Limited Role of Intravenous Propafenone Hydrochloride in the Treatment of Sustained Ventricular Tachycardia: Electrophysiologic Effects and Results of Programmed Ventricular Stimulation

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Propafenone hydrochloride is an experimental antiarrhythmic agent that had been used for treating supraventricular and ventricular tachyarrhythmias (1,2). Its antiarrhythmic activity is mediated mainly through its effect on the fast inward sodium current, although it possesses slow channel blocking and beta-receptor blocking properties (3-6).

Most of the clinical experience with this drug in ventricular arrhythmias has been in treating complex ventricular arrhythmia and nonsustained ventricular tachycardia (7-10). The efficacy of the drug in sustained ventricular arrhythmias as assessed by programmed electrical stimulation remains unknown. We, therefore, studied the effects of intravenous propafenone on: 1) inducibility, mode of initiation and mode of termination, cycle length and morphology of ventricular tachycardia, and 2) intracardiac conduction and ventricular effective refractory periods.

Methods

Study patients. Fourteen patients with spontaneous sustained ventricular tachycardia induced by programmed ventricular stimulation underwent electrophysiologic testing.
Cardiac diagnoses were: coronary artery disease (11 patients), dilated cardiomyopathy (1 patient), restrictive cardiomyopathy (1 patient) and aortic stenosis status after repair of congenital supravalvular aortic stenosis (1 patient). The mean age was 55 years; there were 12 men and 2 women. The clinical presentation was recurrent sustained ventricular tachycardia in eight patients, cardiac arrest in two patients, syncope in two patients, palpitation in one patient and no symptoms in one patient. In 12 of the 14 patients, ventricular tachycardia was induced with one or more conventional antiarrhythmic agents during electrophysiologic study.

**Study protocol.** All patients had at least two baseline inductions of ventricular tachycardia when taken off all medication. Propafenone was given as follows: Patients 1, 2 and 3 received intravenous propafenone (1 mg/kg) and were retested within 30 minutes of the bolus injection. Seven patients (Patients 4 to 10) received 2 mg/kg intravenously and four patients (Patients 11 to 14) received 2 mg/kg intravenously followed by a constant infusion of 2 mg/min. The first 10 patients received propafenone in a double-blind crossover fashion, with both propafenone and placebo administered during the same electrophysiologic study. The dosage was increased from 1 to 2 mg/kg intravenously and the constant infusion was added when none of the first 10 patients had a salutary response to the drug. Our stimulation protocol for induction of ventricular tachycardia has been reported previously in detail (11) and was the same before and after the administration of propafenone.

Termination of ventricular tachycardia both before and after propafenone was accomplished as reported previously (12). Cardioversion was performed if ventricular tachycardia was accelerated by pacing techniques or was poorly tolerated. Stimuli were rectangular pulse widths 1 ms in duration delivered at twice diastolic threshold. Ventricular stimulation was performed with a specially designed programmable stimulator (Bloom Associates, Ltd.).

Sinus cycle length, P wave and QRS duration and PR intervals were measured for three cardiac cycles at paper speeds of 100 to 200 mm/s. P waves and QRS duration were measured from the earliest onset and latest offset on the three simultaneous surface electrocardiographic leads (I, aVF and V1). PR intervals were measured from the earliest onset of the P wave to the earliest onset of the QRS complex in any simultaneous lead. Statistical analysis was performed using the Student’s t test for paired data as appropriate.

**Results**

**Effect of propafenone on conduction times.** Sinus cycle length, P wave duration, PR interval and QRS duration were assessed in the control state and after the administration of propafenone (Fig. 1). Propafenone had no significant effect on sinus cycle length (836 ± 170 ms before and 750 ± 124 ms after propafenone), P wave duration (108 ± 24 ms before and 106 ± 23 ms after propafenone) or PR interval (181 ± 45 ms before and 194 ± 53 ms after propafenone). QRS duration increased significantly from 109 ± 20 to 130 ± 21 ms after the administration of propafenone (p < 0.001).

**Effect of propafenone administration on ventricular effective refractory period.** Ventricular effective refractory periods were measured from the right ventricular apex before and after propafenone in 11 patients. The mean refractory period was 235 ± 24 ms before and 256 ± 19 ms after propafenone (p < 0.005).

**Effect of propafenone on inducibility and mode of initiation of sustained ventricular tachycardia.** Thirteen of 14 patients had sustained ventricular tachycardia that either remained inducible or occurred spontaneously after propafenone. Ventricular tachycardia was induced with the same number of extrastimuli in nine patients, more extrastimuli were required in two patients, two patients had sustained ventricular tachycardia spontaneously after propafenone and one patient had no ventricular tachycardia induced. Additional forms of ventricular tachycardia were seen in six patients. Propafenone tended to prolong the cycle length of ventricular tachycardia (303 ± 73 ms before and 346 ± 143 ms after propafenone), but this did not reach statistical significance (p = 0.15) (Fig. 2). When this analysis was limited to ventricular tachycardia that was the same morphologically before and after propafenone (10 patients), ventricular tachycardia cycle length increased from 302 ± 66 ms before to 368 ± 160 ms after propafenone (p = 0.051).

**Mode of termination of ventricular tachycardia after administration of propafenone.** In four patients, the mode of termination of ventricular tachycardia was the same before and after propafenone (rapid pacing in three patients and cardioversion in one patient). In four of the patients, after propafenone the tachycardia was easier to terminate (one patient), stopped spontaneously (two patients) or one episode of ventricular tachycardia stopped spontaneously and a second episode was easier to terminate (one patient). In the two patients in whom ventricular tachycardia was more easily terminated after propafenone, rapid ventricular pacing was required for termination in the control state and a single extrastimulus terminated ventricular tachycardia after propafenone.

In five patients, ventricular tachycardia was more difficult to terminate after propafenone. Four of these patients required cardioversion after propafenone, whereas rapid ventricular pacing had terminated ventricular tachycardia in the basal state. The reasons for cardioversion were: acceleration of ventricular tachycardia after rapid ventricular pacing that did not accelerate ventricular tachycardia in the basal state (two patients); induction of a more rapid, poorly tolerated ventricular tachycardia (one patient) and incessant ventricular tachycardia of multiple configurations after propafenone.
Figure 1. Electrophysiologic effects of intravenous propafenone on sinus cycle length, P wave duration, PR interval and QRS duration in the control state (C) and after propafenone (P).

Figure 2. Ventricular tachycardia (VT) cycle length during control state (C) and after propafenone (P).

one patient). One patient continued to have ventricular tachycardia that ultimately terminated spontaneously some time after the electrophysiologic study.

There was no relation between the ease of termination of ventricular tachycardia after administration of propafenone compared with baseline and change in cycle length of ventricular tachycardia. In the four patients whose tachycardia was easier to terminate after propafenone, ventricular tachycardia cycle length increased from 325 ± 90 ms before to 336 ± 53 ms after propafenone (p = 0.42). In the five patients whose tachycardia was more difficult to terminate, tachycardia cycle length changed from 313 ± 67 ms before to 399 ± 213 ms after propafenone (p = 0.15).

Discussion

Pharmacologic properties. Propafenone is an experimental antiarrhythmic agent with unique pharmacologic properties. It is known to cause a concentration-dependent decrease in the fast inward sodium current (4). In the same model, propafenone has demonstrated frequency-dependent characteristics (3). Propafenone also has modest effects on the slow inward current of calcium (6), although its calcium antagonistic properties have generally been thought to be
weak (5). Propafenone has also been shown to have modest beta-receptor blocking properties with predominantly a beta₂ affinity (5) and to abolish arrhythmias due to calcium chloride, digitalis intoxication or coronary ligation (13).

Comparison with previous studies. Several studies (7–9) have shown oral propafenone to be effective in suppressing complex ventricular arrhythmias. In one series of 13 patients treated with oral propafenone for complex ventricular ectopic activity (14), the patients exhibited greater than 90% suppression of isolated ventricular premature depolarizations. As in our study, no significant change in heart rate was observed after the administration of propafenone. The PR interval, however, increased by 20% as did the QRS duration Meyer-Estorf et al. (15) also found that propafenone prolonged atrioventricular conduction and used PR prolongation as a clinical index of plasma concentration. We found no significant increase in the PR interval in our patients. The lack of increase in atrioventricular conduction may be due to the mode of administration (that is, oral compared with intravenous propafenone) or may be due to the beta-adrenergic blocking effects of propafenone that may only be evident at higher dose levels. The increase in QRS duration we observed is in agreement with the results of Connolly et al. (14). We found a significant increase in the duration of the ventricular effective refractory period in accord with that observed in a previous report (16).

Present study. Sustained ventricular tachycardia remained inducible in 13 of 14 patients in our study. The cycle length of ventricular tachycardia in the control state and after the administration of propafenone did not differ statistically, probably because of the wide range in cycle lengths of ventricular tachycardia both before and after propafenone. However, in some patients the degree of slowing was dramatic. As with other antiarrhythmic agents, administration of propafenone resulted in ventricular tachycardia whose morphologic features differed from those induced in the basal state. It is unlikely that the low response rate in this group was due to inadequate dosing, because we observed substantial effects on intraventricular conduction and ventricular refractoriness. It is, of course, impossible to assess the effects of active metabolites with acute intravenous dosing, although no such metabolites have been described for propafenone. The spontaneous emergence of sustained ventricular tachycardia in two patients who had been clinically free of arrhythmias for some time before the study raises the possibility that propafenone may facilitate arrhythmias in some patients.

Conclusion. Intravenous propafenone caused no change in intraatrial or atrioventricular conduction, but prolonged intraventricular conduction and ventricular refractoriness. In this regard, it behaved like a type 1A antiarrhythmic agent. Ventricular tachycardia remained inducible in 13 of 14 patients. The mode of initiation, mode of termination and cycle length of ventricular tachycardia were not predictably altered. Propafenone appears to have a limited role in the treatment of recurrent sustained ventricular tachycardia refractory to conventional agents as assessed by programmed ventricular stimulation.

We thank Nancy Walker for the skillful preparation of the manuscript. We also thank Darlene Pembrook-Rogers and Belinda Flores, RN for assistance in completion of the data, and Linda Branco, Joan Brown and Roxellen Auletto for technical assistance during the electrophysiologic studies.

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