Periodic procainamide for paroxysmal tachycardia

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ABSTRACT We evaluated the efficacy of a single oral dose of procainamide to terminate paroxysmal tachycardia, when procainamide was taken shortly after onset of tachycardia, a regimen we have termed “periodic procainamide.” In 12 patients (mean age 15 years) with non–life-threatening tachycardia (orthodromic reciprocating tachycardia, 8/12; ventricular tachycardia, 3/12; atrial flutter, 1/12) in whom intravenously administered procainamide (15 mg/kg at 1 mg/kg/min) terminated tachycardia, efficacy of a single oral dose of procainamide (25 mg/kg) to terminate tachycardia was tested during electrophysiologic study. After oral administration of procainamide, tachycardia was terminated and could not be reinitiated in 11 of 12 patients (9/12 < 75 min, 2/12 > 120 min after administration). Time of tachycardia termination approximately coincided with the time of peak serum concentration of procainamide after the single oral dose. Delayed response or failure of procainamide to terminate tachycardia was associated with delayed and diminished peak serum procainamide concentration. After evaluation, 10 responders were instructed to take a single dose of procainamide when tachycardia occurred. During a mean follow-up of 9 months (range 2 to 17) seven of 10 patients had an opportunity to use periodic procainamide on one to more than 100 occasions; four of 10 patients have not had recurrence of tachycardia. Tachycardia was successfully terminated in six of seven patients using the periodic regimen and could not be terminated on the first out-of-hospital use in one of seven patients. Success of periodic procainamide was predicted during evaluation by rapid termination of tachycardia after oral administration.


TRADITIONAL treatment of patients with paroxysmal tachycardia has been long-term oral prophylaxis with antiarrhythmic drugs to prevent recurrences. With a prophylactic drug regimen, one or more antiarrhythmic drugs are taken on a scheduled basis, one or more times a day, to prevent paroxysmal tachycardia, which may occur relatively infrequently. The risk of adverse side effects and the cumulative expense of medication are recognized disadvantages of long-term prophylactic therapy, especially in young patients with paroxysmal tachycardias. Margolis et al. proposed use of intermittent drug therapy in which a combination of antiarrhythmic drugs in the form of a “cocktail” was taken only after the onset of an episode of tachycardia. Their study established the feasibility of this approach, and they reported success in 24 of 32 patients with supraventricular or ventricular tachycardias.

We evaluated the ability of a single oral dose of procainamide to terminate tachycardia, when procainamide was taken shortly after the onset of tachycardia, a regimen we have termed “periodic procainamide.” Procainamide was selected because, among available antiarrhythmic drugs, it is effective for a variety of tachycardias, it is available for both parenteral and oral administration, and it is well absorbed after oral administration in most patients. We attempted to minimize the influence of interpatient variation in pharmacodynamic properties or “drug effects” by administering the drug orally only to patients in whom the intravenous preparation terminated paroxysmal tachycardia; thereby we hoped to evaluate the pharmacokinetic basis for success or failure of the periodic regimen.

Methods

Patient selection. During electrophysiologic study, we administered procainamide intravenously to 27 patients (17 male, 10 female; ages 0.6 to 38 years) with recurrent paroxysmal tachycardia. Before all procedures, written informed consent

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was obtained. Each patient had had electrocardiographic (ECG) documentation of paroxysmal tachycardia on more than one occasion. In these patients, recurrences of tachycardia usually exceeded 3 hr and often necessitated an emergency visit for termination of the arrhythmia. During spontaneous tachycardia, no patient had syncope and each had demonstrated an ability to tolerate tachycardia for 3 hr or longer.

During electrophysiologic study with either transvenous2-3 or transesophageal catheters,4 all patients had inducible tachycardia (orthodromic reciprocating tachycardia, 14/27; ventricular tachycardia, 7/27; and atrial flutter, 6/27). In each case; ECG features of induced tachycardia were identical to those that had occurred spontaneously.

After initiation of tachycardia, procainamide was administered intravenously by infusion pump (15 mg/kg at a rate of 1 mg/kg/min). During infusion, patients were questioned for symptoms, and blood pressure was measured frequently by sphygmomanometer or continuously by an indwelling arterial line. In 12 patients tachycardia was terminated during the infusion and could not be reinitiated by a stimulation protocol similar to that used before drug infusion. The results of these 12 responders form the basis of this report.

Description of procainamide responders. Of the 12 patients responding to the intravenous preparation of procainamide, eight were male and four female (ages 0.6 to 33 years, mean 15) (table 1). Patient 5 had levo transposition of the great arteries with mild Ebstein's anomaly of the left-sided atrioventricular valve. Patients 3, 4, 6, 9, 11, and 12 exhibited ECG features of Wolff-Parkinson-White syndrome. No patient had other recognized heart disease. No patient had evidence of hepatic or renal dysfunction.

The past history of tachycardia was varied among the 12 procainamide responders. Each had been admitted to the hospital or emergency room for conversion of tachycardia on one or more occasions (mean 3.4, range 1 to 5). Only four patients or their parents acknowledged that tachycardia had ever converted spontaneously without treatment. Three patients had never taken antiarrhythmic drugs except under emergency circumstances; however, nine patients had previously used an average of 2.2 (range 1 to 3) antiarrhythmic drugs (digoxin, propranolol, verapamil, and quinidine sulfate) alone or in combination in an effort to prevent recurrence of tachycardia.

Initial electrophysiologic evaluation of procainamide responders. Each patient underwent electrophysiologic study in the fasting state on two occasions. Before each study written informed consent was obtained. During the initial assessment the response to the intravenous preparation of procainamide was assessed. At the second study, the response of tachycardia to oral administration of procainamide was assessed. The techniques used in this laboratory during transvenous2-3 or transesophageal4 electrophysiologic study have been previously described but are reviewed here briefly.

At the initial study, nine patients underwent transvenous electrophysiologic evaluation. In brief, after percutaneous cannulation of the right femoral and left median basilic or subclavian veins, four No. 6F quadripolar electrode catheters were positioned in the high right atrium, right ventricular apex, across the tricuspid valve to record the His electrogram, and within the coronary sinus by fluoroscopic guidance. Patients were medicated with lidocaine for local anesthesia and diazepam (1.0 to 2.5 mg) as needed for sedation. Atrioventricular and ventriculoatrial conduction and refractoriness were assessed by incremental pacing and extrastimulus testing in the right atrium, right ventricle, and coronary sinus. Additionally, in patients with evidence of accessory atrioventricular connection, short bursts (four to 10 stimuli) at cycle lengths of 200 to 70 msec were delivered in the right atrium and coronary sinus in an effort to initiate atrial fibrillation. Finally, in patients without evidence of accessory atrioventricular connection, efforts were made to induce ventricular tachycardia by a previously described protocol.3 No patient required more than three extra stimuli for initiation of ventricular tachycardia.

In all nine patients undergoing catheter electrophysiologic study, tachycardia with ECG features identical to spontaneously observed tachycardia was initiated. In patients 2, 8, and 10, ventricular tachycardia was present.5 In these three patients, the ECG pattern of right bundle branch block with left axis deviation suggested ventricular tachycardia similar to that described by Lin et al.6 Patients 4, 6, 9, 11, and 12 had ECG features of ventricular preexcitation during sinus rhythm, and during elec-

### TABLE 1
Clinical features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arrhythmia</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Oral dose (mg)</th>
<th>Follow-up time (mo)</th>
<th>Use (No.)</th>
<th>Comment</th>
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</thead>
<tbody>
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<td>110</td>
<td>18</td>
<td>500 (27.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>VT</td>
<td>13</td>
<td>152</td>
<td>42</td>
<td>1000 (23.8)</td>
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<td>ORT</td>
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<tr>
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<td>ORT</td>
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<tr>
<td>7</td>
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<td>157</td>
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AF = atrial flutter; ORT = orthodromic reciprocating tachycardia; VT = ventricular tachycardia.

<sup>a</sup>Data in parentheses are expressed as mg/kg.

<sup>b</sup>Switched to long-term prophylaxis after 1 month.

<sup>c</sup>Concomitant therapy with long-term propranolol.

<sup>d</sup>Wolff-Parkinson-White syndrome.
trophysiologic study they were determined to have accessory atrioventricular connections with bidirectional conduction that participated in orthodromic tachycardia. Patient 7 had no evidence of accessory atrioventricular connection or ventricular tachycardia, but he did have inducible atrial flutter.

Patients 1, 3, and 5 underwent transesophageal electrophysiologic study. A silicone rubber–coated bipolar catheter with 22 mm interelectrode spacing (Medtronic Inc, 6904-A) was inserted through the nares to the minimum pacing threshold site in the distal esophagus. Patients were sedated with meperidine (1 to 2 mg/kg) as needed for sedation. Atrial ventricular conduction and refractoriness were assessed by incremental pacing and extrastimulus testing from the esophageal pacing site. Additionally, short bursts (four to 10 stimuli) at cycle lengths of 200 to 70 msec were delivered in an effort to initiate atrial fibrillation. Based on ventriculoatrial intervals during tachycardia with a normal QRS complex and during transient, rate-related bundle branch block, patients 1, 3, and 5 were thought to have orthodromic reciprocating tachycardia. Patient 3 demonstrated preexcitation during normal sinus rhythm.

During initial electrophysiologic study, each patient received procainamide intravenously (15 mg/kg at 1 mg/kg/min) after initiation of tachycardia. In each patient serum concentration was documented at the completion of the infusion (time 0), and in eight patients serum concentrations were determined at 30, 60, 120, 180, 270, and 360 min after cessation of the procainamide infusion.

Characteristics of tachycardia in procainamide responders. In eight patients with orthodromic reciprocating tachycardia the cycle lengths ranged from 240 to 350 msec (mean 281). During induced atrial fibrillation the minimum interval between preexcited QRS complexes in any patient was 240 msec. During ventricular tachycardia in patients 2, 8, and 10, the cycle length ranged from 270 to 290 msec (mean 278). In patient 7 the ventricular response was irregular during atrial flutter and averaged 390 msec.

Oral administration of procainamide to procainamide responders. At a second electrophysiologic study, performed more than 36 hr after intravenous administration of procainamide and after a fast of 6 hr or longer, tachycardia was reinitiated with a single transvenous (seven patients) or transesophageal (five patients) catheter by a stimulation protocol that had previously initiated tachycardia. Procainamide was administered orally in a dose of approximately 25 mg/kg with available capsule sizes of 250, 375, and 500 mg 15 min after initiation of tachycardia. In the two youngest patients, the contents of the capsule were added to applesauce at the time of ingestion. The oral doses ranged from 250 mg for the smallest patient (8.3 kg) to 2500 mg for the largest patient (110 kg). The average oral dose was 25.9 mg/kg, with a range of 22.7 to 30.0 (table 1).

After oral administration of procainamide, patients were monitored for 3 hr, during which blood pressure was monitored frequently with a sphygmomanometer. If tachycardia was terminated, efforts were made to reinitiate tachycardia by a stimulation protocol similar to that which had previously initiated tachycardia in each individual in the untreated state. After oral administration of procainamide (time 0), serum concentrations were determined at approximately 30, 60, 120, 180, 270, and 360 min. If the time of tachycardia conversion did not coincide with a concentration determination, the procainamide concentration at the time of tachycardia conversion was estimated by linear interpolation from measured values.

Pharmacologic studies. Procainamide and N-acetyl procainamide (NAPA) concentrations were determined in separate assays by means of the Abbott TDx System, an immunoassay that uses fluorescent polarization. The sensitivity of this method is 1 mg/liter for procainamide and 1 mg/liter for NAPA. Model-independent pharmacokinetic analysis was used to determine procainamide elimination half-life and total systemic procainamide clearance. Bioavailability of oral vs intravenous administration of procainamide was determined as the ratio of the areas under the respective procainamide concentration-time curves.

Results

Pharmacokinetic analysis. Pharmacokinetic data from individual patients are presented in table 2. The mean values of procainamide elimination half-life and clearance in patients we studied are similar to those reported by Singh et al.10 in young patients but different than those reported by Lima et al.11 in older patients. The bioavailability of oral vs intravenous administration of procainamide was similar to that observed by Manion et al.12 in young patients.

Results in patient 6 deserve special comment. After oral administration of procainamide, the serum concentration in this patient never exceeded 1 mg/liter, the lower sensitivity of our analysis system. Thus bioavailability could not be determined. However, the area under the concentration-time curve after intravenous administration of procainamide was lower than that for any other patient (6.8 mg hr/liter). Thus the bioavailability in patient 6 may be similar to that observed in other patients.

Intravenous administration of procainamide. In the 12 responders, tachycardia was terminated within 6 to 15 min (mean 12.4) after initiation of the infusion (15 mg/kg at 1 mg/kg/min). At termination of the infusion, the peak procainamide concentration ranged from 6.6 to 29.6 mg/liter (mean = 17.9). After infusion of procainamide, NAPA serum concentrations were always less than 2.0 mg/liter, and the area under the serum NAPA concentration-time curve was 9.2 ± 11.6% of the area under the procainamide concentration-time curve. There were no complications from this infusion regimen.

Oral administration of procainamide. All patients had immeasurable serum concentrations of procainamide and NAPA before oral administration of procainamide. After oral administration, tachycardia was terminated and could not be reinitiated in 11 of 12 responders to intravenous therapy. Tachycardia converted within 75 min of ingestion of procainamide (mean 41, range 23 to 74) in nine patients (Nos. 1, 3, 4, 6, 7, and 9 to 12) (table 2). Tachycardia in patient 6 converted despite a procainamide serum concentration that never exceeded 1 mg/liter. In the remaining eight patients, peak serum procainamide concentration (10.5 ± 3.4 mg/liter, mean ± SD) occurred in less than 120 min, and procainamide concentration estimated by linear interpolation at the time of tachycardia...
The concentration-time curve for NAPA was shown in Figure 1. After oral administration, the serum concentration of procainamide rose slowly, and the peak was not recorded until 180 min after ingestion. Tachycardia was terminated at 155 min and could not be reinitiated. The shape of the concentration-time curve with its marked delay in the time of peak concentration and its reduced peak concentration was quite different than that shown in Figure 1.

Observations at the time of tachycardia conversion. At the time of tachycardia conversion by the intravenous or oral preparation of procainamide, each patient, except for the two youngest ones, acknowledged an abrupt change in heart rate. No patient had any other symptoms. In each case, sinus rhythm promptly resumed. The longest sinus pause after tachycardia conversion was 1.3 sec. In the eight patients with orthodromic tachycardia, procainamide-induced termination of tachycardia occurred after ventricular depolarization (i.e., block in the retrograde limb). After termination, tachycardia episodes exceeding 10 sec could not be induced. Shortly after administration of procainamide, nonsustained orthodromic reciprocating tachycardia was always terminated with ventricular depolarization. Atrial fibrillation exceeding 10 sec could not be induced in the eight patients with accessory connections. In the remaining four patients, the tachycardia rate gradually slowed before termination.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T½β (hr)</th>
<th>CI (l/kg/hr)</th>
<th>F (%)</th>
<th>Cmax (mg/l)</th>
<th>Tmax (min)</th>
<th>Cconv (mg/l)</th>
<th>Tconv (min)</th>
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<td>0.60</td>
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T½β = elimination half-life; CI = total systemic clearance (intravenous study); F = bioavailability; Cmax = maximum measured serum concentration after oral dose; Tmax = time at which Cmax was measured; Cconv = estimated serum concentration at time of conversion to sinus rhythm; Tconv = time of conversion.

*From oral study.

 Could not determine.

 Tachycardia not converted; concentration at 180 min.
Tachycardia episodes exceeding 10 sec could not be induced after procainamide-induced termination of tachycardia.

Follow-up. Ten of 12 patients were discharged and advised to take procainamide orally at the onset of an episode of tachycardia (i.e., periodic procainamide therapy). The dose selected was that demonstrated to be effective during evaluation. Patient 5, in whom conversion could not be achieved after oral administration of procainamide, and patient 8, who required 175 min for termination of tachycardia, were not discharged on the periodic regimen. Patient 11 takes propranolol on a daily basis in addition to using periodic procainamide. During follow-up of 2 to 17 months (mean 9) seven of 10 patients had an opportunity to use periodic procainamide. Patients 1, 2, 3, 6, 9, and 10 have successfully used periodic procainamide on one to more than 100 occasions. Patient 2 opted for long-term therapy within 1 month because of frequent recurrences and the relatively long time (155 min) required for procainamide to terminate tachycardia. In patient 7, the only patient with atrial flutter and the patient with the lowest dose per weight (table 1), the periodic regimen failed in the first out-of-hospital use. Three of 10 patients have not had an opportunity to use the regimen out of the hospital since they have not had recurrence of tachycardia.

**Discussion**

The principal finding of this study is that in selected patients with paroxysmal tachycardia, procainamide administered orally after onset of tachycardia resulted in termination. The time course of this action is rapid enough to be of practical benefit in some patients with paroxysmal tachycardia. Selection of patients for successful application of the periodic regimen appears to be relatively straightforward: non-life-threatening paroxysmal tachycardia, tachycardia termination by intravenous administration of procainamide, and relatively rapid absorption of procainamide after oral administration. Extrapolation of results in the young patients we evaluated to older patients or those with serious associated cardiac disease should be done cautiously.

The response to an antiarrhythmic drug in a periodic regimen is dependent on both the pharmacodynamic and pharmacokinetic properties of the drug. We selected patients for periodic treatment who had a pharmacodynamic response of tachycardia termination during intravenous administration of procainamide. The oral, single-dose regimen appeared promising in nine of 12 patients; the principal cause of failure of the periodic procainamide regimen in three patients appeared to be pharmacokinetic and was related to de-
laidy absorption with diminished peak serum concentration of procainamide. However, in one patient with atrial flutter, the regimen failed in out-of-hospital use in spite of pharmacokinetic features that appeared favorable. Failure in this patient may be related to variation in the pharmacodynamic effect of procainamide on atrial flutter or to intravital variation in the pharmacokinetics of procainamide.

The intravenous infusion protocol of 15 mg/kg administered over 15 min has been a regimen used in our laboratory for several years for procainamide loading during electrophysiologic study, and in patients without congestive heart failure significant hypotension requiring a change in the infusion rate has not been a problem. Similarly, the oral dose of 25 mg/kg is our usual initial loading dose for patients beginning long-term oral therapy; we have encountered no complications from this oral dose. In these short-term studies, the principal antiarrhythmic effect is probably due to procainamide, since the serum concentrations of NAPA were quite low, especially at the time of tachycardia conversion.

In the application of periodic procainamide for termination of tachycardia we attempted to exploit the well-known pharmacokinetic features of rapid oral absorption and short half-life of procainamide, which are usually considered undesirable features when the drug is administered for purposes of long-term prophylaxis. Factors affecting oral absorption of procainamide have been incompletely defined. 12, 14 None of the patients we studied was chronically ill, none had congestive heart failure, and at the time of study all had fasted for 6 hr or longer. The cause for the relatively poor absorption seen in three patients is not apparent.

In a recently published study, Yeh et al. 15 demonstrated in young patients (mean age 34 years) that a single dose combining diltiazem with propranolol was effective in terminating tachycardia caused by reentry within the atrioventricular node or orthodromic reciprocating tachycardia when the drugs were taken shortly after the onset of tachycardia. As emphasized by Yeh et al., 15 the benefits of periodic compared with long-term multiple daily dosing of antiarrhythmic drugs are considerable. Increased convenience and reduced cost of treatment is of substantial benefit in young patients who may require treatment for decades. In the case of procainamide, we are optimistic that periodic treatment will avoid some of the complications of long-term use. 14, 16

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