Pharmacokinetics of lidocaine in man

Plasma levels of lidocaine were measured in 5 normal male volunteers following both intravenous and oral administration of the drug. Each subject received a constant-rate intravenous infusion lasting for 60 minutes and an exponential intravenous infusion which allowed administration of the drug at an ever-decreasing rate having a half-life of 90 minutes. In each case the total dose of lidocaine was 250 mg. The subjects also received a 250 mg and a 500 mg, oral dose administered in tablet form. The plasma lidocaine data were subjected to pharmacokinetic analysis with the use of a two-compartment open model to describe the lidocaine disposition. These calculations suggest that approximately 5 to 7 hours of constant intravenous infusion would be required to approach steady-state plasma levels in human subjects. The plasma lidocaine data after oral administration indicates that approximately 35 percent of the 250 and 500 mg oral doses reached the systemic circulation. Subjective symptoms typical of lidocaine were noted in some cases after the 500 mg oral dose. Since these symptoms were noted when the blood levels of lidocaine were lower than those following intravenous administration, it is suggested that they may, in part, be due to a metabolite formed during the first passage of the drug through the liver.


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In recent years a number of reports have been published concerning the intravenous use of lidocaine (Xylocaine) for the treatment of ventricular arrhythmias, particularly those associated with acute myocardial infarction.6 Data have also been presented by various investigators6-12 which suggest that blood levels of approximately 1.5 to 2.0 mg per milliliter of lidocaine are required for antiarrhythmic activity. This relationship between blood levels of lidocaine and antiarrhythmic activity has resulted in several reports on the possible oral use of lidocaine.6,12 Although these studies are limited in scope, there appears to be a considerable discrepancy in the reported blood levels. Parkinson and associates6 reported levels of lidocaine ranging from approximately 3 to 16 mg per milliliter for 250 and 500 mg oral doses of lidocaine, whereas the highest plasma level found by Eisinger and Hoffer12 was 2.4 mg per milliliter in one subject 30 minutes after 500mg of lidocaine orally. Because of the conflicting data, it is not possi-
sible to predict at this time whether lidocaine would be a useful antiarrhythmic drug when administered orally.

The present study was designed to measure the plasma levels of the drug following both intravenous and oral administration in a group of volunteers. Using these data, classical pharmacokinetic techniques then allowed an appraisal of the factors governing the disposition and elimination of lidocaine following both intravenous and oral administration.

**Methods**

**Subjects.** Five healthy volunteers aged 27 to 43 years and weighing 68 to 89 kilograms participated in the experiments.

**Treatments.** Each volunteer received the following: (1) A constant-rate intravenous infusion of 250 mg. of lidocaine hydrochloride over the period of 60 minutes was given. (2) An exponential intravenous infusion of 250 mg. of lidocaine hydrochloride was given by placing the total dose of lidocaine in a reservoir and by properly adjusting a constant-rate syringe containing saline; the amount of lidocaine delivered to the subject was decreased exponentially with time. The resultant half-time for lidocaine administration was 50 minutes and the infusion was allowed to continue for a total of 240 minutes. (3) A dose of 500 mg. was taken orally as two 250 mg. tablets. (4) A dose of 250 mg. was taken as one tablet. Subjects were fasted for a minimum of 12 hours before each oral dose. The tablets were swallowed whole.

**Blood samples.** Venous blood samples were drawn at the following times after the beginning of administration of each of the lidocaine doses: (1) constant-rate intravenous infusion: 5, 10, 15, 20, 30, 40, 50, 60, 65, 70, 75, 90, 105, 120, 150, 180, 210, and 240 minutes; (2) exponential intravenous infusion and oral doses: 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes. The lidocaine content of these plasma samples was determined with the use of the specific gas chromatographic method described by Svinhufvud and associates.

**Pharmacokinetic analysis of blood level data.** The plasma level data for each volunteer were subjected to pharmacokinetic analysis similar to that described by Boyes and associates. Initially, the constant-rate infusion–blood level data were analyzed by obtaining least-squares agreement between a computer-calculated curve and these data. The computer program used to carry out this procedure was a modified version of SAAM described by Berman and Weiss and the kinetic model used to describe the lidocaine distribution is shown in Fig. 1, in which 3 represents the infusion pump, or the gastrointestinal tract; I represents a central rapidly equilibrating body compartment which includes the blood; 2, a more slowly equilibrating body compartment; V, apparent volume of distribution of Compartment 1; λ13, a fixed zero-order constant when dealing with constant-rate intravenous infusion data, and a variable first-order rate constant when calculating exponential intravenous and oral blood level data; λ12, λ21, the rate constants governing the equilibration of lidocaine between Compartments 1 and 2; λ01, a rate constant representing loss of lidocaine from the body by either excretion or metabolism; λ03, a rate constant used to calculate drug lost before reaching the systemic circulation after oral administration. The computer fitting, therefore, takes place between a theoretical curve calculated for Compartment 1 and the actual blood level data. The values of the constants V, λ21, λ12, and λ01 calculated from the constant-rate infusion data for each subject were then fixed on the computer, and, by allowing λ13 to vary, agreement was obtained between a calculated curve and the exponential infusion blood level data. Since
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The present study was designed to measure the plasma levels of the drug following both intravenous and oral administration in a group of volunteers. Using these data, classical pharmacokinetic techniques then allowed an appraisal of the factors governing the disposition and elimination of lidocaine following both intravenous and oral administration.

**Methods**

**Subjects.** Five healthy volunteers aged 27 to 43 years and weighing 68 to 89 kilograms participated in the experiments.

**Treatments.** Each volunteer received the following: (1) A constant-rate intravenous infusion of 250 mg of lidocaine hydrochloride over the period of 60 minutes was given. (2) An exponential intravenous infusion of 250 mg of lidocaine hydrochloride was given by placing the total dose of lidocaine in a reservoir and by properly adjusting a constant-rate syringe containing saline; the amount of lidocaine delivered to the subject was decreased exponentially with time. The resultant half-time for lidocaine administration was 50 minutes and the infusion was allowed to continue for a total of 240 minutes. (3) A dose of 250 mg was taken orally as two 250 mg tablets. (4) A dose of 250 mg was taken as one tablet. Subjects were fasted for a minimum of 12 hours before each oral dose. The tablets were swallowed whole.

**Blood samples.** Venous blood samples were drawn at the following times after the beginning of administration of each of the lidocaine doses: (1) constant-rate intravenous infusion: 5, 10, 15, 30, 45, 60, 90, 120, 180, 210, and 240 minutes; (2) exponential intravenous infusion and oral doses: 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes. The lidocaine content of these plasma samples was determined with the use of the specific gas chromatographic method described by Sivanand and associates.13

**Pharmacokinetic analysis of blood level data.** The plasma level data for each volunteer were subjected to pharmacokinetic analysis similar to that described by Boyes and associates.8 Initially, the constant-rate infusion—blood level data were analyzed by obtaining least-squares agreement between a computer-calculated curve and these data. The computer program used to carry out this procedure was a modified version of SAAM described by Berman and Weiss2 and the kinetic model used to describe the lidocaine distribution is shown in Fig. 1, in which 3 represents the infusion pump, 1 the gastrointestinal tract, 13 a central rapidly equilibrating body compartment which includes the blood, 2 a more slowly equilibrating body compartment, Vb, apparent volume of distribution of Compartment 1; λ13, a fixed zero-order constant when dealing with constant-rate intravenous infusion data, and a variable first-order rate constant when calculating exponential intravenous and oral blood level data; λ12, λ12, the rate constants governing the equilibration of lidocaine between Compartments 1 and 2; λ01, a rate constant representing loss of lidocaine from the body by either excretion or metabolism; λ03, a rate constant used to calculate drug lost before reaching the systemic circulation after oral administration. The computer fitting, therefore, takes place between a theoretical curve calculated for Compartment 1 and the actual blood level data. The values of the constants Vb, λ13, λ12, and λ01 calculated from the constant-rate infusion data for each subject were then fixed on the computer, and, by allowing λ13 to vary, agreement was obtained between a calculated curve and the experimental infusion blood level data. Since the real value of this constant was known (i.e., t½ = 50 minutes; therefore, λ13 = 0.014 minutes-1), the purpose of this experiment was to ensure that the kinetic model chosen would not only adequately simulate the blood levels but also accurately calculate an exponential input rate. In a similar manner with the use of the values for Vb, λ13, λ12, and λ01 calculated for each subject, attempts were made to obtain least-squares agreement with the blood level data following the 250 and 500 mg oral doses. In these cases, Compartment 3 of Fig. 1 would represent the gastrointestinal tract and λ13 would be a first-order rate constant for absorption. It was necessary to add an extra constant, λ03 (shown by a broken arrow in Fig. 1), when dealing with the oral data in order to account for drug apparently lost during the absorption process, and in some cases a "lag time" in the absorption process was required to adequately define the data. The fraction of the dose actually reaching the systemic circulation was calculated from the relationship shown in Equation 1:

\[
F = \frac{\lambda_{13}}{\lambda_{13} + \lambda_{01}}
\]

where F equals the fraction of the total oral dose reaching the systemic circulation. The derivation of this equation and a more detailed description of the kinetic analysis is given by Boyes and associates.4

**Calculations based on constant-rate intravenous kinetic data.** Knauf-Thiemer used Equation 2 to describe blood levels of drugs in a two-compartment open system similar to Fig. 1 during constant-rate intravenous infusion:

\[
C_t = \frac{D}{V_{IN}} \left[ \frac{(D - \beta)(\lambda_{01} - \beta)}{\lambda_{01}} \right] \left( e^{-\beta t} - e^{-\lambda_{01} t} \right)
\]

where $D$ is the initial intravenous dose; $\lambda_{01}$ is the constant rate of the infusion; $V_{IN}$ is volume of Compartment 1 and:

\[
\lambda_{01} = \frac{D}{V_{IN}}
\]

At infinite time Equation 2 reduces to:

\[
C = \frac{D}{V_{IN}}
\]

where $C_{\text{ss}}$ is the asymptotic blood concentration of drug at infinite time.

To determine how the blood levels approach this asymptote, the following manipulations can be made on Equation 2 and 5. Dividing Equation 2 by Equation 5 yields Equation 6:

\[
\frac{C_t}{C_{\text{ss}}} = \frac{(D - \beta)(\lambda_{01} - \beta)}{\lambda_{01}} \left( e^{-\beta t} - e^{-\lambda_{01} t} \right)
\]

Since the term is considerably larger than $\beta$, it increases the terms $e^{-\beta t}$ and $e^{-\lambda_{01} t}$ approach zero but at different rates. For lidocaine it was found that at values...
of \( t \) greater than 20 minutes, the second term on the right-hand side of Equation 6 became insignificant and, therefore, the equation could be reduced to Equation 7.

\[
\frac{C_t}{C_\infty} = 1 - \frac{(D_0 \beta - \dot{D}) (\lambda_01 - \alpha)}{D_0 (\alpha - \beta)} e^{-\beta t} \quad (7)
\]

\( t > 20 \text{ min.} \)

In the particular application where \( D_0 = 0 \) and \( \lambda_01 < \alpha \), Equation 7 could be reduced and rearranged to Equation 8.

\[
\frac{C_t}{C_\infty} = 1 - \frac{(\alpha - \lambda_01)}{\alpha - \beta} e^{-\beta t} \quad (8)
\]

The term \( C_{\infty} \) therefore represents the fraction of the asymptotic blood concentration at any particular time \( (t) > 20 \text{ minutes} \). As an example, the time to reach 95 per cent of the asymptotic blood concentration for lidocaine at a particular constant infusion rate could be approximated by Equation 9.

\[
t_a = \frac{-\ln 0.95}{(\alpha - \beta)} \left(\frac{\alpha - \lambda_01}{\beta}\right) \quad (9)
\]

In a similar manner the time required to reach 50 or 75 per cent of the asymptotic blood concentration could be estimated.

The usual clinical therapy involves a combination of an initial rapid intravenous injection of lidocaine with a slow infusion. This type of treatment generally results in a blood level curve which reaches a maximum at the end of the initial intravenous injection, then rapidly decreases to a minimum value followed by a prolonged rise in blood concentration to the asymptotic level. Equation 2 could be used to describe the complete shape of this type of blood level curve, but this equation is cumbersome and most of the information obtained is of little value. The important information required would be the initial dose, the infusion rate, the initial and steady-state blood levels, the time at which a minimum blood level is attained, and the approximate value of this minimum. Equation 5 above defines the relationships between the steady-state blood level and the infusion rate (if Equation 5 is rearranged).

\[
\dot{D} = C_\infty \lambda_01 V_s \quad (10)
\]

Establishing the condition that the blood level at zero time must be equal to the steady-state blood level, it is found that Equation 2 reduces to Equation 11.

\[
D_t = \frac{\dot{D}}{\lambda_01} \quad (11)
\]

Therefore, the initial dose is directly related to the infusion rate. If this equality is maintained, the time at which the minimum blood level is attained, can be calculated by setting the derivative of Equation 2 to zero and solving for \( t \). The resultant equation is Equation 12. (The derivation of this equation is given in Appendix 1.)

\[
t = \frac{-\ln \frac{\alpha}{\beta}}{\frac{\alpha - \lambda_01}{\beta}} \quad (12)
\]

It should be noted that Equation 12 is independent of \( D_0 \) and \( \dot{D} \) but requires that they be in a set ratio to each other as given by Equation 11. The actual blood level expected at this minimum can be calculated by substituting the value of \( t \) from Equation 12 into Equation 2, or more appropriately the ratio of this blood level to the steady-state level is determined by substituting \( t \) from Equation 12 into Equation 6.

Results

Following constant-rate intravenous infusion, a mean peak blood level of 1.4 (range 0.9 to 2.5) \( \mu \text{g} \) per milliliter occurred at 60 minutes. During the exponential intravenous infusion, a mean peak blood level of 0.84 (range 0.6 to 1.2) \( \mu \text{g} \) per milliliter was attained at 75 minutes. The mean plasma level data following constant rate and exponential intravenous infusion are summarized in Fig. 2.

The kinetic data calculated from the constant-rate infusion blood level curves
of $t$ greater than 20 minutes, the second term on the right-hand side of Equation 6 became insignificant and, therefore, the equation could be reduced to Equation 7.

$$
\frac{C_t}{C_\infty} = 1 - \frac{(D \beta - D) (\lambda D - \alpha)}{D (\alpha - \beta)} e^{-\frac{t}{\alpha - \beta}} \quad (7)
$$

$t > 20$ min.

In the particular application where $D = 0$ and $\lambda D < \alpha$, Equation 7 could be reduced and rearranged to Equation 8.

$$
\frac{C_t}{C_\infty} = 1 - \frac{(\alpha - \lambda D)}{(\alpha - \beta)} e^{-\frac{t}{\alpha - \beta}} \quad (8)
$$

The term $C_{\infty}$ therefore represents the fraction of the asymptotic blood concentration at any particular time ($t$) > 20 minutes. As an example, the time to reach 95 percent of the asymptotic blood concentration for lidocaine at a particular constant infusion rate could be approximated by Equation 9.

$$
\text{In} \frac{0.05}{(\alpha - \beta)} = \frac{t_{95}}{\alpha - \beta} \quad (9)
$$

In a similar manner the time required to reach 50 or 75 per cent of the asymptotic blood concentration could be estimated.

The usual clinical therapy involves a combination of an initial rapid intravenous injection of lidocaine with a slow infusion. This type of treatment generally results in a blood level curve which reaches a maximum at the end of the initial intravenous injection, then rapidly decreases to a minimum value followed by a prolonged rise to blood concentration to the asymptotic level. Equation 2 could be used to describe the complete shape of this type of blood level curve, but this equation is cumbersome and most of the information obtained is of little value. The important information required would be the initial dose, the infusion rate, the initial and steady-state blood levels, the time at which a minimum blood level is attained, and the approximate value of this minimum. Equation 5 above defines the relationships between the steady-state blood level and the infusion rate (if Equation 5 is rearranged).

$$
\frac{D}{D_x} = \frac{C_x}{C_x} \quad (10)
$$

Establishing the condition that the blood level at zero time must be equal to the steady-state blood level, it is found that Equation 2 reduces to Equation 11.

$$
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$$

Therefore, the initial dose is directly related to the infusion rate. If this equality is maintained, the time at which the minimum blood level is attained, can be calculated by setting the derivative of Equation 2 to zero and solving for $t$. The resultant equation is Equation 12. (The derivation of this equation is given in Appendix 1.)

$$
\text{In} \frac{\alpha}{\beta} = \frac{t}{\alpha - \beta} \quad (12)
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Following constant-rate intravenous infusion, a mean peak blood level of 1.4 (range 0.6 to 2.5) mcg per milliliter occurred at 60 minutes. During the exponential intravenous infusion, a mean peak blood level of 0.84 (range 0.6 to 1.3) mcg per milliliter was attained at 75 minutes. The mean plasma level data following constant rate and exponential intravenous infusion are summarized in Fig. 2. The kinetic data calculated from the constant-rate infusion blood level curves for each subject are given in Table I. Using these data, the values of the constants $\alpha$ and $\beta$ can be calculated from Equations 3 and 4 above. The parameter $\beta$ is of particular importance since it represents the slope of the blood level curve after distribution equilibrium has been established. As shown in Table II, the mean value of this term $\beta = 0.005$ minute$^{-1}$ which is equivalent to a half-life of approximately 87 minutes. Employing Equation 5, it was possible to calculate the steady-state plasma level of lidocaine which would have been reached in each subject had the infusion been carried on indefinitely. These asymptotic plasma concentrations, which range from 1.92 to 4.18 mcg per milliliter, are shown in Table II. The calculated infusion times (using Equation 5) which would be required to reach 50, 75, and 95 per cent of the steady-state blood level in each subject are also given in Table II. These data indicate that in these particular subjects less than 50 per cent of the steady-state
Table II. Calculations based on kinetic parameters determined from constant-rate intravenous infusion blood levels

<table>
<thead>
<tr>
<th>Subject</th>
<th>$\alpha^*$</th>
<th>$\beta^*$</th>
<th>$C_{\infty}^\dagger$</th>
<th>$t_{1/2h}^\ddagger$</th>
<th>$t_{1/2g}^\ddagger$</th>
<th>$t_{1/2t}^\ddagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. E.</td>
<td>0.0716</td>
<td>0.008</td>
<td>2.50</td>
<td>72</td>
<td>152</td>
<td>343</td>
</tr>
<tr>
<td>A. L.</td>
<td>0.298</td>
<td>0.007</td>
<td>3.62</td>
<td>90</td>
<td>190</td>
<td>420</td>
</tr>
<tr>
<td>S. C.</td>
<td>0.123</td>
<td>0.008</td>
<td>4.18</td>
<td>63</td>
<td>144</td>
<td>346</td>
</tr>
<tr>
<td>G. O.</td>
<td>0.129</td>
<td>0.007</td>
<td>3.28</td>
<td>72</td>
<td>171</td>
<td>402</td>
</tr>
<tr>
<td>J. U.</td>
<td>0.183</td>
<td>0.010</td>
<td>1.92</td>
<td>57</td>
<td>128</td>
<td>292</td>
</tr>
<tr>
<td>Mean</td>
<td>0.161</td>
<td>0.008</td>
<td>3.10</td>
<td>71</td>
<td>157</td>
<td>360</td>
</tr>
</tbody>
</table>

*Units = minutes$^{-1}$.
†Units = micrograms per milliliter.
‡Units = minutes.

Blood level would be achieved after one hour and between 5 and 7 hours of continuous infusion would be required to approach asymptotic plasma levels of lidocaine.

After the 250 mg. and 500 mg. oral treatments, peak blood levels ranged from 0.3 to 0.8 and from 0.6 to 1.1 μg per milliliter, respectively. These peak levels generally occurred 45 to 60 minutes following oral administration of the lidocaine tablets. For Subject S. C. the peak levels occurred at 105 and 150 minutes following the 250 and 500 mg. oral doses, respectively.

Two representative curves showing the good agreement between computer-calculated and actual blood level data following oral administration of lidocaine are shown in Fig. 3. The kinetic data related to the oral absorption of the drug are presented in Table III. In the case of the blood level data for Subject S. C. after 500 mg. orally, the peak level was very delayed and, therefore, kinetic analysis was not attempted. The fraction of the oral dose reaching the systemic circulation as shown in Table III was generally quite low and variable between subjects. There does not appear to be any consistent difference in the apparent absorbability of the 250 and 500 mg. doses.

Side effects consisting of light-headedness and numbness of the tongue were noticed by 3 of the 5 subjects after the 500 mg. oral dose. They were minor in nature and usually occurred when the concentration of drug in the venous blood was rising to its maximum. These effects lasted approximately 15 to 20 minutes even though the lidocaine plasma levels remained elevated. The symptoms would appear to be similar to those reported by Eisinger and Hellier and Parkinson and associates during previous studies in which lidocaine was administered orally. It is interesting to note that such effects were not reported during either of the intravenous infusion experiments, although the lidocaine plasma levels were higher than those after the 500 mg. oral doses.

**Discussion**

Because of the extensive intravenous use of lidocaine to control cardiac arrhythmias and the recent suggestion that oral administration of this drug may be of value for maintenance antiarrhythmic therapy, this study was undertaken to evaluate the pharmacokinetic parameters related to the disposition and elimination of lidocaine in man. A two-compartment open model (Fig. 1) was chosen to analyze the blood level data because of the ability of this model to simulate blood levels during and after stopping a constant-rate intravenous infusion. Use of this model also allowed accurate calculation of a known exponential intravenous infusion rate which would tend to mimic the shape of a plasma level curve following oral administration of the drug.

The large values calculated for the apparent volume of Compartment 1 (range 0.41 to 1.19 L. per kilogram, Table I) sug-
blood level would be achieved after one hour and between 5 and 7 hours of continuous infusion would be required to approach asymptotic plasma levels of lidocaine. After the 250 mg. and 500 mg. oral treatments, peak blood levels ranged from 0.3 to 0.8 and from 0.6 to 1.1 μg per milliliter respectively. These peak levels generally occurred 45 to 60 minutes following oral administration of the lidocaine tablets. Subject S. C. the peak levels occurred at 105 and 130 minutes following the 500 and 500 mg. oral doses, respectively. Two representative curves showing the good agreement between computer-calculated and actual blood level data following oral administration of lidocaine are shown in Fig. 3. The kinetic data related to the oral absorption of the drug are presented in Table III. In the case of the blood level data for Subject S. C. after 500 mg. orally, the peak level was very delayed and therefore, kinetic analysis was not attempted. The fraction of the oral dose reaching the systemic circulation as shown in Table III was generally quite low and variable between subjects. There does not appear to be any consistent difference in the apparent absorptivity of the 250 and 500 mg. doses. Side effects consisting of light-headedness and numbness of the tongue were noticed by 3 of the 5 subjects after the 500 mg. oral dose. They were minor in nature and usually occurred when the concentration of the drug in the venous blood was rising to its maximum. These effects lasted approximately 15 to 20 minutes even though the lidocaine plasma levels remained elevated. The symptoms would appear to be similar to those reported by Rüdiger and Hellier and Parkison and associates during previous studies in which lidocaine was administered orally. It is interesting to note that such effects were not reported during either of the intravenous infusion experiments, although the lidocaine plasma levels were higher than those after the 500 mg. oral doses.

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### Table II. Calculations based on kinetic parameters determined from constant-rate intravenous infusion blood levels

<table>
<thead>
<tr>
<th>Subject</th>
<th>α</th>
<th>τ</th>
<th>C = μg</th>
<th>t1/2</th>
<th>τ1/2</th>
<th>t1/2</th>
<th>τ1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. E.</td>
<td>0.0716</td>
<td>0.008</td>
<td>2.50</td>
<td>72</td>
<td>152</td>
<td>343</td>
<td></td>
</tr>
<tr>
<td>A. L.</td>
<td>0.268</td>
<td>0.007</td>
<td>3.62</td>
<td>50</td>
<td>189</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>S. C.</td>
<td>0.133</td>
<td>0.006</td>
<td>4.18</td>
<td>50</td>
<td>144</td>
<td>346</td>
<td></td>
</tr>
<tr>
<td>G. O.</td>
<td>0.139</td>
<td>0.006</td>
<td>3.28</td>
<td>72</td>
<td>171</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>J. U.</td>
<td>0.383</td>
<td>0.010</td>
<td>1.92</td>
<td>57</td>
<td>128</td>
<td>292</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.161</td>
<td>0.008</td>
<td>3.10</td>
<td>71</td>
<td>187</td>
<td>360</td>
<td></td>
</tr>
</tbody>
</table>

*Units = minutes/milliliter.
*Units = minutes.

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### Table III. Kinetic parameters related to the oral absorption of lidocaine in human subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dose</th>
<th>$\tau$ (min.)</th>
<th>$\lambda D$ (min.⁻¹)</th>
<th>$\lambda O$ (min.⁻¹)</th>
<th>$\tau^*$</th>
<th>$\Delta$ (min.)</th>
<th>$\Delta$ (L/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. E.</td>
<td>250</td>
<td>0.009</td>
<td>0.001</td>
<td>0.050</td>
<td>0.0071</td>
<td>0.0023</td>
<td>34.8</td>
</tr>
<tr>
<td>A. L.</td>
<td>250</td>
<td>0.005</td>
<td>0.001</td>
<td>0.047</td>
<td>0.0033</td>
<td>0.0021</td>
<td>42.0</td>
</tr>
<tr>
<td>S. C.</td>
<td>250</td>
<td>0.017</td>
<td>0.001</td>
<td>0.062</td>
<td>0.0043</td>
<td>0.0005</td>
<td>43.8</td>
</tr>
<tr>
<td>G. O.</td>
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<td>0.024</td>
<td>0.001</td>
<td>0.062</td>
<td>0.0161</td>
<td>0.0005</td>
<td>42.0</td>
</tr>
<tr>
<td>J. U.</td>
<td>250</td>
<td>0.026</td>
<td>0.001</td>
<td>0.047</td>
<td>0.0141</td>
<td>0.0027</td>
<td>42.0</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.023</td>
<td>0.002</td>
<td>0.050</td>
<td>0.0061</td>
<td>0.0032</td>
<td>34.8</td>
</tr>
</tbody>
</table>

*$\Delta$ (min.) = $\Delta$ (min.) - $\Delta$ (min.)
*$\Delta$ (L/min.) = $\Delta$ (L/min.) - $\Delta$ (L/min.)

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**Fig. 3. Plasma levels of lidocaine following 500 mg. of oral doses to Subjects G. O. (•) and A. L. (●). Data points represent experimentally determined plasma levels and the continuous lines are the equivalent computer-calculated levels.**
caine in the central compartment is approximately 1,563 ml. per minute. Stenson and associates have calculated that in the individuals with normal liver function the mean extraction ratio for lidocaine by this organ is 72 per cent. If it is assumed that lidocaine clearance occurs completely in the liver, then 1,563 ml. per minute would represent approximately 72 per cent of the hepatic blood flow, and, therefore, the total hepatic blood flow would be estimated at 2,170 ml. per minute. Bradley and associates have reported total hepatic blood flow in human subjects ranging from 1,175 to 2,110 ml. per minute, with the average being 1,509 ml. per minute. The blood flow value calculated from our data and that reported by Stenson and associates may, therefore, be slightly high. This discrepancy may reflect a small clearance of lidocaine by other organs such as the kidney which is not accounted for in our calculation. Nevertheless, the fact that a reasonable estimate of hepatic blood flow is obtained from calculations based on lidocaine blood levels indicates that the liver is probably responsible for the bulk of lidocaine clearance in man.

In Table II it can be seen that the constant β is quite similar for all of the subjects. This parameter represents the slope of the log plasma level against time curve after distribution equilibrium has been established. The mean value of β of 0.008 is equivalent to a half-life of approximately 87 minutes. Thus, although the elimination rate constant (α01) for lidocaine is fairly large (i.e., t½ = 28 minutes), the overall plasma level half-life is considerably longer apparently because of distribution to slowly equilibrating tissues.

The calculated times to reach 75, 90, and 95 per cent of the steady-state blood level shown in Table II are also important to consider. These times indicate that in these 5 subjects approximately 2 to 3 hours of constant infusion would be required to reach 75 per cent of the steady-state level, and even after 5 to 7 hours only 95 per cent of the equilibrium level would be achieved. Although a constant infusion rate of 4.17 mg. per minute was used for these experiments, Equation 8 is independent of the infusion rate, provided that the pharmacokinetic constants of the drug do not change significantly with dose. Therefore, the times to reach 50, 75, and 95 per cent of the steady-state blood level shown in Table II are applicable to all constant-rate infusions of lidocaine in these subjects.

In clinical practice it is generally desirable to establish an effective antiarhythmic blood level of lidocaine as soon as possible after initiating therapy. The ideal situation would be a perfectly constant blood level maintained from the beginning of treatment by the proper manipulation of primary and infusion doses. As Kruger-Thiemer has pointed out, the only way of truly approximating this goal with a drug that distributes itself on the basis of a two-compartment open system (Fig. 1) is by a combination of exponential infusion and constant-rate infusion. The exponential infusion could be accomplished using an apparatus similar to ours, but this is probably not practical in a clinical situation.

Based on the kinetic data in our subjects, it is possible to make some statements regarding the blood levels of lidocaine during the more usual clinical situation in which a rapid intravenous injection is combined with constant-rate infusion therapy. If the initial intravenous dose is calculated using Equation 11, a blood level curve will be obtained such that, at the end of the rapid injection, the blood level will equal the eventual steady-state level. Under these conditions, the blood curve will drop fairly rapidly from its initial value reaching a minimum at a particular time then rise again to the steady-state level. Using Equations 10, 11, and 12 and the mean values of α, β, V₁, and α01 given in Tables I and II, it is possible to predict the general shape of the blood level curve in our volunteers if they had received an initial intravenous dose followed by the infusion. As an example, if the steady-state level
achieved. Although a constant infusion rate of 4.17 mg per minute was used for these experiments, Equation 8 is independent of the infusion rate, provided that the pharmacokinetic constants of the drug do not change significantly with the loading dose. Therefore, the times to reach 50, 75, and 90 percent of the steady-state blood level shown in Table II are applicable to all constant-rate infusions of lidocaine in these subjects.

In clinical practice it is generally desirable to establish an effective antiarrhythmic blood level of lidocaine as soon as possible after initiating therapy. The ideal situation would be a perfectly constant blood level maintained from the beginning of treatment by the proper manipulation of primary and intermittent doses. Kruger-Thiemer has pointed out the only way of truly approximating this goal with a drug that distributes itself on the basis of a two-compartment open system (Fig. 1) is by a combination of exponential infusion and constant-rate infusion. The exponential infusion could be accomplished using an apparatus similar to ours, but this is probably not practical in a clinical situation.

Based on the kinetic data in our subjects, it is possible to make some statements regarding the blood levels of lidocaine during the more usual clinical situation in which a rapid intravenous injection is combined with constant-rate infusion therapy. If the initial intravenous dose is calculated using Equation 11, a blood level curve will be obtained such that, at the end of the rapid injection, the blood level will equal the eventual steady-state level. Under these conditions, the blood curve will show approximately the same blood levels (i.e., 90 mg. loading dose and a 2.0 mg. per minute infusion). These latter values closely approximate the clinically acceptable levels of lidocaine in our volunteers if they had received an initial intravenous dose followed by the infusion. As an example, if the steady-state level was 2.0 mg per milliliter, from Equation 10, this infusion rate would be approximately 4.0 mg per minute. Therefore, from Equation 11 the initial dose would be 160 mg. Using Equation 12, it is found that a minimum blood level would be obtained about 10 minutes after the start of therapy and substituting this value into Equation 6 indicates that this minimum blood level would be approximately 55 percent (1.40 ug per milliliter) of the steady-state level. Thus, it could be predicted that if these subjects were each given an initial rapid intravenous injection of 160 mg. of lidocaine, simultaneously to starting a 4 mg. per minute infusion, the initial plasma levels would range from 2 to 4 ug per milliliter followed by a decline in 19 minutes to minimum levels between 1 and 2 ug per milliliter. Subsequently, the lidocaine plasma levels would rise again slowly to steady-state values between 2 and 4 ug per milliliter.

The applicability of these predictions to clinical practice depends on the relationship between patients with coronary artery disease and normal volunteers. To date no kinetic data in patients have been published, but some general indications of the relationships are available. The mean kinetic data presented herein appears to be applicable to the blood levels reported by Scott and associates following intramuscular injection of lidocaine to patients having suffered a myocardial infarction, except that the apparent volume of distribution in these patients seems to be about half that of the volunteers. If this apparent reduction in volume holds true for the general population of patients, the initial intravenous dose and infusion rate mentioned above could be reduced by a factor of two in order to get approximately the same blood levels (i.e., 90 mg. loading dose and a 2.0 mg. per minute infusion). These latter values closely approximate the clinically acceptable levels of lidocaine in our volunteers if they had received an initial intravenous dose followed by the infusion.

The plasma levels curves for lidocaine following exponential intravenous infusion of 250 mg. were generally the same shape as those observed after oral treatment with the drug. It was also found that the mean calculated value for the exponential phase, and, therefore, from Equation 11 the initial dose would be 160 mg. Using Equation 12, it is found that a minimum blood level would be obtained about 10 minutes after the start of therapy and substituting this value into Equation 6 indicates that this minimum blood level would be approximately 55 percent (1.40 ug per milliliter) of the steady-state level. Thus, it could be predicted that if these subjects were each given an initial rapid intravenous injection of 160 mg. of lidocaine, simultaneously to starting a 4 mg. per minute infusion, the initial plasma levels would range from 2 to 4 ug per milliliter followed by a decline in 19 minutes to minimum levels between 1 and 2 ug per milliliter. Subsequently, the lidocaine plasma levels would rise again slowly to steady-state values between 2 and 4 ug per milliliter.
tion process shown in Table III are comparable to those reported by other authors who have studied the oral absorption of aspirin and amphetamine. Many factors could contribute to the very delayed absorption of lidocaine in Subject S. C.; therefore, from this experiment no definite reason for this phenomenon can be stated.

Our blood level data following oral administration of 250 and 500 mg of lidocaine are not comparable with that reported by Parkinson and associates. Even if all of the orally administered dose reached the systemic circulation intact, it would seem improbable that blood levels as high as those reported would be attained. The most likely explanation for the discrepancy between our results and those presented by Parkinson and associates is that the colorimetric assay procedure used by them was not specific for unmetabolized lidocaine. The fact that they also report clinical efficacy of lidocaine when administered orally is also interesting. Since the blood levels we recorded after comparable doses are generally below those that are considered to have an antiarrhythmic effect, the reported clinical success may in part be due to an active metabolite of the drug.

One point of similarity between our results and those with oral lidocaine and previous reports is the high incidence of reported dizziness. This appears to occur during the first hour after drug administration and in our experiments generally at blood levels of lidocaine lower than those attained after intravenous administration when no symptoms were reported. The dizziness may be caused by a metabolite formed in the liver, since, unlike the intravenously administered lidocaine, virtually all of the oral dose must pass through the liver.

The potential usefulness of orally administered lidocaine as an antiarrhythmic agent must still be questioned. If unmetabolized lidocaine is required for the antiarrhythmic effect, our blood level data and the calculated fraction of the oral dose reaching the systemic circulation would suggest that doses of 250 or 500 mg do not represent a practical means of administering the drug for that purpose. Because of the incidence of dizziness at the 500 mg oral dose, in creating the amount given in an attempt to establish higher blood levels would appear to be impractical. Further experimentation may indicate that a metabolite of lidocaine is capable of suppressing arrhythmias. If this is the case, plasma levels of lidocaine alone may not be directly correlated to its antiarrhythmic action and, therefore, a more detailed evaluation of oral therapy would be warranted.

Summary and conclusions

1. A two-compartment open model has been used to evaluate the kinetic parameters governing the distribution and elimination of lidocaine. This analysis suggested that most of the lidocaine elimination is due to hepatic clearance.

2. The average blood level half-life for lidocaine was approximately 90 minutes.

3. Further calculations based on these pharmacokinetic parameters indicate that after one hour of constant infusion less than 50 per cent of the steady-state blood level would be achieved.

4. Rapid intravenous injections of 160 mg of lidocaine followed by an infusion of 4 mg per minute result in a mean initial and asymptotic plasma level of 2.6 μg per milliliter and a minimum level of approximately 1.4 μg per milliliter being reached 10 minutes after the first injection. Application of this dosage regimen to patients with coronary artery disease requires further evaluation of plasma clearance in patients with coronary artery disease.

5. The mean apparent oral absorption of lidocaine is approximately 35 per cent; this value is in good agreement with the reported hepatic extraction ratio.

6. Plasma levels of lidocaine following oral administration of 250 and 500 mg of lidocaine appear to be less than those reported to cause an antiarrhythmic effect.

7. Oral administration of 300 mg of lidocaine appears to be associated with a high incidence of dizziness. This may be due to a metabolite of lidocaine since it occurs at lower blood levels than those achieved following intravenous administration of the drug.

We wish to acknowledge the assistance of Dr. Ivar Östergren, All Astra, Sweden, for carrying out the plasma level estimations.

References


Appendix 1

Derivation of Equation 12.

If \( C_0 = \frac{D}{\lambda V_L} \), then

\[
\frac{(D - a - \beta)}{\lambda V_L} e^{-\alpha t} = \frac{(D - a - D)\lambda}{\lambda V_L} e^{-\beta t} \quad (1A)
\]

since \( C_0 = \frac{D}{\lambda V_L} \) and letting

\[
A = \frac{(D - a - D)\lambda}{\lambda V_L} e^{-\beta t} \quad (3A)
\]

and

\[
B = \frac{(D - a - \beta)}{\lambda V_L} e^{-\alpha t} \quad (4A)
\]
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lidocaine appears to be associated with a high incidence of dizziness. This may be due to a metabolite of lidocaine itself, since it occurs at lower blood levels than those achieved following intravenous administration of the drug.

We wish to acknowledge the assistance of Dr. Bope Ostergren, Albertsun, Sweden, for carrying out the plasma level estimations.

References


Appendix 1

Derivation of Equation 12.

If: $C_t = \frac{D}{V_t}$

\[ (D - \frac{D}{V_t} - \frac{\beta}{V_t} \alpha - \frac{\beta}{V_t} \alpha) = \frac{D}{V_t} \alpha - \frac{\beta}{V_t} \alpha \]

(1A)

and letting: $A = \frac{D}{V_t} \alpha - \frac{\beta}{V_t} \alpha$  

$B = \frac{D}{V_t} \alpha - \frac{\beta}{V_t} \alpha$  

(1B)

since $C_t = \frac{D}{V_t}$

(2A)

(1C)