Termination of paroxysmal supraventricular tachycardia with a single oral dose of diltiazem and propranolol

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ABSTRACT The efficacy of a single oral dose combination of 120 mg diltiazem and 160 mg propranolol in terminating paroxysmal supraventricular tachycardia (PSVT) was evaluated in 15 patients. All 15 patients underwent electrical induction of PSVT that lasted longer than 15 min, and all underwent randomized crossover placebo and diltiazem and propranolol studies on 2 consecutive days. On each day PSVT was induced and placebo or diltiazem and propranolol was administered 15 min later. Electrical conversion of PSVT was performed when severe symptoms occurred or at the end of 240 min. With placebo PSVT lasted 164 ± 89 (mean ± SD) min; four patients had spontaneous conversion. With diltiazem and propranolol PSVT lasted 39 ± 49 min (p < .001); 14 patients had spontaneous conversion in an average of 27 ± 15 min. None of the 14 patients had electrical reinduction of sustained PSVT after conversion. The sinus nodal recovery time during spontaneous or electrical conversion of PSVT was 911 ± 459 msec with placebo and 1076 ± 270 msec with diltiazem and propranolol (NS). Two patients developed transient second-degree atrioventricular block and junctional rhythm while on diltiazem and propranolol. Serum diltiazem and propranolol levels (ng/ml) after diltiazem and propranolol in five patients were, respectively, 49 ± 26 and 108 ± 101 at 15 min, 232 ± 147 and 228 ± 148 at 30 min, 254 ± 169 and 370 ± 393 at 45 min, 280 ± 115 and 209 ± 189 at 60 min, 188 ± 72 and 268 ± 264 at 120 min, and 118 ± 57 and 265 ± 148 at 240 min. Follow-up study after 5.6 ± 0.9 months revealed 51 spontaneous episodes of PSVT in the patient group; 50 of the 51 episodes were converted after the single oral dose of the diltiazem and propranolol combination, with a conversion time of 21 ± 16 min. In conclusion, a single oral dose combination of diltiazem and propranolol effectively terminates acute episodes of PSVT and may be considered the therapeutic regimen of choice in selected patients.


PAROXYSMAL supraventricular tachycardia (PSVT) that fails to convert to sinus rhythm with simple vagal maneuvers is usually terminated by parenteral drug administration. The prophylaxis of recurrent PSVT is dependent on long-term administration of antiarrhythmic drugs. Margolis et al. used intermittent drug therapy in which antiarrhythmic medication was taken only at the onset of an episode of tachycardia. This approach was effective in terminating both supraventricular and ventricular tachyarrhythmias in 24 of 32 patients and obviated some of the need for hospitalization and long-term drug treatment. They, however, did not systematically evaluate the efficacy of a specific therapeutic regimen in terminating a specific type of tachycardia. Since most paroxysmal tachycardias convert spontaneously to sinus rhythm without intervention, the efficacy of a specific therapy cannot be determined without a strictly controlled comparison. The present study was undertaken to define the efficacy of a single oral dose of a combination of diltiazem and propranolol in terminating acute episodes of PSVT. Our results suggest that this approach may be the therapy of choice in most patients with PSVT.

Materials and methods

Patient selection. The study group consisted of 15 patients (11 men and four women) ranging in age from 19 to 52 years (mean ± SD 34 ± 10). Of these 15 patients, two had atrioventricular nodal reentrant tachycardia, and 13 had atrioventricular reentrant tachycardia utilizing a retrogradely conducting accessory pathway. Of the former two patients, one had the slow-fast form, and the other the fast-slow form of atrioventricular nodal reentrant tachycardia. Of the latter 13 patients, eight had ventricular preexcitation and five had a concealed accessory path-
way. The average frequency of PSVT was 11 ± 5 episodes/year. Previous drug regimens that failed to control the arrhythmia satisfactorily included digoxin in seven patients, propranolol in two patients, combination of digoxin and propranolol in two patients, diltiazem in three patients, verapamil in four patients, quinidine in four patients, and disopyramide in two patients. All 15 patients underwent electrical induction of sustained PSVT that lasted longer than 15 min.

Electrophysiologic study. Each patient gave informed written consent. Cardiac medications were discontinued for at least five plasma half-lives before the study. A No. 7F quadrupolar electrocatheter was percutaneously introduced into the right femoral vein, advanced to the right atrium, and positioned across the tricuspid valve. The proximal two electrodes were used for His bundle recording and the distal two electrodes for right ventricular pacing. A second No. 7F hexapolar electrocatheter was introduced into the right antecubital vein by a small incision and advanced to the right atrium and then to the coronary sinus. The distal two electrodes were used to record the left atrial electrogram from the coronary sinus, the middle two electrodes were used to record the right atrial electrogram, and the proximal two electrodes were used to stimulate the right atrium. The distal two electrodes of the hexapolar electrocatheter as well as the quadrupolar electrocatheter were also positioned at different sites in the coronary sinus and the right atrium to map the atrial activation sequence during induced episodes of PSVT. Multiple surface and intracardiac electrograms were simultaneously recorded on a multichannel oscilloscopic recorder (Electronics for Medicine VR-16) at a paper speed of 100 mm/sec. Stimuli were provided by a programmable digital stimulator (DTU PC 100, Bloom and Associates) and were approximately twice the diastolic threshold and 2 msec in duration.

As previously described, conduction intervals and anterograde and retrograde refractory periods were measured and defined by incremental pacing and extrastimulus testing. The diagnoses of atrioventricular nodal reentry and atrioventricular reentry were made according to the previously described criteria. Anterograde weak link of the reentrant circuit refers to termination of echoes or PSVT occurring with an atrial response not followed by a ventricular response. Retrograde weak link of the reentrant circuit refers either to termination of echoes or tachycardia occurring with a ventricular response not followed by an atrial response, or to achievement of an atrioventricular interval that is longer than the control critical atrioventricular interval without induction of atrial echoes or PSVT. After the control studies the quadrupolar electrode catheter was removed while the hexapolar electrode catheter was withdrawn from the coronary sinus, advanced to the right ventricle, and was used for subsequent electrophysiologic studies. The proximal two electrodes of the hexapolar catheter were kept at the junction of the superior vena cava and the right atrium, as during the control study. The distal two electrodes were used for ventricular pacing during subsequent electrophysiologic studies.

Study protocol. After the initial electrophysiologic study, PSVT was electrically induced and allowed to continue for 15 min while each patient was observed. After the observation period each patient underwent a randomized crossover trial with placebo or a single oral dose combination of 120 mg diltiazem and 160 mg propranolol on 2 consecutive days. To enhance absorption, the placebo or the combination of diltiazem and propranolol was crushed into powder form and given orally with water. Electrocardiographic tracings were recorded continuously on a tape recorder for 240 min after intervention. Electrical termination of PSVT was performed only when severe symptoms occurred or at the end of 240 min. Sinus nodal recovery time during spontaneous or electrical termination of PSVT was measured as the interval from the last QRS complex during PSVT to the first sinus P wave after conversion. Blood pressure and heart rate were taken every 15 min for the first hour and every 30 min thereafter. In five patients multiple blood samples were taken for measurements of serum diltiazem and propranolol concentrations. The serum diltiazem concentration was measured by the thin-layer chromatography of Tanabe Seiyaku Co, Ltd.; Osaka, Japan. The serum propranolol concentration was measured by a high-performance liquid chromatographic procedure. The study protocol was reviewed and approved by the Subcommittee on Human Research of the Chang Gung Memorial Hospital.

Data analysis. Data are expressed as mean ± SD and were analyzed with the paired Student t test, the chi-square test, and analysis of variance.

Results

Termination of PSVT. With placebo four of the 15 patients had spontaneous conversion of PSVT to sinus rhythm and 11 patients required electrical termination of PSVT. Among the 11 patients requiring electrical termination, four had symptoms of nausea and extreme dizziness and in seven PSVT was terminated at the end of 240 min. The total duration of PSVT with placebo was 164 ± 89 (range 30 to 240) min. The mode of termination could be determined in two of the four patients with spontaneous conversion and in both patients, the weak link occurred in the anterograde direction. The sinus nodal recovery time in these 15 patients was 911 ± 459 (range 400 to 1800) msec.

With diltiazem and propranolol 14 patients had spontaneous conversion of PSVT to sinus rhythm. The total duration of PSVT in these 14 patients was 27 ± 15 (range of 4 to 56) min as compared with 158 ± 90 min in patients on placebo (p < .001); in 10 patients PSVT was converted within 30 min, in one at between 30 and 45 min, and in three at between 45 and 56 min. In only one patient did PSVT require electrical termination (at 210 min) because of nausea and vomiting. The total duration of PSVT in patients on diltiazem and propranolol was 39 ± 49 (range of 4 to 210) min, which was significantly shorter than that in patients on placebo (p < .001). The mode of termination could be determined in 12 of the 14 patients with spontaneous conversion. The weak link occurred in the anterograde direction in 10 patients and in the retrograde direction in one. In the remaining patient PSVT was terminated after a spontaneous premature ventricular beat. The sinus nodal recovery time in these 15 patients was 1076 ± 270 (range of 500 to 1480) msec after diltiazem and propranolol, which is not significantly different from that after placebo (NS). Electrophysiologic study was repeated immediately after PSVT conversion in the 14 patients in whom PSVT converted spontaneously after diltiazem and propranolol. Six of the 14
patients had induction of nonsustained PSVT that terminated within 30 sec, seven had induction of a single atrial echo, and one had induction of neither echo nor PSVT. In all 14 patients, the weak link occurred in the anterograde direction. The longest atrial paced cycle length that induced second-degree atrioventricular block increased from 300 ± 28 to 431 ± 96 msec after diltiazem and propranolol (n = 11, p < .01). The anterograde effective refractory period of the atrioventricular conduction system that was measured at an identical cycle length of either 600 or 500 msec before and after drug intervention increased from 243 ± 23 to 379 ± 118 msec after diltiazem and propranolol (n = 11, p < .01). There was no significant change in anterograde and retrograde properties of the accessory pathway. In the patient with the fast-slow form of atrioventricular nodal reentry, the longest ventricular paced cycle length that induced ventriculocartrial block increased from 280 to 330 msec after diltiazem and propranolol. In the patient with the slow-fast form of atrioventricular nodal reentry, before diltiazem and propranolol the longest ventricular paced cycle length that induced ventriculocartrial block was at 280 msec and there was no ventriculocartrial conduction after drug administration.

**Rate of PSVT.** With placebo, PSVT rate increased initially and stabilized after 45 min (figure 1). The PSVT rate (beats/min) was 182 ± 27 before placebo and 183 ± 28 at 15 min (NS), 193 ± 21 at 30 min (NS), 202 ± 22 at 45 min (p < .02), 205 ± 17 at 60 min (p < .01), 199 ± 28 at 90 min (NS), 203 ± 25 at 120 min (p < .05), 201 ± 23 at 150 min (p < .01), 196 ± 23 at 180 min (NS), 199 ± 28 at 210 min (NS), and 194 ± 21 at 240 min (NS) after placebo.

After diltiazem and propranolol PSVT rate progressively slowed until spontaneous conversion occurred (figure 1). The PSVT rate was 197 ± 27 before diltiazem and propranolol and 183 ± 23 at 15 min (p < .01), 179 ± 21 at 30 min (p < .001), and 167 ± 35 at 45 min (p < .02) after the drugs. The PSVT rate at 30 min after diltiazem and propranolol was significantly slower than that at a comparable measurement time in the patients on placebo.

**Blood pressure during PSVT.** With placebo the systolic pressure decreased slightly (figure 2). It was 101 ± 20 (mm Hg) before placebo and 102 ± 19 at 15 min (NS), 101 ± 19 at 30 min (NS), 102 ± 18 at 45 min (NS), 99 ± 18 at 60 min (NS), 95 ± 20 at 90 min (NS), 94 ± 20 at 120 min (p < .05), 90 ± 22 at 150 min (p < .05), 93 ± 20 at 180 min (p < .02), 89 ± 20 at 210 min (p < .05), and 87 ± 17 at 240 min (p < .05) after placebo. The diastolic pressure did not change significantly: 77 ± 16 before placebo and 77 ± 16 at 15 min, 80 ± 15 at 30 min, 81 ± 16 at 45 min, 77 ± 20 at 60 min, 77 ± 17 at 120 min, 82 ± 20 at 150 min, 78 ± 20 at 180 min, 70 ± 17 at 210 min, 74 ± 22 at 240 min after placebo.

Systolic pressure (mm Hg) was 97 ± 17 before administration of diltiazem and propranolol and 93 ± 12 at 15 min, 90 ± 10 at 30 min, and 89 ± 5 at 45 min

**FIGURE 1.** Change in PSVT rate in patients on placebo as compared with those on the oral combination of diltiazem and propranolol. The number of patients are indicated next to each measurement. *p < .05 as compared with time 0 (immediately before intervention). #p < .05 for comparison of placebo with oral combination of diltiazem at comparable measurement times.

**FIGURE 2.** Change in systolic pressure during PSVT in patients on placebo as compared with those on the oral combination of diltiazem and propranolol. Conventions and abbreviations are as in figure 1.
after drug administration (figure 2). Although the systolic pressure was slightly lower in patients on diltiazem and propranolol as compared with that in those on placebo, the difference was statistically significant only at 15 min (p < .05). The diastolic pressure (mm Hg) did not change significantly with drug administration. It was 76 ± 13 before diltiazem and propranolol and 76 ± 11 at 15 min, 73 ± 7 at 30 min, and 76 ± 5 at 45 min after diltiazem and propranolol.

**Side effects.** During PSVT dizziness, chest tightness, nausea, vomiting, and diaphoresis occurred in eight patients on placebo and in seven patients on diltiazem and propranolol (NS). After conversion to sinus rhythm, orthostatic dizziness with mild hypotension occurred in four patients on diltiazem and propranolol. One of these had transient second-degree atrioventricular block and another had sinus bradycardia with junctional escape rhythm. None of the four patients required special therapy. Heart rate was slower and systolic and diastolic pressures were lower in patients on diltiazem and propranolol as compared with during sinus rhythm before drug administration. The decrease in heart rate and blood pressure reached a nadir at 90 min and then gradually returned to the pretreatment level. The heart rate was 87 ± 16 beats/min before and 59 ± 10 beats/min at 90 min after diltiazem and propranolol (p < .001). The systolic and diastolic pressures were, respectively, 111 ± 11 and 77 ± 10 mm Hg before and 88 ± 9 and 66 ± 9 mm Hg after diltiazem and propranolol (p < .001).

**Serum drug concentrations.** Serum diltiazem concentration was measured in five patients after oral administration of diltiazem and propranolol (figure 3) and was 49 ± 26 ng/ml at 15 min, 232 ± 147 ng/ml at 30 min, 254 ± 169 ng/ml at 45 min, 280 ± 115 ng/ml at 60 min, 227 ± 70 ng/ml at 90 min, 118 ± 72 ng/ml at 120 min, 162 ± 78 ng/ml at 150 min, 160 ± 75 ng/ml at 180 min, 150 ± 78 ng/ml at 210 min, and 118 ± 57 ng/ml at 240 min after drug administration.

Serum propranolol concentration was measured in five patients after oral administration of diltiazem and propranolol (figure 3) and was 108 ± 101 ng/ml at 15 min, 228 ± 148 ng/ml at 30 min, 370 ± 393 ng/ml at 45 min, 209 ± 189 ng/ml at 60 min, 259 ± 264 ng/ml at 90 min, 268 ± 264 ng/ml at 120 min, 282 ± 257 ng/ml at 150 min, 218 ± 194 ng/ml at 190 min, 126 ± 139 ng/ml at 210 min, and 265 ± 148 ng/ml at 240 min after drug administration.

**Follow-up data.** The 14 patients in whom PSVT was effectively terminated by the single oral dose combination of diltiazem and propranolol were discharged on the same regimen for PSVT termination. The dosage of diltiazem was kept at 120 mg in all 14 patients; however, the dosage of propranolol was decreased to 80 or 120 mg in those four patients who developed sinus bradycardia, junctional rhythm, or mild hypotension after diltiazem and propranolol. The patients were instructed to crush their tablets before taking them. A total of 51 spontaneous episodes of PSVT were reported in a period of 5.6 ± 0.9 months; 50 of the 51 episodes were converted after the single oral dose regimen. The conversion time (estimated by the patients) after drug administration was 21 ± 16 min. None of the patients reported any significant side effects.

**Discussion.**

Acute episodes of PSVT can be terminated by physiologic maneuvers such as carotid massage, eyeball compression, and the Valsalva maneuver. Nonetheless, termination of PSVT frequently requires emergency room visits for parenteral drug administration. The administration of pressor agents such as phenylephrine and aramine, or acetylcholinesterase inhibitors such as edrophonium and neostigmine usually results in conversion of PSVT to sinus rhythm within a few minutes after drug intervention. Adenosine or adenosine-5'-triphosphate has also been shown to be an effective agent in the termination of PSVT when given parenterally. The proven efficacy and safety of intravenous verapamil for the termination of acute episodes of PSVT has made it the drug of choice for parenteral termination of this tachycardia. Emergency room visits for parenteral drug administration are inconvenient and impractical for those patients suffering frequent attacks. In these patients prophylaxis with long-term daily drug administration in multiple doses is required to prevent recurrence. Long-term multiple daily dosing of a drug or drugs is not only
inconvenient, but also carries the risk of producing side effects. Invasive therapeutic modalities, including implantation of an antiarrhythmic pacemaker,\textsuperscript{12} surgical incision,\textsuperscript{13} cryoaablation,\textsuperscript{13} or electrocoagulation\textsuperscript{14} of the normal or the accessory pathway are available, but they cannot be advocated for most patients with PSVT. It is desirable, therefore, to develop an effective and safe way for patients to self-terminate PSVT that would eliminate emergency room visits and/or long-term drug use.

The most significant electrophysiologic effect of calcium-channel blockers is that they depress atrioventricular nodal function. As a consequence, both verapamil\textsuperscript{9-11} and diltiazem,\textsuperscript{15-18} when given intravenously, are very effective in terminating acute episodes of PSVT. Long-term oral administration of verapamil\textsuperscript{19, 20} or diltiazem\textsuperscript{21} is also effective in PSVT prophylaxis. However, the effect of calcium-channel blockers on the atrioventricular node may sometimes be abrogated by reflex changes in autonomic activity resulting from peripheral vasodilation. Schlepper et al.\textsuperscript{22} found that after a single oral dose of 240 mg of verapamil effects on the atrioventricular were seen at 2 hr and peaked at 5 hr.\textsuperscript{22} On the other hand, Wu et al.\textsuperscript{23} found that after multiple oral doses of verapamil the peak effect on the atrioventricular node was seen at 1 and 2 hr after the last dose, and the effect correlated well with the plasma verapamil concentration. The discrepancy between results of these two studies was explained by the differences in the study designs. A secondary reflex increment in sympathetic tone after a single large dose of verapamil could have negated the initial effect of verapamil on the atrioventricular node in the study of Schlepper et al.\textsuperscript{22} Evidence of increased sympathetic tone after multiple oral doses of verapamil was not observed in the study of Wu et al.\textsuperscript{23}; heart rate and blood pressure were unchanged. The electrophysiologic effect of diltiazem on the atrioventricular node after a single large oral dose has not been studied previously. It is possible that reflex augmentation of sympathetic tone resulting from peripheral vasodilation may also occur. In this study propranolol was added to mitigate this possibility.

The absorption of both diltiazem and propranolol is rapid and satisfactory when given orally. Smith et al.\textsuperscript{24} showed that after a single oral tablet of 60 or 90 mg diltiazem an early plasma diltiazem peak was observed at 1.8 ± 0.5 hr. The present study showed that a high serum concentration was achieved within 30 min when the diltiazem tablet was crushed into powder form. The gastrointestinal absorption of propranolol has been shown to be nearly complete, but the high first-pass hepatic extraction, particularly following a single dose, has made it necessary to administer a large dose of the drug to achieve a therapeutic plasma level.\textsuperscript{25} The conversion time of PSVT in this study correlated well with the serum concentrations of both diltiazem and propranolol. The postconversion electrophysiologic study demonstrated a profound atrioventricular nodal depressant effect of the single dose combination of diltiazem and propranolol, with prolongation of both the longest atrial paced cycle length that induced atrioventricular block and the atrioventricular nodal effective refractory period. This profound atrioventricular nodal depressant effect was responsible for conversion of PSVT, since the weak link was noted in the anterograde direction. Since a high serum concentration of both diltiazem and propranolol was achieved within 30 min, our study does not preclude the possibility that diltiazem or propranolol alone would be effective in terminating acute episodes of PSVT. However, propranolol alone is not likely to be effective, since intravenous propranolol is not effective in preventing induction of sustained PSVT, particularly in patients with atrioventricular reentrant tachycardia incorporating an accessory pathway.\textsuperscript{26, 27}

This study has some limitations. First, the long-term phase of this study was neither randomized nor controlled. Although the results were favorable, a solid conclusion cannot be made without further studies. Second, the safety of this approach was not tested in patients who had anterograde preexcitation and a history of atrial fibrillation, or in patients who had heart failure or hypotension associated with PSVT. In these patients the efficacy and safety of this therapy should be evaluated with a complete electrophysiologic study before therapy is begun.

In conclusion, we have demonstrated that a single oral dose combining diltiazem and propranolol is highly effective and safe in terminating acute attacks of PSVT. This therapeutic regimen avoids the inconvenience of long-term multiple daily dosing of antiarrhythmic agents as well as their potential side effects and should be a therapy of choice in most patients with PSVT. Ideal candidates include those patients in whom PSVT does not cause serious symptoms and in whom the frequency of PSVT does not require long-term daily antiarrhythmic prophylaxis. A complete electrophysiologic evaluation before this form of therapy is instituted is advised to ensure its efficacy and safety.

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