The Electrophysiologic Effects of Lidocaine in Patients with Intraventricular Conduction Defects

By F. Kunkel, M.D., M. Rowland, M.D., and M. M. Scheinman, M.D.

SUMMARY

A 6 mg/kg lidocaine infusion was administered (over 22 min) to 10 patients with the electrocardiographic findings of bundle branch block. His bundle electrograms, heart rate, blood pressure, and plasma lidocaine levels were obtained before, every 5 min during, and for 20 min after the infusion was terminated. Control atrioventricular nodal conduction time (AH) was prolonged in two patients (130-175 msec) and infranodal conduction time was abnormally prolonged in four (60-100 msec). Therapeutic lidocaine levels were achieved in all patients and peak levels ranged from 3.3-11.0 µg/ml. No significant changes in mean heart rate, blood pressure, AH, His-Purkinje conduction time, or QRS duration were noted between control values and during or after the lidocaine infusion. Toxic central nervous system side effects including somnolence, dysarthria, and euphoria were noted in five subjects. Therapeutic levels of lidocaine were effective in the eradication of premature ventricular beats and safe in the sense that no higher degrees of atrioventricular or intraventricular conduction block were found; however, mild symptoms of central nervous system toxicity were commonly observed.

Additional Indexing Words:
Lidocaine               Atrioventricular conduction
Heart block
His bundle electrograms

LIDOCAINE has proved to be an effective agent for the treatment of cardiac dysrhythmias.1-12 Its rapid onset of action, lack of significant cardiovascular side effects, and short half-life have made it an ideal agent for the treatment of cardiac patients. Previous studies performed in man with intact cardiac conduction showed that the drug has little effect on atrioventricular (A-V) or intraventricular (IV) conduction.13 Nonetheless, reports of complete heart block and other serious dysrhythmias following the administration of lidocaine in man have appeared and caution in its use in the presence of conduction defects has been stressed.2, 14-18 The exact nature of the risk involved in administration of lidocaine in the presence of AV and/or IV conduction defects, however, remains to be defined. His bundle electrocardiography allows for estimation of A-V nodal and infranodal conduction time and was therefore used in this study to assess the effects of lidocaine on A-V conduction in patients with IV conduction delay. In addition, we attempted to correlate changes in A-V conduction, the frequency of ventricular premature beats (VPBs), and the symptoms suggestive of toxicity with plasma lidocaine levels.

Materials and Methods

Ten patients with chronic complete right or left bundle branch block19 and ventricular dysrhythmias were studied. A complete history and physical examination, a standard electrocardiogram, and serum electrolyte measurements and blood tests to assess hepatic and renal function were obtained in all patients. Patients with recent (less than 1 month) myocardial infarction or severe congestive heart failure were excluded and no patients were receiving digitalis preparations or any other antiarrhythmic agents at the time of the study. Informed consent was obtained and the study conducted in accordance with a protocol approved by the University of California Committee on Human Experimentation, San Francisco.

His bundle recordings were obtained using previously described techniques20, 21 and the catheter was not repositioned during the course of study. External scalar leads X, Y, and inverse Z leads of the Frank orthogonal system were recorded and displayed simultaneously with the His electrograms at a paper speed of 100 mm/sec. Atrioventricular nodal conduction time, (AH interval), was measured from the earliest rapid deflection of the atrial electrogram to the initial deflection of the His bundle depolarization. The His-Purkinje conduction time (HQ interval) was measured from the initial His deflection to the earliest onset of ventricular depolarization on the surface electrocardiogram. The duration of ventricular depolariza-
tion and the total ventricular depolarization-repolarization time were measured from the surface leads (QRS and QT intervals, respectively). Other serial observations included 1) clinical status of the patient, 2) pulse rate, 3) blood pressure, and 4) presence and frequency of ventricular premature beats (VPBs). The recorded intervals were measured by means of a specially calibrated grid, as previously described. All records were analyzed independently by two of the authors and the maximal intraobserver error was ± 3.0%.

For each patient 6 mg/kg of lidocaine (Xylocaine) was diluted in 50 ml of 5% dextrose and water and infused into a peripheral vein by means of a constant infusion pump over a period of 22 min. A polyethylene catheter inserted into a vein in the opposite arm allowed for periodic blood sampling. Control measurements of the cuff systemic pressure, heart rate, AH, HQ, QRS, and QT intervals were recorded every 5 min during the infusion and for 25 min thereafter. In addition, 60 sec recordings (at a paper speed of 10 mm/sec) were obtained at these same 5 min intervals in order to count the number of VPBs. The patients were closely observed and asked to report any symptoms during the study. Blood specimens were obtained simultaneously with each recording and plasma lidocaine levels were measured by gas chromatography. Where applicable, the data were analyzed using Student’s paired t-test and a P value of < 0.05 was considered significant. Mean values are expressed as the mean ± the standard deviation.

Results

The pertinent clinical information, peak plasma lidocaine levels, and the electrophysiologic data for the 10 patients with chronic IV conduction disturbances and VPBs are summarized in table 1.

Plasma lidocaine levels. Plasma lidocaine levels increased progressively during the infusion and peak levels (mean 6.2 ± 0.84) were achieved in all patients at the termination of the infusion (fig. 1). In one patient marked drowsiness required cessation of the infusion after 15 min. Therapeutic levels of lidocaine (2-5 μg/ml) were achieved in all patients and five of the 10 patients had peak levels in excess of 5.5 μg/ml. Serum lidocaine levels tended to be higher in patients with congestive heart failure (three patients) or hepatic disease (two patients) than in subjects without these diagnoses; however, the small sample size precludes statistical analyses of differences among these groups.

Effects on sinus rate, A-V and IV conduction. There was no significant difference between mean control heart rate (77 ± 3.2 beats/min) and mean rates during or after the infusion. For the group as a whole, there was a small (2.5 mean %) decrease in heart rate at peak lidocaine concentration compared with the control rate.

Mean control A-V nodal conduction time was 103 ± 10.7 msec and was abnormally prolonged (> 120 msec) in only two patients. There was no significant difference between mean control AH interval and mean AH intervals during or after the infusion. At peak lidocaine concentration, the group as a whole showed a 4.3 mean % increase in AH time. Although control HQ intervals were prolonged in four subjects, no significant differences were found between mean control HQ (51.5 ± 6.9 msec) and HQ intervals during or after the infusion. At peak plasma lidocaine levels there was a 1.9% increase in mean infranodal conduction time. Similarly, there were slight but insignificant changes between mean QRS or QT duration before and after lidocaine administration.

Arrhythmia control. In four of the 10 subjects (Nos. 3, 4, 9, 10) control records showed VPBs sufficiently frequent (> 5/min) to allow for valid comparison of change in frequency before, during, and after lidocaine infusion (fig. 2). In these patients, VPBs began to diminish within 5 min of the start of the infusion at plasma lidocaine levels between 0.9 and 2.3 μg/ml. Ventricular premature beats virtually disappeared by 15 min at lidocaine levels between 2.1 and 7.8 μg/ml. In only one of these patients did VPBs recur during the period of observation following the completion of the infusion. No higher degrees of A-V block or new cardiac arrhythmias were noted during or after lidocaine administration.

Toxic side effects. Varied manifestations of effects on the central nervous system were commonly observed during the infusion (table 1). The most common symptom was drowsiness, which occurred in five subjects. One patient had dysarthria and another became euphoric during the study. The majority of these toxic side effects occurred at plasma lidocaine

![Figure 1](https://example.com/image1)

**Figure 1**

Plasma lidocaine levels are shown for each patient before, at the end (solid parallel lines), at 5 min, and at 20 or 25 min following the infusion. Shaded area represents mean ± standard error of lidocaine levels.

![Figure 2](https://example.com/image2)

**Figure 2**

The effects of lidocaine on frequency of VPBs in four patients with > 5 VPBs/min. The premature beats decreased within 5 min after start of the infusion and disappeared within 15 min.
**Clinical and Electrophysiologic Data**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Cardiac diagnosis</th>
<th>Congestive heart failure</th>
<th>Hepatic disease</th>
<th>Electrocardiogram</th>
<th>Arrhythmia</th>
<th>Peak lidocaine level (µg/ml)</th>
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<td>RBBB/LAHB</td>
<td>VPB</td>
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<td>VPB</td>
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<tr>
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<td>APB, VPB*</td>
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<td>VPB</td>
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<td>8</td>
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<td></td>
<td>RBBB</td>
<td>VPB*</td>
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</table>

Mean C

Mean P

*Abbreviations: APB = atrial premature beats; JPB = junctional premature beats; VPB = ventricular premature beats; 1° AVB = first degree atroventricular block; RBBB = right bundle branch block; LBBB = left bundle branch block; LAHB = left anterior hemi-block; C = control values; and P = values at peak lidocaine levels.

*Greater than 5 VPBs/min.

Concentrations that were well within the accepted therapeutic range; in only two instances were plasma levels grossly elevated (11.0 and 10.3 µg/ml). These symptoms were most common near the time of peak plasma lidocaine concentration and were generally mild (severe drowsiness necessitated termination of the infusion in only one subject) and transient. The symptoms usually disappeared within 5-10 min after cessation of the infusion. In addition, there was no significant change in either mean systolic or diastolic pressure before, during, or after the infusion. Finally, none of the patients complained of any subjective symptoms or showed objective signs of increased congestive heart failure or new cardiac arrhythmias during the study.

**Discussion**

Previous workers have defined the electrophysiologic effects of lidocaine on the transmembrane action potential of the ventricular specialized conduction system and ventricular muscle. Their studies have shown that the major effect of this drug is to reduce the action potential duration and that this effect is most marked in distal Purkinje fibers. In addition, therapeutic concentrations of lidocaine were shown to attenuate phase 4 diastolic depolarization, but variable effects on the maximal rate of phase 0 depolarization in part related to extracellular potassium concentration have been reported. The therapeutic concentrations of lidocaine in the intact dog are associated with little change in sinoatrial automaticity or in intratraet, A-V, and IV conduction. Very large doses of lidocaine (40-50 mg/kg) are, however, associated with impaired A-V conduction and sinus node depression. Previous studies in man have adequately documented the efficacy of this drug in abolishing ventricular arrhythmias due to a variety of causes, but only two previous studies of

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the effects of this drug on the cardiac conduction system in man are available.

Our studies are unique in that we assessed the effects of lidocaine in patients with IV conduction disturbances and correlated these effects with simultaneous measurements of plasma lidocaine concentration. Therapeutic plasma levels of lidocaine (in five of the 10 subjects peak lidocaine levels actually exceeded the accepted therapeutic range) were associated with minor and inconsistent effects on A-V or IV conduction. These findings are in close agreement with previous lidocaine studies in which His bundle electrograms were obtained in patients with essentially normal cardiac conduction. Our studies, therefore, extend these observations to subjects with IV conduction disturbances and establish the safety of acute intravenous lidocaine infusion for these patients.

In contrast, our review of the literature uncovered four reports of development of either higher degrees of A-V block or ventricular asystole in patients following intravenous lidocaine administration, and one author suggested consideration of prophylactic insertion of a temporary ventricular pacemaker for patients with electrocardiographic findings of bifascicular block who require lidocaine therapy. Gianelly et al. reported two instances of complete A-V block following lidocaine infusions. Both patients had recent myocardial infarctions and in one the heart block persisted for several days following cessation of lidocaine. The electrocardiogram in the second patient showed second degree A-V block before the lidocaine infusion, and development of transient complete A-V block following lidocaine. The complete A-V block in the first patient was almost certainly due to ischemic damage to the A-V conduction system (as suggested by the authors) and, likewise, this possibility cannot be excluded in the second patient. Similarly, Rydén and Korsgren reported a patient with second degree A-V block who had ventricular asystole following lidocaine. This patient, however, had had previous Stokes-Adams attacks (a ventricular pacemaker was actually in place), and coincidental development of ventricular asystole due

<table>
<thead>
<tr>
<th>Systemic pressure (mmHg)</th>
<th>RR (msec)</th>
<th>AH (msec)</th>
<th>HQ (msec)</th>
<th>QRS (msec)</th>
<th>QT (msec)</th>
<th>Symptoms of toxicity</th>
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<td>C 200/60</td>
<td>960</td>
<td>135</td>
<td>60</td>
<td>145</td>
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<td>Drowsiness</td>
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<tr>
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<td>150</td>
<td>60</td>
<td>165</td>
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<td>95</td>
<td>55</td>
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<tr>
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<td>138</td>
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<tr>
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to chronic underlying disease of the cardiac conduction system is a strong possibility. Josephson et al.18 reported a patient with left bundle branch block (LBBB) who during catheter recording of the His bundle potential had transient complete A-V block localized to the level of A-V node after lidocaine (Xylocaine) administration. Although this complication was attributed to lidocaine toxicity, an equally plausible explanation is catheter-induced injury to the A-V node and/or the His bundle. We have observed similar findings in patients with LBBB undergoing catheter recordings of His bundle depolarization.31 Finally, and most difficult to explain is the report by Lichstein et al.16 of a patient with bifascicular block in whom transient complete A-V block developed on two separate occasions following a 50 mg bolus intravenous injection of lidocaine. The second injection was given at the time of the His bundle recording and showed a control infranodal conduction time of 100 msec with the subsequent development of A-V block; the level of block was localized distal to the common bundle. This patient had no evidence of congestive heart failure or liver disease and although plasma lidocaine levels were not obtained it is unlikely that inordinately high plasma lidocaine levels were achieved. It is unclear from this report if the patient suffered an acute myocardial infarction or if spontaneous complete A-V block unassociated with lidocaine administration was observed on follow-up evaluation. Furthermore, we studied one patient with LBBB and comparable prolongation of the HQ interval (fig. 3) who showed no changes in A-V conduction after a much larger dose of lidocaine. In addition, extensive experience with the use of lidocaine both therapeutically and for arrhythmia prophylaxis in patients with acute infarction (including patients with bilateral bundle branch block) has not indicated an association between lidocaine administration and the development of complete A-V block.32, 33 Finally, the discrepancy between our findings and the case reports cited above may be related to differences in extracellular potassium concentration. Lidocaine administration to patients with raised serum potassium levels could conceivably produce depression of A-V conduction.27 All of the patients in the present study were normokalemic while no mention of serum potassium levels are made in the previously cited reports.

While some have stressed that serious toxic effects of lidocaine on the nervous system (convulsions and stupor) are associated with plasma lidocaine levels in excess of 9 μg/ml,2 others have reported milder toxic reactions at lower dose levels.34, 35 Our own studies document the frequent occurrence of central nervous system toxicity at plasma lidocaine levels generally considered to be within the therapeutic range. These symptoms generally appeared near the time of peak plasma lidocaine concentration, well after therapeutic effects were manifest, and were readily reversible on discontinuation of the infusion. The clinician as well as the coronary care nurse should search for these symptoms and make appropriate change in lidocaine administration when detected. In addition, no significant changes in heart rate, blood pressure, QRS duration, or QT interval were noted, and these findings are in agreement with many previous studies.13, 28-30

In summary, intravenous administration of lidocaine appears to be both effective for control of ventricular arrhythmias and safe in patients with chronic IV conduction delay. A note of caution is in order lest these results be extrapolated to all patients with IV conduction disturbances. First, none of the patients in our study had evidence of severe congestive heart failure, severe impairment of hepatic function, hypoxia, or electrolyte abnormalities. It is conceivable that lidocaine administration (comparable to the dose used in our study) in these patients may produce inordinately high blood levels and/or toxic effects on A-V conduction.36-38 In addition, at least one report of sinus arrest in a patient with the sick sinus syndrome19 suggests that caution be used when administering this drug to patients with impaired sinoatrial node function.

References


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![Figure 3](image-url)

Control tracing showing simultaneous recordings of X, Y, and inverse Z leads of the Frank orthogonal leads together with the His bundle electrogram (HBE) showing marked prolongation of infranodal conduction time (HQ). There are no significant changes in HQ at peak lidocaine concentration (5 μg/ml). Atrial pacing was used to validate the His deflection in this patient.
EFFECTS OF LIDOCAINE ON CONDUCTION


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