to monoethylglycylxylidide was a major metabolic pathway in man. Apart from this proposal, very little is known about the metabolism of lidocaine in man, even though some information is available in animals.[6-9]

Results of the present study clarify the apparent discrepancies that exist between estimations of half-life based on clinical observation of pharmacologic effects of the drug and calculations made from limited clinical determinations. The disposition kinetics of lidocaine were studied in normal volunteers, and this information has helped establish suitable dosage regimens in patients with ventricular arrhythmias.

Methods and Materials

Experimental

Each of 10 normal volunteers (9 male, 1 female), ages 28–54, received 50 mg of lidocaine hydrochloride as an i.v. bolus over a period of approxi-

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mately one minute. Subjects were supine throughout most of the experiment, and blood samples were drawn at 0, 2, 5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, and occasionally, 360 minutes after the injection. In five of these subjects urine was collected for 24 hours after the injection. In five subjects, the study was repeated with a 100-mg dose infused over two minutes. On another occasion, three of these subjects received a bolus followed by a 120-minute infusion of lidocaine, the regimen being calculated from previous kinetic information obtained in these volunteers. All samples were stored at −10° C until analyzed.

Chemical Analysis

The general scheme of analysis is depicted in FIGURE 1. To 0.5–2.0 ml of blood or plasma was added 1 ml of an aqueous solution containing equal amounts of two internal markers, m-methyl N-diethylglycylanilide hydrochloride (methyl DEGA) and m-methoxy N-diethylglycylanilide hydrochloride (methoxy DEGA). Usually, 1 μg of each was added, but when low levels (0.4 μg/ml or less) of lidocaine were expected, either 0.5 μg or 0.2 μg of each standard (marker) was used. The solution was shaken with 7 ml of freshly distilled diethyl ether for two minutes and centrifuged, and as much as possible of the organic layer was transferred to another tube containing 1 ml of 0.1 N HCl. The tube was shaken for two minutes and centrifuged, and the ether layer was siphoned off and discarded. One-half ml of 0.5 N sodium hydroxide was added to the aqueous layer, which was then extracted with 7 ml freshly distilled diethyl ether and centrifuged, and the ether layer was transferred to another tube containing a washed carborundum boiling chip. The ether extract was then concentrated on a 45° C water bath to approximately 100 μl. The remaining ether was slowly evaporated at ambient temperature, and the residue was reconstituted in 50–100 μl freshly distilled chromatographic grade carbon disulfide. Less carbon disulfide was used when low concentrations of lidocaine were expected. Three to five μl of the concentrate was injected into the gas chromatograph. The peak height ratio of the lidocaine to each standard was calculated, and the concentration of lidocaine in the biological sample was determined by reference to-standard calibration curves. Lidocaine standards in phosphate buffer (pH 7.4) were run with each batch of samples. Urine was analyzed in a similar manner, except that the sample was made basic with 0.1 N sodium hydroxide prior to the initial extraction.

Chromatographic Conditions

A Varian 1200 gas chromatograph was used, containing 3% OV-17 coated onto 100–120 mesh Chromosorb W DMCS/AW HP packed into a six-foot-long, 1/8-inch outer diameter, glass column. The packing was conditioned for 24 hours at 280° C without gas flow and for another 24 hours at this temperature with gas flow. Operating conditions were: oven temperature 210° C; detector and injector port, 260° C; nitrogen and hydrogen flow, each 20 ml/minute; and air flow, 300 ml/minute. The GLC was connected to a 10-inch model 20 Varian recorder.

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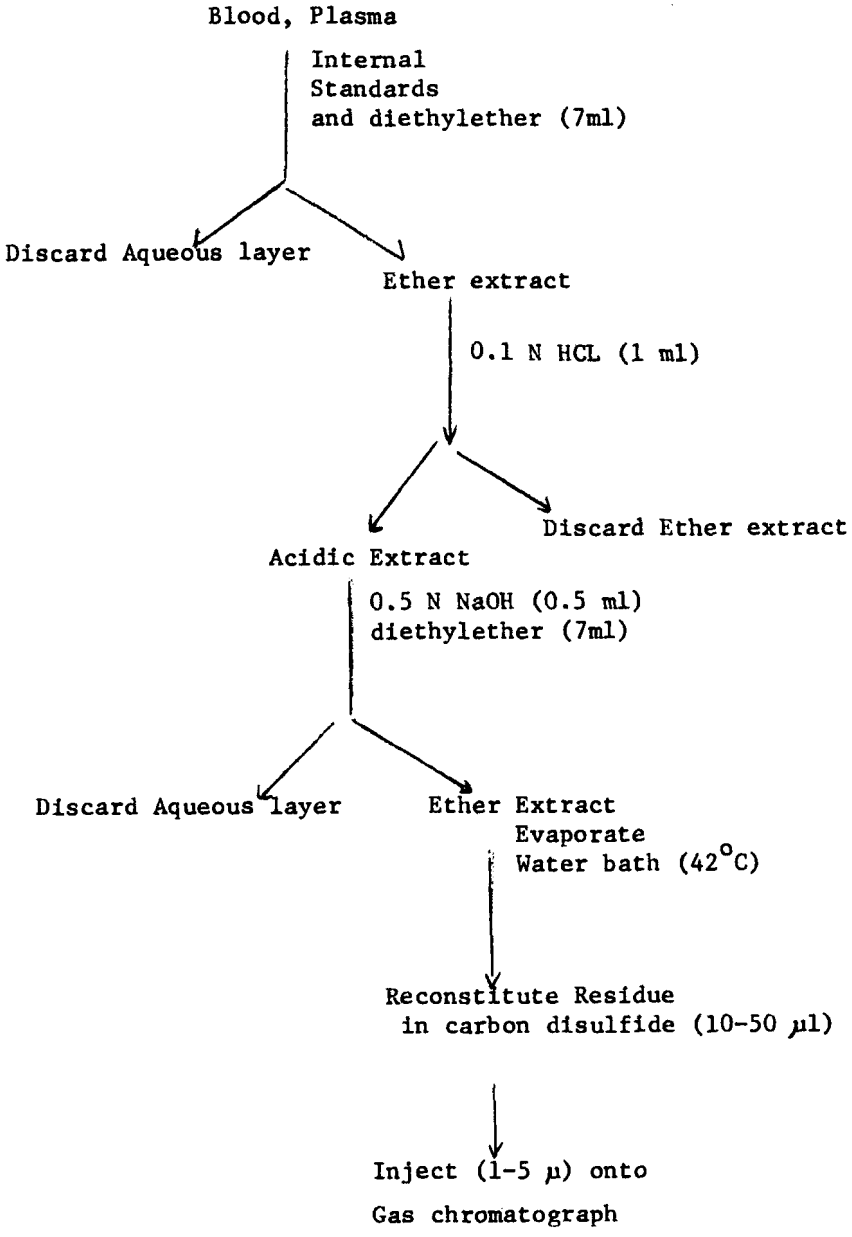

FIGURE 1. Schematic Diagram for the Analysis of Lidocaine.

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Pharmacokinetic Analysis, I.V. Bolus

In all subjects, over the period of the study, the plasma-concentration (C_p) time curve could be fitted by a biexponential equation of the form

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where A and B are the zero time intercepts of the data plotted on semilogarithmic paper and α and β are the rapid- and slow-rate constants, respectively. All data were fitted with use of a BMDX85T nonlinear regression analysis program on an IBM 360-50 computer. Each datum point was weighted by the reciprocal of the variance of the assay assuming linearity of the variance between concentrations at which the assay variance was calculated. This curve is consistent with, and was interpreted in terms of, a two-compartment open model[10] (FIGURE 2). The initial dilution space (V_p), volume of distribution at

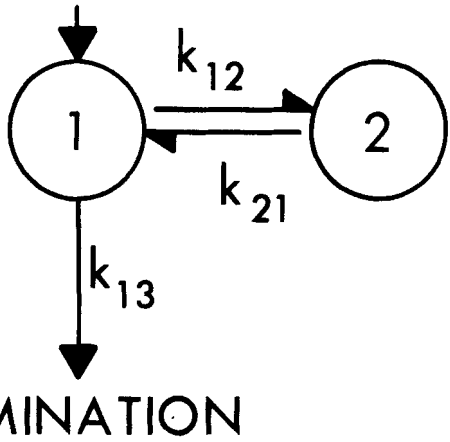

FIGURE 2. Two-compartment open model describing the disposition kinetics of lidocaine. Drug distributes between compartments one and two and is eliminated via compartment one.

steady state ($V_{d_{ss}}$) and mass rate constants k_{12}, k_{21}, and k_{13} associated with the model were calculated from A, B, α, and β in the usual manner.[10] The total body plasma clearance was calculated by dividing the dose by the area under the plasma concentration time curve ($A/\alpha + B/\beta$).

Intravenous Bolus and Constant Infusion

Dividing Equation 1 by the dose administered (D_o) yields

$$\frac{C_p}{D_o} = A'e^{-\alpha t} + B'e^{-\beta t} \quad (2)$$

where A′, B′ are the intercepts divided by the dose and correspond to $(k_{21} - \alpha)/V_p(\beta - \alpha)$ and $(k_{21} - \beta)/V_p(\alpha - \beta)$ in terms of the compartmental model.[10]

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When a bolus is given at zero time followed by a constant infusion (rate k_o) starting and finishing at times θ_s and θ_E, the plasma-concentration time curve is given by

$$C_p = A' \left[D_o - k_o \frac{(e^{+\alpha\theta_1} - e^{+\alpha\theta_2})}{\alpha} \right] e^{-\alpha t} + B' \left[D_o - k_o \frac{(e^{+\beta\theta_1} - e^{+\beta\theta_2})}{\beta} \right] e^{-\beta t} \quad (3)$$

where

$$\theta_1 = \begin{cases} t \text{ when } t < \theta_s \\ \theta_s \text{ when } \theta_s \leqslant t \end{cases}$$

and

$$\theta_2 = \begin{cases} t \text{ when } t < \theta_E \\ \theta_E \text{ when } \theta_E \leqslant t \end{cases}$$

The entire plasma level data before (if infusion was started after the bolus), during, and after the infusion was fitted according to Equation 3 with use of the BMDX85T program, and the parameters associated with the model were calculated from A', B', α and β.

Dosage Regimens

The object of giving a bolus followed by a constant-rate infusion is to attain rapidly and maintain the desired concentration (C_p^*) for any length of time. When the disposition kinetics of a drug are described by a two-compartment open model, the above situation is theoretically most rapidly and readily achieved by commencing infusion at a time (t^*), after the bolus, when the amount in the peripheral compartment has reached a maximum. (See FIGURE 3.) At that time the rates of drug entering and leaving the peripheral compartment are equal. Then, by infusing the drug at that time at a rate equal to the rate of loss of drug from the body, the desired constant level of drug in the body is maintained.

Provided the system is linearly related to dose, the time t^* is dose-independent and is given by

$$t^* = \frac{\ln\left(\frac{\alpha}{\beta}\right)}{\alpha - \beta} \quad (4)$$

and at that time

$$\text{the fraction of the initial dose in compartment 1} = \frac{k_{21} e^{-\beta t^*}}{\alpha} \quad (5)$$

So that the bolus required to give the desired plateau concentration, C_p^* (and the amount $V_p C_p^*$ in compartment 1) at t^* is

$$\text{Initial bolus (Dose}_2\text{)} = V_p C_p^* \frac{\alpha}{k_{21}} \cdot \left(\frac{\alpha}{\beta}\right)^{\beta/\alpha - \beta} \quad (6)$$

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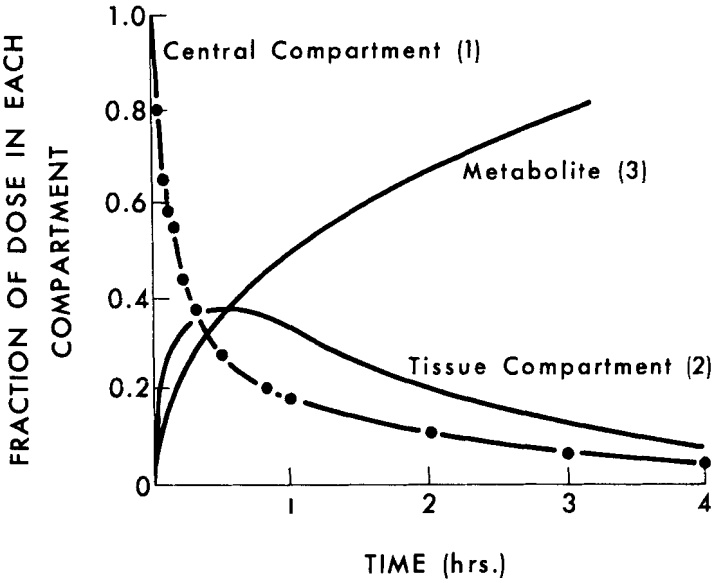

FIGURE 3. Analog computer-generated curves for the amount of lidocaine in various compartments after an i.v. 50-mg bolus. Circles are the calculated amount of lidocaine in compartment 1. Note that as much as 30% of the lidocaine is metabolized within 30 minutes of injection and that the maximum amount in the tissue compartment is reached within 25 minutes.

where the subscript "2" after "dose" denotes that the calculations are based on a two-compartment model. The infusion rate required to maintain this concentration is then given by

$$\text{Infusion rate } (k_{0,2}) = V_p k_{13} C_p^* \tag{7}$$

Were the infusion rate started immediately instead of at t^* then the fraction of the initial dose that would be infused up to time t^* $[(k_{0,2}) \cdot t^*/\text{Dose}_2]$ is given by

$$\frac{(k_{0,2}) \cdot t^*}{\text{Dose}_2} = \frac{\beta}{\alpha - \beta} \cdot \frac{\ln\left(\frac{\alpha}{\beta}\right)}{\left(\frac{\alpha}{\beta}\right)^{\beta/\alpha-\beta}} \tag{8}$$

Frequently the initial, rapidly declining phase is ignored when calculating dosage regimens, and the drug is assumed to be spontaneously distributed in such a way that the body acts as a single compartment with respect to the drug. The corresponding apparent volume of distribution V_d of the drug, given by Dose/B, is equal to V_p $(\alpha - \beta/k_{21} - \beta)$.[10] The initial bolus required to achieve the concentration C_p^* would then be

$$\text{initial bolus } (\text{Dose}_1) = V_d C_p^* = V_p C_p^* \frac{\alpha - \beta}{k_{21} - \beta} \tag{9}$$

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where $Dose_1$ denotes the initial dose assuming a one-compartment model. Then the infusion rate would start immediately at a rate defined by

$$\text{infusion rate } (k_{0,1}) = V_d C_p^* \beta. \tag{10}$$

In assessing the difference between the two models it is appropriate to examine the ratio of doses derived from Equations 6 and 9 together with Equations 7 and 10.

$$\text{Ratio of initial bolus } \frac{Dose_2}{Dose_1} = \frac{\alpha (k_{21} - \beta) \left(\frac{\alpha}{\beta}\right)^{\beta/\alpha - \beta}}{k_{12} (\alpha - \beta)}. \tag{11}$$

$$\text{Ratio of infusion rates } \frac{k_{0,2}}{k_{0,1}} = \frac{\alpha (k_{21} - \beta)}{k_{21} (\alpha - \beta)}. \tag{12}$$

Results and Discussion

Assay

The gas-chromatographic assay proved suitable for the determination of lidocaine in blood, plasma, or urine. In no case was a peak observed at the retention time of lidocaine in blank samples. The use of two internal standards, one on either side of lidocaine, was helpful. A constant ratio between methylDEGA and methoxyDEGA was taken as evidence of a good chromatogram. Occasionally, the ratio of the former to the latter was higher, an indication of an additional peak at the same retention time as methylDEGA, and then analyses were based only on the methoxyDEGA peak. As expected, being tertiary amines, lidocaine and the standards were found stable in carbon disulfide. This organic solvent was chosen because of its lack of response in the flame ionization detector, thereby reducing the solvent peak and permitting low levels of lidocaine to be determined. Identical linear calibration curves were achieved whether lidocaine was placed in blood, plasma, urine, or distilled water. A large peak with a long retention time previously noted by Reynolds and Beckett,[11] which eventually interfered with their assay, was not observed. When spurious peaks were seen, these invariably originated from contaminated extraction tubes. The coefficients of variance of the assay at 2.0, 0.5, and 0.2 μg lidocaine/ml plasma were 5.1 (N = 6), 5.9 (N = 6), and 6.5% (N = 6) respectively. The assay used has many similarities to the assay proposed by Tucker[12] for the determination of bupivacaine, mepivacaine, and related anilides.

Pharmacokinetics

Attempts to fit the plasma concentration time curve of lidocaine satisfactorily, after an i.v. bolus of the drug, with a single exponential equation proved unsuccessful. All the data could be fitted by a biexponential equation using the nonlinear regression analysis program BMDX85T. Tables 1 and 2 contain the coefficients and exponents associated with each exponential term of the plasma level time curve following a 50-mg and 100-mg bolus, respectively. The data were interpreted in terms of a two-compartment open model, and the

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TABLE 1

PHARMACOKINETIC PARAMETERS DESCRIBING THE DISPOSITION KINETICS OF LIDOCAINE FOLLOWING A 50-MG BOLUS

Subject	Age (Yrs)	Wt. (kg)	A (μg/ml)	α (min^{-1})	B (μg/ml)	β (min^{-1})	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	Plasma Clearance (ml/min/kg)	V_p/kg (L/kg)	V_d/kg (L/kg)	$V_{d_{ss}}$/kg (L/kg)	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})
PT	34	70	0.935	0.107	0.374	0.00725	6.7	96	11.9	0.55	1.90	1.39	0.054	0.035	0.022
SM	24	59	0.507	0.047	0.321	0.00516	14.7	134	11.7	1.03	2.60	1.91	0.019	0.022	0.011
PH	26	70	2.23	0.116	0.279	0.00518	5.9	133	9.7	0.28	2.60	1.39	0.070	0.018	0.035
MR	30	69	1.37	0.207	0.590	0.00955	3.3	73	10.4	0.37	1.23	1.02	0.120	0.069	0.029
NS	28	90	1.44	0.139	0.497	0.00762	5.0	91	7.3	0.29	1.12	0.84	0.079	0.041	0.026
PE	30	93	1.06	0.107	0.538	0.00578	6.7	120	5.3	0.34	1.00	0.58	0.039	0.054	0.015
FG	29	80	1.61	0.067	0.240	0.00555	10.3	125	12.1	0.74	2.60	1.23	0.023	0.034	0.016
ES	55	82	1.45	0.146	0.450	0.00755	4.8	92	8.8	0.32	1.40	1.01	0.086	0.040	0.027
PF	53	93	3.00	0.182	0.400	0.00527	3.8	131	6.2	0.16	1.34	0.92	0.125	0.026	0.037
HH	57	82	1.27	0.108	0.528	0.00837	6.4	83	8.2	0.34	1.16	0.83	0.055	0.038	0.024
Mean		78.7	1.38	0.123	0.42	0.00673	6.76	108	9.16	0.44	1.69	1.11	0.0660	0.038	0.0242
% Standard Deviation of the Mean			54	39	28	23	50	21	26	59	39	34			

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TABLE 2

PHARMACOKINETIC PARAMETERS DESCRIBING THE DISPOSITION KINETICS OF LIDOCAINE FOLLOWING A 100-MG BOLUS

Subject	A (μg/ml)	α (min^{-1})	B (μg/ml)	β (min^{-1})	$t_{1/2_\alpha}$ (min)	$t_{1/2_\beta}$ (min)	Plasma Clearance (ml/min/kg)	V_p/kg (L/kg)	V_d/kg (L/kg)	$V_{d_{ss}}$/kg (L/kg)	k_{12} min^{-1}	k_{21} min^{-1}	k_{13} min^{-1}
PH	2.53	0.089	0.70	0.0082	7.8	85	12.6	0.44	2.0	1.14	0.043	0.026	0.028
MR	2.00	0.090	0.92	0.0083	7.7	83	10.8	0.50	1.43	1.00	0.068	0.029	0.025
ES	1.52	0.078	0.70	0.0070	8.9	99	10.2	0.55	1.70	1.25	0.037	0.029	0.019
PF	2.85	0.116	0.75	0.0062	6.0	112	7.4	0.30	1.60	1.10	0.042	0.034	0.022
HH	1.00	0.050	1.00	0.0083	14.0	83	8.7	0.61	1.21	0.93	0.015	0.029	0.014
Mean	1.98	0.85	0.81	0.0076	8.84	92.3	9.94	0.48	1.58	1.08	0.041	0.029	0.022
% Standard Deviation of the Mean	37	28	17	12.5	34	14	20	25	19	11	46	9.7	25

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rate constants, k_{12}, k_{21}, k_{13}, and the volume constants, V_p, $V_{d_{ss}}$, associated with the model, are also shown in the tables.

An early rapid decay in lidocaine plasma levels following a 50-mg bolus (mean half-life 7.0 minutes, TABLE 1) agrees with the rapid decline in pharmacological activity associated with i.v. doses of this drug. However, there is a much shallower phase (mean half-life 108 minutes), which relates to the elimination of this drug. Although these studies were extended only up to 240 minutes and occasionally 360 minutes after the injection, the average value of 108 minutes (TABLE 1) agrees closely with the elimination half-life of 96–108 minutes, noted by Beckett and associates[4] from urinary lidocaine data collected serially for 12 hours. Elimination is primarily due to metabolism, since less than four percent of unchanged lidocaine was found in the 24-hour urine collected after the bolus. As commonly occurs, the variance of the half-life of the first exponent was greater than that associated with the slower second exponent. In addition, note the relatively narrow range in the elimination half-life (73–133 minutes) among these normal subjects. No difference in the disposition kinetics of lidocaine was seen between the young and older subjects, the latter being age-matched to patients having ventricular arrhythmias. It appears that there are significant differences in the half-lives of the fast and slow phases and in the volume constants among individuals. This dispersion of individual characteristics will be described in a later paper.

No special meaning was associated with values of the rate constants k_{12}, k_{21}, and k_{13}. They were used simply to calculate the amount of drug in the peripheral compartment of the model (FIGURE 3), the volume of distribution of lidocaine at steady state ($V_{d_{ss}}$), and dosage regimens using the two-compartment model. The initial dilution space, V_p (0.44 1/kg), and the $V_{d_{ss}}$ (1.11 1/kg) are greater than the plasma volume and body-water spaces respectively, implying extravascular concentration of lidocaine. These values correspond closely with those in dogs.[13] The high concentrations of lidocaine in kidney, liver, lung, spleen, and other viscera in mice and rats[14] indicate probable sources of localization in man. The rate of equilibration of lidocaine between plasma and heart and other highly perfused organs is probably very rapid. Central and cardiac effects are noted within seconds after the bolus was administered. Additionally, after an intraperitoneal (i.p.) injection into mice, there is a parallel decline of a basic extract (lidocaine and perhaps some metabolite) in plasma, kidney, liver, brain, spleen, and heart,[14] tending to confirm rapid equilibration of this drug between plasma and these tissues.

Increasing the dose to 100 mg gave a proportional increase in the concentration of lidocaine in plasma. Comparison of the values describing the disposition kinetics of lidocaine in TABLES 1 and 2 appears to indicate changes with dose. However, there was no consistent trend. Larger doses were not given because of the known toxicities associated with higher plasma levels of lidocaine. Nonetheless, the data that Wahlquist[15] collected in humans up to 40 minutes after an i.v. injection of 200 mg lidocaine are, as expected, proportionately higher than those found in the present study. These data suggest that the disposition kinetics of lidocaine are independent of dose over the therapeutic dose range of this antiarrhythmic agent. From information gained from the bolus studies, dosage regimens involving a bolus and an infusion were calculated that would rapidly attain and maintain a constant level of 1 μg lidocaine/ml plasma. The bolus and infusion rates, given in TABLE 3, yielded the desired plasma level (e.g. FIGURE 4), indicating the appropriateness of these dosage regimens.

Zero- and first-order infusions of drugs have been conducted in man and

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TABLE 3

PHARMACOKINETIC PARAMETERS DEFINING THE DISPOSITION OF LIDOCAINE FOLLOWING A BOLUS EITHER WITH OR WITHOUT A CONSTANT INFUSION

Subject	Dose	Infusion Rate (mg/min)	Infusion Time (min)		A' (ug/ml/mg)	α (min^{-1})	B' (ug/ml/mg)	β (min^{-1})	$t_{1/2_\alpha}$ (min)	$t_{1/2_\beta}$ (min)	Clearance/kg (ml/min/kg)
			Start	Finish							
MR	50	—	—	—	0.0274	0.207	0.0118	0.0096	3.3	73	10.4
	100	—	—	—	0.020	0.090	0.0092	0.0083	7.7	83	10.8
	110	0.75	30	150	0.0174	0.046	0.0100	0.0073	15.0	95	8.4
HH	50	—	—	—	0.0254	0.108	0.0105	0.0084	6.4	83	8.2
	100	—	—	—	0.0100	0.050	0.0100	0.0083	14.0	83	8.7
	77	0.75	0	120	0.0323	0.101	0.0061	0.0068	6.9	102	10.0
PF	50	—	—	—	0.060	0.182	0.0080	0.0053	3.8	131	6.2
	100	—	—	—	0.0285	0.116	0.0075	0.0062	6.0	112	7.4
	128	0.74	0	120	0.0106	0.100	0.0061	0.0071	7.0	98	9.4

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animals in whom the disposition kinetics of the drug have been previously determined after an i.v. bolus. The stability and appropriateness of the pharmacokinetic model were then demonstrated by the similarity of the known rate to that calculated from the resultant plasma or blood concentration time curve.[13,16,17] In the present study this was not done; instead, on the basis of the known size of the bolus and the infusion rate, coefficients and exponents defin-

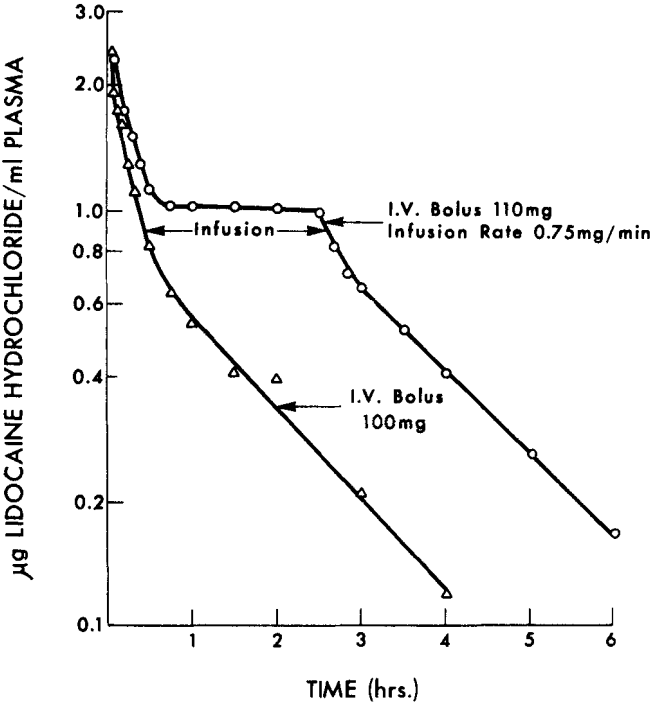

FIGURE 4. Plasma concentrations of lidocaine following a bolus and bolus plus infusion on separate occasions (Subject, MR). The continuous lines are the computer-fitted curves.

ing the disposition kinetics of lidocaine were estimated from the entire plasma curve with the use of the computer. The data are presented in TABLE 3, and for comparison, the corresponding values following the 50-mg and 100-mg boluses are also given. Differences in the parameters are seen, but there are no clear trends, and it would appear that reasonable estimates of the parameters can be derived from infusion data. This is particularly important, since in a clinical setting a single bolus is rarely given but is usually immediately followed by an i.v. lidocaine infusion, and it becomes necessary to gain pharmacokinetic information from the resultant concentration of drug in plasma related to time (plasma level-time curve).

When an infusion is given alone, plasma levels will continue to rise until a plateau is reached when input equals output. It takes at least three to four half-lives to reach the plateau[18] that corresponds from five and one-half to

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seven hours for lidocaine. This contrasts with the statement by Gianelly and colleagues[3] that the plateau was reached within two hours. The reason for this discrepancy is not apparent. Based on a two-compartment model and using averaged data (TABLE 1), the initial bolus (Equation 6) and infusion rate (Equation 7) necessary to attain rapidly and to maintain 1 μg/ml plasma in a 70-kg man are 126 mg and 0.80 mg/min lidocaine hydrochloride, respectively. Theoretically, the infusion should be started 25 minutes (t*), (Equation 4) after the bolus has been given, but in practice, infusion of additional drug (20 mg), (usually commencing simultaneously with the bolus), will do little to alter the overall picture. Ignoring the distribution phase and assuming a single-compartment model, the corresponding bolus and infusion rates are 122 mg [$V_dC_p^*$, V_d = 122L (TABLE I)] and 0.82 mg/minute ($V_dC_p^*\beta$), with the bolus being immediately followed by the infusion. The difference between the two ways of calculating the dosage is negligible, because, while on the one hand the clearance of 911 ml/min ($V_d\beta$) assuming a one-compartment model, is much higher than the 700 ml (V_pk_{13}) based on the two-compartment model, on the other hand, the amount of drug in the body at the plateau level is much smaller (84 mg, $V_{d_{ss}}C_p^*$) than the 122-mg ($V_dC_p^*$) assuming a single compartment. Consequently, utilizing the elimination rate constant (β) and the volume of distribution assuming a single compartment model (V_d) is sufficiently accurate when calculating dosage regimens for lidocaine.

The above considerations relating to i.v. dosage regimens can be considered in a more general sense. For any drug exhibiting a biexponential disposition curve and $\alpha > 2k_{21} > 6\beta$ then, it may be seen, by appropriate substitution in Equation 11 that the ratio of initial doses based on a two- versus a single-compartment model is not greater than 1.14. Similarly, the corresponding ratio for the infusion rates will be not less than 0.8 (Equation 12), and the fraction of the initial dose that would be infused had the infusion started simultaneously with the bolus would not be greater than 0.25 (Equation 8). It is clear that for practical purposes these differences are insignificant, and there is no merit in going to the more complicated two-compartment model when calculating such dosage regimens. This is especially true for drugs such as digoxin,[19] digitoxin,[20] warfarin,[21] bishydroxycoumarin,[22] salicylic acid,[23] and others that distribute rapidly but are slowly eliminated. However, it is also true for drugs such as penicillin,[24] spectinomycin,[25] and others that are eliminated rapidly, and probably for the majority of drugs. Only in rare instances would the single-compartment model lead to a widely differing answer, but even then, it is doubtful that it would be clinically significant.

In general, these recommendations for the dosage regimen of lidocaine agree with those suggested on clinical considerations: to attain a plateau concentration of 1 μg/ml plasma, the present results suggest an infusion rate of 0.80 mg/minute or 10 μg/minute/kg (average weight 78.7 kg). Assuming a linearity between the infusion rate and the plateau concentration, this corresponds to an infusion rate of 40 μg/kg/minute for 4 μg/ml. This calculated value of 4 μg/ml agrees closely with the plateau concentration of 3.5 μg/ml blood found by Gianelly and co-workers.[3] The difference between the actual and the computed numbers may be partially accounted for by the concentration ratio of 0.9 for lidocaine between whole blood and plasma. Also, Gianelly and colleagues[3] attempted to establish a relationship between infusion and plateau level in a group of patients receiving different infusion rates of lidocaine. Attempts of this sort are generally inappropriate, since at the plateau concentration, infusion rate equals the product of clearance ($V_d\beta$) and plateau concentration. Hence, no linearity between infusion rate and plateau con-

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centration is expected unless either the clearance is the same in all subjects, or corrections are made for clearance before plotting the data. In the case of the data of Gianelly and associates,[3] it is not known whether the disproportionately high plateau concentrations at high infusion rates are due to a decrease in lidocaine clearance with dose or whether the few patients examined at these high infusion rates had low clearance values, relative to the general population. With regard to the initial dose, the practice of giving two 50-mg boluses, one soon after the other, rather than 100 mg or more in a single dose, to a patient with ventricular fibrillation is both clinically prudent and basically sound. This approach would be expected to decrease the maximum peak concentration of drug in the blood and to result in less risk to the patient. The divided dosage schedule still would yield essentially the same mean concentration of lidocaine.

The total body plasma clearance of lidocaine in normal subjects is high (TABLE 1), corresponding to 642 ml/minute/70 kg man. The partition ratio of lidocaine between whole blood and plasma is 0.90, so that the total body blood clearance of lidocaine is 720 ml/minute/70 kg. Therefore, during the rapidly declining phase, with a large fraction of the dose in the vascular system, a large amount of the drug is eliminated mainly by metabolism, since very little appears in the urine unchanged. Sometimes the early phase is stated to be primarily due to distribution of the drug into tissues. However, as can be seen, up to 40% of the dose is metabolized during the "distribution" phase (FIGURE 3). Consequently, if this phase is ignored and the body is assumed to act as a single compartment, for a 70-kg man estimation of the apparent volume of distribution (Dose/B; 122L) is much larger than $V_{d_{ss}}$ (84L), which takes all the data into consideration. The discrepancy between the two systems arises because a greater fraction of the dose has been eliminated from the body during distribution phase than that calculated by assuming the body to be a single compartment.

Assuming that man is similar to animals with respect to the metabolism of lidocaine and that the liver is the major site for drug elimination,[8] since blood flow to the liver is 1.38 L/minute[26] and the blood clearance for lidocaine is about 800 ml/minute, one would anticipate that as much as 60% of an oral dose of lidocaine might be cleared before entering the systemic circulation. This could account for the relatively low lidocaine plasma levels noted after 500 mg oral lidocaine hydrochloride.[27]

This raises the question whether a drug, with a high hepatic clearance, is a suitable candidate for oral administration. A great deal will depend upon the toxicity of the metabolite. Since a much larger dose is required orally than by i.v. administration, in order to attain the same concentration of drug in the blood, there would be a much higher concentration of metabolites circulating after oral administration. If these metabolites are toxic, side effects not seen if the drug is given parenterally may be noted when the metabolites are present in the body after oral administration.

The present study has been concerned with the disposition kinetics of lidocaine in normal subjects. The applicability of this base-line information to the clinical setting depends largely upon whether the disposition of lidocaine in patients with ventricular arrythmias is similar to the present normal population. Major differences will necessitate modification of the dosage regimen in order to ensure efficacy without toxicity.

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DISCUSSION OF THE PAPER

DR. STANLEY C. GLAUSER (*Temple University School of Medicine, Philadelphia, Pa.*): In lidocaine pharmacokinetics, it appeared from the slides that about 90% of the drug had a six-and-one-half minute half-life, and about 10% had a half-life of two hours. This would mean that there would not be too much accumulation, if this is indeed right in normals. The question was, if this interpretation is roughly correct, does this distribution of amount of drug with each half-life change? In other words, do you get more or less of the long half-life type in heart failure? One couldn't determine this from your data.

DR. MELMON: What was presented was the decline in plasma concentration of lidocaine following an i.v. bolus. The initial rapid decline is predominately due to distribution of drug away from plasma into other tissues, although there is also some metabolism. The slower phase does reflect elimination of the drug from the body and is influenced by distribution, in that the more extensive the sequestering of drug away from the metabolic site, the longer the corresponding half-life. In patients with heart failure, the clearance of lidocaine is lower than in normal subjects, but the plasma levels are always higher, so that the fraction of the dose metabolized in the early phase, although not measured, may not differ significantly.

Regarding metabolism, with use of radioactive lidocaine the majority appears in the urine mostly as metabolites when the drug is given intravenously. If it is given orally, the same percentage of the total counts representing lidocaine plus metabolites appear in the urine, indicating complete absorption of oral lidocaine. However, larger oral doses are necessary to give lidocaine plasma levels equivalent to those following i.v. administration. Consequently, metabolite levels are higher, and if these, which are unknown at this time, have toxicity associated with them, there is a potential risk to the patient.

DR. GLAUSER: In the cases of heart failure patients who have had all of these changes, whether the mechanism of that rapid phase is disappearance or metabolism, I am willing to go along with you. It's a mixture. Was there a smaller percentage of the rapid phase present in the heart failure patients, or does the distribution of half-lives seem about the same?

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