The Usefulness of Electrophysiological-Pharmacologic Studies in the Long-term Therapy of Paroxysmal Tachycardias

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In 96 cases of paroxysmal tachycardia, results of chronic pharmacological assessment (CPA) were compared with acute electrophysiological-pharmacologic assessments (EPA) to evaluate the usefulness of EPA. I. Patients with sustained VT (31 cases): Sustained VT and repetitive ventricular response (RVR) could be induced in 61% and 23% respectively. More than one effective drug was found by EPA for 23 of 24 subjects. Of the 22 followed by CPA, the effectiveness of medication was excellent for 14 (64%), moderate for 1, slight for 4, and ineffective for 3 (14%). II. Patients with non-sustained VT (23 cases): RVR could be induced in 52%. Effective medication was identified by EPA for 8 of 10 patients. Of the 7 followed by CPA, the effectiveness of medication was excellent for 2 (28.5%), moderate for 2, and ineffective for 3. III. Patients with PSVT (42 cases): PSVT could be induced in 90% of cases. Effective medication was found for all 31 cases which underwent EPA. Of the 23 cases followed by CPA, the chronic efficacy of drugs was excellent for 7 (30%), moderate for 5 (22%), slight for 7 (30%), and noneffective for 4 (18%).

Therefore, we conclude that the usefulness of EPA differs according to the type of tachycardia. EPA is most useful in predicting chronic results for patients with sustained VT, especially when the sustained VT is readily reproducible by electrical stimulation. It is less useful for nonsustained VT and PSVT. With nonsustained VT, EPA is limited by difficulty in repeatedly inducing RVR, and by difficulty in predicting the appropriate medication for chronic oral therapy. With PSVT, even though the PSVT can be induced with greater success, EPA is limited by variations in pharmacologic effects over time, which create discrepancies between EPA and CPA.

THE onset of paroxysmal tachycardia (PT) is sudden and transitory, rendering the selection and evaluation of appropriate antiarrhythmic medication difficult. In order to clinically evaluate drug efficacy against PT, induction and termination of PT by electrical stimulation is being utilized¹⁻⁸. This method is

called clinical electrophysiological-pharmacologic assessment (EPA). Though EPA has gained wide acceptance for the evaluation of paroxysmal supraventricular tachycardias (PSVT), it is also generating considerable interest for the evaluation of ventricular tachycardias (VT)⁴⁻⁸. This provocative-objective approach to VT, however, risks ventricular fibrillation, hemodynamic deterioration, mental/physical stress and patient anxiety. Recently some authors have reported the successful prediction of the long-term effectiveness of drugs for treatment of recurrent

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VT by this method.⁹⁻¹¹ However, its usefulness and limitations have not been established. The purpose of this study is to evaluate the chronic efficacy of oral drug regimens determined by EPA.

MATERIALS AND METHODS

Materials: Ninety-six patients (56 males and 40 females) were studied. They ranged in age from 14 to 77 years, average age being 41. PTs were classified into three groups: sustained VT, nonsustained VT and PSVT.

The sustained VT group consisted of 31 cases (23 males, 8 females), average age being 33 (range, 14–77 years). Of these, 11 had myocardial disease, 2 had myocardial infarction and 18 were of unknown etiology. Syncopal attacks were observed in 7 cases, faintness in 14, and palpitations in 27. The average interval from the onset of symptoms was 63 months (1 month to 20 years), and the mean duration of chronic therapy was 17 months (range, 5–35 months).

The nonsustained VT group consisted of 23 cases (5 males and 18 females), average age being 43 (range, 17–65 years). Three cases had myocardial disease, 2 had prolapsing mitral valves, and 18 were of unknown etiology. Syncopal attacks were observed in 7 cases, faintness in 13 and palpitations in 18. The average interval from the onset was 44 months (range, 4–87 months), and the mean duration of chronic therapy was 19 months (range, 5–31 months).

The PSVT group consisted of 42 cases (27 males and 15 females), average age being 42 (range, 15–77 years). Three cases had myocardial disease, one had an atrial septal defect and 37 were of unknown etiology. Syncopal attacks were observed in 5 cases, faintness in 13, and palpitations in 48. The average interval from the onset was 168 months (range, 5 months to 43 years and 3 months), and the mean duration of chronic therapy was 19 months (range, 5–45 months).

Method of EPA: Our electrical stimulation protocol consisted of single and double extra-stimuli during paced rhythm, rapid pacing and burst pacing. The pharmacological protocol of our laboratory has already been reported in detail.⁸ Drugs were administered in the following manner: procainamide (PA) 500–1000 mg i.v., disopyramide (DP) 100 mg i.v., quinidine (Q) 600 mg/day, propafenone (Propaf) 50–70 mg i.v., aprindine (Ap) 100 mg i.v., lidocaine (Lid)

50–100 mg i.v., mexiletine (Mex) 125 mg i.v., tocainide (Toc) 200–400 mg i.v., propranolol (Prop) 2–4 mg i.v., and verapamil (Ver) 5–10 mg i.v.. As a general rule, EPA was repeated until an effective drug was found. An average of 3.8 drugs (1–7) were tried per subject. Plasma concentration of PA, DP and Lid were determined by the enzyme immunoassay method, Mex by gas chromatography and Ver by high performance liquid chromatography. We considered a drug to have a preventive effect if it prevented the induction of tachycardias or repetitive ventricular response (RVR) after its administration. A drug was considered to have a terminating effect if the induced sustained tachycardia was spontaneously halted in 10 or fewer complexes, or if the spontaneous or induced VT was halted after its intravenous administration.

Method of chronic therapy: Chronic medication was administered orally, based on a drug's proven acute effectiveness in preventing and/or terminating tachycardias. Administration of the various drugs was as follows: PA 1000–2000 mg/day, DP 300–400 mg/day, Q 600–800 mg/day, Propaf 300–800 mg/day, Mex 300–600 mg/day, Toc 600–1200 mg/day, Prop 60–120 mg/day, and Ver 120–360 mg/day. The efficacy of chronic oral drug administration was assessed by a method called chronic pharmacological assessment (CPA), which evaluated the incidence, duration and symptoms of tachycardia attacks, as well as by Holter ECGs and plasma concentrations. For the sustained VT and PSVT groups, effectiveness was considered excellent if attacks disappeared; moderate if attacks were shortened in duration and decreased in incidence; slight if attacks were shortened or decreased; and deteriorative if they were increased or prolonged. For the nonsustained VT group, effectiveness was considered excellent if the incidence of VT decreased by more than 90%, and moderate if it decreased by 50–90%.

Definitions: Sustained VT was defined as VT that lasted for over 100 complexes and required either pharmaceuticals, pacing, or DC cardioversion for its termination. Nonsustained VT was defined as VT with a duration of greater than 3 complexes but spontaneously terminating within 100 complexes. RVR was defined as 1–4 nonstimulated ventricular beats that occurred after a paced ventricular premature beat following paced ventricular rhythm.

Fig.1. Breakdown of sustained VT group.

RESULTS

(1) Sustained VT Group

In 19 of 31 patients with recurrent sustained VT, the VT was easily and repeatedly initiated by programmed electrical stimulation, and could be terminated by burst pacing except for one case. Both QRS morphology and frontal plane

axis of the induced VT were identical to the spontaneous tachycardias in 18 of the 19 cases. In 17 of these 18 cases, at least one drug could be found which acutely prevented or terminated VT. In one case, however, all 5 drugs tested were ineffective. In 16 of 17 cases, the chronic effectiveness of the oral drugs could be assessed. One patient left the study and could not be assessed.

RVR was induced by electrical stimulation in 7 cases. In 5 of these the QRS morphology was identical to that of the spontaneous VT. EPA was also performed in 6 of the 7 cases in which RVR was induced, and effective drugs for its prevention were found. In 5 cases (16%), neither VT nor RVR could be induced by electrical stimulation (Fig. 1).

Table I shows the chronic efficacy of the drugs found to be effective by EPA. These were Ver in 6 cases, Mex in 3 cases, DP in 4 cases, Toc in 3 cases, Propaf in 2 cases, Q in 1 case, and combinations of Q + Ver, Q + DP, and Q + Digoxin in single cases. Table II shows a comparison between EPA and CPA. In 14 of 22 cases, spontaneous VTs were prevented for an average of 17 months by medication determined

TABLE I EFFECT OF CHRONIC VARIOUS ORAL REGIMENS IN SUSTAINED VT GROUP

Drugs	Cases	CPA			
		Excellent	Moderate	Slight	Ineffective
Verapamil	6	2	1	3	
Disopyramide	4	3			1
Mexiletine	3	2			1
Tocainide	3	1		1	1
Quinidine	1	1			
Propafenone	2	2			
Quinidine + Disopyramide	1	1			
Quinidine + Verapamil	1	1			
Quinidine + Digoxin	1	1			

TABLE II EFFECT OF CHRONIC THERAPY IN PATIENTS WITH SUSTAINED VT AND RVR INDUCED BY ELECTRICAL STIMULATION

Electrophysiological study	CPA			
	Excellent	Moderate	Slight	Ineffective
Induced sustained VT	11 (69%)	1 (6%)	3 (19%)	1 (6%)
Induced RVR	3 (50%)		1 (17%)	2 (33%)
	14 (64%)	1 (4%)	4 (18%)	3 (14%)

Fig. 2. Case 1, in which a combination of quinidine and verapamil proved effective (male, 32 years old).

Fig. 3. Effect of chronic oral drug administration against VT (for same patient as Fig. 2). Upper section indicates drug and period of administration. Lower section indicates number of VT episodes over time. Following administration of verapamil and quinidine, VT subsided for 2 years except when patient forgot medication.

Fig.4. Case 2, in which a combination of disopyramide and quinidine prolonged the duration of efficacy (male, 54 years). Vertical scale indicates VT zone (solid line) and blood concentration of disopyramide (dotted line) and horizontal indicates post oral and/or intravenous administration time. Upper left is for disopyramide 100 mg i.v., upper right for quinidine 200 mg p.o., lower graph for combined administration of 200 mg quinidine p.o. and 100 mg disopyramide i.v. Note disopyramide alone was effective beyond concentration levels of 1.7 $\mu\text{g}/\text{ml}$ for 2 hours, whereas when combined with quinidine, which was ineffective by itself, VT was suppressed for 5 hours and the effective concentration level was decreased to 1.25 $\mu\text{g}/\text{ml}$.

by EPA. Five of the 22 cases exhibited fewer and/or shortened episodes of VT, and VT could not be prevented in 3 cases. Of the 16 cases in which sustained VT was induced by electrical stimulation, the pharmacological effectiveness was excellent in 11 (69%), moderate in 1 (6%), slight in 3 (19%), and not effective in 1 (6%). Of the 6 patients with RVR induced by pacing,

efficacy was excellent in 3 patients (50%), slight in 1 (17%), and not effective in 2 (33%).

Figure 2 shows a case in which neither Q nor Ver could prevent VT induction, but the combination of the two drugs prevented the induction of VT for more than 90 minutes. Other drugs (PA, DP, Prop and Lid) were not effective. As shown in Fig. 3, this patient had a history of

Fig.5. Effect of chronic oral drug administration against VT (for same patient as Fig. 4). Following administration of disopyramide and quinidine, VT could be suppressed, although higher dosages of disopyramide alone were ineffective.

Fig.6. Breakdown of nonsustained VT group.

VT for roughly 13 years and received more than 10 DC shocks when medication proved ineffective. Following oral administration of Q and Ver, he had only two episodes of palpitations, which terminated spontaneously after a short while. These episodes only occurred when the patient was negligent about taking his prescribed medication.

Figure 4 shows a case in which DP gave excellent results in preventing VT induced by ventricular burst pacing. The drug was effective for 2 hours after 100 mg intravenous adminis-

tration, and the minimum plasma concentration that prevented VT at the time of the first admission was $1.70 \mu\text{g/ml}$ (Fig. 4, upper left). However, as shown in Fig. 5, chronic oral administration of 400 mg/day of DP failed to prevent recurrent VT for 14 months post discharge, and was found to be ineffective especially against VT occurring immediately before the next administration. At the time of the second admission, although a single administration of Q was not effective (Fig. 4, upper right), a combination of Q and DP was effective for over 5 hours and the minimum effective plasma concentration was found to be less than $1.25 \mu\text{g/ml}$ (Fig. 4, bottom). After oral administration of Q and DP, no VT attack occurred over a period of 2 years (Fig. 5).

(2) Nonsustained VT Group

In 12 of 23 patients with nonsustained VT, RVR could be induced by electrical stimulation. The QRS morphology of RVR was identical to the spontaneous VT in 6 cases, and differed in 6 cases. The efficacy of drugs against RVR could be assessed in 10 cases, but could not be assessed in 2 cases because RVR could not be reproduced. More than one drug that acutely prevented RVR could be found for 8 of these 10 patients in which RVR was induced. In 7 of the 8 patients, the efficacy of chronic oral regimens was assessed (Fig. 6). As shown in Table III, drugs successful in preventing RVR were PA, DP, Toc, Ap, Prop,

TABLE III EFFECT OF VARIOUS CHRONIC ORAL REGIMENS IN NONSUSTAINED VT GROUP

Drugs	Cases	CPA		
		Excellent	Moderate	Ineffective
Disopyramide	1		1	
Procainamide	1			1
Aprindine	1	1		
Tocainide	1			1
Propranolol	1	1		
Mexiletine	1			1
Propafenone	1		1	
	7	2 (28.5%)	2 (28.5%)	3 (43%)

TABLE IV EFFECT OF VARIOUS CHRONIC ORAL REGIMENS IN PSVT GROUP

Drugs	Cases	CPA			
		Excellent	Moderate	Slight	Ineffective
Verapamil	10	2	2	4	2
Disopyramide	7	4	2	1	
Quinidine	1	1			
Propranolol	2		1		1
Verapamil + Digoxin	1			1	
Verapamil + Propranolol	1			1	
Disopyramide + Propranolol	1				1
	23	7 (30%)	5 (22%)	7 (30%)	4 (18%)

Fig.7. Breakdown of PSVT group.

Mex, and Propaf (for single cases). The effect of chronic oral administration in preventing nonsustained VT was excellent in 2 cases (28.5%), moderate in 2 cases and ineffective in 3 cases.

(3) PSVT Group

In 33 of 42 patients with PSVT, PSVT could be induced by programmed electrical stimulation. In 5 out of 9 patients in which PSVT could not be induced, PSVT was induced by electrical stimulation after the administration of isoproterenol or atropine. The efficacy of drugs against induced PSVT was evaluated in 31 cases, and more than one effective drug could be identified for all patients. Twenty-three patients were treated by chronic oral regimens. The other eight were monitored without medication. Table IV shows acutely effective drugs, which were Ver in 10 cases, DP in 7 cases, and Prop in 2 cases, Q, Ver + Digoxin, Ver + Prop and DP + Prop in single cases. As shown in Table IV,

Fig.8. Induction rate of EPA and effective rate of CPA in sustained VT group, nonsustained VT group and PSVT group.

7 of the 23 (30%) patients treated chronically with the drug had an excellent effect, 5 of 23 (22%) patients had a moderate effect, 7 of 23 (30%) patients had a slight effect, and 4 of 23 (18%) patients had no effect. The effect of verapamil was excellent in 2 cases, moderate in 2 cases, slight in 4 cases, and it was not effective in 2 cases.

DISCUSSION

The usefulness of the electrophysiological-pharmacologic approach for the selection and assessment of anti-arrhythmic drugs is thought to differ between various types of paroxysmal tachycardia. However, until now there has been no study which directly compares PSVT, sustained VT and nonsustained VT within the same institution to assess the efficacy of EPA. Figure 8 compares the induction rate of EPA and the efficacy of CPA between the sustained VT, the nonsustained VT and the PSVT groups.

(1) Sustained VT Group

It is reported that sustained VT can be induced by electrical stimulation in 50–100% of patients with recurrent sustained VT^{4,12–15}. This wide variance may be due to underlying disease, VT origin, pacing site, number of extrastimuli during rapid ventricular pacing, cycle length and isoproterenol administration, etc.

The relatively low induction rate (61%) obtained in this study is thought to be due to the

fact that many patients lacked an obvious underlying etiology, that we did not employ triple extrastimuli, and the fact that the study included few patients undergoing left ventricular pacing.

Although the definitions of RVR and non-sustained VT differ between authors, Engel et al.¹³ report that nonsustained VT could be induced in 3 of 11 patients (27%). This is similar to our RVR induction rate of 23%. Mason et al. report that either sustained VT or nonsustained VT could be induced in 19 of 24 patients (85%) with clinical sustained VT⁵. This is similar to our induction rate for sustained VT and RVR.

Whether an effective drug can be found by EPA is determined in part by the number of drugs investigated, the dosage, the time of testing after drug administration, and the criteria for evaluating efficacy, etc. Horowitz⁴ and Josephson¹⁶ report acute successes in 34 of 54 (63%) cases with A, DP, PA, Lid, Prop and DPH. Mason et al.^{5,17} investigated single as well as combined administration of Q, DP, PA, Lid and DPH, and had success rates of roughly 70%.

The higher success rate (94%) achieved in this study is thought to be due to the following: a maximum of 7 drugs was tried until an effective one was found; both single and combined administrations were utilized; new drugs such as Mex, Toc, and Propaf were available; and many patients had no obvious underlying etiology.

The chronic efficacy of drugs chosen by EPA

is reported to be 80–100%.^{15,16} Horowitz reports success in 13 out of 13 patients followed for 3–27 months.⁴ Mason et al. report 4 out of 30 (13%) failures within the first 2 months and 2 out of 30 (7%) late failures after a mean of 9.8 months.⁵ In our study, 14 of 22 patients (64%) were free of symptomatic sustained VT, but when those whose frequency and/or duration of VT was decreased were included, the success rate became (86%). Success in patients with induced VT (94%) tended to be higher than in those with induced RVR (67%).

In assessing the efficacy of drugs by EPA, we considered prevention and termination separately.⁸ If an induced VT ceased spontaneously within 10 complexes, the drug was considered to be capable of terminating but not capable of preventing VT. Previous studies have not made this distinction and have assessed efficacy by the duration of VT before its termination. For example, Boxton et al. considered a drug to be effective if it halted VT within 15 complexes,²¹ and Denes considered a drug effective if it turned induced sustained VT into nonsustained VT.¹⁸ In our study, Ver had both a preventive and terminating effect in 2 of 6 cases, but only a terminating effect in only 4 cases. (The acute efficacy of Ver has been reported in another study by our institution.²² However, its chronic efficacy is noteworthy.) During chronic therapy, the patients with preventive and terminative effects were free of symptomatic VT, while those with terminative effects alone experienced fewer incidences and/or shortened episodes of VT. Thus, the importance of distinguishing prevention from termination is emphasized.

The role of antiarrhythmic drugs in EPA is not necessarily the same as in CPA. During EPA, a drug is expected to influence the initiation and maintenance mechanism of VT induced by electrical stimulation. However, during CPA the drug's ability to counter VPB, which triggers VT, plays a more important role.

This study concentrated on the chronic efficacy of drugs that were found to be effective by EPA. However, the chronic efficacy of drugs ineffective during EPA needs to be considered also. The success rate in patients chronically treated with acutely ineffective drugs is reported to be 0–40%.^{5,20} As mentioned above, this could be due to the drug's ability to suppress VPB. The fact that EPA cannot measure a drug's effect on VPB is one of its inherent limitations.

Ruskin et al.¹⁹ and Denes et al.¹⁸ report

mortality in the course of their follow-up. The fact that this study did not encounter any is thought to be due to differences in underlying cardiac disease.

(2) Nonsustained VT

Nonsustained VT includes various pathogeneses with a wide variance in their clinical significance, ranging from no symptoms to sudden death. Relatively few studies on EPA for nonsustained VT are found in comparison to similar studies on sustained VT. Vandepol et al. report that nonsustained VT with QRS configurations identical to spontaneous VT was induced by programmed electrical stimulation in 21 of 33 patients (64%).¹⁴ However, in our study the corresponding induction rate was only 26%, and 52% if RVR with different QRS configurations was included. This difference is thought to be due to underlying etiology and stimulation method, etc. Vandepol et al.¹² report that sustained VT and VF could not be induced by electrical stimulation in patients with clinical nonsustained VT.¹⁴ Our results were generally similar.

In our study, 10 of the 12 patients with induced RVR were given EPA. Two patients were excluded due to lack of reproducibility. At least one effective drug could be found for 8 patients (80%). Success with chronic oral therapy was 57.0%, with excellent effect in 28.5% of cases and moderate effect for 28.5%. Schaeffer et al.²¹ report a high success rate for chronic therapy in cases in which RVR could be induced. However, the induction rates of nonsustained VT and RVR, and their reproducibility, were lower. Therefore, the usefulness of EPA in patients with nonsustained VT is thought to have limitations.

(3) PSVT Group

PSVT which is induced and terminated by electrical stimulation is thought to result from a re-entrant mechanism, and includes sinus nodal re-entrant tachycardia, intra-atrial re-entrant tachycardia, A-V nodal re-entrant tachycardia and the WPW syndrome. Therefore, the effect of medication is expected to differ according to the site that it influences. Since the various re-entry circuits include the atrium, A-V node (α , β pathway), the Purkinje system, ventricles, and accessory pathways, drugs can affect the conductivity and refractoriness of each re-entrant circuit. Also, the response of antegrade and

retrograde conduction to drugs can differ. Accordingly, the efficacy of drugs against PSVT is expected to vary considerably with the various types of PSVT. In this study, A-V nodal re-entrant tachycardia and re-entrant tachycardia with antegrade conduction of the A-V node and retrograde conduction of the accessory pathways were examined.

Among the PSVT group, programmed electrical stimulation induced PSVT in 33 of 42 patients (79%). This figure was 90% if PSVT induced after drug administration was included. An effective medication was found for all 31 patients on whom EPA was conducted. However, chronic oral therapy was only administered to 23 patients because others had few incidences of PSVT and remained asymptomatic.

Until now there have been few reports on the chronic efficacy of drugs chosen by EPA for PSVT. In our study, PSVT disappeared in only 30% of cases, although episodes were decreased or shortened in 52%. Discrepancies between EPA and CPA were more pronounced for Ver, which did not decrease the number of PSVT episodes and only shortened their duration in 4 out of 10 cases. Rinkenberger et al²⁴ and Klein²⁵ also report that the ability of Ver to terminate reciprocating tachycardia by bolus injection does not necessarily predict its ability to prevent tachycardia when administered orally. This is thought to be due to the fact that Ver can affect the induction and sustenance of tachycardia by prolonging the effective refractory period of the A-V node, but cannot suppress atrial premature beats nor always prevent the atrial echo. DP, by comparison, can suppress tachycardia by inhibiting atrial and ventricular premature beats, and by prolonging the effective retrograde refractory period of the accessory pathway. On the other hand, since DP enhances A-V nodal conduction by indirect vagolytic action and increases the effective antegrade refractory period of the accessory pathway, it increases the re-entry echo zone. It can also enhance tachycardia if the cycle length is extended beyond the increase of the effective refractory period of the circuit. Therefore, medication can have contradictory effects on PSVT, and for this reason it is difficult to correlate the chronic results with those obtained by EPA.

In addition to pharmacologic influences, the conductivity and refractoriness of the re-entrant circuit are affected by the autonomic nervous

system and catecholamines, especially in the A-V node. Therefore, predicting the chronic efficacy of acutely effective drugs for patients with PSVT is thought to be more difficult than for patients with VT.

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