Clinical Electrophysiologic Effects of Tocainide

JEFFREY L. ANDERSON, M.D., JAY W. MASON, M.D., ROGER A. WINKLE, M.D.,
PETER J. MEFFIN, PH.D., ROBERT E. FOWLES, M.D.,
FLORA PETERS, R.N., AND DONALD C. HARRISON, M.D.

SUMMARY The electrophysiologic properties of tocainide were evaluated by electrophysiologic studies in 11 patients before, during and after a constant intravenous infusion of the drug for 15 minutes. Peak plasma tocainide concentrations averaged 11.0 ± 1.7 µg/ml (SEM), range 3.7 to 22.7. AH, HV, QRS, QTc and RR intervals were measured every 5 minutes during sinus and atrial-paced rhythms and showed small changes which were not statistically significant for HV and QRS. Mild shortening of RR was significant (P < 0.05) at 15 minutes only. AH tended to increase slightly for spontaneous (but not paced) rhythm, becoming significant at 15 minutes only (P < 0.05). QTc decreased slightly, a change which was significant (P < 0.05) for paced but not spontaneous rhythm. A progressive rise in mean arterial pressure occurred during drug infusion and persisted through 30 minutes (P < 0.001). Comparison of electrophysiologic studies at 0 and 30 minutes showed decreases in mean effective refractory periods of atrium, A-V node, and right ventricle by 17, 22, and 23 msec, respectively (P < 0.05, 0.01, 0.01). Functional refractory period of the A-V node showed an average decrease which was not significant. Sinus node recovery time and Wenckebach cycle length were unchanged. The drug was well tolerated in all 11 patients. Hypotension in a twelfth patient may or may not have been drug related. These results obtained at therapeutic plasma concentrations suggest qualitative similarities between the conduction system effects of tocainide and those published for lidocaine.

TOCAINIDE (2-amino-2',6'-propionoxylidide HCl), a primary amine congener of lidocaine, has recently been shown to be an orally effective antiarrhythmic in man.\(^1\)\(^2\) Studies in conscious dogs indicated a marked antiarrhythmic effect against ischemia-induced ventricular arrhythmias with elevation of ventricular fibrillation threshold.\(^3\)\(^4\) In man, tocainide administered every 8 hours suppressed ventricular ectopic beats by more than 70% in 11 of 15 patients (average reduction 91 ± 10%) in a placebo-controlled multi-dose study.\(^5\) Following oral administration, tocainide is rapidly absorbed and has linear kinetics with a plasma elimination half-life of 12 to 15 hours.\(^6\)\(^7\) Both renal and nonrenal elimination occur. Toxicity, mainly neurologic, has been mild and rarely limiting in studies to date. Based on these preliminary observations, tocainide appears to have several favorable attributes, including excellent oral bioavailability, a long plasma half-life, and antiarrhythmic activity in the absence of severe toxicity.

No consistent effects on electrocardiographic intervals have been apparent in early studies.\(^1\)\(^2\) To further characterize the actions of tocainide on the cardiac conduction system in man, we performed intracardiac electrophysiologic studies during acute intravenous drug infusions in patients undergoing cardiac catheterization.

Methods

Patient Characteristics

Twelve patients without overt heart failure or limiting valvular disease were studied at the time of cardiac catheterization. Patient characteristics are summarized in table 1. The group consisted of eleven males and one female, aged 37 to 69 (mean 49.3 years). Eight patients had significant coronary artery disease, one patient had atypical chest pain with mild coronary artery disease, one patient had idiopathic cardiomyopathy, and two patients had mild to moderate valvular insufficiency. One patient had left anterior hemiblock, one patient showed left bundle branch block, and the remaining ten patients had normal resting electrocardiographic conduction patterns. Seven patients were taking maintenance propranolol and two were on chronic digoxin therapy. Propranolol was discontinued prior to catheterization as noted in table 1. Digoxin was omitted for 29 hours in patient 9 and continued in patient 11. Electrolytes were normal in all patients.

The experimental protocol was approved by the Stanford University Medical Committee on the Use of Human Subjects in Research, and written informed consent was obtained in each case. Cardiac catheterization was performed for clinical indications in the postabsorptive state under light sedation with diazepam 10 mg given orally.

Electrophysiologic Methods and Definitions

Electrophysiologic studies were undertaken at least 30 minutes following left ventriculography. A #6F or #7F quadripolar recording-stimulating electrode catheter was placed perversely in the high right atrium, and a #6F tripolar or #5F bipolar electrode catheter for His bundle recording was inserted through a femoral vein and positioned across the tricuspid valve. Surface electrocardiographic leads I, aVF, and V1 were recorded simultaneously with atrial and His bundle electrograms. Equipment and technique were similar to those in a previous report.\(^6\)

The experimental protocol is outlined in figure 1. A control electrophysiologic study consisting of sinus node recovery time (SNRT), Wenckebach cycle length (WCL), refractory periods, and blood pressure and electrographic interval measurements was performed prior to initiating the drug infusion. The atrial and ventricular paced stimuli used were pulsed square wave potentials of 2 msec duration and of amplitudes equal to twice diastolic threshold.

To assess sinus node recovery, the initial sinus pause and subsequent ten sinus cycles were measured after pacing for one minute at each of 3 or 4 cycle lengths (600, 500, 460, 400...
msec). The same set of cycle lengths was used for both studies in any one patient. The SNRT taken for analysis in each separate study was the maximum SNRT, i.e., the longest AA interval occurring following pacing at any cycle length.

The WCL, the longest cycle length at which atrioventricular (A-V) nodal Wenckebach consistently occurred, was determined to the nearest 10 msec. In some patients, pacing was terminated for considerations of patient safety before WCL was reached.

An atrial pacing rate was then selected for each patient at a heart rate 10 to 15 beats per minute above the spontaneous sinus rate, or at 75 beats/minute, whichever was greater (hereafter referred to as base atrial pacing rate). The base atrial pacing rate for individual patients was the same during both control and post-drug studies. Atrial, A-V nodal, and His-Purkinje refractory periods were determined to the nearest 5–10 msec by the extrastimulus technique. A premature stimulus (S2) was introduced following every eight paced beats (S1). The sequence of stimuli was programmed on a WPI digital stimulator. The S1–S2 interval was reduced by 10 msec intervals until absolute atrial refractoriness was reached. A-V nodal and His-Purkinje conduction times and refractory periods of atrium, A-V node, and His-Purkinje system were measured at the base atrial pacing rate as previously defined and reviewed below.6,7

Effective refractory period (ERP) of the atrium is defined as the longest S1–S2 interval at which S2 fails to depolarize the atrium. A-V nodal ERP is the longest A1–A2 interval at which A2 fails to depolarize the His bundle. A-V nodal functional refractory period (FRP) is the shortest H1–H2 interval resulting from an A1–A2 as long as A-V conduction is not limited by atrial refractoriness or, if so, is associated with a series of H1–H2 intervals that has reached a minimum and begun to increase prior to atrial refractoriness.

To determine right ventricular refractoriness, the His electrode catheter was advanced across the tricuspid valve to the right ventricular apex. A ventricular extrastimulus was introduced following every eight spontaneous sinus beats. The R–S1 interval was reduced by 5–10 msec until ventricular capture failed. The longest Q–S1 interval at which S1 consistently failed to cause ventricular depolarization was taken as the effective refractory period of the right ventricle. In one patient ventricular irritability precluded this measurement.

At the completion of the control electrophysiologic study and immediately prior to drug infusion spontaneous heart rate, PA, AH and HV intervals, surface QRS and QT intervals, and aortic pressure were recorded during both spontaneous rhythm and base atrial-paced rhythm. Aortic pressure was measured through a #7F end-hole pigtail catheter attached to a Statham P23Db transducer. AH interval,

*Numbers in brackets following propranolol dosage represent time of last dose in hours prior to study.

Abbreviations: MI = myocardial infarction; LVH = left ventricular hypertrophy; LAE = left atrial enlargement; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LMCA = left main coronary artery; RCA = right coronary artery; LAD = left anterior descending coronary artery; LV = left ventricle; CAD = coronary artery disease; AR = aortic regurgitation.

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**Table 1. Clinical Information on Patients Receiving Tocainide**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>ECG findings</th>
<th>Diagnoses</th>
<th>Drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 2</td>
<td>F</td>
<td>51</td>
<td>Minor ST segment abnormality</td>
<td>Progressive angina (mild &lt;40% narrowing of LMCA; no other CAD)</td>
<td>Isosorbide dinitrate, propranolol (40 mg bid, [32] mercapto thiobenzoate, hydralazine, nitroglycerine)</td>
</tr>
<tr>
<td>3 &amp; 4</td>
<td>M</td>
<td>69</td>
<td>Old anterolateral MI; diffuse T-opacification</td>
<td>Post-2 MIs (40% RCA, 95% LAD, apical LV aneurysm)</td>
<td>Tocainide, Hydralazine, Nifedipine</td>
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<tr>
<td>5 &amp; 6</td>
<td>M</td>
<td>45</td>
<td>Probably normal</td>
<td>Mitral valve prolapse with moderate mitral regurgitation</td>
<td>None</td>
</tr>
<tr>
<td>7 &amp; 8</td>
<td>M</td>
<td>51</td>
<td>Old inferior MI</td>
<td>Post-MI (posterosobal hypokinesia, severe 3 vessel CAD)</td>
<td>Propranolol (15 mg qid [31]), Isosorbide dinitrate, Hydrochlorothiazide</td>
</tr>
<tr>
<td>9 &amp; 10</td>
<td>M</td>
<td>41</td>
<td>Old anterolateral MI; LAHB</td>
<td>Post-MI (obstruction of 2nd obtuse marginal)</td>
<td>Propranolol (15 mg qid [21]), Isosorbide dinitrate</td>
</tr>
<tr>
<td>11 &amp; 12</td>
<td>M</td>
<td>52</td>
<td>Old inferior MI; sinus bradyarrhythmia</td>
<td>Post-inferior MI, CAD</td>
<td>Isosorbide dinitrate</td>
</tr>
<tr>
<td>13 &amp; 14</td>
<td>M</td>
<td>46</td>
<td>LBBB</td>
<td>Idiopathic cardiomyopathy</td>
<td>Digoxin, (0.25 mg/day), Furosemide, Hydrochlorothiazide, Isosorbide dinitrate</td>
</tr>
<tr>
<td>15 &amp; 16</td>
<td>M</td>
<td>52</td>
<td>Normal</td>
<td>Angina (2-vessel CAD)</td>
<td>Tocainide (40 mg qid [31])</td>
</tr>
</tbody>
</table>

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**Figure 1. Outline of experimental protocol.** Time (T) in minutes is indicated on horizontal scale. Tocainide (TOC) was infused between 0 and 15 minutes. INT/SP indicates interval (AH, HV, QRS, QT, RR) and blood pressure measurements, with and without pacing, taken at 5 minute intervals. Blood samples for plasma tocainide concentration (CP) were drawn at 0 and 195 minutes as indicated. Complete electrophysiologic (CEP) studies were completed at (A) just prior to infusion (control study) and initiated again at (B) (drug study, 30 minutes).
defined in our laboratory as the interval from the onset of the high right atrial electrogram to the onset of the His bundle deflection, is normally 60 to 130 msec. The HV interval, a measure of His-Purkinje conduction, is taken from the initial His deflection to the earliest part of ventricular depolarization (normally 35–50 msec). The PA interval was measured from earliest onset of P activity in the surface or high atrial leads to the first rapid A deflection in the low atrial lead. For paced rhythm the stimulus to low atrial (SA) interval was used. QT interval was corrected to a cycle length of 1 second by the formula:

\[ \text{QTc} = \frac{\text{QT}}{\sqrt{R-R}} \]

Drug Administration

Tocainide was administered intravenously by a constant-rate infusion pump for a 15 minute period at either 0.5 mg/kg/min (two patients) or 0.75 mg/kg/min (10 patients) (table 2). From the antecubital vein of the other arm, blood samples were obtained at 0, 1, 5, 10, 15, 20, 25, 30, 45, 75, and 195 minutes after the beginning of the infusion. Plasma tocainide concentrations (Cp) were determined by a high-pressure liquid chromatographic method.*

Measurements of paced and spontaneous AH, HV, QRS, QT, and RR intervals and blood pressure were repeated every 5 minutes for 30 minutes. The start of the drug infusion was defined as zero time and all noncontrol measurements are reported in minutes from this time (fig. 1). After these measurements were obtained at 30 minutes, an electrophysiologic study similar to the pre-drug control was repeated.

Statistical Analysis

Electrophysiologic data were compared with control measurements by the two-tailed Student’s t-test for paired data. Patient 12 experienced nausea and became hypotensive and somewhat bradycardic at 13 minutes. The study was terminated and he was treated with intravenous fluids, atropine, and atrial pacing with prompt recovery of blood pressure. Insufficient comparative data had been measured to include this patient in statistical analysis; the patient is discussed separately below.

Results

Plasma Tocainide Concentrations

Plasma concentrations of tocainide (Cp) obtained in this study with infusions of 0.5 or 0.75 mg/kg/min for 15 minutes are shown in figure 2A and table 3. The mean Cp for the two patients receiving the lower dose did not differ sufficiently to warrant separate analysis; therefore means for the entire group are presented. Peak plasma tocainide concentrations averaged 11.0 ± 1.7 μg/ml (SEM), range 3.7 to 22.7. By 30 minutes, Cp had entered a relative plateau phase. At that time, Cp averaged 7.4 ± 0.6, range 3.1 to 10.0. Individual data for 30 minutes are given in table 2.

Electrophysiologic data are presented in tables 2 and 3 and summarized below.

**Table 2. Individual Patient Data from Electrophysiologic Studies**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Dose (mg/kg/min)</th>
<th>Side effects</th>
<th>Cp (μg/ml)</th>
<th>SCL (mm Hg)</th>
<th>BP (mm Hg)</th>
<th>SNRT (msec)</th>
<th>BAP-CL (msec)</th>
<th>AERP (msec)</th>
<th>AVN-ERP (msec)</th>
<th>AVN-FRP (msec)</th>
<th>WCL (msec)</th>
<th>RV-ERP (msec)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>.5</td>
<td>p</td>
<td>940</td>
<td>98</td>
<td>1.23</td>
<td>800</td>
<td>340</td>
<td>530</td>
<td>510</td>
<td>520</td>
<td>300</td>
<td>290</td>
</tr>
<tr>
<td>2</td>
<td>.5</td>
<td>p</td>
<td>990</td>
<td>100</td>
<td>1.54</td>
<td>800</td>
<td>290</td>
<td>380</td>
<td>480</td>
<td>420</td>
<td>355</td>
<td>310</td>
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<tr>
<td>3</td>
<td>.75</td>
<td>(a) 900</td>
<td>100</td>
<td>1.72</td>
<td>800</td>
<td>220</td>
<td>330</td>
<td>485</td>
<td>520</td>
<td>285</td>
<td>240</td>
<td>240</td>
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<tr>
<td>4</td>
<td>.75</td>
<td>p, m</td>
<td>765</td>
<td>100</td>
<td>1.30</td>
<td>600</td>
<td>220</td>
<td>360</td>
<td>465</td>
<td>510</td>
<td>260</td>
<td>260</td>
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<tr>
<td>5</td>
<td>.75</td>
<td>p, v</td>
<td>720</td>
<td>78</td>
<td>1.50</td>
<td>600</td>
<td>240</td>
<td>320</td>
<td>410</td>
<td>410</td>
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<td>240</td>
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<tr>
<td>6</td>
<td>.75</td>
<td>p, a</td>
<td>1120</td>
<td>82</td>
<td>1.19</td>
<td>800</td>
<td>250</td>
<td>-</td>
<td>470</td>
<td>300</td>
<td>290</td>
<td>290</td>
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<tr>
<td>7</td>
<td>.75</td>
<td>p, m</td>
<td>1180</td>
<td>80</td>
<td>1.16</td>
<td>800</td>
<td>300</td>
<td>-</td>
<td>400</td>
<td>340</td>
<td>260</td>
<td>260</td>
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<tr>
<td>8</td>
<td>.5</td>
<td>p</td>
<td>845</td>
<td>84</td>
<td>1.64</td>
<td>800</td>
<td>280</td>
<td>-</td>
<td>525</td>
<td>-</td>
<td>330</td>
<td>-</td>
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<tr>
<td>9</td>
<td>.75</td>
<td>p</td>
<td>875</td>
<td>76</td>
<td>1.50</td>
<td>700</td>
<td>280</td>
<td>-</td>
<td>350</td>
<td>300</td>
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<td>300</td>
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<tr>
<td>10</td>
<td>.75</td>
<td>p</td>
<td>835</td>
<td>91</td>
<td>1.47</td>
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<td>470</td>
<td>280</td>
<td>280</td>
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<tr>
<td>11</td>
<td>.75</td>
<td>p</td>
<td>815</td>
<td>114</td>
<td>1.56</td>
<td>600</td>
<td>210</td>
<td>300</td>
<td>515</td>
<td>460</td>
<td>255</td>
<td>255</td>
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<tr>
<td>12</td>
<td>.75</td>
<td>p, h</td>
<td>806</td>
<td>108</td>
<td>1.47</td>
<td>540</td>
<td>200</td>
<td>-</td>
<td>330</td>
<td>-</td>
<td>210</td>
<td>-</td>
</tr>
</tbody>
</table>

Mean (pts. 1-11) | - | 888 | 90 | 1.44 | 714 | 258 | 346 | 464 | 449 | 298 |

| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

| | | | | | | | | | | | | |

**Abbreviations:** p = parenthesis; a = auditory change; v = visual change; m = mental change; b = hypotensive resection; Cp = plasma tocainide at 30 minutes; SCL = sinus cycle length; BP = mean systemic pressure (sinus rhythm); SNRT/RR = ratio of sinus node recovery time (SNRT) to spontaneous cycle length (RR); BAP-CL = base atrial pacing cycle length; AERP = atrial effective refractory period; AVN-ERP = AV nodal effective refractory period; AVN-FRP = AV nodal functional refractory period; WCL = Wenckebach cycle length; RV-ERP = right ventricular effective refractory period.

**Footnotes:**

(a) control (pre-infusion) study (time = 0).

(b) drug study (time = 30 minutes).

**NS** = not significant.
Sinus Node

Cycle length (RR interval) was either unchanged (four patients) or showed a modest decrease (seven patients) at the end of tocainide infusion. Measurement of mean sinus cycle lengths at 5 minute intervals are plotted in figure 2B. Only the mean decrease from 868 ± 53 to 812 ± 45 msec at 15 minutes was significant (P < 0.05). Individual effects on rate were similar whether initial resting heart rates were relatively low or high (table 2).

Sinus node recovery time (SNRT), as a percentage of spontaneous cycle length, is plotted for each patient before and after drug infusion (fig. 3). Increases occurred in 6 patients and decreases in 5 patients. The mean SNRT/RR ratio (1.44 ± 0.05 control vs 1.45 ± 0.05 drug study) for the group was unchanged. Four patients had initial SNRT/RR ratios greater than 1.50. No significant change occurred in this subgroup following drug (1.65 ± 0.03 to 1.59 ± 0.06). When corrected by subtracting resting RR interval, mean SNRT for the whole group was 371 ± 51 before and 378 ± 37 after drug, an insignificant change.

Atrium

Individual effects of tocainide on atrial effective refractory period (AERP) are shown in figure 4A. AERP decreased in eight patients, was unchanged in one patient, and increased in two patients. The mean decrease of 17 msec accompanying drug infusion (258 ± 14 to 241 ± 9 msec) reached significance at the level of P < 0.05.

No change occurred in PA interval after drug (table 3).

Atrioventricular Node

Atrioventricular conduction time as judged by AH intervals showed variable small changes (usually small increases...
or no change) during sinus and paced rhythms (fig. 2D). Small mean changes were significant only at 15 minutes during sinus rhythm (113 ± 6 to 119 ± 7 msec, P < 0.05), but were not significant during atrial-paced rhythm. Mean values for 0, 15, and 30 minutes appear in table 3. No case of A-V block was induced by tocainide and no patient showed more than a 10% increase in AH interval during drug. Two patients had resting AH above 130 msec, the upper limit of normal. In patient 3, AH was 140 msec and was unchanged during drug infusion (Cp at 15 minutes = 9.8 μg/ml). In patient 8, resting AH was 145 msec and at 15 minutes (Cp = 4.0 μg/ml) was 155 msec.

Wenckebach cycle length (WCL), determined in seven patients, decreased in two, increased in two, and remained unchanged in three (fig. 5). In these patients WCL was 449 ± 30 before and 454 ± 26 msec after drug, an insignificant change. Three of these patients had baseline WCL prolonged to 500 msec or over, but tocainide did not cause further prolongation.

The A-V nodal effective refractory period (AVN-ERP) could be measured both before and after tocainide in seven patients and decreased by a mean of 22 msec (346 ± 22 to 324 ± 20 msec), a significant change (P < 0.01). Individual changes included a decrease in six and a slight increase in one patient (fig. 4C). In another patient, the AVN-ERP decreased from 240 msec to ≤ 210 msec. The AVN-ERP could not be measured in three other patients due to earlier atrial refractoriness.

The functional refractory period of the A-V node (AVN-FRP), which could be determined in 10 patients, decreased in six, was unchanged in one, and increased in three patients (fig. 4D). The mean decrease of 14 msec (464 ± 21 to 450 ± 26 msec) was not significant.

![Figure 4. Refractory period measurements. A) Atrial effective refractory periods (ERP). B) Right ventricular effective refractory periods (RV-ERP). C) A-V nodal effective refractory periods (ERP). D) A-V nodal functional refractory periods (FRP).](image)

![Figure 5. Wenckebach cycle lengths (WCL).](image)
His-Purkinje System

His-Purkinje conduction, as measured by the HV interval, showed no significant change with tocainide infusion (table 3). Similarly, the QRS duration was unchanged (table 3). In individual patients, increases in HV and QRS never exceeded 5-10%, and no case of intraventricular conduction delay occurred. Patient 3 had an initially prolonged HV interval of 70 msec; at peak tocainide Cp (15 minutes) it measured 75 msec. Patient 9 had a control QRS which was prolonged to 110 msec; after tocainide infusion (15 minutes) it measured 115 msec. Patient 11 had a prolonged control QRS of 160 msec; it was unchanged by tocainide.

Effective refractory period of the His-Purkinje system (HP-ERP) could not be determined because preferential block did not occur in any patient below the His bundle. The relative and functional refractory periods of the His-Purkinje system could be measured in one patient, and both decreased (by 55 and 35 msec, respectively).

Ventricular Refractoriness and Repolarization

The effective refractory period of the right ventricle (RV-ERP) was measured in 10 patients and decreased by a mean of 23 msec (298 ± 14 to 275 ± 11), a significant change (P < 0.01). Individual values are represented in table 2 and in figure 4B. In nine patients a decrease, and in only one an increase in RV-ERP was noted after tocainide.

Ventricular repolarization time during sinus and atrial-paced rhythms, as reflected by QTc interval, was unchanged or decreased slightly with drug infusion. Mean values are presented in table 2 and shown graphically in figure 2E. There was no significant change in QTc during sinus rhythm at any time when compared with control. The overall decrease at 15 minutes (447 ± 10 to 436 ± 11 msec) in QTc during atrial pacing reached significance at P < 0.05.

Arterial Pressure

A moderate, progressive rise in aortic pressure occurred during tocainide infusion, persisting through 30 minutes (fig. 2C, tables 2, 3). Mean aortic pressures during sinus (or paced) rhythm increased from 89.6 ± 3.3 (92.4 ± 3.1) mm Hg pre-drug to 105.6 ± 2.4 (107.4 ± 2.7) at the end of infusion (15 minutes, P < 0.001) and to 106.9 ± 3.2 (108.7 ± 3.1) at 30 minutes (15 minutes postinfusion, P < 0.001). Average systolic and diastolic pressures also increased significantly (P < 0.001 - 0.01) by 15 minutes and remained elevated above control at 30 minutes.

Side Effects

Severe adverse reactions did not occur in patients 1 through 11. Mild paresthesias was common, however, occurring in eight of these patients (table 2). A feeling of coolness, occasionally numbness or burning, about the lips, face, throat, limbs or chest was the most common subjective description of drug effect. Minor changes in visual perception, in auditory perception, increased alertness, and mild confusion each occurred in one case. These minor neurologic effects were initially noted between 2 and 11 minutes (average 6.25 minutes) of drug infusion and correlated poorly with Cp. Plasma tocainide concentrations during these events ranged from 0.7 to 19.9 µg/ml (average 7.3 µg/ml). Three patients, achieving average Cp of 8.1 µg/ml, perceived no drug effects. Paresthesias disappeared within 5 minutes after the infusion ended. No nausea or vomiting, tremor, seizures, or other serious neurologic effects occurred. Moderate elevations in arterial pressure were unaccompanied by clinical adverse effects. Urinalysis and blood chemistries, including electrolytes, hematologic, renal, and liver function tests, were checked before and 24 hours after infusion and showed no significant abnormalities or changes. Nausea, hypotension and bradycardia noted at 13 minutes in patient 12 were felt clinically to represent a vasovagal reaction; however, a reaction to tocainide cannot be excluded. The study was terminated and the patient was treated with atropine 0.6 mg, intravenous fluids and atrial pacing, with prompt response. Plasma tocainide at 10 minutes in this patient was 7.3 µg/ml, with an unusually steep rise to 25.5 µg/ml at 15 minutes. It was unclear whether this rise caused, was secondary to, or was unrelated to the hypotension.

Discussion

The clinical electrophysiologic effects of intravenous tocainide were ascertained for mean plasma levels in the therapeutic range in this study. We have previously shown oral tocainide to be effective and well tolerated for suppressing premature ventricular contractions at plasma concentrations subject to wide individual variation but usually ranging between 4 and 10 µg/ml. The infusion rates used here were designed to provide tocainide concentrations in the range shown to be effective and clinically well tolerated for orally administered drug. Mean plasma concentrations (Cp) at the end of the infusion (10.6 ± 1.8 µg/ml) and at 30 minutes (7.4 ± 0.6 µg/ml) demonstrate these doses to be appropriate. The broad ranges of Cp are noteworthy, however, and reflect large individual differences in drug distribution.

Tocainide resulted in mean decreases in all refractory periods measured although individual variations occurred. The mean changes in AERP and AVN-ERP (17 and 22 msec) are similar to those induced by therapeutic concentrations of lidocaine. Josephson and associates gave lidocaine (1 mg/kg bolus, then 1 mg/kg/min infusion) and noted mean decreases in atrial and A-V nodal ERP in 14 patients of 13 and 24 msec respectively. These changes did not reach statistical significance, however. His-Purkinje ERP decreased by 15-25 msec in three of four of their patients.

Right ventricular ERP decreased in nine of 10 patients following tocainide, for a mean decrease of 23 msec (P < 0.01). Olsson et al. noted a directionally similar trend following a 75 mg lidocaine bolus, with a decrease or no change in RV-ERP in eight of 10 patients. The overall small decrease in RV-ERP in their study was not significant, however. Engel et al. determined RV-ERP in 11 patients following lidocaine boluses totaling 0.7 or 1.4 mg/kg, and found no significant change in RV-ERP. This result, obtained at plasma lidocaine concentrations ranging from 1.9 to 5.8 µg/ml, held for RV-ERP during spontaneous, ventricular, and atrial-driven rhythms. In their study, changes in ventricular-driven rates were associated with small decreases in RV-ERP of approximately 1 msec per 10 msec decrease in cycle length. In our study, a significant change in heart rate between the control and the 30 minute drug study to explain the decrease in RV-ERP observed did not occur.
Tocainide/Anderson et al.

No change or mild facilitation of sinus node automaticity following tocainide was evidenced by a lack of effect on sinus node recovery time and no change or a slight increase in heart rate. QRS was not affected by tocainide, and QTc was unchanged or decreased slightly. Similarly, lidocaine in therapeutic concentrations did not cause significant changes in electrocardiographic intervals (RR, PR, QRS, QT) in human subjects in the study of Kermayer:QTc shortening occurred but did not reach significance. The small mean decreases in QTc noted here for tocainide reached significance at P < 0.05 for paced but not sinus rhythms.

Tocainide induced no change or minor increases in atrioventricular conduction time, as measured by AH intervals. HV interval, a measure of His-Purkinje conduction, was unchanged. Similarly, lidocaine (50–100 mg boluses) caused minimal changes in His bundle measurements (AH, HV); occasionally slight depression, usually no change, but no acceleration of intraventricular conduction occurred.

The moderate rise in mean arterial pressure noted here is similar to findings in a recent study of the hemodynamic effects of intravenous tocainide and is a consequence of increased vascular resistance. It has not been determined whether this represents an indirect (autonomic) or a direct effect on vascular tone. This change is directionally similar to, although quantitatively greater than, that of lidocaine (1 mg/kg, injection) and contrasts with that of intravenous procaïnanide.

It is evident from the preceding discussion that the effects of tocainide on electrophysiologic and blood pressure measurements resemble those of lidocaine in many respects, with a few apparent differences. The use of bolus injections of lidocaine, associated with rapidly changing plasma concentrations, or of lidocaine infusions, but without adequate data on plasma concentration, in previously reported studies make exact comparisons of the effects of lidocaine and tocainide difficult. Further studies of lidocaine will be required if more quantitative comparison of these drugs is to be made.

Mexiletine, another lidocaine-like agent, is said to cause no consistent changes in heart rate, AH or HV intervals, or atrial or A-V nodal refractory periods. However, there has been a significant incidence of unacceptable bradycardia and hypotension, increased conduction block, and neurologic toxicity during the intravenous use of this agent.

The actions of tocainide and lidocaine on isolated conduction tissue remain to be compared, but might be expected to be similar. At therapeutic (1–4 µg/ml) to somewhat higher plasma concentrations, lidocaine induces small but consistent decreases in action potential amplitude and duration, conduction velocity, and automaticity in Purkinje fiber bundles. Effective refractory period decreases but to a lesser extent than does action potential. The voltage-time course of repolarization is accelerated. The probable mechanisms by which these changes lead to the antiarrhythmic action of lidocaine have been discussed elsewhere.

Tocainide was generally well tolerated by intravenous infusion in the present study. Blood pressure increases and the provocation of minor paresthesias did not result in clinical intolerance. The occurrence of hypotension at high tocainide plasma concentrations may have been drug-related in patient 12, although a vasovagal reaction was suspected clinically. Two other patients with peak Cp over 19 µg/ml showed increases in blood pressure at 15 minutes.

In summary, tocainide seems to be a relatively safe antiarrhythmic drug with little depressant effect on the conduction system and myocardium at therapeutic plasma concentrations. Although lidocaine may continue to be the preferred agent for intravenous use, the excellent oral bioavailability and patient tolerance, prolonged elimination half-life, and antiarrhythmic efficacy of tocainide appear to support its continued use as an oral agent for short-term and chronic testing.

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