Pharmacokinetics and Electrophysiological Effects of Verapamil in Patients with Paroxysmal Supraventricular Tachycardia

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Ten mg of verapamil was administered intravenously to eight patients with paroxysmal supraventricular tachycardia. After drug administration, investigation of the pharmacokinetics of verapamil was carried out, and the relationship between plasma verapamil concentration and its electrophysiological effects was studied. After verapamil administration, pharmacokinetic parameters were calculated using a two-compartment open model. Biological half-life ranged from 2.91 to 4.55 hours and apparent volume of distribution ranged from 1.28 to 3.18 L/kg. Total body clearance ranged from 216 to 733 ml/min.

Verapamil significantly prolonged the AH interval but did not prolong the HV interval. The effective and the functional refractory period of the AV node (ERPAVN and FRPAVN) were also prolonged after verapamil administration. The antegrade echo zone and the supraventricular tachycardia zone were also narrowed in most patients. A concentration-dependent relationship between plasma verapamil and percent increase of both ERPAVN and AH interval was observed.

Key words : verapamil, paroxysmal supraventricular tachycardia, pharmacokinetic parameter, electrophysiological effect

Verapamil was originally introduced as a coronary vasodilator¹⁾. Its antiarrhythmic effect on various experimentally induced arrhythmias was explored during the 1960's²⁾³⁾⁴⁾. It has also been

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demonstrated that verapamil's antiarrhythmic mechanism differs from those of other antiarrhythmic drugs^{5,6}. Due to its inhibition of AV nodal conduction, verapamil is effective clinically in atrial flutter, atrial fibrillation and paroxysmal supraventricular tachycardia (PSVT)^{7,8,9,10}. Although there are numerous reports on the antiarrhythmic effects of verapamil, relatively few reports have been published on the pharmacokinetic effects of this drug^{11,12,13,14,15}. However, to understand the antiarrhythmic mechanism of verapamil both its pharmacokinetics and pharmacodynamics must be studied simultaneously. Correlation between plasma verapamil levels and electrophysiological and hemodynamic effects have been demonstrated in animal studies^{16,17,18}. However, there is little comparable clinical data available¹⁹. Therefore, we have attempted to clarify the relationship between pharmacokinetics of verapamil and its electrophysiological effects in patients with PSVT.

Materials and Methods

Patients : Eight patients, four males and four females, with a history of recurrent supraventricular tachycardia participated in this study. Ages ranged from 45 to 67 years (mean 57.1) and body weights ranged from 46 to 67.5 kg (mean 53.4). Normal liver and kidney function were verified by laboratory function tests. None had electrocardiographic evidence of the Wolff-Parkinson-White syndrome. Details of patient characteristics are shown in Tab. 1.

Methods : All drugs were withdrawn 48 hours prior to study. Patients were informed, and written consents were obtained. The electrophysiological studies were performed in post-absorptive and non-sedative state.

Four tri- or quadripolar electrode catheters were inserted, and positioned as follows : high in the right atrium ; in the coronary sinus (or pulmonary artery) ; in the right ventricle to record and stimulate ; and the fourth catheter was positioned across the tricuspid valve to record

Tab. 1 Patient Characteristics

Patient	Age (y)	Sex	Body weight (kg)	SGOT (K.U.) ¹	SGPT (K.U.) ¹	Serum creatinine (mg/dl)	Ccr ² (ml/min)
1	45	M	58	11	7	1.2	76.0
2	49	F	52	15	7	0.7	91.4
3	63	M	67.5	20	29	0.8	81.0
4	67	F	47	22	21	0.9	74.2
5	48	M	58	28	29	1.1	--
6	56	M	52	29	30	0.8	107.3
7	65	F	46.5	10	7	0.7	92.5
8	64	F	46	12	8	0.6	98.3
Mean	57.1		53.4	18	17	0.9	88.7
SD	8.8		7.4	7.5	11.0	0.2	12.2

1: Karmen Unit

2: Creatinine clearance

His bundle electrogram using the technique described by Sherlag et al.²⁰ Intracardiac electrograms were recorded simultaneously on a multichannel oscilloscopic photographic recorder (Hewlett-Packard 4568) with standard electrocardiographic leads at a paper speed of 50 or 100 mm/sec. The effective and the functional refractory period of the AV node (ERPAVN and FRPAVN) and the effective refractory period of the right atrium, as described by Wit et al.²¹, were determined using the right atrial extrastimulus technique. The antegrade echo zone (EZ), which is the zone of coupling interval resulting in atrial echoes, and the EZ in which more than one atrial echo could conduct to the ventricle (SVTZ) were also measured using the technique above-mentioned. Thereafter, the ventriculoatrial (V-A) conduction time, the refractory period of the V-A conduction both over the concealed accessory pathway and the normal conduction system, and the effective refractory period of the right ventricle were determined by the right ventricular extrastimulus technique.

After the control measurement, 10 mg verapamil was administered intravenously and the same stimulation program was repeated 15 min after injection. Verapamil injection was completed within a two minute time period. The AH interval (AH), the HV interval (HV), ERPAVN, FRPAVN, the effective refractory period of the atrium, EZ, SVTZ, the V-A conduction time, the refractory period of the V-A conduction over the right ventricle were determined at 15, 30, 60, 90 and 120 min thereafter.

Control blood sample was drawn prior to drug administration. Blood was taken 5, 15, 30, 60, 90 and 120 min during the electrophysiological studies and 3, 4, 6 and 8 hr after intravenous injection of verapamil. Blood samples were centrifuged and separated plasma was stored at

-20°C prior to analysis.

Verapamil analysis: Plasma verapamil was measured by the fluorometric method described by McAllister and Howell²².

Pharmacokinetic analysis: Plasma verapamil concentration after intravenous injection was analyzed using a two-compartment open model. The plasma concentration vs time curve was obtained by least square fitting:

$$C_p(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (\text{Eq. 1})$$

where $C_p(t)$ is the plasma concentration at time t after intravenous injection, A and B are the zero time intercepts, and α and β are the slopes of the distribution and elimination with apparent half-lives $t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively. The apparent volume of distribution ($V_{d\text{area}}$) of the drug was calculated with the use of the following formula:

$$V_{d\text{area}} = \frac{I. V. \text{dose}}{\beta \times \text{AUC}} \quad (\text{Eq. 2})$$

where AUC is the area under plasma concentration vs time curve calculated by means of the trapezoidal rule and extrapolated to infinity. Total body clearance (Cl_b) was calculated as follows:

Fig. 1 Mean plasma verapamil concentration after intravenous injection of 10 mg in 8 patients with paroxysmal supraventricular tachycardia (PSVT). Each value represents as Mean $\pm$ SD.

Tab. 2 Verapamil Pharmacokinetic Parameters after Intravenous Injection of 10 mg in Patients with Paroxysmal Supraventricular Tachycardia (PSVT)

Patient	α (hr ⁻¹)	β (hr ⁻¹)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	K_{el} (hr ⁻¹)	K_{12} (hr ⁻¹)	K_{21} (hr ⁻¹)	V_{darea} (L/Kg)	V_1 (L/Kg)	V_2 (L/Kg)	V_{dss} (L/Kg)	Cl_b (ml/min)	AUC (hr•ng/ml)
1	4.81	0.18	0.14	3.85	1.04	3.12	0.83	1.94	0.33	1.25	1.58	338.23	532.82
2	4.09	0.20	0.17	3.48	1.04	2.47	0.78	2.62	0.47	1.49	1.96	453.05	394.73
3	6.43	0.18	0.11	3.80	1.21	4.42	0.97	1.83	0.22	0.99	1.21	339.00	591.44
4	5.30	0.16	0.13	4.38	1.22	3.55	0.69	2.31	0.30	1.54	1.84	286.14	606.38
5	5.90	0.24	0.12	2.91	1.40	3.73	1.01	3.18	0.54	2.01	2.55	733.51	244.50
6	2.63	0.21	0.26	3.30	0.69	1.35	0.80	1.28	0.39	0.66	1.05	233.37	717.09
7	5.79	0.17	0.12	4.11	0.59	3.71	1.67	1.73	0.50	1.11	1.61	226.95	746.28
8	5.80	0.15	0.12	4.55	1.29	3.98	0.69	1.86	0.22	1.28	1.50	216.79	804.67
Mean	5.09	0.19	0.15	3.80	1.06	3.29	0.93	2.09	0.37	1.29	1.66	353.38	579.74
SD	1.23	0.03	0.05	0.55	0.29	0.98	0.32	0.59	0.12	0.40	0.47	172.56	187.79

Glossary of symbols

A	zero time intercept of 'alpha' or 'distribution' phase
B	zero time intercept of 'beta' or 'elimination' phase
α	exponent for 'alpha' or 'distribution' phase
β	exponent for 'beta' or 'elimination' phase
$t_{1/2\alpha}$	biological half-life of 'alpha' or 'distribution' phase
$t_{1/2\beta}$	biological half-life of 'beta' or 'elimination' phase
K_{el}	elimination rate constant
K_{12}	transfer rate constant from central to peripheral compartment
K_{21}	transfer rate constant from peripheral to central compartment
V_{darea}	apparent volume of distribution
V_1	volume of central compartment
V_2	volume of peripheral compartment
V_{dss}	volume of distribution at steady-state
Cl_b	total body clearance
AUC	area under plasma concentration vs time curve

$$Cl_b = \beta \times V_{darea} \quad (\text{Eq. 3})$$

The transfer (K_{12} , K_{21}) and elimination (K_{el}) rate constant were calculated by using the values of the slopes (α , β) and intercepts (A, B)^{23,24}. Statistical analysis : Pretreatment control period mean and post verapamil administration mean of electrophysiological data were compared using the paired, two-tailed Student's t-test. A p value of less than 0.05 was regarded as the minimum

level of statistical significance. Individual concentration-effect relationship data was analyzed by using linear regression by the least square method. Data is expressed as Mean $\pm$ SD.

Results

Pharmacokinetics : The semilogarithmic plots of drug plasma level vs time for 8 patients are shown in Fig.1. After intravenous injection, plasma

Tab. 3 Time Course of Electrophysiological Effects of Verapamil in Patients with PSVT

Patient	CL	AH					HV					ERP/VN				
		c	15 min	30 min	60 min	90 min	120 min	c	15 min	30 min	60 min	c	15 min	30 min	60 min	120 min
1	660	100	175	155	152	137	139	40	40	40	40	<230	260	260	260	280
2	600	120	180	170	120	110	110	40	40	40	40	300	380	330	-	-
3	-	-	-	-	-	-	-	-	-	-	-	<250	-	<260	<240	<300
4	700	80	150	120	115	110	105	35	35	35	35	<280	<340	<300	<300	<300
5	800	90	110	110	120	110	110	35	35	35	35	<290	360	340	340	340
6	720	120	140	120	120	120	120	35	35	35	35	290	340	340	340	320
7	600	90	177	-	-	-	-	55	55	55	55	<250	440	-	-	-
8	650	95	120	130	120	120	-	55	55	55	55	<280	280	300	300	280
Mean		99	150	134	124	117	116	42	42	42	42	295	343	314	314	305
S.D.		15	28	23	13	10	13	9	9	9	9	7	66	34	34	30
t-test		p<0.01														
n		7														
		NS														
		7														
		2														

Tab. 3 (Continued)

ERP/VN	FRP/VN										Plasma verapamil (ng/ml)					
	90 min	120 min	c	15 min	30 min	60 min	90 min	120 min	15 min	30 min	60 min	90 min	120 min	15 min	30 min	60 min
260	280	-	450	460	465	480	460	480	158.6	113.9	83.2	67.4	-	158.6	113.9	83.2
290	-	-	480	535	545	495	490	490	148.5	105.0	69.0	45.0	36.0	148.5	105.0	69.0
<260	<220	-	-	-	-	-	-	-	200.5	101.7	-	67.3	55.9	200.5	101.7	-
<300	<300	-	395	590	575	535	490	515	214.8	98.4	66.3	54.0	52.8	214.8	98.4	66.3
290	280	-	455	490	485	470	430	420	73.4	56.9	51.7	28.8	28.6	73.4	56.9	51.7
300	300	-	410	420	410	385	380	375	287.9	234.5	140.8	84.2	83.6	287.9	234.5	140.8
-	-	-	440	535	-	-	-	-	184.3	107.2	85.5	91.1	85.5	184.3	107.2	85.5
300	-	-	410	460	460	460	470	-	214.6	147.5	100.4	82.8	63.9	214.6	147.5	100.4
288	286	-	434	498	490	470	453	456	185.3	120.6	85.2	65.0	58.0	185.3	120.6	85.2
16	11	-	30	58	60	49	42	57	62.1	52.1	29.0	21.4	21.7	62.1	52.1	29.0
			p<0.05													
			7													

Abbreviations: CL, cycle length; AH, AH interval; HV, HV interval; ERP/VN, effective refractory period of the AV node; FRP/VN, functional refractory period of the AV node; c, control. Measurements of electrophysiological parameters are expressed as milliseconds. Differences in electrophysiological parameters between control value and 15 min value after intravenous injection of verapamil were determined by the paired, two-tailed Student's t-test.

Tab. 4 Time Course of Electrophysiological Effects of Verapamil on EZ and SVTZ in Patients with PSVT

Patient	CL	EZ (width)					
		c	15 min	30 min	60 min	90 min	120 min
1	660	230-300(70)	none(0)	none(0)	none(0)	none(0)	285(5)
2	600	310-385(75)	390-400(10)	350-460(110)	-	320-380(60)	-
3	-	250-260(10)	-	260-270(10)	240-280(40)	260-280(20)	220-260(40)
4	700	280-320(40)	340-520(180)	300-500(200)	300-460(160)	300-400(100)	300-420(120)
5	800	290-370(80)	380-400(20)	360-400(40)	360-480(120)	300-420(120)	290-380(90)
6	720	300-320(20)	none(0)	none(0)	none(0)	none(0)	320(5)
7	600	250-320(70)	none(0)	-	-	-	-
8	650	280-320(4)	320-360(40)	320-340(20)	300-340(40)	320-380(60)	-

Tab. 4 (continued)

SVTZ (width)		15 min	30 min	60 min	90 min	120 min
c						
230-300(70)	none(0)	none(0)	none(0)	none(0)	none(0)	none(0)
310-385(75)	390-400(10)	350-460(110)	-	320-380(60)	-	-
250-260(10)	-	260-270(10)	240-280(40)	260-280(20)	220-260(40)	
280-320(40)	340-520(180)	300-500(200)	300-460(160)	300-400(100)	300-420(120)	
290-370(80)	none(0)	none(0)	none(0)	none(0)	none(0)	
300-320(20)	none(0)	none(0)	none(0)	none(0)	320(5)	
250-300(50)	none(0)	-	-	-	-	
280-320(40)	none(0)	none(0)	none(0)	none(0)	-	

Abbreviations: CL, cycle length; EZ, antegrade echo zone; SVTZ, supraventricular tachycardia zone; c, control. Values of EZ and SVTZ are expressed as milliseconds.

Fig. 2 Relationships between the percent increase of AH and plasma verapamil concentration.

verapamil levels declined biexponentially. Data was analyzed in accordance with a two-compartment open model.

Relevant pharmacokinetic parameters are listed in Tab. 2. The apparent half-life of initial distribution phase ($t_{1/2\alpha}$) ranged from 0.11 to 0.26 hours. The apparent half-life of elimination phase ($t_{1/2\beta}$) ranged from 2.91 to 4.55 hours. The apparent volume of distribution ($V_{d_{area}}$) ranged from 1.28 to 3.18 L/kg, and total body clearance ranged from 216 to 733 ml/min. AUC of verapamil ranged from 394.73 to 804.67 hr·ng/ml.

Electrophysiological effects: Maximal effect was obtained 15 minutes after intravenous injection of verapamil. Thereafter, it decreased gradually. The time course of electrophysiological effects is shown in Tab. 3 and 4. AH was significantly prolonged from 99 ± 6 to 150 ± 11 msec in His bundle electrocardiogram 15 minutes after injection ($p<0.01$, $n=7$) (Tab. 3). Mini-

mal concentration of verapamil required to prolong AH was 29 ng/ml. On the other hand, HV was not changed by verapamil. Verapamil also prolonged both ERPAVN and FRPAVN from 295 ± 7 to 360 ± 28 msec and from 434 ± 11 to 499 ± 22 msec, respectively 15 min after injection (not significant for ERPAVN, $n=2$ and $p<0.05$ for FRPAVN, $n=7$) (Tab. 3). Minimal concentrations which prolonged ERPAVN and FRPAVN were 29 ng/ml and 36 ng/ml, respectively.

Verapamil did not effect the refractory period of the atrium, the refractory period of the V-A conduction system over the accessory pathway or the effective refractory period of the right ventricle. The width of EZ was narrowed in 5 of the 7 patients and width of SVTZ was narrowed in 6 of 7 patients 15 min after intravenous injection of verapamil (Tab. 4).

Relationship between plasma concentration and electrophysiological effect: There were positive correlations between the percent increase of AH

Fig. 3 Relationships between the percent increase of ERPAVN and plasma verapamil concentration.

Tab. 4 Relationships between the percent increase of FRPAVN and plasma verapamil concentration.

and plasma verapamil concentration, and verapamil's this correlation was significant in 3 out of 6 patients (Fig. 2). Concerning the verapamil's

effect on ERPAVN, although control values were obtained in only two patients, there was a strong positive correlation between the percent increase

of ERPAVN and plasma verapamil concentration, and this correlation was found to be significant in patient 6 (Fig. 3). With regard to the effect on FRPAVN, positive correlations between percent increase of FRPAVN and verapamil concentration were observed in 4 out of 6 patients. Correlation was significant in 2 patients (Fig. 4).

Discussion

Previously, little had been published concerning disposition kinetics of verapamil in man. The first report that appeared in 1976 demonstrated that plasma verapamil levels showed a biexponential decline and the elimination half-life ($t_{1/2\beta}$) ranged from 3 to 7 hr in normal subjects¹¹.

The previous study of the pharmacokinetics and relationship between serum concentration and surface electrocardiographic changes demonstrated that the biological half-life of verapamil characteristically ranged between 3 and 4 hr, and that there was a significant correlation between the prolongation of PQ interval and the increase of serum verapamil concentration¹². These findings concurred with earlier animal experiments¹⁶.

The present study was conducted to explore both the pharmacokinetics of intravenous verapamil and the relationship between verapamil concentration and electrophysiological effects in patients with PSVT.

In our present study, there was a two-fold difference in the apparent volume of distribution in patients, but little individual difference between $V_{d\text{area}}$ and $V_{d\text{ss}}$. There was a three-fold difference in the total body clearance among them. Most pharmacokinetic parameters approximated those of normal subjects as Koike et al. reported previously¹². The elimination half-life

observed in our study was identical to that observed by Eichelbaum¹⁴ and was longer than that reported by Dominic¹³. Recently, Kates et al.¹⁵ reported longer elimination half-life of verapamil. The authors collected blood samples for over 24 hr after intravenous infusion and the data was analyzed using a three-compartment open model. These differences may be attributed to the duration of sampling time. The volume of distribution and plasma clearance were less than those observed in other studies¹¹⁾⁽¹³⁾⁽¹⁴⁾⁽¹⁵⁾. Discrepancy between our data and others may be due partly to differences in populations.

Verapamil's electrophysiological effect works selectively on the sinus node and the AV node⁶⁾⁽²⁵⁾⁽²⁶⁾⁽²⁷⁾. More selectively, it has been demonstrated that verapamil depresses the AV node more selectively than the sinus node¹⁷. The membrane potential of both nodal cells depends upon inward current through the slow channel. Since verapamil interferes with this slow channel, it depresses the intranodal conduction time and prolongs the refractory period of the AV node⁷⁾⁽²⁶⁾⁽²⁸⁾.

Many clinical reports have shown that verapamil prolonged the AV nodal conduction as well as ERPAVN and FRPAVN, but did not prolong the HV interval^{29)–33)}. Our results were in agreement with these studies. Furthermore, verapamil narrowed the width of EZ and SVTZ in all of the patients studied. This effect indicates the efficacy of the drug in terminating PSVT. Since most supraventricular tachycardia results from reentry and the AV node is an antegrade limb of the reentry circuit, prolongation of ERPAVN decreases the absolute width of EZ during which atrial premature impulse may induce the reentry and prevents the atrial echo from returning to the ventricle and initiating tachycardia.

In regard to correlation between plasma vera-

pamil concentration and electrophysiological effects, Mangiardi et al.¹⁷⁾ demonstrated in animal experiment that there was a significant correlation between plasma verapamil concentration and AH interval prolongation. The authors also reported that the functional and the effective refractory period of the AV node increased in a concentration dependent manner.

Our present studies demonstrated that the prolongation of the AH interval and the increase of ERPAVN were dependent upon plasma verapamil concentration throughout both distribution and elimination phases. Because of the correlation between plasma verapamil concentration and electrophysiological effects, it was speculated that the pharmacodynamic effects of verapamil were dependent upon the concentration (or amount) of the drug in the central compartment. In addition, the minimal effective plasma concentration of verapamil which prolonged the AH interval and ERPAVN was found to be between 30-40 ng/ml. But in clinical therapy of arrhythmias, the "minimal effective therapeutic concentration" may be a high level than those mentioned above because critical prolongation of ERPAVN and the effective decrease of width of EZ are required in order to terminate supraventricular tachycardia. In fact, Sung et al.³⁴⁾ reported that plasma verapamil concentrations that successfully terminated supraventricular tachycardia ranged from 72 to 195 ng/ml. In our clinical experience, a concentration range of 50-150 ng/ml verapamil has been sufficient to terminate supraventricular tachycardia (unpublished observation).

The present study confirmed our previous observation that verapamil's physiological disposition in patients with PSVT does not differ from that in normal subjects. It also demonstrated that intravenous injection of verapamil prolonged

the AV nodal conduction time and increased the effective and the functional refractory period of the AV node. The drug narrowed the width of EZ and SVTZ in most patients. The electrophysiological results indicate that verapamil is effective treatment of PSVT. In addition, the prolongation of the AH interval and the increase of the refractory period of the AV node were dependent upon plasma verapamil concentration. These facts indicate that rapid injection may possibly produce inappropriate elevation of plasma verapamil concentration, inducing occurrence of adverse effects such as atrioventricular block.

Thus, one should avoid rapid injection of verapamil. Furthermore, it appears that monitoring the concentration of verapamil is a useful way to determine the optimal therapeutic dosage regimen and avoid adverse effects.

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