Interrelationships of Hepatic Blood Flow, Cardiac Output, and Blood Levels of Lidocaine in Man

By ROBERT E. STENSON, M.D., ROBERT T. CONSTANTINO, M.D., and DONALD C. HARRISON, M.D.

SUMMARY

Factors that regulate the arterial level of lidocaine during a constant infusion were investigated in 17 patients undergoing cardiac catheterization. Lidocaine was administered by a 50 mg bolus, followed by a constant infusion of 40 μg/kg/min until steady state conditions were achieved. Cardiac output and estimated hepatic blood flow were also determined. An inverse relationship between arterial lidocaine levels and cardiac index was observed. With a low cardiac index of 1.9 ± 0.3 liters/min/m² the arterial level was 2.4 (±0.4 SEM) μg/ml, while with a normal cardiac index of 3.3 ± 0.8 liters/min/m² it was 1.5 (±0.2 SEM) μg/ml.

A linear relationship was also observed between estimated hepatic blood flow and cardiac index. Therefore, an inverse relationship between arterial lidocaine levels and estimated hepatic blood flow was noted. At steady-state conditions, the liver accounted for 70% (±16% SEM) of the metabolism or removal of the lidocaine administered. These studies suggest that the administration of smaller doses of lidocaine will produce effective therapeutic levels when reduced hepatic blood flow exists.

Additional Indexing Words: Steady-state lidocaine blood levels, Lidocaine metabolism

LIDOCAINE was synthesized in 1943 and used for many years as a local anesthetic agent. However, during the past decade it has also become one of the most frequently used drugs for the treatment and prevention of ventricular arrhythmias. Previous studies from this laboratory and other institutions have demonstrated that the effective therapeutic blood level for lidocaine is between 1.2 and 5.5 μg/ml blood. In patients without congestive heart failure, hypotension, or evidence of a low cardiac output, this level is generally achieved by an infusion rate of 20 to 50 μg/kg/min. Higher blood levels of lidocaine have been noted with similar infusion rates in those patients with circulatory depression. In addition, clinical evidence suggests that a higher incidence of toxicity to lidocaine occurs in those patients with markedly depressed circulatory function. Accordingly, we designed this study to define factors that are important in regulating the blood level of lidocaine for any given infusion rate, specifically the effects of cardiac output, hepatic blood flow, and metabolism or removal of lidocaine by the liver.

Methods

These studies were carried out in 17 patients undergoing cardiac catheterization for diagnostic
Table 1

Clinical Data on Patients Studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Result of liver function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.P.</td>
<td>55</td>
<td>M</td>
<td>Aortic insufficiency</td>
<td>Normal</td>
</tr>
<tr>
<td>C.E.</td>
<td>48</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>BSP 9%</td>
</tr>
<tr>
<td>R.H.</td>
<td>21</td>
<td>M</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>E.T.</td>
<td>45</td>
<td>M</td>
<td>Mild pulmonic insufficiency</td>
<td>Normal</td>
</tr>
<tr>
<td>A.G.</td>
<td>48</td>
<td>F</td>
<td>Mitral stenosis</td>
<td>Alkaline phosphatase 14</td>
</tr>
<tr>
<td>R.A.</td>
<td>16</td>
<td>M</td>
<td>Pulmonic stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>L.W.</td>
<td>44</td>
<td>M</td>
<td>Mitral insufficiency</td>
<td>Bilirubin 1.2</td>
</tr>
<tr>
<td>J.L.</td>
<td>23</td>
<td>M</td>
<td>Mild pulmonic stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>M.G.</td>
<td>40</td>
<td>F</td>
<td>Postop aortic homograft</td>
<td>Normal</td>
</tr>
<tr>
<td>M.N.</td>
<td>42</td>
<td>F</td>
<td>Mitral stenosis</td>
<td>Bilirubin 1.3</td>
</tr>
<tr>
<td>V.P.</td>
<td>53</td>
<td>M</td>
<td>Mitral stenosis; aortic insufficiency; tricuspid insufficiency</td>
<td>Bilirubin 3.2; alkaline phosphatase 18; prothrombin time 49%; LDH 360</td>
</tr>
<tr>
<td>V.O.</td>
<td>58</td>
<td>M</td>
<td>Aortic stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>N.K.</td>
<td>52</td>
<td>F</td>
<td>Mitral stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>E.H.</td>
<td>50</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>Normal</td>
</tr>
<tr>
<td>S.G.</td>
<td>39</td>
<td>F</td>
<td>Mitral and aortic stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>F.B.</td>
<td>57</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>Normal</td>
</tr>
<tr>
<td>E.H.</td>
<td>58</td>
<td>F</td>
<td>Mitral and aortic stenosis</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Normal values are: bilirubin <1.0 mg/100 ml; alkaline phosphatase <12 King-Armstrong units; SGOT <45 international units; LDH <185 international units; prothrombin time >60%; BSP retention <5%. Liver function tests not specifically listed were in the normal range.

purposes. The study group included 11 males and six females ranging in age from 16 to 58 years (table 1). All patients had a complete history, physical examination, series of cardiac X-rays, electrocardiograms, routine laboratory tests, and hepatic and renal function tests, including those for bilirubin, alkaline phosphatase, prothrombin time, serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), creatinine, BUN, and sulfobromophthalein (BSP) retention (table 1).

The protocol and procedure to be followed were discussed in detail with each patient, and informed consent was obtained. All patients underwent diagnostic catheterization by standard right and left heart techniques; then the lidocaine study was performed. Carbocaine (mepivacaine) was used as the local anesthetic in all cases. An end-hole Brockenbrough catheter was placed into the femoral vein, by the Seldinger technique. The tip of the catheter was then advanced under fluoroscopic control and wedged into the right hepatic vein. In all cases, the right hepatic vein was easily catheterized upon slow withdrawal of the catheter from the right atrium into the inferior vena cava, with the distal curve pointing horizontally to the right. When the catheter was wedged into position, the patient would frequently experience pain radiating to the right shoulder upon deep inspiration.

A radiopaque polyethylene catheter was placed in the central aorta via the right brachial artery. The right heart catheter, previously inserted, was positioned in the main pulmonary artery to serve as the route for infusion of lidocaine and indocyanine green (Cardio-Green). In three patients, a double-lumen catheter was used in the pulmonary artery and right ventricle, so that samples could be obtained from the right ventricle when infusions were made into the main pulmonary artery. This was done for determination of total body clearance of lidocaine. Pressures were recorded in the central aorta and main pulmonary artery prior to and at frequent intervals during the 100-min period of infusion. Standard indocyanine green dye cardiac outputs were determined in duplicate before beginning the lidocaine study and at the end of the 100-min lidocaine infusion. Lidocaine was administered as a 50 mg loading bolus into the main pulmonary artery during an interval of 1 to 2 min. This was followed by constant infusion of 40 μg/kg/min with a calibrated Harvard infusion pump. Arterial blood was sampled at control time, 20, 40, 60, 80, 90, and 100 min, and hepatic vein blood at 60, 80, 90, and 100 min for lidocaine measurements. All blood specimens were refrigerated after they were collected. Lidocaine levels were determined by a gas chromatographic method at the Analytical Division of the Astra Pharmaceutical Laboratories in Worcester, Massachusetts.5

In order to obtain estimated hepatic blood flows so that the effect of hepatic blood flow on steady-state arterial levels of lidocaine could be
determined, we used indocyanine green as an indicator. In this study, two methods were employed for the measurement of hepatic blood flow. The single intravenous bolus method utilized the principle described previously by Wiegard. In five patients, a bolus dose of 0.8 mg/kg was administered, and aortic and hepatic vein plasma decay curves were measured at 3-min intervals for 18 min. The constant infusion method utilized techniques previously described by Caesar. In six patients, a loading dose of 15 mg was followed by a constant infusion of 0.5 mg/min with a calibrated Harvard infusion pump. After allowing 60 min for equilibration, during which time arterial levels of indocyanine green were monitored, paired heparinized samples were withdrawn from the hepatic vein and central aorta at 10-min intervals over the next 40 min. In order to infuse lidocaine and indocyanine green in the same syringe, we added 1 cc of human serum albumin to the mixture for stabilization.

After centrifugation, the plasma concentration of indocyanine green was read against a blank of the patient's serum obtained prior to infusion on a Beckman Model B spectrophotometer at a wave length of 800 m. A calibration curve ranging from 0.5 to 10 mg/liter indocyanine green was then constructed for each patient by mixing his own plasma and a specific quantity of indocyanine green from a calibrated pipette. Using a standard formula, we performed the following calculations for each patient: the half-life time, the average slope of the decay curve, the plasma clearance rate, the hepatic extraction ratio, and the estimated hepatic blood flow.

The statistical calculations made in this study were performed on an IBM 360 Model 50 digital computer, by standard programs for calculation of correlation coefficient and regression lines.

**Results**

**Clinical Observations**

A majority of the patients had organic heart disease (table 1), classes 3 and 4 of the New York Heart Association classification. Most of the patients had normal liver function tests, as measured by standard enzyme and bilirubin determinations, and by sulfobromophthalein retention. One patient, V.P., had significantly abnormal liver function tests, as shown by a bilirubin concentration of 3.2 mg/100 ml, an elevated alkaline phosphatase concentration, and a decreased prothrombin time. These abnormalities were attributed to passive congestion of the liver secondary to right heart failure. During the study, frequent measurements of the central aortic and right heart pressures were made. Hemodynamic stability was manifested by the fact that pressures and cardiac output at the end of the study were not significantly different from control values.

**Relationship Between Cardiac Output and Blood Lidocaine Levels**

An inverse relationship between steady-state arterial lidocaine levels and the cardiac index was observed in the 16 patients in whom this measurement was made (fig. 1). Steady-state arterial lidocaine levels were assumed after 1 hour, since arterial blood levels had reached a plateau. When the reciprocal of the steady-state lidocaine concentration is plotted against the cardiac index, an approximately linear
The relationship between the estimated hepatic blood flow and cardiac index. Lower cardiac indices were associated with lower hepatic blood flows.

Relation is obtained with a correlation coefficient of 0.83, the equation for this regression line is

\[ y = 0.13x + 0.207 \]

It was possible to separate the patients into two groups: those with a cardiac index of less than 2.5 liters/min/m² and those with an index above this value. The average cardiac index for those with a low cardiac output was 1.9 ± 0.3 (SEM) liters/min/m², while the group with a normal cardiac index averaged 3.3 ± 0.8 (SEM) liters/min/m². At the same rate of infusion, the steady-state arterial lidocaine level averaged 2.4 ± 0.4 (SEM) µg/ml in those patients with a low cardiac index, and 1.5 ± 0.2 (SEM) µg/ml in those patients with a normal cardiac index. The steady-state arterial levels are statistically significantly different (P < 0.02).

Relationship Between Steady-State Arterial Lidocaine Levels and Estimated Hepatic Blood Flow

The relationship between estimated hepatic blood flow and cardiac index was approximately linear (fig. 2). The correlation coefficient for this relationship was \( r = 0.75 \). There was, therefore, an inverse relationship between steady-state arterial lidocaine levels and estimated hepatic blood flow (P < 0.05) (fig. 3). When the reciprocal of the arterial lidocaine level is considered in relationship to the estimated hepatic blood flow, an approximately linear relationship is found, with a correlation coefficient of \( r = 0.75 \) and a regression line with the slope

\[ y = 0.0004x + 0.255 \]

The relationship of the steady-state arterial lidocaine levels to the estimated hepatic blood flow. The solid square is the average lidocaine level for patients with hepatic flows of less than 800 ml/min/m², and the solid triangle is the average for patients with hepatic flows of greater than 800 ml/min/m².

The relationship between the arterial-hepatic venous differences and the estimated hepatic blood flow.
Table 2

Hemodynamic and Laboratory Data on Patients Studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cardiac index (liters/min/m²)</th>
<th>Cardiogreen extraction ratio (%)</th>
<th>Estimated hepatic blood flow (ml/min/m²)</th>
<th>Estimated hepatic blood flow (% cardiac index)</th>
<th>Arterial lidocaine concentration (µg/ml)</th>
<th>Hepatic venous lidocaine concentration (µg/ml)</th>
<th>Arterio-venous lidocaine difference (µg/ml)</th>
<th>Lidocaine metabolized by liver (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.P.</td>
<td>2.3</td>
<td>53</td>
<td>615</td>
<td>26</td>
<td>2.6</td>
<td>0.9</td>
<td>1.7</td>
<td>56</td>
</tr>
<tr>
<td>C.E.</td>
<td>2.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>R.H.</td>
<td>3.6</td>
<td>75</td>
<td>1160</td>
<td>32</td>
<td>1.3</td>
<td>0.3</td>
<td>1.0</td>
<td>89</td>
</tr>
<tr>
<td>E.T.</td>
<td>3.0</td>
<td>81</td>
<td>1075</td>
<td>36</td>
<td>1.3</td>
<td>0.3</td>
<td>1.0</td>
<td>59</td>
</tr>
<tr>
<td>A.G.</td>
<td>2.3</td>
<td>87</td>
<td>980</td>
<td>42</td>
<td>1.9</td>
<td>0.6</td>
<td>1.3</td>
<td>76</td>
</tr>
<tr>
<td>R.A.</td>
<td>4.4</td>
<td>93</td>
<td>935</td>
<td>21</td>
<td>1.5</td>
<td>0.4</td>
<td>1.1</td>
<td>71</td>
</tr>
<tr>
<td>L.W.</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>1.0</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>J.L.</td>
<td>4.2</td>
<td>90</td>
<td>1575</td>
<td>38</td>
<td>1.4</td>
<td>0.6</td>
<td>0.8</td>
<td>87</td>
</tr>
<tr>
<td>M.G.</td>
<td>3.2</td>
<td>84</td>
<td>810</td>
<td>25</td>
<td>1.5</td>
<td>0.2</td>
<td>1.3</td>
<td>77</td>
</tr>
<tr>
<td>M.N.</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>0.7</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>V.P.</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V.O.</td>
<td>2.0</td>
<td>60</td>
<td>800</td>
<td>40</td>
<td>2.8</td>
<td>1.0</td>
<td>1.8</td>
<td>83</td>
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<tr>
<td>V.K.</td>
<td>1.8</td>
<td>65</td>
<td>525</td>
<td>29</td>
<td>2.6</td>
<td>1.0</td>
<td>1.6</td>
<td>57</td>
</tr>
<tr>
<td>E.H.</td>
<td>1.5</td>
<td>50</td>
<td>625</td>
<td>42</td>
<td>2.2</td>
<td>0.4</td>
<td>1.8</td>
<td>81</td>
</tr>
<tr>
<td>S.G.</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.5</td>
<td>1.3</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>F.B.</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.1</td>
<td>1.3</td>
<td>1.8</td>
<td>-</td>
</tr>
<tr>
<td>E.H.</td>
<td>2.7</td>
<td>53</td>
<td>475</td>
<td>18</td>
<td>2.2</td>
<td>1.0</td>
<td>1.2</td>
<td>36</td>
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<tr>
<td>Mean</td>
<td>2.53</td>
<td>71.9</td>
<td>870</td>
<td>31.7</td>
<td>2.0</td>
<td>0.7</td>
<td>1.3</td>
<td>70.2</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.89</td>
<td>16.2</td>
<td>324</td>
<td>8.5</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td>16.3</td>
</tr>
</tbody>
</table>
Those patients with higher blood flows to the liver had smaller hepatic arterial-venous differences in concentration of lidocaine (fig. 4). This finding would be anticipated only if the liver were a major site for the metabolism or removal of lidocaine from the circulation. If the assumption is made that at steady-state the rate of metabolism equals the rate of infusion, the percentage of lidocaine metabolized by the liver can be estimated from the hepatic arterial-venous difference in concentration of lidocaine and the estimated hepatic blood flow (table 2). In these patients, the hepatic metabolism of lidocaine varied between 36 and 89% of the total metabolism, with an average value of 70 ± 16%. Inherent in this calculation of hepatic metabolism of lidocaine is the assumption that arterial lidocaine levels were, in fact, measured at steady-state. While this assumption is probably not absolutely correct, it was verified in three patients in whom lidocaine was infused into the pulmonary artery through a double-lumen catheter and mixed right ventricular blood samples were analyzed for lidocaine concentration. With the knowledge of the arterial and venous concentration of the drug and the amount being infused per minute and the assumption that steady-state had been reached, the cardiac output can be calculated on the basis of the Fick principle for lidocaine. In these patients, the values for cardiac output determined by standard indocyanine green methods and by this Fick method, with lidocaine as an indicator, were in agreement to within ± 10%.

Discussion

These studies clearly demonstrate that there is a relationship between circulatory function and the steady-state blood level of lidocaine. Clinically, we have frequently noted that patients who have severe congestive heart failure and/or cardiogenic shock develop toxic side effects to infusion rates of lidocaine that are commonly considered to be in the therapeutic range. Toxicity at low infusion rates, however, does not always occur, and the factors affecting this have been difficult to document precisely. Previous work by Hollunger and Katz have demonstrated in rabbit and rat experiments that the chief site of metabolism of lidocaine appears to be in the liver. To our knowledge, the present study is the first to demonstrate that the liver is a major site of metabolism or removal of lidocaine in man. The techniques employed in our study do not differentiate between lidocaine metabolism and excretion by the liver, but do demonstrate removal of lidocaine, as such, from the blood.

The inverse relationship between the arterial level of lidocaine and cardiac performance has been previously noted. However, in the present study, this correlation has been more clearly demonstrated by the almost linear relationship of the reciprocal of the steady-state arterial lidocaine concentration to the cardiac index. It would appear that a reduction in cardiac index leads to an approximately proportional reduction in the estimated hepatic blood flow. This in turn increases the arterial-venous difference across the hepatic bed and also increases the steady-state arterial levels. There is, however, no clear relationship between the estimated hepatic blood flow per square meter and the percentage of lidocaine metabolized by the liver at steady-state conditions as they were measured in this study.

The liver accounts for the majority of lidocaine metabolized or removed from the circulation, but does not appear to be the only site. The site of removal or metabolism of the remainder of the lidocaine was not identified in the present study. In one patient, the renal vein was unintentionally catheterized. Virtually no arterial-venous difference could be demonstrated across the renal bed. This observation is in agreement with results reported by Thomson et al., who demonstrated that less than 5% of an administered dose of lidocaine was excreted unchanged in the urine.

Since indocyanine green dye is excreted almost exclusively by the liver, it provides a safe, easy method for estimation of hepatic blood flow. Either a bolus technique with
rapid serial determinations of the rate of decrease of the concentration of indocyanine green dye or constant infusion at a known rate may be utilized. The latter is more reliable in those patients with a reduced cardiac index and prolonged intravascular mixing. With determination of hepatic blood flow and the simultaneous infusion of a second drug, lidocaine in the present study, a quantitative determination can be made of the contribution of the liver to total body metabolism of the drug. The technique may be easily used at the time of cardiac catheterization, and involves little discomfort to the patient. The only requirements are that the drug under study is nontoxic and that steady-state may be reached in a reasonable period of time. We anticipate much wider application of this technique in the study of drug metabolism.

Although the patients in the present study did not have myocardial infarction, the findings should be relevant to those patients in Coronary Care Units. Cardiac output is frequently depressed after infarction, and there may be a redistribution of blood flow away from the splanchnic bed during the acute phase. It seems likely that effective hepatic blood flow may be disproportionately reduced during the acute stages. These considerations probably account for the somewhat higher blood levels of lidocaine which were observed in patients shortly after myocardial infarction when similar infusion rates were utilized. In addition, none of the patients in this study had significantly impaired hepatic function apart from that which might be attributed to passive congestion or poor perfusion. Superimposed hepatic damage from other causes might well alter the lidocaine levels observed at various cardiac outputs.

It is our clinical observation that in patients who are in low output states and/or who have underlying liver disease, the dose of lidocaine administered may be reduced while still obtaining blood levels adequate for production of an antiarrhythmic effect. In these conditions it appears necessary to reduce these infusion rates in order that production of extremely high blood levels and clinical toxicity might be avoided.

References
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