Electrophysiologic Evaluation of Antiarrhythmic Drugs on Supraventricular Tachyarrhythmias

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The effects of the intravenous administration of three drugs, i.e., verapamil, disopyramide, and procainamide, on paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (Af) and atrial flutter (AF) were evaluated electrophysiologically.

Efficacy on PSVT was 94.7% (36/38) with verapamil, 61.5% (13/18) with disopyramide and 100% (4/4) with procainamide. Efficacy on Af and AF was 9.1% (1/11) with verapamil and 80.0% (12/15) with disopyramide.

PSVT termination mechanisms were as follows: 1) Verapamil: A-H block in 5 cases and H-A block in 5 cases with Type 1 A-V nodal reentrant tachycardia (AVNRT). H-A block in 6 cases with Type 2 and Type 3. A-H block in 17 of 18 cases with A-V reciprocating tachycardia (AVRT). Cycle length alternans were observed in 13 of 34 cases. 2) Disopyramide: H-A block in 2 cases with AVNRT and V-A block in 2 cases with AVRT. 3) Procainamide: V-A block in 4 cases with AVRT.

These results suggest that verapamil and disopyramide are most effective on PSVT and Af, respectively.

THE search for an ideal antiarrhythmic agent has continued up to the present time and several new drugs are now under clinical investigation. Although intravenous administration of verapamil and disopyramide has been widely used to treat supraventricular tachyarrhythmias (SVTAs) for several years in Europe and recently intravenous verapamil in the United States, they are not yet approved for general use in Japan.

It has been demonstrated that paroxysmal supraventricular tachycardia (PSVT) consists of various mechanisms. PSVT due to A-V nodal reentry, i.e., A-V nodal reentrant tachycardia

(AVNRT), is the most common type of PSVT except for PSVT due to reentry *via* an accessory pathway, i.e., A-V reciprocating tachycardia (AVRT)! Three types are known in AVNRT! Accordingly, not all of these mechanisms were considered to be equally responsive to the same drug. We studied the efficacy of these drugs on SVTAs together with an old antiarrhythmic drug, procainamide, and termination mechanisms of these drugs were evaluated.

MATERIALS AND METHODS

Three types of SVTAs were induced electrophysiologically in 80 patients whose chief complaint was palpitation. PSVT was induced in 57 patients, atrial fibrillation (Af) in 15 and atrial flutter (AF) in 8. PSVT mechanisms were demonstrated electrophysiologically. AVNRT

Key Words:

Verapamil
Disopyramide
Procainamide
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A-V reciprocating tachycardia

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TABLE I EFFICACY OF VERAPAMIL ON TERMINATION OR INDUCTION OF SUPRAVENTRICULAR TACHYARRHYTHMIAS

Type of Arrhythmia	No. of Cases	Termination		Induction		Usefulness (%)	Induced Other Arrhythmia
		Yes	No	No	Yes		
SVT							
AVNRT	20	17	0	3	0	20 (100)	0
SANRT	2	—	—	2	0	2 (100)	0
MWPW	12	9	1	2	0	11 (91.7)	sinus arrest (1)
CWPW	14	10	1	3	0	13 (92.9)	Af (1)
Af	7	0	7	—	—	0 (0)	0
AF	4	1	3	—	—	1 (25)	sinus arrest (1)
Total	59	37	12	10	0		3 (5.1%)

AVNRT = A-V nodal reentrant tachycardia, SANRT = S-A nodal reentrant tachycardia, MWPW = manifest WPW syndrome, CWPW = concealed WPW syndrome, Af = atrial fibrillation, AF = atrial flutter, — = not performed. Abbreviations are the same in the succeeding tables.

TABLE II EFFICACY OF DISOPYRAMIDE ON TERMINATION OF SUPRAVENTRICULAR TACHYARRHYTHMIAS

Type of Arrhythmia	No. of Cases	Termination		Induction		Usefulness (%)	Induced Other Arrhythmia
		Yes	No	No	Yes		
SVT							
AVNRT	4	2	1	0	1	2 (50.0)	0
SANRT	1	—	—	0	1	0 (0)	0
MWPW	7	3	3	1	0	4 (57.1)	0
CWPW	5	3	1	1	0	4 (80.0)	0
Af	11	7	2	2	0	9 (81.8)	AF (1)
AF	5	2	1	2	0	4 (80.0)	0
Total	33	17	8	6	2		1 (3.0%)

Abbreviations are the same as in Table I.

was identified in 23 patients, S-A nodal reentrant tachycardia (SANRT) in 3 and AVRT in 33, including concealed WPW syndrome in 16.

Informed consent was obtained from all patients before study. The electrophysiologic study was performed with the same technique described previously² Furthermore, 23 cases of AVNRT were divided into 3 types according to Akhtar's classification¹: Type 1: the atrial echo (Ae) on the His bundle electrogram almost always follows and seldom, if ever, occurs simultaneously with or precedes the onset of His bundle deflection. The retrograde P (P') wave during tachycardia is partially or completely obscured by the QRS complex. Type 2: the H-Ae intervals are significantly longer than the Ae-H intervals. The P' wave is, therefore, outside

the ST-T segment, and clearly identifiable, preceding the next QRS complex. Type 3: a pattern of PSVT intermediate between the two types. The Ae response clears the V wave and the P' wave may be identifiable in ST and T segment. Thus, there were 15 patients of Type 1, 3 of Type 2 and 5 of Type 3.

To evaluate the efficacy of the 3 kinds of antiarrhythmic drugs, they were administered intravenously as a single bolus during attacks in some patients and during non-attacks in the remaining patients. When the arrhythmia terminated or they were not inducible electrophysiologically after administration of the drug, the efficacy was judged as positive.

Intravenous administration protocol of these drugs was as follows: 10 mg of verapamil was

TABLE III EFFICACY OF PROCAINAMIDE ON TERMINATION OR INDUCTION OF SUPRAVENTRICULAR TACHYARRHYTHMIAS

Type of Arrhythmia	No. of Cases	Termination		Induction		Usefulness (%)	Induced Other Arrhythmia
		Yes	No	No	Yes		
SVT							
MWPW	2	2	0	—	—	2 (100)	0
CWPW	2	2	0	—	—	2 (100)	0
AF	1	0	1	—	—	0 (0)	VT (1)
Total	5	4	1				1 (20%)

VT = ventricular tachycardia. Other abbreviations are the same as in Table I.

TABLE IV TERMINATION MECHANISM OF A-V NODAL REENTRANT TACHYCARDIA BY VERAPAMIL

Type of Arrhythmia	No. of Cases	Site of Block	
		A-H	H-A (V-A)
AVNRT			
I	10	5	5
II	2	0	2
III	4	0	4
MWPW	8	7	1*
CWPW	10	10	0
Total	34	22	11 (1*)

* In this case spontaneous termination could not be ruled out. Abbreviations are the same as in Table I.

TABLE V MODE OF TERMINATION OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA BY VERAPAMIL

Mechanism	No. of Patients	Increase in A-H	
		LSC (—)	LSC (+)
AVNRT	17	13	4
WPW	17	8	9

LSC = long-short cycle. Other abbreviations are the same as in Table I.

TABLE VI TERMINATION MECHANISM OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA BY DISOPYRAMIDE AND PROCAINAMIDE

Type of PSVT	No. of Cases	Site of Block	
		A-H	H-A (V-A)
AVNRT (Type I)			
D	2	0	2
MWPW			
D	2	0	2
P	2	0	2
CWPW			
P	2	0	2
Total	8	0	8

D = disopyramide, P = procainamide, V-A = ventriculo-atrial conduction.

Other abbreviations are the same as in Table I.

RESULTS

Efficacy of Drugs on SVTAs

Verapamil: Table I shows the efficacy of verapamil on termination or induction-inhibition of PSVT.

Verapamil converted AVNRT to sinus rhythm in all 17 cases and inhibited induction of AVNRT and SANRT in all 5 cases. Verapamil terminated AVRT in 19 out of 21 cases and prevented induction of AVRT in all 5 cases. Verapamil was not able to terminate Af in 7 cases or AF in 3 out of 4 cases.

Disopyramide: Results of the disopyramide study are shown in Table II. Disopyramide terminated AVNRT in 2 out of 3 cases, but could not prevent induction of AVNRT and SANRT in one case each.

injected within one minute, 100 mg of disopyramide and 500 mg procainamide over 5 min.

Plasma verapamil levels were measured using the GC-Ms method and disopyramide substrate levels in plasma using a high performance liquid chromatographic method.

Fig. 1. Plasma concentration of verapamil administered intravenously (10 mg).

Fig. 2. Plasma concentration of disopyramide administered intravenously (100 mg) in patients with paroxysmal supraventricular tachycardia.

Disopyramide converted AVRT to sinus rhythm in 6 out of 10 cases and inhibited induction of AVRT in both the 2 cases.

Disopyramide converted Af to sinus rhythm in 7 out of 9 cases and AF in 2 out of 3 cases. In addition, the drug prevented induction of Af and AF in one case each.

Procainamide: Table III illustrates effects of procainamide on termination and induction-inhibition of SVTAs. The drug terminated

Fig. 3. Plasma concentration of disopyramide administered intravenously (100 mg) in patients with atrial fibrillation.

AVRT in all 4 cases, but could not prevent induction of AF in one case.

Electrophysiologic Mechanisms in Terminating SVTAs

Electrophysiologic mechanism in the termination of AVNRT by verapamil is shown in Table IV.

In 10 cases with Type 1 AVNRT, tachycardia terminated with an A-H block in 5 cases and with a H-A block in 5 cases. In Type 2 and Type 3, all 6 cases showed termination with a H-A block. AVRT terminated with an A-H block in 17 out of 18 cases and with a V-A block in one case, in which spontaneous termination could not be ruled out.

Before termination of PSVT by verapamil, cycle length alternans associated with increase in A-H intervals were observed in 13 out of 34 cases (Table V).

Disopyramide: Disopyramide terminated AVNRT (Table I) with a H-A block in 2 cases and AVRT with a V-A block in 2 cases (Table VI).

Procainamide: Procainamide terminated AVRT with a V-A block in all 4 cases (Table VI).

Plasma Concentration of Drugs

Verapamil: Figure 1 shows plasma concentrations of verapamil administered intravenously in 6 cases. In one patient with AVNRT, which terminated 100 sec after the beginning of the injection, the plasma concentration was 530 ng/ml at that moment. In 3 patients with Af the concentration 5 min after the beginning of

the injection was lower, showing 142, 157 and 73 ng/ml, respectively.

Disopyramide: Figure 2 shows the plasma concentration of disopyramide administered intravenously in 5 cases with PSVT. The average level 5 min after the beginning of the injection was $5.53 \pm 3.39 \mu\text{g/ml}$. Figure 3 shows the plasma levels in 4 cases with Af. The average level 5 min after the beginning of the injection was $6.45 \pm 2.72 \mu\text{g/ml}$.

Side Effects

In 97 episodes of SVTAs in which drugs were administered intravenously as a single bolus, ventricular tachycardia was induced by procainamide in one case and sinus arrest by verapamil in 2 cases.

DISCUSSION

Efficacy of Three Drugs on SVTAs

Our results show potent antiarrhythmic effects of verapamil on PSVT and disopyramide on Af. The conversion rate of PSVT by verapamil in this study was 94.7% (36/38), being consistent with other reports (70–100%)^{3–10}. Conversion from PSVT to sinus rhythm occurred less than 2 min after a 10 mg dose of intravenous verapamil.

Conversion from Af to sinus rhythm by verapamil did not occur in our study, although large multicenter studies have reported that conversion rate of Af was 16% (230/1474).^{11,12} Our results show that intravenous verapamil has no role in the conversion of Af to sinus rhythm except its rate control action of Af.

Since conversion rate of PSVT by disopyramide was 61.5% (8/13), its efficacy seemed to be slightly lower than that of verapamil. Considering the favorable electrophysiologic effects of disopyramide on an accessory pathway (AP) in WPW syndrome,¹³ it is natural to consider that this drug may be more effective on AVRT than on AVNRT. In only 3 of 6 cases in our study, however, AVRT associated with manifest WPW syndrome were converted to sinus rhythm by disopyramide.

It is noteworthy that in 7 out of 9 cases (81.8%) Af was converted to sinus rhythm with 100 mg of intravenous disopyramide. Deano et al.¹⁴ have reported that disopyramide administration resulted in the conversion to sinus rhythm in 2 out of 10 patients with Af and in 3 out of 8 patients with AF. This difference might be attributable to the fact that the duration of Af

was relatively short in our cases.

Mechanisms of Terminating PSVT by These Drugs

The mechanisms of PSVT termination by intravenous verapamil were different in each type of AVNRT. In Type 1 A-H block without significant effects on retrograde conductions occurred in 5 cases, while H-A block with an increase in antegrade conduction time occurred in 5 cases. This finding suggests that the A-V node has nonuniform functional property and that there are cells less sensitive to slow channel blocker or cells not composed of fibers dependent on the slow inward current in either antegrade pathway or retrograde pathway.⁷ In the former case, participation of an AP cannot be ruled out because termination of PSVT occurred without prolongation of the retrograde conduction time by verapamil.

Termination of PSVT with a H-A block in all cases of Type 2 and Type 3 represented a relative weakness of the retrograde pathway.

We expected to observe that AVRT would be terminated due to an A-H block by verapamil because an AP is known to be unresponsive to verapamil.^{6,15} In one case, however, AVRT was terminated by a V-A block. It could not be judged whether this was induced spontaneously or if verapamil was truly effective on the AP.

Disopyramide and procainamide terminated PSVT with V-A or H-A block in all cases of AVRT. These effects are due to common depressive properties of the drug on the AP, since they belong to Class 1 agents.

Several workers have reported cycle length alternans before the termination of PSVT during the administration of verapamil.^{7,10,16,17} It occurred in 13 out of 34 of our patients (38.2%). Spurrell et al.¹⁶ have postulated unmasking of three pathways, i.e., one for retrograde conduction and two for antegrade conduction (a slow and a fast pathway). Rinkenberger et al.⁷ have asserted that the occurrence of a form of resonance related to the effects of change in cycle length on A-H interval. Namely, the cycle length with the shorter A-H interval might allow the succeeding cycle an insufficient time for complete recovery of A-V nodal refractoriness, thereby prolonging the A-H interval in the next cycle. The subsequent long A-H interval might provide more time for complete recovery of A-V nodal refractoriness and permit a shorter A-H interval in the next cycle. Relatively frequent occurrence of cycle length alternans after

verapamil administration as observed in our patients suggests that the latter mechanism is more likely.

Plasma Drug Concentration

The paucity of pharmacokinetic data on verapamil in man has been pointed out.¹⁸ According to Hollman et al.,¹⁹ an antiarrhythmic effect resulting from a conduction prolongation within the A-V node can be expected at a plasma concentration of verapamil above 70 ng/ml. The plasma verapamil level at the moment of termination of AVNRT was 530 ng/ml in one case in the present study. Considering a higher conversion rate of PSVT by verapamil, it seems that verapamil would be sufficient to terminate PSVT with a plasma level of less than 530 ng/ml. The average plasma level after 100 mg of intravenous disopyramide (5 min after the beginning of the injection) was slightly higher in the Af group than in the PSVT group. This higher plasma level may be necessary to terminate Af, although Sandler²⁰ have reported that disopyramide could not suppress Af even at the higher level (9.0, 7.5 µg/ml).

Clinical Implication

Verapamil was most effective on PSVT irrespective of the AP. Verapamil seems to be the first choice of drug for PSVT because of its rapid effects and few side effects. The effects of disopyramide on PSVT seems to be less and slower than verapamil, but the side effects were fewer than procainamide. Disopyramide should be elected first for conversion of Af to sinus rhythm, although only verapamil may be sufficient if one wishes to control the Af rate.

Verapamil induced sinus arrest in 2 patients with apparent normal sinus nodal function. This suggests that verapamil should be used with caution in patients with sinus nodal dysfunction, such as sick sinus syndrome.

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