

Serial electrophysiologic testing of drug therapy in supraventricular tachycardia related to accessory pathways

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■ Data are limited on the use of serial electrophysiologic testing of drug therapy in patients with supraventricular tachycardia associated with accessory pathways, including the Wolff-Parkinson-White syndrome. Twenty-four highly symptomatic patients (aged 36 ± 11 years) with SVT related to accessory pathways underwent electrophysiologic studies to select an effective chronic oral treatment. Conventional (verapamil, propranolol, quinidine, disopyramide) and investigational (amiodarone, aprindine, propafenone) drugs were used alone and in combination if necessary. It was determined that serial electrophysiologic studies could identify potentially effective treatments in 66% of patients with reentrant SVT involving accessory pathways, and the findings were highly predictive of long-term clinical outcome.

□ INDEX TERMS: ELECTROPHYSIOLOGY; TACHYCARDIA, SUPRAVENTRICULAR; CLEVE CLIN J MED 1990; 57:622-626

SEVERAL EFFECTIVE treatments have evolved for tachyarrhythmias associated with accessory atrioventricular pathways, including arrhythmias that complicate the Wolff-Parkinson-White (WPW) syndrome.¹ Therapeutic alternatives include antiarrhythmic drugs² aimed at the prevention of tachyarrhythmias; surgical³ and catheter ablation⁴ aimed at eradication of the arrhythmogenic substrate; and antitachycardia pacing⁵ aimed at rapid, automatic termination of tachycardia episodes. Despite the unquestioned benefits of surgical therapy in subsets of patients,⁶ pharmacologic therapy is the mainstay of treatment for most.

Reciprocating tachycardias in patients with accessory

pathways can be reliably reproduced during electrophysiologic studies (EPS). The results of these studies define the pathways involved in the reentrant circuit and enable investigation of the effects of drugs on them. Because the characteristics of these reentrant circuits are fairly constant, the EPS findings should predict the response to long-term therapy. For example, a drug that modifies the reentrant circuits and prevents induction of the reciprocating tachycardia should effectively suppress the clinical arrhythmia. Therefore, serial electrophysiologic assessment of pharmacologic effects has been recommended as a way to achieve the greatest therapeutic benefit for patients with supraventricular tachycardia (SVT) related to accessory pathways,⁷ but published data on the value and limitations of this approach are limited.⁸

We report the results of serial electrophysiologic testing of drugs in a group of symptomatic patients with reciprocating tachycardia involving accessory pathways,

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TABLE 1
TREATMENT REGIMENS TESTED

Drug	Intravenous bolus dose	Oral dosage
Verapamil (single or combined with disopyramide, quinidine, or propranolol)	5-15 mg	80-120 mg q6-8h
Disopyramide (single or combined with verapamil)	100-150 mg	100-200 mg q6-8h
Quinidine (combined with verapamil or propranolol)		200-400 mg q6-8h
Propranolol	0.15 mg/kg	20-40 mg q6-8h
Amiodarone		2,400-3,600 mg (loading dose for 3-5 d), then 200-400 mg bid
Aprindine	100-200 mg	50-100 mg bid
Propafenone	50-80 mg	150-300 mg tid

and comment on the relationship between the results of such studies and long-term clinical outcome.

METHODS

Study population

The study population consisted of 24 patients referred to the University of Cairo between June 1984 and June 1987 for evaluation of documented recurrent symptomatic SVT and in whom EPS confirmed the participation of an accessory pathway during reciprocating tachycardia. Patients who had both Wolff-Parkinson-White syndrome and spontaneous atrial fibrillation were excluded from this study.

The group included 19 men and 5 women age 36 ± 11 years. The WPW pattern was present in 18 patients. Concealed accessory pathways were present in 6, and 4 patients had evidence of structural heart disease (3 with dilated cardiomyopathy and 1 with Ebstein's anomaly). The mean heart rate with documented previous SVT was 195 ± 20 beats per minute. All patients had needed at least one hospitalization for tachycardia termination. The frequency of episodes ranged from eight per day to twice a year. Half of the patients had more than one attack of symptomatic SVT per week. Dizziness was the most severe symptom in 10 patients, palpitations in 9, chest pain in 3, and dyspnea in 2.

Baseline electrophysiology studies

After obtaining verbal informed consent, baseline EPS was performed for each patient in the postabsorptive, nonsedated, drug-free state. Four quadripolar catheters were positioned in the high right atrium, in

the right ventricular apex, across the tricuspid valve for His bundle recording, and in the coronary sinus.

A standard stimulation protocol was followed for induction of SVT.⁹ Briefly, it included (1) incremental pacing of the high right atrium, the coronary sinus, or both, at cycle lengths of 600 to 200 msec for 30 to 60 seconds; (2) single and double atrial extrastimuli during atrial paced rhythm at two cycle lengths; and (3) incremental ventricular pacing and ventricular extrastimuli, also introduced during a ventricular paced rhythm at two different cycle lengths. The induction of atrial fibrillation was specifically sought during these studies.

The participation of retrogradely conducting accessory pathways during an orthodromic reciprocating tachycardia was confirmed by an eccentric pattern of atrial activation, the ability to preexcite the atria with ventricular extrastimuli introduced during tachycardia at time of His bundle refractoriness, or the two findings together.⁹

Serial testing of drugs

After elucidating the mechanism of reciprocating tachycardia and localizing the accessory pathways, intravenous drugs were given to test acute termination and prevention of induction of reciprocating tachycardia. If the first drug was unsuccessful, a second was tested intravenously in the same setting. At the end of this baseline study, two catheters were left in place at the right ventricular apex and high right atrium for subsequent testing of oral drugs.

Patients were then started on oral therapy. After four to five half-lives at a maximum tolerated dose, repeat EPS was performed; at this time, the predicted plasma levels were lowest. Amiodarone was tested at a regimen of 200 mg to 400 mg bid after administration of 2,400 mg to 3,600 mg daily for 3 to 5 days (Table 1).

Drug selection

A drug was not tested if a patient had previously not responded to it, or if it had been associated with side effects the patient had not tolerated. Conventional drugs¹⁰⁻¹² were used first and investigational agents were reserved for resistant cases. When single agents proved ineffective, combination therapy was attempted; generally, a drug active at the atrioventricular node, such as verapamil or propranolol, was combined with another that acted on the accessory pathways, such as a Class I antiarrhythmic. Whenever feasible, the same drug was tested in both intravenous and oral routes. The testing endpoint was prevention of induction of

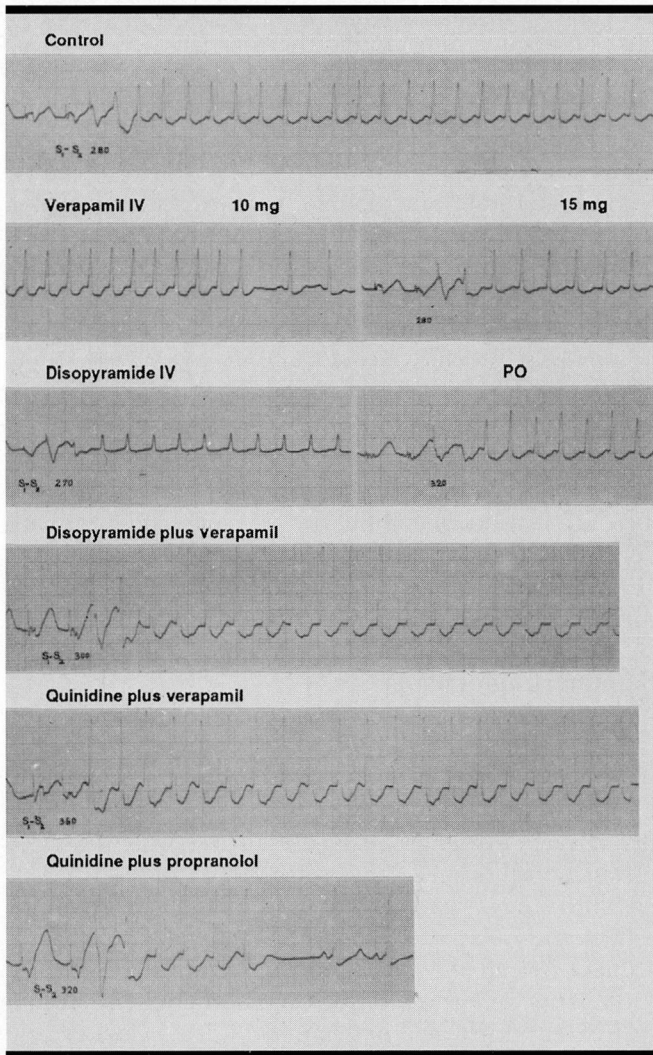


FIGURE 1. Testing of multiple drugs to find an effective therapy. From top: Orthodromic reciprocating tachycardia was induced by single ventricular extrastimulus during control electrophysiologic study. Tachycardia was terminated by intravenous verapamil (left, but was still inducible (right)). Reciprocating tachycardia was inducible after intravenous and oral disopyramide, after oral verapamil and disopyramide, and after oral quinidine and verapamil. Only the combination of quinidine plus propranolol was effective (bottom tracing) as shown by induction of only short runs of reciprocating tachycardia.

reciprocating tachycardia after completion of the stimulation protocol.

Follow-up

Patients were discharged on an oral drug regimen predicted to be successful by serial drug testing. If no such regimen was found, the patient was treated with a “par-

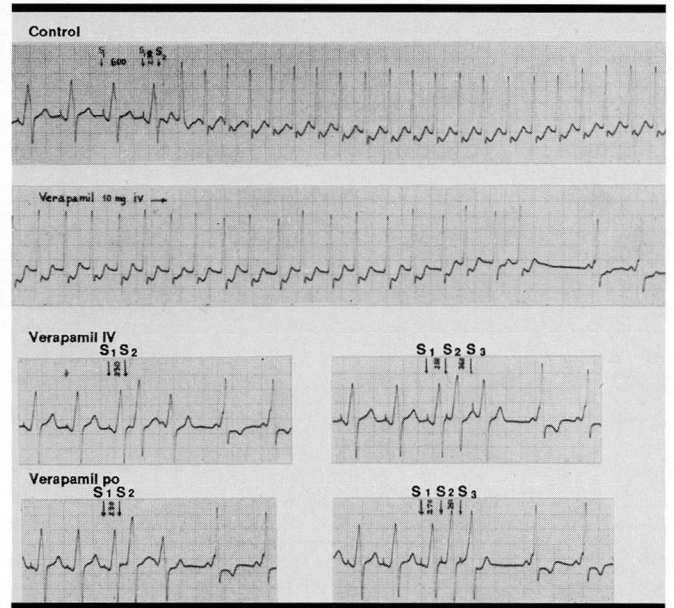


FIGURE 2. Predictive value of intravenous therapy. An induced reciprocating tachycardia by single coronary sinus extrastimulus during the control study (top) was terminated by intravenous verapamil (second tracing) and could not be induced by single or double extrastimuli after either intravenous or oral verapamil (lower tracings).

tially effective” regimen (eg, one that lengthened the cycle of induced reciprocating tachycardia or made it poorly sustained). At 1- to 2-month intervals, each patient was evaluated for evidence of symptomatic recurrence of supraventricular tachycardia or drug toxicity. These evaluations also included Holter monitoring.

RESULTS

EPS findings

All but one of the 24 patients presented with spontaneous orthodromic reciprocating tachycardia, and in all of these the arrhythmia was induced by baseline EPS. The remaining patient had spontaneous antidromic reciprocating tachycardia, and this arrhythmia was induced as well. Atrial stimulation effectively induced reciprocating tachycardia in 74% of the patients, while ventricular stimulation was effective in 95%.

Intravenous drug therapy was tested on 37 occasions. Therapy converted the reciprocating tachycardia to sinus rhythm in 21 instances, but achieved subsequent suppression of induction in only 11.

The 24 patients underwent 44 trials of oral drug therapy (1 to 4 trials per patient; mean, 2). Successful

treatment regimens were found for 16 patients (66%).

Seven patients responded to monotherapy: six to verapamil, one to disopyramide. Nine patients required combination therapy: verapamil plus quinidine in three, verapamil plus propranolol in three, quinidine plus propranolol in two (Figure 1), and verapamil plus disopyramide in one. A "partially effective" regimen was selected for five patients: verapamil plus disopyramide in two; and in the other three, verapamil with either quinidine, amiodarone, or aprindine. The remaining three patients did not respond to any tested regimen.

Among the 14 patients in whom the same drug was tested orally and intravenously, the results of intravenous administration accurately predicted the results of oral testing (Figure 2).

Follow-up

All patients but one were followed for a mean of 16 ± 8 months (range, 6 to 28). Among 16 patients discharged on a successful regimen (as predicted by EPS), 13 were free of SVT. Two patients had occasional transient episodes of SVT (lasting less than 10 minutes) and one had frequent longer attacks lasting 10 to 30 minutes.

In three patients taking quinidine plus verapamil, the regimen was discontinued because of intolerable fatigue, resulting in frequent recurrence of sustained SVT. Of seven patients followed on ineffective drugs (including those with "partial responses"), six (87.5%) had recurrent SVT requiring hospitalization. Two of this group underwent repeat EPS which identified effective regimens. Empiric trials were partially effective in another three patients. Surgical resection of the accessory pathways was performed in the remaining two patients.

DISCUSSION

Although tachyarrhythmias related to accessory pathways may be considered a "surgical disease"⁶ in the future, current practice reserves ablative therapy for selected patients. Only tertiary care centers possess the electrophysiologic and surgical expertise to perform these procedures.^{3,6,13} Pharmacologic therapy is still the initial and preferred mode for most patients with reciprocating tachycardia and accessory pathways, either empiric or guided by serial EPS.

The most important observation from this study is that the results of testing reliably predicted long-term outcome. During a mean follow-up of 16 months, 94% of patients discharged on predicted effective treatment remained free of symptomatic sustained SVT. Conversely,

86% of patients discharged on therapy that did not prevent induction of SVT (including the "partial responders") had recurrent SVT requiring hospitalization. These data support previous findings.⁸

Oral regimens prevented sustained tachycardia induction following successful termination of SVT by intravenous therapy in only 44% of trials. This suggests that acute termination of SVT by an antiarrhythmic drug administered intravenously is a poor predictor of long-term efficacy on the oral form of the same drug. On the other hand, results of reinduction after intravenous administration, particularly verapamil, consistently predicted the results of oral drug testing in the 14 patients in whom the same drug was tested by both routes.^{12,14}

Recommendations

Traditional empiric therapy may be reasonable for patients with well-tolerated arrhythmias. Such therapy is best evaluated in patients who have frequent episodes of SVT so that the utility of therapy can be readily determined.

EPS-guided therapy of SVT provides an objective and quickly attainable therapeutic endpoint; ie, prevention of the induction of reciprocating tachycardia by programmed stimulation. Suppression of induced reciprocating tachycardia by drugs in the laboratory setting is a valuable predictor of long-term efficacy. This approach quickly identifies either effective regimens or patients who are unresponsive and require other therapies.

EPS-guided therapy is clearly indicated in several situations.⁷ These include uncertain diagnosis, severe symptoms such as hypotension or syncope during SVT, SVT that is refractory to empirical drug therapy, inaccessibility of a medical facility, and patient preference. In patients with WPW, EPS will give valuable information about the antegrade conducting properties of the accessory pathways—mainly the ventricular response during induced atrial fibrillation.¹ These data may help in reaching a decision about treatment.

Because EPS is invasive, it has a few disadvantages, including the low risk and mild discomfort related to an endovascular procedure.¹⁵ In our series, even when catheters were left in place for as long as 1 week, there were no instances of sepsis or venous thrombosis.

Given today's emphasis on cost containment, the major drawback of EPS-guided therapy is the need for a relatively long hospital stay.¹⁶ Transesophageal atrial pacing—an inexpensive, ambulatory procedure—may be a cost-effective alternative to EPS for selected patients with SVT.¹⁷ The good correlation between in-

travenous and oral verapamil in the suppression of reciprocating tachycardia induction may obviate the need for repeated EPS testing in patients who respond to the intravenous preparation of verapamil. Unfortunately, this correlation does not apply to all drugs. For example, the effects of IV amiodarone¹⁸ and encainide¹⁹ differ from the effects of oral administration because of active metabolites and complex pharmacokinetics.

Newer drugs, such as class IC agents^{20,21} and amiodarone,^{22,23} are effective in many patients with reciprocating tachycardia and accessory pathways. However, amiodarone has long-term toxicity,²⁴ and the results of the Cardiac Arrhythmia Suppression Trial,²⁵

although not strictly applicable to SVT patients, raised concern about the safety of class IC agents.^{26,27} We strongly believe that when ablative therapy is not being considered, conventional therapy should be given a trial—ideally, assessed with serial EPS—before turning to amiodarone or a class IC agent.

The present study demonstrates that serial EPS, using multiple antiarrhythmic agents singly or together, is a useful way to identify effective prophylactic oral therapy in highly symptomatic patients with reciprocating tachycardia related to accessory pathways. At the same time, EPS rapidly identifies resistant cases that may benefit from other therapeutic approaches.

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