Electrophysiologic Effects of Procaine Amide in Patients with Intraventricular Conduction Delay

By Melvin M. Scheinman, M.D., Alan N. Weiss, M.D., Eugene Shafton, M.D., Neal Benowitz, M.D., and Malcolm Rowland, Ph.D.

SUMMARY
In 16 patients with intraventricular conduction delay (IVCD) and cardiac arrhythmias, procaine amide (PA) was infused intravenously at rates of 30-40 mg/min until a maximum dose of 750-1,000 mg was administered. His bundle electrograms and plasma PA levels were obtained every 5 min during infusion and for 25 min thereafter. The mean peak PA level (10.2 ± 3.4 μg/ml) was achieved at the end of infusion. Mean control A-V nodal conduction times (A-H: 99.5 ± 34 msec) and A-V at peak PA levels (90 ± 15.3) did not differ significantly. However, the mean infranodal conduction time (H-Q) at peak PA (68.1 ± 14.8 msec) was significantly higher than control measurements (57.6 ± 13 msec) (P < 0.001), with a mean percent increase of 18% (11 msec), and maximal prolongation of H-Q occurred at peak PA blood levels. There was no statistically significant correlation between maximum absolute or percent change in H-Q and control H-Q, control QRS duration, or peak PA levels. One patient with sinus bradycardia had further decreases in rate and a junctional rhythm after PA. Intravenous administration of PA appears safe and effective for patients with IVCD in terms of arrhythmia control and absence of high degree A-V block, ventricular ectopic beats, or standstill, but caution should be used in treating patients with sinus bradycardia.

Additional Indexing Words:
Procaine amide  His bundle electrocardiography  Atrioventricular conduction
Cardiac arrhythmias

The Effectiveness of Procaine Amide Hydrochloride in the treatment of supraventricular as well as ventricular arrhythmias has been well documented.1–4 Previous studies in subjects with normal atrioventricular (A-V) and intraventricular (IV) conduction demonstrated that infusion of procaine amide results in impaired conduction and increased refractoriness of the His-Purkinje system.5, 6 Moreover, procaine amide administration has been implicated as the cause of high degree A-V block in patients with cardiac disease.7–9 The risk of procaine amide administration inducing higher degrees of A-V block or serious ventricular arrhythmias in patients with IV conduction delays is unknown.

Catheter recordings of the His bundle electrical activity allows more precise localization and quantification of A-V conduction disorders. This technique was used to assess the safety of intravenous administration of procaine amide in patients with IV conduction delay and cardiac arrhythmias. In addition, the relationship between differing clinical states and plasma procaine amide levels achieved and the relationship of these blood levels and the degree of A-V conduction impairment were also investigated.
**PROCVAINE AMIDE ON IV CONDUCTION**

**Materials and Methods**

Sixteen patients with stable IV conduction disturbances and chronic or acute cardiac arrhythmias requiring suppressive therapy were included in the study. Patients with recent (less than 1 month) myocardial infarction or severe heart failure were excluded from the study. A complete medical history, physical examination, serum electrolytes, blood tests to evaluate hepatic and renal function, and 12 lead electrocardiographic tracings documenting the rhythm disturbances were obtained before study in all cases. No patient was receiving drugs known to affect A-V conduction, except three with atrial fibrillation or atrial flutter who were receiving digoxin prior to and during the study. The study was approved by the University of California Committee on Human Experimentation and informed consent was obtained from each patient prior to the study.

His bundle recordings were obtained as described previously using standard techniques. His bundle electrograms and scalar leads X, Y, and inverse Z leads of the Frank orthogonal lead system were simultaneously displayed and recorded at a paper speed of 100 mm/sec. The A-V nodal conduction time (A-H interval) was measured from the initial rapid deflection of the atrial electrogram to the initial deflection of the His bundle depolarization. The His-Purkinje conduction time (H-Q) was measured from the initial His deflection to the earliest onset of ventricular activation detected in the surface electrograms. The normal ranges for A-H and H-Q for our laboratory are 70-120 msec and 35-55 msec, respectively. The QRS duration and the interval from the earliest onset of ventricular depolarization to the end of ventricular repolarization (QT interval) were measured from the surface leads.

Procaine amide, 750-1,000 mg, was diluted to a volume of 50 ml of 5% dextrose and water and a 5 ml aliquot was removed for determination of procaine amide concentration. The remaining 45 ml solution was infused into a peripheral vein by a Harvard constant infusion pump over a 22 min interval (infusion rate of 30-40 mg/min). A polyethylene catheter was inserted into a vein in the other arm opposite to the infusion site for periodic blood sampling. Plasma procaine amide levels were determined by a spectrophotometric technique. Control measurements of the cuff systemic pressure, heart rate, A-H, H-Q, P-A, QRS, and QT intervals were recorded and repeated every 5 min during and at the termination of the infusion and for 25 min after procaine amide infusion. In addition, 30 sec recordings at a paper speed of 25 mm/sec were obtained at the same 5 min intervals in order to count the number of premature beats. Blood samples for determination of procaine amide concentration were obtained simultaneously with each recording. The procaine amide infusion was terminated prior to completion of the study in two patients (table 1) because of hypotension (P.J.) and hypotension and junctional rhythm (F.B.), respectively. Because of the anticipated small changes in the measured intervals, great care was taken in the measurement of this data. The various intervals obtained from both the surface and intracardiac electrograms were measured by a specially designed grid which was calibrated at 0.5 mm intervals and the mean percent interobserver error was 4.6 ± 2.84 msec. The position of the catheter was not changed during the study and although beat to beat variation in atrial, His, and ventricular electrograms (most likely attributable to catheter motion) were frequently noted, this never resulted in significant changes in the measured intervals. Seven to 10 consecutive beats were analyzed for each 5 min study period and the average values obtained were used in the study.

All records were analyzed independently by two of the authors (A.W. and G.S.) and the interobserver differences were never greater than ±3%. These data were analyzed by Students paired t-test and a P value of <0.05 was considered significant.

A total of 16 patients with IV conduction delay were studied and the pertinent clinical information, peak plasma procaine amide levels, and electrophysiologic data are summarized in table 1.

**Results**

**Plasma Procaine Amide Concentration**

During infusion, plasma concentration of procaine amide rose to a mean peak level of 10.2 ± 3.4 (SD) µg/ml near the end of infusion (fig. 1) in all patients. A slight decline in plasma drug level occurred in some patients between 20 and 22 min and was probably due to a slight delay in synchronizing blood sampling at the actual completion of infusion. The plasma procaine amide concentration fell rapidly in the first 5 min postinfusion and then more slowly over the ensuing 20 min. The mean plasma procaine amide level was 4.9 ± 3.2 µg/ml at the termination of the study. Wide variability of plasma procaine amide concentrations occurred despite

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### Table 1

Clinical and Electrophysiologic Data for 16 Patients with Bundle Branch Block Before and at Peak Plasma Procaine Amide Concentration

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>ECG</th>
<th>Arhythmia</th>
<th>Peak procaine amide level (ug/ml)</th>
<th>Systemic pressure (mm Hg)</th>
<th>R-R</th>
<th>A-H</th>
<th>H-Q</th>
<th>QRS</th>
<th>QT</th>
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<tr>
<td>T.W.</td>
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<td>RBBB</td>
<td>PVCs</td>
<td>9.0</td>
<td>148/98</td>
<td>600</td>
<td>72</td>
<td>50</td>
<td>160</td>
<td>375</td>
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<tr>
<td></td>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td>P 134/90</td>
<td>70</td>
<td>62</td>
<td>160</td>
<td>375</td>
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<tr>
<td>F.G.</td>
<td>HCVD</td>
<td>RBBB</td>
<td>PVCs</td>
<td>6.4</td>
<td>170/110</td>
<td>790</td>
<td>110</td>
<td>65</td>
<td>150</td>
<td>300</td>
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<tr>
<td></td>
<td>LBBB</td>
<td></td>
<td></td>
<td></td>
<td>P 170/110</td>
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<td>80</td>
<td>160</td>
<td>302</td>
<td></td>
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<td>A.R.</td>
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<td>APCs</td>
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<td>140/90</td>
<td>600</td>
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<td>52</td>
<td>130</td>
<td>380</td>
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<td>92</td>
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<td>150</td>
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<td>A.O.</td>
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<td>87</td>
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<td>140</td>
<td>365</td>
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<td>H.T.*</td>
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<td>Atrial flutter</td>
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<td>128/80</td>
<td>850</td>
<td></td>
<td></td>
<td>170</td>
<td></td>
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<tr>
<td></td>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td>P 99/80</td>
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<td>F.B.*</td>
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<td>PVCs</td>
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<td>200</td>
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<td>J.H.*†</td>
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<td>LBBB</td>
<td>PVCs</td>
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<td>730</td>
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<td>65</td>
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<td>390</td>
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<td>H.A.§</td>
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<td>PVCs</td>
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<td>138/100</td>
<td>705</td>
<td>90</td>
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<td>125</td>
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<tr>
<td>W.H.*</td>
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<td>LBBB</td>
<td>Atrial flutter</td>
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<td>90/70</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P 89/70</td>
<td>95</td>
<td></td>
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<tr>
<td>P.J.*‡</td>
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<td>LBBB</td>
<td>Atrial fibrillation</td>
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<td>160/70*</td>
<td>675</td>
<td></td>
<td>68</td>
<td>150</td>
<td>380</td>
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<td>M.L.</td>
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<td>APCs</td>
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<td>370</td>
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<tr>
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<td>CAD</td>
<td>LBBB</td>
<td>APCs</td>
<td>8.0</td>
<td>140/80</td>
<td>705</td>
<td>125</td>
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<td>165</td>
<td>380</td>
</tr>
<tr>
<td>F.S.‡</td>
<td>HCVD</td>
<td>LBBB</td>
<td>PVCs</td>
<td>7.8</td>
<td>150/100</td>
<td>760</td>
<td>80</td>
<td>52</td>
<td>110</td>
<td>350</td>
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<tr>
<td></td>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td>P 148/100</td>
<td>745</td>
<td>82</td>
<td>52</td>
<td>115</td>
<td>365</td>
</tr>
</tbody>
</table>

Mean ± SD:

- 10.2 C 45 ± 27 S 748 ± 106 99.5 ± 34 57.0 ± 13.0 142 ± 19.7 383 ± 30.4 ± 3.41 C 130 ± 26 S 742 ± 95 90 ± 15.3 68.1 ± 14.8 154 ± 21.5 394 ± 33.4

- **Abbreviations:** HCVD = hypertensive cardiovascular disease; CAD = coronary artery disease; C = control recording; P = recording at peak procaine amide levels; RBBB = right bundle branch block; LBBB = left bundle branch block; LAD = left axis deviation; PVCs = premature ventricular contractions; APCs = atrial premature contractions; AVB = atrioventricular block; S = systolic; D = diastolic; and J = junctional rhythm.

- *Showed evidence of mild heart failure at the time of study (S, gallop with or without pulmonary rales).
- †Infusion terminated at 5 min because of hypotension and junctional rhythm all of which normalized 12 min after cessation of procaine amide infusion.
- ‡Mild renal insufficiency.
- §Cirrhosis.
- §§Infusion terminated at 15 min because of decrease in systolic pressure.
normalization of the procaine amide dose for body weight and rate of infusion (fig. 2). There was no correlation between plasma procaine amide levels and presence of congestive heart failure, renal insufficiency or hepatic disease, but the number of patients with these diagnoses was small (table 1). The highest blood level of drug was found in the one patient (W.H.) who had evidence of congestive heart failure and decreased peripheral perfusion.

A-V Conduction

Control A-H intervals were within normal limits in 12 patients and prolonged in one. Atrial flutter (with variable A-V conduction) or fibrillation was present in three. There was no significant correlation between change in A-H and plasma procaine amide levels. At the peak procaine amide concentration, three patients had depression of A-V nodal conduction, two had increased conduction, and seven subjects had essentially no change in A-V nodal conduction time (<2 msec difference). The group as a whole showed an over-all mean percent decrease in A-H time of 9.5%.

Control H-Q intervals were abnormal in eight of the 16 patients (with a range of 60-60 m/sec). The H-Q interval increased during infusion in 14 patients and remained unchanged in two. Although there was marked variability in the magnitude of change in H-Q intervals between patients, changes in His-Purkinje conduction were parallel with the rising procaine amide concentration, and maximal prolongation always occurred at the time of peak drug concentration (fig. 1). For the group as a whole, mean H-Q time at the end of infusion was 68.1 ± 14 m/sec and significantly higher than the mean control time of 57.8 ± 13.0 m/sec (P < 0.001) with a mean percent increase of 18% (11 m/sec). The relationship between plasma procaine amide concentration and effects on A-V conduction was studied by comparing changes in infranodal conduction time with plasma levels during and after the infusion. In those patients showing prolongation of the H-Q interval (14 of 16), two types of responses were noted. In each of two subjects (L.C., F.C.) (fig. 3) similar effects on infranodal conduction time were noted for a given plasma level both during and after infusion while in the remaining subjects (12 of 14) the degree of H-Q prolongation was greater for a given plasma level after cessation of the infusion compared with similar plasma levels achieved during the infusion.

For the group as a whole there was no statistically significant correlation between maximal absolute or percent change in the H-Q interval and control H-Q, control QRS duration or peak procaine amide concentration. The group was divided into two subgroups: ten patients had less than 15 m/sec maximal lengthening of H-Q interval and six had H-Q prolongation equal to or greater than 15 m/sec. Although the latter subgroup tended to have slightly greater control H-Q and QRS intervals as well as

![Figure 2](image_url)

**Figure 2**

Procaine amide levels normalized to a standard infusion rate of 35 mg/min in a 70 kg man (corrected plasma level = actual plasma level × 0.5 mg/min/kg/actual infusion rate (mg/min/kg)).

For the sake of clarity, data from seven patients are depicted but similar curves were inscribed for the remaining nine subjects.

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higher peak drug levels, there was no significant difference between the two groups with respect to these variables. The data were similarly analyzed with respect to H-Q times in the subsets of patients who showed either right bundle branch block (seven patients) or left bundle branch block (nine patients) at the time of study. Mean control H-Q time for patients with right bundle branch block was 52.8 ± 8.6 msec before and 64.8 ± 13.6 msec after the infusion. Mean control H-Q interval for patients with left bundle branch block was 61.3 ± 15 msec and increased to 70.5 ± 16 msec following the infusion. There was no statistically significant difference between the mean percent change in H-Q for each subgroup before or after the infusion.

**Effect on Sinus Rate**

In 13 patients with sinus rhythm mean heart rate increased slightly but not significantly from control R-R intervals of 748 ± 106 to 742 ± 95 msec at the end of infusion. One patient with documented episodes of sinus bradycardia before the study had a decrease in sinus rate 5 min after starting procaine amide infusion that was followed by hypotension and a junctional rhythm. The blood pressure and sinus rhythm returned within 12 min after termination of the infusion (fig. 4).

**QRS Duration and QT Interval**

Control QRS duration was equal to or greater than 120 msec in 15 patients and one had intermittent right bundle branch block. Prolongation of the QRS occurred in 11 patients during infusion and maximal prolongation always occurred at the time of peak procaine amide concentration. For the group as a whole, there was a small but significant prolongation of the QRS duration (mean change of 14 msec) at peak drug levels (P < 0.001) (fig. 2). The QT prolongation tended to parallel and was, in part, due to prolongation of the QRS duration.

**Blood Pressure**

There was no significant change in diastolic pressures before and during infusion; however, a significant decrease in systolic pressure (mean change of 15.2 mm Hg) occurred at the end of infusion.

![Figure 4](https://circ.ahajournals.org/)

*Figure 4*

A, control tracings of simultaneous X, Y, and inverse Z leads of the Frank orthogonal lead system and the His bundle electrogram from patient F.B. showing sinus rhythm at a rate of 65 beats/min. There is prolongation of A-V nodal (A-H) and infranodal (H-Q) conduction times. B, 5 min after initiation of infusion, sinus bradycardia (47 beats/min) developed at the time when the plasma procaine amide concentration (PA) was 4.9 μg/ml. C, 5 min later at a plasma procaine amide concentration of 7.0 μg/ml, hypotension and a junctional rhythm with 1:1 retrograde conduction (arrows depict inverted P waves in lead Y) at a rate of 52 beats/min developed and the infusion was terminated. D, 12 min after termination of infusion, the patient's rhythm returned to sinus bradycardia at a rate of 49 beats/min.
In two patients (P.J. and F.B.) infusion was terminated because of significant (>30 mm Hg) falls in systolic pressure. In both patients the fall in systolic pressure was transient and returned to control levels within 10 min after termination of infusion. There was no significant correlation between the absolute or percent change in systolic pressure and peak procaine amide concentration.

Arrhythmia Control
In nine of the 16 patients the atrial and/or ventricular beats were sufficiently frequent (>5/min) to allow for meaningful comparisons between control, intra- and postinfusion recordings. In seven of the nine patients the arrhythmia was either completely abolished (five subjects) or the number of premature beats was significantly decreased (two subjects). The frequency of premature beats decreased as therapeutic levels of procaine amide were achieved, and in some patients the arrhythmia recurred as plasma drug levels fell (fig. 5). Although small increases in A-V conduction time were observed, development of high degree A-V block, increased ventricular ectopic beats, or cardiac asystole did not occur in any patient during the study.

Discussion
Procaine amide is widely recognized as an effective antiarrhythmic agent. Previous work in the intact animal demonstrated that this agent causes prolongation of A-V nodal and intranodal conduction times.12-15 Studies in man also demonstrated delayed A-V conduction with depression of conduction localized primarily to the ventricular specialized conduction system.5,6 Furthermore, clinical studies implicated procaine amide as the cause of A-V block in patients with cardiac disease.7-9 Conceivably, patients with pre-existent IV conduction disturbances might be especially sensitive to this agent, and therefore, at greater risk for development of higher degrees of A-V block. Our study is unique in that we studied the electrophysiologic effects of procaine amide in patients with IV conduction disturbances.

Atrioventricular and IV Conduction
Our results establish the safety of intravenous administration of procaine amide in patients with bundle branch block insofar as high degree A-V block, ventricular ectopic beats, or cardiac asystole does not develop during or after procaine amide infusion. However, procaine amide infusion was associated with small and variable effects on A-V nodal conduction and consistent depression of intranodal conduction. The mean percent maximal lengthening of the H-Q interval was 18% (11 msec). These findings are in close agreement with those of previous studies of patients with normal A-V nodal and IV conduction.5,6 In the present study, the degree of H-Q prolongation could not be predicted on the basis of control QRS duration, bundle branch block pattern, H-Q interval, or peak procaine amide level achieved. Although there was marked variability in magnitude and time course of the H-Q prolongation among our patients, maximal values were always achieved at the time of the peak procaine amide plasma level. Similarly, there was a small but statistically significant increase in QRS duration and the maximal change occurred at the time of the peak procaine amide plasma level. The surface recordings of only one patient (W.H.) showed an increase in QRS duration greater than 25% and the procaine amide level reached in this patient (19.6 µg/ml) was the highest observed in this study.

Procaine Amide Levels
Therapeutic plasma levels of procaine amide (4-8 µg/ml)12 were achieved in all patients, and in 12 of the 16 patients peak plasma levels exceeded the usually accepted therapeutic range. In the vast majority of subjects the effects on the H-Q interval and QRS duration were greater at the same concentrations of plasma procaine amide after the infusion (fig. 3), suggesting either slower equilibration with intracardiac receptor sites or a lag in tissue respon-
siveness relative to given blood levels. Marked variations in plasma procaine amide levels among the subjects were noted despite normalization for body weight and rates of infusion. Plasma levels achieved were related primarily to tissue perfusion and drug distribution since the time course of infusion was such that negligible amounts of drug were cleared from the plasma by either hepatic metabolism or renal excretion. 16, 17 Koch-Weser clearly demonstrated that patients with congestive heart failure have a diminished volume distribution of procaine amide and hence higher plasma levels are achieved in these patients compared with normal subjects after comparable doses of the drug. In our study, however, there was no statistically significant correlation between the presence of cardiac failure and the plasma procaine amide levels achieved, but only three patients had clinical evidence of heart failure at the time of study. Equally significant, however, is the finding that a patient with heart failure and evidence of diminished peripheral perfusion (W. H., table 1) had the highest procaine amide levels. Further studies are needed to clarify the effects of heart failure and/or decreased cardiac output on plasma procaine amide levels, but caution should be used in administering large intravenous bolus infusions of procaine amide in patients with impaired cardiac function.

Clinical Implications
Our study demonstrated that acute intravenous infusions of procaine amide as administered in the study produced clinically effective plasma levels and were safe for patients with IV conduction disturbances in that no high degree of A-V block, ventricular ectopic beats or cardiac asystole resulted from procaine amide administration. Although most of the patients had prolongation of infranodal conduction at the peak procaine amide concentration, the magnitude of change was generally small (mean change, 11 ms) and probably of little clinical significance. It should be stressed, however, that these results are applicable only to the use of acute intravenous infusions of procaine amide. The safety of chronic oral or parenteral administration of this agent for these patients remains to be studied. Similarly, effects of this drug on patients with arterial hypoxemia, acid-base and/or electrolyte imbalance have not been defined, and therefore, appropriate caution should be used in the administration of this agent in these settings until more experience is available. Finally, caution should be used in the administration of this agent to patients with sinus bradycardia. Although the group as a whole showed no significant change in heart rate, one patient with pre-existent sinus bradycardia showed a pronounced fall in sinus rate during the infusion. One additional patient with sinus bradycardia (who was not included in the present study because plasma procaine amide samples were not processed for technical reasons) developed a slowing of sinus rate and had episodes of atrioventricular dissociation during the infusion. Given the above limitations, our studies indicate that acute intravenous administration of procaine amide appears to be both safe and effective for patients with intraventricular conduction delay.

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