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OBJECTIVES
We tested the efficacy of two drug treatments, flecainide (F) and the combination of diltiazem and propranolol (D/P), administered as a single oral dose for termination of the arrhythmic episodes.

BACKGROUND
Both prophylactic drug therapy and catheter ablation are questionable as first-line treatments in patients with infrequent and well-tolerated episodes of paroxysmal supraventricular tachycardia (SVT).

METHODS
Among 42 eligible patients (13% of all screened for SVT) with infrequent (<5/year) well-tolerated and long-lasting episodes, 37 were enrolled and 33 had SVT inducible during electrophysiological study. In the latter, three treatments (placebo, F, and D/P) were administered in a random order 5 min after SVT induction on three different days.

RESULTS
Conversion to sinus rhythm occurred within 2 h in 52%, 61%, and 94% of patients on placebo, F and D/P, respectively (p < 0.001). The conversion time was shorter after D/P (32 ± 22 min) than after placebo (77 ± 42 min, p < 0.001) or F (74 ± 37 min, p < 0.001). Four patients (1 placebo, 1 D/P, and 2 F) had hypotension and four (3 D/P and 1 F) a sinus rate <50 beats/min following SVT interruption. Patients were discharged on a single oral dose of the most effective drug treatment (F or D/P) at time of acute testing. Twenty-six patients were discharged on D/P and five on F. During 17 ± 12 months follow-up, the treatment was successful in 81% of D/P patients and in 80% of F patients, as all the arrhythmic episodes were interrupted out-of-hospital within 2 h. In the remaining patients, failure occurred during one or more episodes because of drug ineffectiveness or drug unavailability. One patient had syncope after D/P ingestion. During follow-up, the percentage of patients calling for emergency room assistance was significantly reduced as compared to the year before enrollment (9% vs. 100%, p < 0.0001).

CONCLUSIONS
The episodic treatment with oral D/P and F, as assessed during acute testing, appears effective in the management of selected patients with SVT. This therapeutic strategy minimizes the need for emergency room admissions during tachycardia recurrences. (J Am Coll Cardiol 2001;37:548–53) © 2001 by the American College of Cardiology

Paroxysmal supraventricular tachycardia (SVT) is commonly due to atrioventricular (AV) nodal reentry or AV reentry secondary to an AV accessory pathway. In patients with frequent episodes of SVT, long-term oral prophylaxis with antiarrhythmic drugs treatment has been used to prevent clinical recurrences. However, both the daily intake of antiarrhythmic agents, sometimes in multiple doses or drug combinations, and the risk of drug-related adverse effects are recognized disadvantages of long-term prophylactic therapy. In addition, despite optimal drug administration and compliance, relapses are not infrequent in these patients (1).

Recently, radiofrequency catheter ablation has been introduced in clinical practice and proven to be a highly effective curative therapy for SVT. However, major complications have been reported in up to 3% of patients undergoing this therapy (2); this finding suggests that catheter ablation should be primarily recommended in those patients in whom paroxysmal SVTs indeed produce a detrimental impact on their life quality.

Not infrequently, patients with SVT may present with episodes that are rare and well-tolerated but long enough to require emergency room admission. In these patients, long-term oral prophylaxis or catheter ablation may not represent the most appropriate first-line treatment. Rather, an optimal approach in this group of patients might be an “episodic treatment” consisting of a single-dose oral ingestion of an antiarrhythmic drug at the time and site of arrhythmia onset (3,4). This type of treatment has already been investigated in patients with paroxysmal atrial fibrillation (5–8), but not yet in patients with paroxysmal SVT, except for subgroups with frequent episodes (9–11).

The aims of this study were to verify: 1) the efficacy of
antiarrhythmic drugs as an acute oral dose to terminate SVT in patients with infrequent, long-lasting and well-tolerated episodes of this tachycardia, and 2) verify the out-of-hospital feasibility and safety of this treatment. To this purpose, we have utilized in a controlled design oral flecainide (F) and oral diltiazem plus propranolol (D/P). These drugs were chosen because of the encouraging results reported in the literature (10,11).

METHODS

Inclusion criteria were as follows: 1) age between 18 and 75 years; 2) infrequent (≤5/year), well-tolerated episodes of electrocardiographically documented paroxysmal SVT prompting for treatment in an emergency room at least once each year; 3) electrocardiogram (ECG) during tachycardia suggestive of AV nodal or AV reentrant tachycardia (12,13). The SVT episodes were defined as well-tolerated if they were not associated with severe symptoms, including dyspnea, presyncope or syncope, and did not prevent normal activities, such as walking and driving.

Patients were excluded if they had one or more of the following findings: ventricular preexcitation; ischemic heart disease; resting sinus rate <50 beats/min; left ventricular dysfunction (i.e., ejection fraction <50% and/or history of heart failure); very severe general diseases; recent myocardial infarction or stroke or other acute diseases; a need for long-term treatment with beta-blockers, calcium antagonists, digitalis or other antiarrhythmic drugs; a history of documented sustained atrial or ventricular tachyarrhythmias.

The study protocol was approved by the ethic committees of the two recruiting institutions (Ospedale Civile, Cento, and Arcispedale S. Maria Nuova, Reggio Emilia, Italy) and patients were required to give written informed consent.

All patients underwent clinical, chest X-ray and two-dimensional echocardiographic examination. Other diagnostic investigations, such as exercise stress testing, were performed only when clinically indicated.

Electrophysiologic study. All patients in a nonsedated state underwent an electrophysiologic study according to standard techniques. A single quadripolar catheter was percutaneously introduced into the right femoral vein and advanced to the right atrium, where a programmed electrical stimulation consisting of incremental pacing and extra-stimulus testing (S1, S2, S3) was performed. If the clinical SVT was not induced, the catheter was advanced into the right ventricular apex and programmed stimulation repeated. After induction of SVT, the catheter was moved to the His bundle area, the coronary sinus, or other areas to enable accurate identification of the type of tachycardia. If the SVT was an AV nodal or AV reentrant tachycardia (14,15), the patient was enrolled and underwent each of the following three treatments: 1) placebo, 2) single oral dose of F (about 3 mg/kg), and 3) single oral dose combination of 120 mg D and 80 mg P. The three treatments were investigated on three consecutive days according to a random order. The catheter was left in situ for three days. A distinct computer-generated randomization sequence was used by each center. To enable a more rapid absorption, tablets were crushed and administered with sugar. All drugs were administered 5 min after induction of stable SVT, and the time-to-SVT termination was carefully monitored. Electrical termination of SVT was attempted if no spontaneous conversion to sinus rhythm had occurred within 2 h from drug administration or arrhythmia-related severe symptoms were observed earlier on and treatment was considered ineffective. Blood pressure and heart rate were taken before the induction of SVT, 1 min after induction, every 10 min during tachycardia, and 1 and 15 min after tachycardia interruption. If SVT was noninducible or lasted <5 min during one of the three electropharmacological studies, the patient was excluded from analysis because it was not possible to evaluate and compare the efficacy of the treatments.

Follow-up. Patients were discharged on the most effective treatment (showing the shortest conversion time; F or D/P). If this treatment had induced severe adverse effects, including symptomatic arterial hypotension, systolic blood pressure lower than 80 mm Hg, sinus bradycardia less than 50 beats/min and 2nd or 3rd degree AV block, the other treatment was prescribed. Patients in whom none of the two active drug treatments had proven effective were referred for catheter ablation of the clinical arrhythmia.

Before discharge, all patients were instructed to crush their tablet and to swallow it 5 min after the onset of the clinical arrhythmia. Patients were also requested to carefully report in an appropriate form the number of arrhythmia episodes, whether the drug was effective in interrupting them, the time duration between drug intake and termination of symptoms and the adverse effects. Finally, patients were advised not to take more than one oral dose during a 24-h period and to refer to an emergency room if the arrhythmia had not terminated within 2 h from drug ingestion. After discharge, patients were followed in the outpatient clinic every four months.

Statistical analysis. The data were analyzed using the chi-square or Fisher exact test, analysis of variance with or without Benferroni correction, and paired Student t test, as appropriate. Significance was established at p < 0.05. Results were given as mean ± standard deviation.
RESULTS

The trial profile and the results of acute testing are reported in Figure 1. Out of 320 patients referred between March 1995 and June 1998 for treatment of SVT (12,13), 42 patients (13%) met the eligibility criteria. Of these, 37 (16 men; 47 ± 11 years; range 25 to 75 years) gave written informed consent and were enrolled in the study. Two patients had hypertensive cardiovascular disease, whereas no signs of underlying heart disease were found in the remaining 35. In the year preceding hospital admission, the frequency of SVT episodes per patient had been 3.6 ± 1.3 and the number of emergency room admissions per patient 1.8 ± 0.8. Twenty-one patients (58%) had been or still were under oral antiarrhythmic prophylaxis prior to hospital admission.

Electrophysiologic study. In 33 patients, a regular SVT was inducible at time of electrophysiologic study: AV nodal reentrant tachycardia in 25 (76%) and orthodromic AV reentrant tachycardia in 8 (24%) patients. In all cases, during electrophysiologic study the 12-lead ECG of the induced tachycardia matched the 12-lead ECG morphology of the spontaneous arrhythmia. In four patients (11%) SVT was noninducible or lasted <5 min; these patients were excluded from analysis and referred for catheter ablation. Of the 33 patients with inducible SVT, conversion to sinus rhythm without pacing was achieved within 2 h in 17 (52%) after placebo, in 20 (61%) after F, and in 31 (94%) patients after D/P (p < 0.001).

Adverse effects. Hypotension after drug administration requiring electrical termination of SVT appeared in four patients: in one after placebo, in two after F and in one patient after D/P. Sinus bradycardia (heart rate <50 beats/min) following SVT bradycardia was observed in four patients: in one after placebo and in three after D/P. Minor side
effects (nausea, cephalgia, sweating) were observed in four patients after placebo, in five after F and in three after D/P. No patient showed 2nd or 3rd degree AV block following SVT termination.

**Conversion time.** The conversion time to sinus rhythm was evaluable in 32 patients after placebo, in 31 after F and in 32 after D/P. It was shorter after D/P (32 ± 22 min) than it was after placebo (77 ± 42 min, p < 0.001) or F (74 ± 37 min, p < 0.001). The conversion time after F did not significantly differ from that after placebo. The treatment associated with the shortest conversion time was placebo in 6 patients (20%), F in 2 (8%), and D/P in 21 (72%). The D/P was more effective than placebo (p < 0.001) and F (p < 0.001), whereas the efficacy of F did not significantly differ from that of placebo.

**Follow-up.** Of the 33 patients with inductible SVT, 2 were referred for catheter ablation because, according to the study design, both drugs (F and D/P) were ineffective or had induced severe adverse effects. Of the remaining 31 patients, 26 were discharged on D/P and 5 on F; the choice was based on acute efficacy results. During 17 ± 12 months’ follow-up (range, 4 to 48 months), 140 episodes of the clinical arrhythmia were reported, 115 (4.4 per patient) occurring in patients assigned to D/P and 25 (5.0 per patient) in patients assigned to F. Twenty-three episodes were self-terminating within 5 min from the onset and, therefore, they have not been treated, according to the study design.

Of the 26 D/P patients, the treatment was successful in 21 (81%) as all the arrhythmic episodes were interrupted out-of-hospital within 2 h. In the remaining five patients, at least one episode lasted more than 2 h because of ineffectiveness of the treatment in three (11%) and of drug unavailability in two (8%) patients. These five patients reported treatment failure during nine arrhythmic episodes. The conversion time of the treated episodes was 41 ± 24 min and was similar to that observed during acute testing. Three patients (11%) called for emergency room assistance for SVT termination.

Of the five F patients, the treatment was successful in four (80%) and in the remaining patient the drug was unavailable during one arrhythmic episode, and this lasted more than 2 h. The conversion time of the treated episodes was 43 ± 18 min. No patient called for emergency room assistance.

A failure of the out-of-hospital treatment occurred during one or more episodes in 6 of the 31 patients (19%, 95% CI, + 5%, + 33%) because of drug ineffectiveness or drug unavailability.

During follow-up, the percentage of patients calling for emergency room assistance was significantly reduced as compared to the year before enrollment (3/31 [9%] vs. 31/31 [100%], p < 0.0001).

Adverse effects during one or more arrhythmic episodes were reported in 11 patients: in 10 patients after D/P (asthenia lasting several hours in 6 patients, nausea in 1, vomiting in 1, cephalalgia in 1, and syncope with trauma in 1) and in 1 patient after F (vomiting).

In seven patients (27%), the episodic treatment was discontinued after 13 ± 6 months follow-up: in one patient because of syncope with trauma, in one because of concomitant atrial fibrillation requiring long-term prophylactic antiarrhythmic treatment, and in five patients because the arrhythmic episodes became more frequent and the patients underwent catheter ablation. At the end of follow-up, 24 patients (73%) were satisfied with the treatment and were advised to continue with it.

**DISCUSSION**

**Main finding of the study.** The main finding of the present study was that a single-dose of self-administered D/P or F at the time of arrhythmia onset appears an effective treatment of patients with infrequent, long-lasting and well-tolerated SVTs. Selection of drug treatment was based on the acute drug efficacy in terminating electrically induced SVT in the individual patient. This therapeutic strategy proved highly effective to minimize the need for emergency room admission during the SVT recurrences and was associated with a low incidence of severe adverse events.

**Selection of patients and therapeutic strategy.** The prevalence, among patients with paroxysmal SVT, of those with infrequent and well-tolerated episodes, though long enough to call for emergency room assistance, is not known. In the present study, these patients accounted for 13% of all patients referred for treatment of SVT during the enrollment period, thus representing a small group. The remaining patients reported more frequent episodes and/or severe symptoms and/or short, self-terminating episodes. Single-dose oral ingestion of an antiarrhythmic drug for termination of arrhythmia is an appealing form of treatment for rarely symptomatic patients (16) because it prevents the disadvantages of long-term oral prophylaxis (1) and the potential complications associated with catheter ablation (2).

Although other drugs had also been investigated (9), D/P and F were selected for evaluation in this study because they appeared to be effective in patients with frequent SVT (10,11). The mode of action of single-dose oral ingestion of D/P and F has been previously investigated (10,11). When both tablets are crushed into powder form, oral D/P is readily absorbed and high serum levels are achieved within 30 min (11).

In a study by Yeh et al. (11), administration of a single oral dose (D 120 mg; P 160 mg) of this combination was associated with termination within 3 h of drug intake of electrically induced SVT in 14 (93%) out of 15 cases. Of note, at the dosage administered by the investigators, two patients (13%) developed 2nd degree AV block after SVT interruption. In the Yeh et al. (11) study, 50 out of 51 SVT episodes occurring during 5 ± 1 months follow-up were converted within 3 h (conversion time, 21 ± 16 min) after
a single D/P oral dose; no major drug-related adverse effects were reported.

In another study by Musto et al. (10), the efficacy of a single oral dose of F (about 3 mg/kg) to terminate electrically induced SVT in 25 children and young adults was tested using a noncontrolled design. Although this therapy was associated with SVT termination within 3 h of drug intake in 22 patients (88%) (conversion time, 80 ± 34 min), the true efficacy of F could not be assessed in the absence of a placebo arm.

**Efficacy of drug treatment at time of acute testing.** In the present study, we chose to select the antiarrhythmic drug based on its efficacy to terminate electrically induced SVT in the individual patient. Because of the risk of induction of 2nd degree AV block, as reported by Yeh et al. (11), a dose of 80 mg rather than 160 mg P was used in combination with D. Also, for a successful single-dose drug treatment during the electrically induced SVT, we arbitrarily selected a time limit of 2 h rather than 3 h, as previously reported (10,11). This decision was based on a more conservative approach for assessment of drug efficacy in the clinical setting before calling for emergency room assistance.

During the acute testing, the true drug efficacy was investigated by comparing the time of SVT conversion into sinus rhythm of the two drug treatments with that of placebo. In general, D/P, but not F, proved effective to shorten the conversion time compared to placebo.

**Efficacy of drug treatment during follow-up.** Selection of drug therapy based on the results of acute testing was associated with a satisfactory clinical outcome during the follow-up. In fact, oral D/P interrupted within 2 h all out-of-hospital arrhythmic episodes in 81% of the patients and oral F in 80%; in the remaining patients, a failure occurred during one or more episodes because of drug ineffectiveness or drug unavailability.

A remarkable impact of the proposed treatment strategy was the dramatic reduction in emergency room admissions for medical care. These data are of clinical significance, because emergency room admission often represents the most important concern for these patients.

A not unexpected finding was that the clinical course of these patients may deteriorate with time. This was the case in five patients (16%) of this study, in whom the occurrence of more frequent episodes required discontinuation of the investigated therapeutic strategy after 13 ± 6 months follow-up; all five patients were referred for catheter ablation.

**Drug-related adverse effects.** During follow-up, one patient had syncope with trauma 15 min after D/P ingestion, and drug treatment was discontinued. Although paroxysmal SVT may cause syncope (17,18), no previous such episodes were reported in this patient population. Therefore, it is likely that this symptom represents a true drug-related adverse effect. Although rarely reported, the possibility of syncope should prompt physicians to recommend the patient at least to take a sitting position when using a self-administered single-dose oral treatment. Given the administration modality, minor drug-related adverse effects were accepted by patients in comparison with the associated clinical benefit.

**Clinical implications.** Although useful to identify the most effective drug treatment on an individual basis, the strategy introduced here appears of questionable practicability in daily clinical routine. Given its documented superiority to placebo and F, D/P could reasonably be tested as a first-choice treatment during a single electropharmacological study. Based on the data from the present study, an acute success rate of about 70% would be expected (considering the possibly of SVT noninducibility and of severe side effects). Treatment of nonresponders remains to be investigated, and, at this time, may include testing of alternative drugs as well as other forms of therapy. Because the episodic treatment with D/P was not tested in patients with ventricular preexcitation, sinus bradycardia and left ventricular dysfunction, the therapeutic strategy used in the present study cannot be proposed in these patient categories.

**Study limitations.** Owing to the study design, we cannot exclude that some potentially eligible patients with SVT were excluded because of an inaccurate diagnosis of the clinical arrhythmia on 12-lead ECG.

In about 10% of the patients with infrequent episodes of paroxysmal SVT, tachycardia is noninducible during electrophysiological study or lasts <5 min; therefore, in these patients it is not possible to test an episodic treatment.

During follow-up, arrhythmic episodes and concomitant drug treatment were assessed based on patient symptoms. We cannot exclude that some of these episodes were secondary to arrhythmias other than SVT (i.e., atrial fibrillation, atrial tachycardia, etc.). However, the efficacy of the tested therapeutic strategy was investigated with a clinical rather than an electrophysiological purpose, and the reported rates of success appear clinically valuable, regardless of the specific arrhythmia associated with the patient symptoms.

During the follow-up period, the time between drug intake and tachycardia termination was measured by the patient and, therefore, it cannot be considered very precise.

Selection of out-of-hospital drug treatment was based on its acute efficacy on electrically induced SVT. Although it was associated with a low incidence of patients calling for emergency room assistance during follow-up, this method is invasive and requires multiple electropharmacological studies. A more practical approach would be an empiric one. Whether an empiric approach could result in a clinical efficacy similar to that of the mode introduced in the present study remains to be investigated.

Finally, in the absence of a randomized controlled design for out-of-hospital management of arrhythmic episodes, it is not possible to ascertain conclusively whether the favorable impact on clinical outcome of the tested strategy is inherently related to the drug efficacy or to the strategy itself.
CONCLUSIONS

Data from the present study show that episodic treatment with oral D/P and F, as assessed on an individual basis at time of acute testing, appears effective in about 70% of patients with infrequent and well-tolerated episodes of AV nodal reentrant tachycardia or orthodromic AV reentrant tachycardia. The incidence of severe adverse events appears low; however, safety will have to be evaluated in a larger group of patients. Using this method, D/P appears an interesting therapeutic approach in these patients; in particular, this therapeutic strategy minimizes the need for emergency room admission during the acute event. Before being prescribed, D/P must be tested in hospital for assessment of efficacy and safety during a single electro-pharmacological study or during a spontaneous SVT attack.

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REFERENCES