The Clinical Pharmacology of Lidocaine as an Antiarrhythmic Drug

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SUMMARY

This article reviews current knowledge about lidocaine, with reference to its chemistry, metabolism, electrophysiology, hemodynamic effects, antiarrhythmic uses, pharmacokinetics, and side effects. The critical importance of blood levels and their relation to lidocaine’s antiarrhythmic and toxic effects is noted, with special emphasis given to patients with compromised clearance due to heart failure. On the basis of this information, we present our current approach to the clinical use of lidocaine in the treatment of ventricular arrhythmias, with particular reference to patients with acute myocardial infarction.

LIDOCAINE was first synthesized in 1943 and was used for many years as a local anesthetic agent. Its first reported use as an antiarrhythmic drug was in 1950. Anesthesiologists subsequently adopted lidocaine for treating arrhythmias occurring during surgery, and in 1963 its successful use in treating arrhythmias occurring during and after cardiac operations was described. Lidocaine has since been used extensively in treating ventricular arrhythmias, and administered intravenously is probably the most widely used agent for the treatment and prevention of cardiac arrhythmias after acute myocardial infarction.

Chemistry and Metabolism

The chemical structure of lidocaine is an aromatic group, 2,6-xylidine, which is coupled to diethylglycine via an amide bond. Lidocaine appears to be metabolized chiefly by the liver. Studies on hepatic tissue homogenates have shown that the microsomal enzyme system is primarily responsible for the hepatic metabolism of lidocaine. Its major degradative pathway (fig. 1) appears to be conversion to monoethylglycinexylidide by oxidative N-de-ethylation followed by hydrolysis to 2,6-xylidine. Evidence exists for a cyclic intermediate in the N-de-ethylation reaction. A stable cyclic form, N-ethyl-2-methyl-N-(2,6-dimethylphenyl)-4-imidazolidinone, has also been isolated from the urine of humans receiving oral lidocaine. Further conversion of 2,6-xylidine to 4-hydroxy-2,6-xylidine appears to occur in man, since the latter compound excreted in urine over a 24-hour period has accounted for over 70% of an orally administered dose of lidocaine. A number of other degradative pathways produce small amounts of 3-hydroxylidocaine, 3-hydroxymonoethylglycinexylidide, and glycineexylidide, as well as small amounts of the intermediate compounds in its major metabolic pathway, monoethylglycinexylidide and xylidine. Hydroxylation of the aromatic nitrogen also occurs, resulting in the formation of N-hydroxylidocaine and N-hydroxymonoethylglycinexylidide, both of which have been identified in the urine of patients given oral lidocaine. Lidocaine is a weak base with a pKa of 7.85 and up to 10% of lidocaine in unchanged form may be excreted in the urine, depending on the urinary pH. Acid urine results in a larger fraction being excreted in the urine. Extensive biliary secretion of lidocaine metabolites occurs in rats, but most of these metabolites are absorbed in the intestine and then eliminated via the urine. There is no evidence that biliary secretion and intestinal absorption of lidocaine metabolites occur in man.

Electrophysiology

The electrophysiologic effects of lidocaine on
cardiac tissue have been studied extensively. Though controversy remains, the results of these studies may be summarized as follows.

Lidocaine causes a slight decrease in automaticity (spontaneous phase 4 depolarization) of pacemaker tissue in rabbit atrial tissue in tissue baths at lidocaine concentrations of 3 and 5 µg/ml, and in rabbit sinoatrial node at 2.54 µg/ml. Larger decreases in automaticity than found in atrial tissue occur in canine Purkinje fibers at extracellular lidocaine concentrations of 2.34 µg/ml and 5 µg/ml. These lidocaine concentrations are in the range of therapeutic blood levels (1.4 to 6.0 µg/ml) in man (discussed below). The diastolic threshold requisite for depolarization in rabbit atrial tissue is increased at extracellular lidocaine concentrations of 3 and 5 µg/ml. In humans, the ventricular diastolic threshold is either slightly increased or unchanged after 1–2 mg/kg intravenous bolus injection. Spontaneous repetitive discharge after a premature stimulus is prevented by extracellular lidocaine concentrations of 5 µg/ml in canine ventricular tissue and 10 µg/ml in canine Purkinje tissue. Lidocaine increases the ventricular fibrillatory threshold in intact rabbit hearts at perfusion concentrations of 1.5–6.2 µg/ml, and in acutely ischemic hearts in dogs, at blood levels of 1.2–5.5 µg/ml.

The effect of lidocaine on the duration of cardiac action potential and effective refractory period has been studied.11, 13, 16, 17 The action potential duration in canine Purkinje fibers is decreased at extracellular lidocaine concentrations of 2.34 µg/ml and 5 µg/ml. Lidocaine also shortens the action potential duration in ventricular muscle at extracellular concentrations of 3 µg/ml in tissue from rabbits and 2.34 µg/ml in tissue from dogs. A more prominent effect is noted on Purkinje fibers than on ventricular muscle.

The effective refractory period is relatively prolonged compared to the action potential duration in both Purkinje fibers and ventricular muscle. Lidocaine’s effect on the maximum rate of depolarization and membrane responsiveness has been the subject of controversy. The reported differences are probably due to the extracellular potassium concentrations in the tissue baths at which these two properties are measured.11, 16, 18, 19 At physiologic potassium levels (5.6 mM), the maximum rate of depolarization and membrane responsiveness in rabbit ventricular muscle is decreased by extracellular lidocaine concentrations of 3 µg/ml. Hypokalemic solutions (3.0 mM), however, cause hyperpolarization of the cell membrane so that tenfold increases in lidocaine concentration are needed before depression of membrane

Figure 1

Metabolic pathways of lidocaine degradation.
responsiveness or maximum rate of depolarization occurs. Conduction velocity in Purkinje fibers in hypokalemic (3.0 mM) bath preparations appears to be slightly decreased by lidocaine concentrations of 5–50 μg/ml.

Atrioventricular (A-V) node and intraventricular conduction time in man are not significantly changed after intravenous injections of lidocaine of 1–2 mg/kg. However, A-V node conduction time is increased in dogs given high-dose intravenous injections of lidocaine (5–20 mg/kg).

These electrophysiologic effects cannot be correlated precisely with lidocaine’s antiarrhythmic actions in humans at this time, but can be used to speculate upon its mode of action in certain specific instances. Ventricular arrhythmias due to acceleration of ectopic foci may be responsive to lidocaine because of its effect on decreasing automaticity by slowing the rate of spontaneous phase 4 depolarization. Lidocaine has been shown to abolish the gating function of distal Purkinje tissue by reducing the nonuniformity of action potential duration in Purkinje tissue, resulting in more uniform recovery of excitability, and to abolish slowing of conduction in Purkinje tissue. Reentrant ventricular arrhythmias may thus be abolished by lidocaine, due to its effect on action potential durations resulting in altered conduction velocity and excitability.

The results reviewed here were obtained mostly from in vitro animal muscle preparations that were studied in well-oxygenated baths, in contrast to the in vivo situation, where arrhythmias possibly originate from ischemic myocardium. Another difference would be that in vivo the microcirculation would be perfused, at least partially, whereas no such perfusion would exist in vitro. This might change the oxygen availability at different areas in the myocardium, and different lidocaine concentrations at different areas in the myocardium might exist in both instances. Similar extensive electrophysiologic studies with lidocaine in vitro in damaged or ischemic myocardial tissue have not been reported, though a recent report has demonstrated that lidocaine does affect differently the electrophysiologic properties of normal and ischemic dog Purkinje fibers. The reported differences, in part, may have resulted from use of tissues from different animal species and thus reflect species variation in response to lidocaine. Tissue was used from different areas of myocardium, which may also have caused different responses to lidocaine. In addition, different extracellular potassium concentrations, which had previously been shown to alter the electrophysiologic changes induced by lidocaine in the same tissue, were used in these experiments. These potassium-related differences might have clinical relevance with regard to lidocaine’s antiarrhythmic mechanism and efficacy, since they were noted at extracellular potassium concentrations which occur in many clinical instances, i.e., 3 mM and 5.6 mM. A summary of the findings of electrophysiologic effects of lidocaine from several studies is presented in table 1.

**Hemodynamic Effects**

The hemodynamic effects of lidocaine have been studied in isolated muscle preparations, isolated perfused hearts, awake and anesthetized animals, animal models with acute myocardial infarction, anesthetized man, and in awake man with acute myocardial infarction.

Lidocaine has been shown to depress the contractility of bath preparations of isolated guinea pig right ventricular muscle. In anesthetized dogs, rapid intravenous injections of lidocaine of 2, 4, and 8 mg/kg resulted in dose-dependent transient decreases of cardiac output, stroke work, arterial pressure, and peripheral vascular resistance. Heart rate increased slightly. Awake dogs showed less marked changes, and when the drug was injected over one minute, negligible depressant effects were seen. Lidocaine has caused dose-dependent depression of ventricular contractility as measured by left ventricular dp/dt in anesthetized dogs when given in i.v. injections of from 0.5 to 30 mg/kg. Large doses of lidocaine (i.e., 5 mg/kg) given as a bolus have produced significant transient depression of ventricular contractility (left ventricular dp/dt), arterial pressure, heart rate, and cardiac output in anesthetized dogs with experimental acute myocardial infarction. However, when the same dogs were given a continuous infusion of 200 μg/kg/min, minimal circulatory changes developed.

When a 2.2 mg/kg i.v. injection was given over one minute to anesthetized adult human males without cardiovascular disease, heart rate did not change, and arterial blood pressure did not decline. In half the patients, there were actually small increases in the arterial pressure. In awake patients with heart disease, rapid i.v. injections of lidocaine, 1 mg/kg over one minute and 1.5 mg/kg over one-half minute, caused no significant depression of ventricular function. However, one study has shown: transient minimal depression of ventricular function in half of the patients given 100 mg bolus doses. The effect of bolus doses of lidocaine up to 2.0 mg/kg given to anesthetized patients undergoing cardiac surgery has been studied. Minimal decreases were seen in right ventricular contractile force as measured by a strain gauge attached directly to the right ventricle, and no significant changes in arterial pressure or heart rate were noted.
In awake patients with acute myocardial infarction, bolus doses of lidocaine, 1–2 mg/kg and 100 mg, caused no significant depression of cardiac output, heart rate, or arterial pressure. In one patient who received a 5 mg/min continuous infusion of lidocaine, a marked fall of arterial pressure was observed and sinus bradycardia developed. In another study in patients with acute myocardial infarction, continuous infusion of lidocaine up to 3 mg/min for up to one hour caused no significant change in left ventricular contractility, stroke work index, cardiac output, arterial pressure, or heart rate.

Lidocaine appears to cause no, or minimal, decrease in ventricular contractility, cardiac output, arterial pressure, or heart rate. This generalization would seem to apply to normal individuals, patients with cardiac disease, and patients with acute myocardial infarction. With excessive doses, however, marked depression of cardiac function in patients with acute infarction would likely develop. Extrapolating from dog studies, rapid intravenous bolus injections of lidocaine leading to very high blood levels would be more likely to cause depression of cardiac function than more slowly administered (1–5 min) bolus injections, and it should always be administered in the latter way in patients with depressed cardiac function.

**Antiarrhythmic Actions**

Lidocaine administered intravenously has been highly effective in terminating ventricular premature beats and ventricular tachycardia occurring during general surgery, during and after cardiac surgery, following acute myocardial infarction, and in the course of digitalis intoxication. It has also been suggested for the prevention and treatment of ventricular arrhythmias occurring during cardiac

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**Table 1**

*Electrophysiologic Effects of Lidocaine on Cardiac Muscle*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Therapeutic conc.</th>
<th>Toxic conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrical threshold</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atria (rabbit)</td>
<td>low K →</td>
<td>low K slightly ↑</td>
</tr>
<tr>
<td>Purkinje fiber (canine)</td>
<td>normal K ↑</td>
<td>normal K ↑</td>
</tr>
<tr>
<td></td>
<td>low K →</td>
<td>low K ↑</td>
</tr>
<tr>
<td><strong>Automaticity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atria (rabbit)</td>
<td>low K →</td>
<td>low K slightly ↓</td>
</tr>
<tr>
<td>Purkinje fiber (canine)</td>
<td>normal K slightly ↓</td>
<td>normal K slightly ↓</td>
</tr>
<tr>
<td></td>
<td>low K ↓</td>
<td>low K ↓</td>
</tr>
<tr>
<td><strong>Action potential duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atria (rabbit)</td>
<td>low K →</td>
<td>low K ↑</td>
</tr>
<tr>
<td>ventricular muscle (rabbit)</td>
<td>normal K ↑</td>
<td>normal K ↑</td>
</tr>
<tr>
<td>ventricular muscle (canine)</td>
<td>low K → or ↓</td>
<td>low K ↓</td>
</tr>
<tr>
<td>Purkinje fiber (canine)</td>
<td>low K ↓</td>
<td>low K ↓</td>
</tr>
<tr>
<td><strong>Effective refractory period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atria (rabbit)</td>
<td>low K →</td>
<td>low K ↑</td>
</tr>
<tr>
<td>ventricular muscle (canine)</td>
<td>low K → or ↓</td>
<td>low K ↑</td>
</tr>
<tr>
<td>Purkinje fiber (canine)</td>
<td>low K ↓</td>
<td>low K ↓</td>
</tr>
<tr>
<td><strong>Maximum rate of depolarization</strong> (phase 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>atria (rabbit)</td>
<td>low K →</td>
<td>low K ↓</td>
</tr>
<tr>
<td>ventricular muscle (rabbit)</td>
<td>normal K ↓</td>
<td>normal K ↓</td>
</tr>
<tr>
<td>ventricular muscle (canine)</td>
<td>low K →</td>
<td>low K ↓</td>
</tr>
<tr>
<td>Purkinje fiber (canine)</td>
<td>low K → or slightly ↑</td>
<td>low K slightly ↓ or ↓</td>
</tr>
<tr>
<td><strong>Conduction velocity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atria (rabbit)</td>
<td>low K →</td>
<td>low K ↓</td>
</tr>
<tr>
<td>ventricular muscle (rabbit)</td>
<td>normal K ↓</td>
<td>normal K ↓</td>
</tr>
<tr>
<td>Purkinje fiber (canine)</td>
<td>low K ↓</td>
<td>low K ↓</td>
</tr>
</tbody>
</table>

Conc. = concentration; ↑ = increased; ↓ = decreased; → = no change.
catheterization. However, ventricular fibrillation is best treated by electrical cardioversion, to be followed by lidocaine infusion.

The general experience has been that lidocaine has not been very effective in the treatment of atrial or A-V junctional arrhythmias. In isolated atrial tissue, poor response of ectopic tachycardias to lidocaine has been shown.12 Perhaps the most important use for lidocaine after acute myocardial infarction is to suppress ventricular premature beats which often occur in the early postinfarction period. Most cases of ventricular tachycardia and fibrillation after acute infarction are preceded by ventricular premature beats. On the basis of these observations, criteria have been developed for the treatment of ventricular arrhythmias occurring after acute infarction.33, 34 We have recommended suppression of ventricular premature beats when: a) more than five per minute of unifocal origin occur, b) R-on-T ventricular premature beats are noted, c) multifocal ventricular premature beats occur, d) two or more ventricular premature beats in a row occur, i.e., short bursts of ventricular tachycardia.35 In addition, after ventricular tachycardia or fibrillation has been terminated, lidocaine is administered prophylactically for 24 hours, in an attempt to prevent the recurrence of ventricular arrhythmias.

Several studies have been carried out to determine the maintenance dose of intravenous lidocaine necessary to prevent ventricular premature beats. In one study, it was found that ventricular premature beats above a frequency of five per minute were suppressed or terminated in 80% of patients by a lidocaine blood level of 1.4 to 6.0 μg/ml (fig. 2).33 This level was achieved by constant infusion rates of 20–55 μg/kg/min (1.4–4.0 mg/min in a 70 kg patient) (fig. 3).34 Lower rates are recommended in patients with overt congestive heart failure or liver failure (see below.) Under a similar program of treatment, one coronary care unit reported that occurrence of ventricular tachycardia or fibrillation was extremely rare.35 Studies have been performed in which lidocaine was used in standard therapeutic doses prophylactically after acute myocardial infarction, in a random manner.36, 37 In the patients receiving lidocaine, the frequency of ventricular arrhythmias of all types was clearly lower. However, because side effects from lidocaine administration do occur, we do not presently advocate usage of this drug for all patients after myocardial infarction, but instead prefer to administer lidocaine when premonitory signs of life-threatening cardiac arrhythmias occur.

**Pharmacokinetics**

The pharmacokinetics of intravenous lidocaine administration has been studied in normal healthy humans.38–42 After an intravenous bolus of lidocaine, or after discontinuing a constant infusion, the plasma concentration changes describe a biphasic curve that can be fitted into two exponential components (fig. 4). There is an early rapid fall in concentration, followed by a later slower decrease in plasma concentration. An average half-life of about 8 min was found in one study for the early rapid fall, though considerable variation was present within the group.38 Another report placed the average value of half-life at 17 min.43 The half-life of the later slow decrease in plasma concentration of drug has been reported to average 108 minutes38 and 87 minutes41 in normal subjects.

The two-compartment open model (fig. 5) has been formulated to explain the biphasic curve observed for the plasma disappearance of lidocaine.38, 41 The first or central compartment (CPT 1) includes the intravascular space, though the calculated volume of distribution exceeds plasma volume.38 The second or peripheral compartment (CPT 2) is larger. When equilibration is attained for all tissues, the volume of distribution exceeds total body water,38 and implies intracellular concentration of lidocaine. In rats, tissue lidocaine levels in numerous organs are higher than blood levels, tending to confirm the intracellular concentration of lidocaine.43

![Figure 2](http://circ.ahajournals.org/)

> Interval histograms obtained before therapy (left) and during treatment (right) with lidocaine, 2 mg/min (32 μg/kg of body weight/minute). The abscissa of the interval histogram represents the R-R interval in milliseconds, and the ordinate the number of beats at a given R-R interval. Lidocaine markedly reduced the number of premature beats. Total beats in each panel = 160.

[Reprinted with permission of Gianelly et al. and New Engl J Med38]
The two phases for the elimination of lidocaine can be observed best after a steady-state is achieved and infusion of lidocaine is stopped. The first rapid phase is due to changes in distribution of lidocaine within the two compartments and hepatic metabolism of that in the central compartment. The liver extraction ratio for lidocaine is approximately 70% in individuals with normal liver function. The second, slower phase of elimination is dependent at least in part upon the slower net transfer of drug from the larger peripheral compartment (CPT 2) to the smaller central compartment. Thus, the influence of the slow phase of elimination dominates the calculation of half-life, yielding the value of 87 to 108 min.

Based on the principle that during constant infusion about five half-life times are required to approach plateau levels of an infused drug, and considering a half-life of 108 min, up to 9 hours would be required...
to reach plateau levels of lidocaine. Higher rates of infusion yield higher steady-state levels, but the time to plateau is unchanged. After discontinuing an infusion at a steady-state level, the dominant elimination half-life is approximately two hours.

Attempting to reach therapeutic levels (i.e., 1.4–6.0 μg/ml) by using conventional rates of constant infusion alone (i.e., 20–55 μg/kg/min) can take several hours, depending on the rate of infusion. Constant infusion technique alone, then, would not acutely provide effective blood levels in life-threatening arrhythmias. Intravenous injections of lidocaine can provide therapeutically effective levels within 1 to 2 min, as indicated by clinical observations of prompt responses of ventricular arrhythmias and by determination of plasma levels after bolus doses. However, bolus administration alone is not useful for managing persistent ventricular arrhythmias because lidocaine plasma levels fall rapidly below the therapeutic level due to rapid clearance from the central compartment, and ventricular arrhythmias have been observed to return within 15 to 20 minutes after an injection. The practical clinical approach is to give a bolus dose at the same time constant infusion is initiated, in order to achieve persistent therapeutic levels from the onset of administration. With this approach, it would be expected that an initial peak level would be present followed by a rapid decline to some minimal level, and followed then by a slow rise to plateau concentrations. Using the two compartment model, it has been computed for an average normal individual that a 160 mg lidocaine i.v. injection (2.3 mg/kg in a 70 kg person) simultaneously given at the onset of a 4 mg/min infusion (55 μg/kg/min in a 70 kg person) would produce initial blood levels of 2 to 4 μg/ml, followed by a decline to a minimal level between 1 to 2 μg/ml at 20–40 min. The lidocaine blood level then rises to plateau levels of 2 to 4 μg/ml (fig. 6). Other investigators have computed similar results and shown by actual measurements in normal individuals that a 100 mg injection of lidocaine followed by an infusion of 1 mg/min would produce a minimal plasma level of just over 1 μg/ml. Using the regimen of constant infusion following an initial i.v. injection, it is thus possible to maintain therapeutic lidocaine levels at all times after starting the infusion.

Clinical observations demonstrate an increased incidence of lidocaine toxicity, primarily manifested by central nervous system disturbances in patients with severe liver disease and severe congestive heart failure. Blood levels in excess of 9 μg/ml are frequently associated with toxic effects, though toxicity has been noted when blood and plasma levels have been in the 5–9 μg/ml range. In one patient with advanced heart failure who was receiving lidocaine at low doses (i.e., 50 mg followed by 1 mg/min infusion), near toxic levels of lidocaine were measured at 2 hours (fig. 7). If the infusion had been continued, plateau levels near 12 μg/ml would probably have been reached. Another patient in cardiogenic shock had lidocaine plasma levels in excess of 8.8 μg/ml at 24 hours while receiving an infusion of only 0.7 mg/min.

Higher blood levels of lidocaine due to decreased
clearance have been demonstrated by infusing lidocaine and simultaneously measuring cardiac output, hepatic clearance of lidocaine, and hepatic blood flow in patients with stable congestive heart failure.\(^{44}\) In this study, lidocaine blood levels varied inversely with cardiac output, with higher blood levels present in patients with depressed cardiac output. Hepatic blood flow was linearly related to cardiac output. Higher blood levels correlated well with the degree of decreased cardiac output (fig. 8), decreased hepatic blood flow (fig. 9), and decreased lidocaine clearance. These data suggest that the clearance of lidocaine during steady-state is primarily limited by hepatic blood flow. Animal studies have also confirmed the correlation between decreased cardiac output and hepatic blood flow, resulting in decreased lidocaine clearance and elevated blood concentrations compared to control animals.\(^{51, 52}\)

In a study of lidocaine pharmacokinetics in patients with advanced liver disease, the steady-state volume of distribution was increased on the average by a factor of nearly two, the central compartment volume of distribution was unchanged, and the plasma clearance was decreased by almost half, compared to normal subjects.\(^{40}\) The half-life of the slow phase of elimination was prolonged. As expected, higher than usual lidocaine plasma levels were present during constant infusion. Changes in plasma protein or tissue affinity for lidocaine have been suggested as the cause for the increased volume of distribution.\(^{40}\) Reduced liver enzyme activity or reduced hepatic blood flow are other possible reasons for the decrease in plasma clearance. Care must be used in extrapolating data from computer models of distribution to man.

However, patients with acute myocardial infarction often have depressed cardiac output and there may be a redistribution of blood flow away from the splanchnic bed during the acute phase. Hepatic blood flow is reduced disproportionately to the reduction in flow elsewhere during the acute stages of infarction, thus causing reduced lidocaine clearance in patients with acute failure compared with patients with chronic congestive failure. This possibility is supported by the observation that somewhat higher levels of lidocaine were present in patients shortly after acute infarction, compared with later stages of recovery, when similar rates of infusion were used.\(^{18}\)

**Figure 8**

The relationship between the arterial lidocaine blood level and the cardiac index in 16 patients is shown. The dotted vertical line represents the lowest normal value for cardiac index in our laboratory of 2.5 L/min/m\(^2\). The solid square is the average lidocaine level and cardiac index for 8 patients with abnormally low cardiac indices, and the solid triangle the average values for the 8 patients with normal cardiac indices. [Reprinted with permission of Stenson et al. and Circulation\(^{44}\)]

**Figure 9**

The steady-state arterial lidocaine level related inversely to the estimated hepatic blood flow in ten patients is illustrated. The solid square is the average lidocaine level for five patients with hepatic flows of less than 800 ml/min/m\(^2\), and the solid triangle is the average for five patients with hepatic flows of greater than 800 ml/min/m\(^2\). [Reprinted with permission of Stenson et al. and Circulation\(^{44}\)]
Another study has shown higher than expected steady-state plasma levels of lidocaine (i.e., 1.0–2.5 μg/ml) in a group of patients with acute infarction and congestive heart failure receiving lidocaine infusions of 0.7 mg/min. The mean plasma half-life in these patients was prolonged (T1/2 = 200 min) following cessation of infusion after steady-state levels had been achieved. The long half-life was in part attributed to slow release of lidocaine from peripheral tissues and impaired hepatic clearance, probably due to diminished perfusion. The plasma clearance of lidocaine was also reduced in these patients and wide ranges of values were found for the apparent volume of distribution. Another group of patients with acute infarction but without severe heart failure have been studied in a similar manner. In these patients, mean plateau levels of 2.25 μg/ml were achieved by constant infusion of lidocaine of 30 μg/kg/min (i.e., 2.1 mg/min in a 70 kg person). Infusion alone, not preceded by a bolus dose, had not provided therapeutic blood levels by 40 minutes. When a 1 mg/kg injection preceded the infusion, initial therapeutic levels of approximately 1.4 μg/ml were achieved, followed by a transient drop below therapeutic levels. Subsequently, blood levels rose slowly to steady-state between 8 and 12 hours. After discontinuing the infusion at steady-state levels, an initial plasma half-life of 120 minutes was found. A later phase was also present with a half-life of approximately ten hours. Calculations have been made of expected blood levels in patients with acute infarction, based on data from normal individuals and the assumption that the volume of distribution is one-half of normal in patients with acute infarction. An 80 mg injection followed by a 2 mg/min infusion would be expected to produce eventual lidocaine blood levels between 2 and 4 μg/ml, with minimal levels of 1 to 2 μg/ml between 20 and 30 minutes. These figures roughly correlate with the data presented above during actual clinical testing, though the calculated blood levels are slightly higher.

Therapeutic Dosage

On the basis of these data reviewed above, and our own experience, dosage recommendations for the use of lidocaine can be made. In patients with presumed normal cardiac output and normal hepatic function and blood flow, an initial injection of 2 mg/kg followed by a 55 μg/kg/min infusion should provide therapeutic lidocaine plasma levels at all times after the initial injection. These doses are equivalent to a 140 mg dose and approximately 4 mg/min infusion in a 70 kg person. In patients with acute infarction or moderately reduced cardiac output, an initial injection of 1.5 mg/kg, followed by 30 μg/kg/min infusion, is recommended. These doses correspond approximately to a 100 mg dose, followed by a 2 mg/min infusion in a 70 kg person. Another approach would be to give the two smaller bolus doses of 0.75 mg/kg each, with the second injection following the first by about 15 minutes. The drug should always be injected over several minutes, since very rapid injection might lead to transiently high plasma levels, with possible toxic side effects. Slower rates of injection would tend to prevent such high plasma levels, without reduction in antiarrhythmic effectiveness. In patients with markedly reduced cardiac output or shock, we recommend a dose of no more than 0.75 mg/kg, followed by an infusion of 10–20 μg/kg/min. This would correspond approximately to a 50 mg injection, followed by an infusion of 0.7 to 1.4 mg/min, in a 70 kg person. Even these doses may be too high in some instances. In such critically ill cardiac patients in whom the use of lidocaine is required, monitoring of lidocaine plasma levels, if available, should serve as a guide to the proper dose of lidocaine. Several hours must elapse before new constant blood levels are approached when increasing or decreasing the rate of infusion. Thus, toxic effects of lidocaine during chronic infusion might persist for a significant period of time after stopping the infusion. One half-life time (approximately 2 hours) is needed for a 50% decrease in the plasma level, so that significantly decreased plasma levels with reduction in toxic effects would take more than just a few minutes. If a higher plasma level of lidocaine during constant infusion is desired to control an arrhythmia, increasing the rate of administration from 2 to 3 mg/min would require several hours to reach new steady-state levels. In any case, significantly increased plasma levels would not develop acutely. In such an instance, we recommend an injection of 25 mg or less at the time acutely increased plasma levels are required. This can be repeated every 15 to 20 minutes as necessary to control the arrhythmia.

Since the clearance of lidocaine may be reduced in patients with liver disease, with up to 50% reductions noted in some patients with severe cirrhosis, the recommendation has been made for reduction of infusion rates of lidocaine. Reduction to one-half the rates for normal would seem appropriate. However, individualization of doses should be made based on plasma level determinations, since lidocaine disposition may vary markedly among patients with liver disease.

Patients with chronic renal disease on hemodialysis show normal pharmacokinetics of lidocaine with regard to half-life times, plasma clearance, and volume of distribution. However, lidocaine
metabolites are excreted almost entirely in the urine, and some of these metabolites have pharmacologic and possibly toxic effects (see below). Although there has been no reported additional incidence of toxic effects during lidocaine administration in patients with chronic renal failure,24 this may be due to the brief period of infusion. Lidocaine metabolites would probably accumulate in the plasma during long infusions, a collection which might result in toxic effects even when the plasma levels of lidocaine are not elevated. Though data are not available on this topic, caution is urged in patients with renal disease receiving prolonged infusions of lidocaine.

It is a well-known pharmacologic principle that plasma levels of certain drugs may be altered by the concomitant use of another or several other drugs. Patients receiving lidocaine are likely to be receiving a number of other drugs also, including sedatives, analgesics, inotropic agents, other antiarrhythmic agents and anticoagulants. The effect of such drugs on lidocaine disposition in man has not been determined. However, some information is available from animal studies. In vitro studies show that phenobarbital increases lidocaine metabolism, whereas drugs such as isoniazid and chloramphenicol decrease lidocaine metabolism,55 presumably by altering liver microsomal enzyme activity. One author has shown that the liver extraction of lidocaine is markedly increased in phenobarbital pretreated dogs,56 probably due to enhanced enzymatic metabolism. A different type of drug interaction is illustrated by propranolol, isoproterenol, and glucagon, in which drug-induced hemodynamic change is the factor that alters another drug’s disposition. Propranolol administered to dogs results in increased lidocaine levels compared to control, by diminishing cardiac output, hepatic blood flow, and lidocaine clearance.92 In contrast, glucagon given to dogs and monkeys57 and isoproterenol given to monkeys58 cause increased hepatic blood flow and thereby increased clearance of lidocaine. Whether or not these animal and in vitro studies apply to lidocaine disposition and plasma levels in humans is speculative. Clinical studies are needed for elucidation of drug interactions with lidocaine in humans.

Lidocaine Blood Levels

With the increasing availability of lidocaine assay, lidocaine therapy can be followed accurately, especially in patients with compromised elimination or in long-term therapy, allowing accurate adjustment of lidocaine infusion rates to achieve the desired plasma level and clinical effect. Lidocaine levels are reported as either blood or plasma levels. Simultaneously analyzed samples show that the value obtained for plasma is about 120% of that obtained for blood, and the plasma:erythrocyte ratio is approximately 1.34:1.58 Until recently, lidocaine levels were reported as the hydrochloride form. Currently, many laboratories are reporting the base form, which is 80% of the equivalent hydrochloride form.

Other Routes of Administration

Intramuscular injection of lidocaine has been suggested in an attempt to treat arrhythmias in patients with acute infarction or suspected infarction when they are first seen by a physician outside the hospital.59 Intramuscular injections of 10% lidocaine in a 4 mg/kg dose into the deltoid muscle provide blood levels within the therapeutic range of 1.4 μg/ml or greater, persisting for 60 to 120 min after initial injection in all patients with myocardial infarction tested (fig. 10).34,60 Injection into the deltoid muscle provides higher and more rapid blood60 and plasma61 levels than does injection into the gluteal muscle, and thus the former site is recommended. One study has shown an average reduction of 75% in the number of ventricular premature beats after intramuscular lidocaine injection in patients with acute myocardial infarction.62 We currently recommend lidocaine, 3 to 4 mg/kg intramuscularly, for patients with acute infarction seen at home by a physician, when premature beats are detected and bradycardia is not present.

Orally administered lidocaine has not been shown to provide effective therapeutic levels (fig. 11).41,63 Since lidocaine is metabolized primarily in the liver, it is substantially inactivated by passage through the liver after oral administration. A high incidence of mild central nervous system side effects has also been reported after oral administration41 (see below).
LIDOCAINE PHARMACOLOGY

PHARMACOLOGY OF LIDOCAINE

Lidocaine Resistance

Patients with ventricular arrhythmias resistant to lidocaine have been reported. A study of such patients referred to a university hospital has been made.44 Some patients in the study were responsive, but only to high blood levels greater than 5 µg/ml, and were refractory to ordinary therapeutic levels (fig. 12). Other patients were considered truly unresponsive to lidocaine, even at elevated blood levels of 10 µg/ml and after toxic central nervous system side effects begin to appear. (fig. 13). In some of these patients unresponsive ventricular arrhythmias were due to a parasystolic foci. On the other hand, other patients in the study were responsive to lidocaine in the usual therapeutic range, suggesting that lidocaine administration was inadequate. Also, failure to administer a bolus injection before beginning constant infusion may result in therapeutically ineffective blood levels for several hours, resulting in apparent unresponsiveness.

Side Effects

Serious toxic side effects on the central nervous system include focal and grand mal seizures, psychosis, and rarely, respiratory arrest.49, 63 Drowsiness, decreased hearing, paresthesias, disorientation, and muscle twitching may occur, and some patients become acutely disturbed and agitated. The treatment of central nervous system side effects includes withdrawal of lidocaine and administration of sedatives. Convulsive disorders respond well to intravenous barbiturates or diazepam. True allergic reactions to lidocaine are probably extremely rare,64, 65 though this has been challenged.66

The contribution of the metabolic products of lidocaine degradation to its toxic effects is not clear. The N-dealkylation metabolites, monoethylglycinexylidide and glycinexylidide may be responsible for central nervous system symptoms in some cases.67 In one patient who was confused and had visual hallucinations, the lidocaine plasma level was in a low therapeutic range, while levels of both monoethylglycinexylidide and glycinexylidide were considerably elevated, suggesting an etiologic relationship between the elevated levels of these metabolites and the toxic symptoms.67 These two metabolites are apparently not pharmacologically inert. Monoethylglycinexylidide

Circulation, Volume 50, December 1974
Sinus bradycardias may be further slowed or induced by lidocaine. Sinus arrest has been reported in the "sick sinus syndrome" after lidocaine administration and when used in association with other antiarrhythmic drugs. Sinus arrest has been induced in a patient with acute anterior infarction in normal sinus rhythm who received large bolus doses of lidocaine, probably resulting in toxic blood levels. However, in a normally conducting heart with a normal sinus rhythm, therapeutic levels of lidocaine cause little or no decrease in A-V conduction and minimal cardiac slowing. Furthermore, His bundle studies performed in patients with conduction abnormalities have shown that increased levels of block induced by lidocaine are probably the exception and not the rule. In patients with first degree heart block and prolonged H-V times, one study has shown no significant effect of lidocaine on H-V times. In another study, patients with prolonged A-H and H-V times and bilateral bundle branch block were given lidocaine, without subsequent significant change in A-H or H-V times. In both reports, lidocaine suppressed the patients' ventricular premature beats.

These studies would appear to establish that therapeutic doses of lidocaine may be used safely in patients with conduction abnormalities. Although lidocaine may induce heart block or sinus node depression, it probably does so infrequently, and mainly when toxic doses have been given. Either abnormality should not necessarily be a contraindication to the cautious use of lidocaine. The failure to suppress ventricular arrhythmias by withholding lidocaine may place the patient at greater risk of subsequent complications than the risk of inducing heart block or bradycardia by giving lidocaine. Lidocaine may be safely used in treating ventricular premature beats in patients with artificial ventricular pacemakers, without fear of altering pacemaker capture, since the threshold response to artificial pacing does not seem to be significantly changed by lidocaine.

Acceleration of ventricular response in atrial tachyarrhythmias after lidocaine administration has been reported, presumably due to enhanced A-V conduction. This would seem paradoxical in view of most studies which point out either unchanged or slightly diminished A-V conduction by lidocaine. An increase in the number of ventricular ectopic beats in patients with acute myocardial infarction has been reported, using low dose lidocaine infusion. In addition, re-entry ventricular beats were increased by lidocaine in animal models of acute infarction in some instances in one study. These reports of paradoxical effects of lidocaine would appear to need further confirmation.

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Lack of response of ventricular arrhythmias to high dose lidocaine infusion. [Reprinted with permission of Harrison and Alderman and Mod Treatam]
PHARMACOLOGY OF LIDOCAINE

Acknowledgments

Some of the studies cited were carried out in the Coronary Care Unit at Stanford University Hospital with the collaboration of Dr. Alfred Spivack and the nursing staff, and the cooperation of several former cardiac fellows and faculty, who permitted these studies in their patients. Finally, we have had the excellent editorial assistance of Mrs. Dorothy McCain in the preparation of this manuscript.

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The Clinical Pharmacology of Lidocaine as an Antiarrhythmic Drug
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Circulation. 1974;50:1217-1230
doi: 10.1161/01.CIR.50.6.1217
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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the World Wide Web at:
http://circ.ahajournals.org/content/50/6/1217

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