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Effects of Intravenous Diltiazem on Supraventricular Tachyarrhythmias

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SUMMARY : The effects of intravenous diltiazem on supraventricular tachyarrhythmias were studied in 16 patients : 6 with paroxysmal supraventricular tachycardia using an accessory pathway retrogradely, 6 with atrial fibrillation, 3 with atrial flutter and 1 with chronic atrial tachycardia. Diltiazem (0.1 or 0.2 mg/kg) was administered intravenously over 5 minutes.

Termination of paroxysmal supraventricular tachycardia was achieved in 6 out of 10 episodes during or just after the injection. Diltiazem slowed the ventricular conduction from 2 : 1 to 4 : 1 in atrial flutter, but sinus rhythm was not restored in either case. Diltiazem increased the ventricular response through an accessory pathway in a patient with atrial fibrillation associated with Wolff-Parkinson-White syndrome. Atrial rate in a case of chronic atrial tachycardia did not change significantly. There were no adverse clinical effects.

It is concluded that diltiazem is effective in slowing ventricular rate in atrial fibrillation and flutter and in terminating paroxysmal supraventricular tachycardia. However, diltiazem may be contraindicated in atrial fibrillation associated with Wolff-Parkinson-White syndrome.

INTRODUCTION

Diltiazem, a 1, 5-benzothiazepine derivative, is one of the compounds blocking the inward flux of calcium during cellular depolarization[1]. Diltiazem, originally introduced for the treatment of angina pectoris[1], has been shown to have antiarrhythmic properties[2, 3]. However, there are a few detailed reports about the effects of intravenous diltiazem on supraventricular tachyarrhythmias[4~8].

In this report we present the effects of intravenous diltiazem on various types of supraventricular tachyarrhythmias.

SUBJECTS AND METHODS

Study patients : Diltiazem was administered intravenously to 16 patients with supraventricular tachyarrhythmias on 22 occasions. The clinical features of the patients are summarized in **Tables 1 and 2**. The patients were divided into four groups according to the type of supraventricular arrhythmias.

Group A was composed of 6 patients with 10 spontaneous episodes of paroxysmal supraventricular tachycardia using the atrioventricular node antegradely and an accessory pathway retrogradely, which was demonstrated at elec-

trophysiological study (4 with manifest Wolff-Parkinson-White syndrome and 2 with concealed Wolff-Parkinson-White syndrome).

Group B consisted of a patient with chronic atrial tachycardia (repetitive type). Diltiazem was administered on 2 separate occasions to this patient.

Group C consisted of 3 patients with 3 episodes of atrial flutter.

Group D included 6 patients with atrial fibrillation (5 with paroxysmal and 1 with chronic atrial fibrillation).

Intravenous administration of diltiazem: Informed consent was obtained from all patients for the administration of diltiazem intravenously. All patients received a bolus injection of diltiazem at a dose of 0.1 mg/kg (4 occasions) or 0.2 mg/kg (18 occasions), administered by hand infusion over 5 minutes. When supraventricular tachyarrhythmias were converted to normal sinus ryhthm during the injection, the bolus injection was stopped immediately.

Continuous electrocardiographic monitoring and direct slow speed recording were performed during diltiazem administration and continued 3 hours after the injection.

Blood pressure was measured immediately before the injection of diltiazem and at 1, 3, 5, 10, 15, 30, 60, 120 and 180 minutes afterwards.

Blood samples were drawn for plasma diltiazem measurements just before the administration and at 5, 15, 30, 60, 120, 180 and 240 minutes after the beginning of the injection. Diltiazem plasma concentration was measured by a gas chromatographic method[9].

Statistical analysis: Differences in heart rate and blood pressure measured before and after diltiazem administration were analyzed for sig-

Table 1. Clinical Features of Patients and Response to Diltiazem (Group A and B)

Patient	Age (years) & sex	Cardiac Diagnosis	Dose mg/kg (Total)	Response to diltiazem
Group A (Paroxysmal Supraventricular Tachycardia associated with WPW)				
1A	44M	Normal Manifest WPW	0.1 (5.0)	Slowed (190/min → 110/min)
1B			0.2 (10.0)	Slowed (155/min → 97/min)
2A	18M	Normal Concealed WPW	0.2 (6.7)	Terminated *(165 sec)
2B			0.2 (13.4)	Terminated *(360 sec)
2C			0.2 (10.2)	Terminated *(240 sec)
3A	61M	Normal Manifest WPW	0.2 (4.0)	Terminated *(90 sec)
3B			0.2 (10.6)	Terminated *(240 sec)
4	14M	Normal Manifest WPW	0.2 (8.0)	Terminated *(200 sec)
5	11F	Normal Operated Concealed WPW	0.2 (7.0)	Slowed (170/min → 140/min)
6	56F	Normal Manifest WPW	0.2 (12.2)	Slowed (168/min → 152/min)
Group B (Chronic Atrial Tachycardia)				
7A	21F	Normal	0.1 (4.3)	ectopic P-R interval 0.19 sec to 0.24 sec.
7B			0.2 (8.6)	ectopic P-R interval 0.21 sec to 0.24 sec.

*Time elapsing from the beginning of diltiazem injection to termination of supraventricular tachycardia.
Abbreviatiion: WPW = Wolff-Parkinson-White Syndrome.

Table 2. Clinical Features of Patients and Response to Diltiazem (Group C and D)

Patient	Age (years) & sex	Cardiac Diagnosis	Dose mg/kg (Total)	Mean Heart Rate (beats/min) C	*D	Response to Diltiazem	Previous therapy
Group C (Atrial Flutter)							
8	69F	Normal	0.2 (8.4)	155	98	Ventricular rate decreased ; atrial flutter 2 : 1 mostly 4 : 1	
9	49M	PS associated with ASD	0.2 (9.8)	144	80	Ventricular rate decreased ; atrial flutter 2 : 1 mostly 4 : 1	Methyldigoxin 0.1 mg
10	66M	MS, AR	0.1 (5.5)	146	81	Ventricular rate decreased ; atrial flutter 2 : 1 mostly 4 : 1 conversion to atrial fibrillation at 15 minutes	Lanatoside C 0.4 mg i. v. 3 hours before
Group D (Atrial Fibrillation)							
11	51F	Normal, Paroxysmal AF	0.2 (11.0)	162	142		
12	59M	IHD, Chronic AF	0.2 (9.8)	72	53		
13	52M	OMI, Paroxysmal AF	0.2 (11.4)	79	54	Ventricular rate decreased	
14	57M	Normal, Paroxysmal AF	0.2 (13.0)	99	67		
15	41M	HOCM, Paroxysmal AF	0.1 (4.6)	117	80		
16A	44M	Normal, Paroxysmal AF associated with WPW	0.2 (12.4)	118	83	Ventricular rate decreased ; A-V conduction slowed ; *Accessory pathway conduction unchanged*	Procainamide 520 mg i. v. 30 minutes before.
16B			0.2 (12.4)	119	73	Ventricular rate decreased ; A-V conduction slowed, but *Accessory pathway conduction unchanged*	

*Minimal ventricular rate within 30 minutes of diltiazem adiministration.
Abbreviations : AF = atrial fibrillation, AR = aortic regurgitation, ASD = atrial septal defect, C = control, D = diltiazem, HOCM = hypertrophic obstructive cardiomyopathy, IHD = ischemic heart disease, MS = mitral stenosis, OMI = old myocardial infarction, PS = pulmonary stenosis, WPW = Wolff-Parkinson-White syndrome.

nificance using a t test. A p value of 0.05 or less was considered statistically significant.

Definitions : Participation of an accessory atrioventricular pathway during supraventricular tachycardia and the diagnosis of chronic atrial tachycardia were established using criteria described previously[10~12].

Ventricular rate during atrial fibrillation and atrial flutter, and atrial rate of chronic atrial tachycardia was determined by averaging over 60 seconds.

RESULTS

Group A —Paroxysmal Supraventricular Tachycardia Associated with Wolff-Parkinson-White Syndrome.

Four patients had left lateral accessory pathways that conducted bidirectionally and two patients had concealed left lateral accessory pathways. In all patients, the conduction during supraventricular tachycardia proceeded antegradely in the atrioventricular node and retrogradely in the accessory pathway.

Diltiazem was administered on 10 spontaneous episodes to the 6 patients with paroxysmal supraventricular tachycardia. The drug was injected twice or 3 times in Patients 1, 2 and 3 (**Table 1**), for episodes of supraventricular tachycardia occurring on different days.

A bolus injection of 0.2 mg/kg was administered 9 times in 6 patients with paroxysmal supraventricular tachycardia. Supraventricular tachycardia terminated after a bolus injection in 3 patients (6 times in total), whereas the ventricular rate decreased after the injection in the remaining 3 patients (3 times in total).

Fig. 1 shows the change in the ventricular rate of paroxysmal supraventricular tachycardia in 6 episodes of 3 cases which terminated after the injection of 0.2 mg/kg. The ventricular rate began to decrease gradually during the injection (169±32/min (mean±standard deviation) to 155±24/min) and conversion to sinus rhythm was achieved after a mean interval of 3.6±1.5 minutes from the onset of the injection.

Fig. 2 shows the change of the ventricular rate after intravenous diltiazem of 0.1 or 0.2 mg/kg in the remaining 3 cases of paroxysmal supraventricular tachycardia which did not termi-

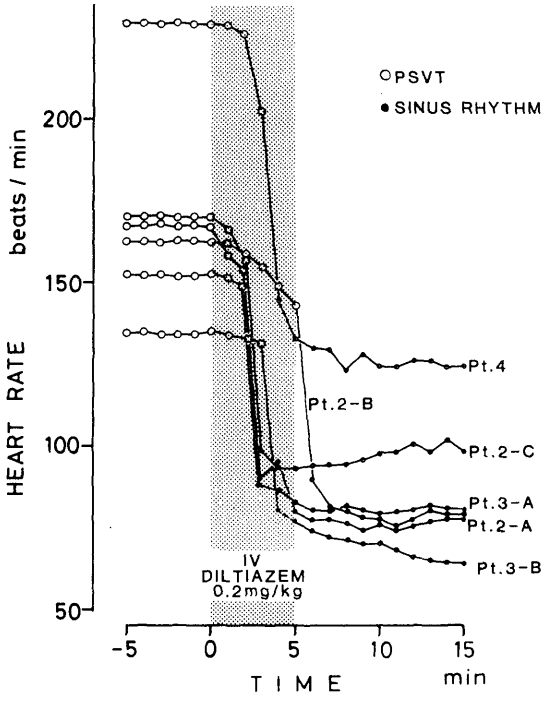

Fig. 1. The change in the ventricular rate of paroxysmal supraventricular tachycardia (PSVT) in 3 patients (6 episodes) which terminated after the injection of diltiazem (0.2 mg/kg). Unfilled circles indicate supraventricular tachycardia and the filled circles sinus rhythm.

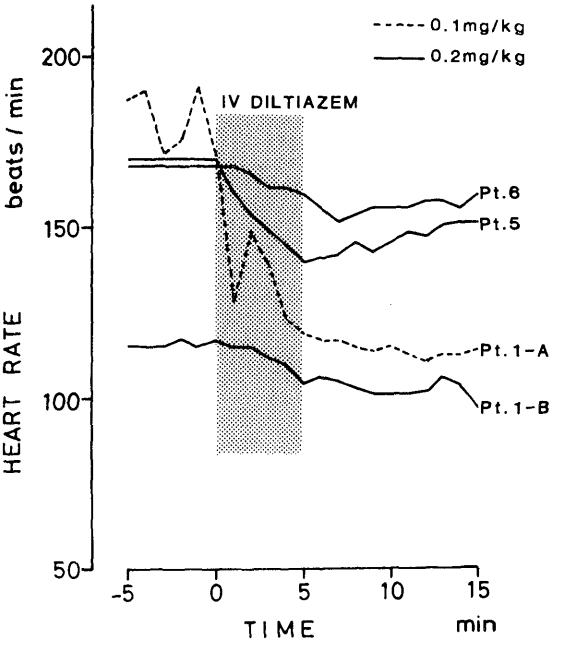

Fig. 2. The ventricular rate after intravenoous diltiazem of 0.1 or 0.2 mg/kg in the 3 cases of paroxysmal supraventricular tachycardia which did not terminate, but slowed. In the case shown with the broken line (Case 1-A), the ventricular rate was markedly decreased by diltiazem even at a dose of 0.1 mg/kg.

nate, but slowed.

In Patient 1, diltiazem was administered in two dosages : 0.1 and 0.2 mg/kg. The ventricular rate before the injection changed markedly within a short time (170/min to 190/min) (**Fig. 2,** Pt 1-A).

Initially 0.1 mg/kg was administered and the ventricular rate decreased from 190/min to 110/min 15 minutes after the injection. However, supraventricular tachycardia did not terminate and 0.2 mg/kg was administered 4 hours later (**Fig. 2,** Pt 1-B). The ventricular rate decreased further, from 115/min to 97/min, 15 minutes after the injection. Although supraventricular tachycardia did not terminate spontaneously, it could be terminated easily by a Valsalva maneuver done 30 minutes after the injection of 0.2 mg/kg.

Group B — Chronic Atrial Tachycardia.

Diltiazem at doses of 0.1 and 0.2 mg/kg was administered on different days in a case with chronic atrial tachycardia of repetitive type (**Table 1**). The atrial rate (139/min) remained unchanged 15 minutes after the injection of 0.1 mg/kg. However, P-R interval prolonged from 0.19 second to 0.24 second. The atrial rate failed to slow even after a further injection of 0.2 mg/kg, despite P-R interval prolongation.

Group C — Atrial Flutter.

Patient 10 received 0.1 mg/kg of diltiazem, and Patients 8 and 9 received 0.2 mg/kg (**Table 2**). Both doses slowed the ventricular rate markedly 15 to 30 minutes after the injection and atrioventricular conduction changed from 2 : 1 to 4 : 1. However, there was no significant

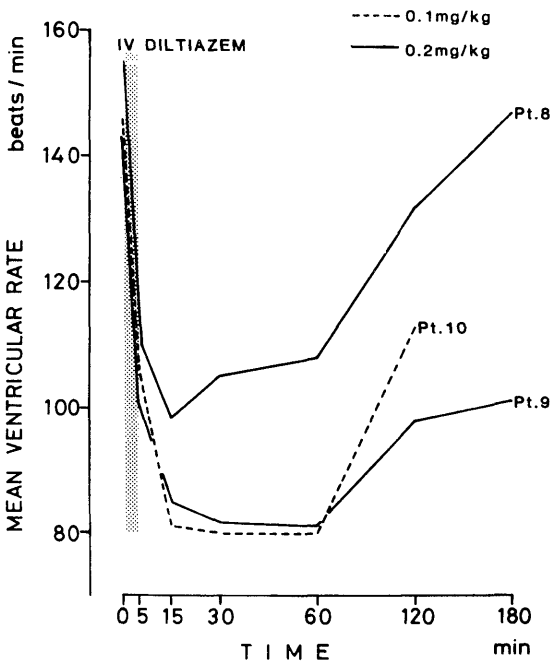

Fig. 3. The change in the mean ventricular rate of atrial flutter after intravenous diltiazem. The broken line indicates 0.1 mg/kg and the solid lines 0.2 mg/kg. At both doses the ventricular rate decreased markedly 15 to 30 minutes after the injection and the atrioventricular conduction changed from 2 : 1 to 4 : 1. The ventricular rate began to increase gradually 1 hour after the injection, but the effect of the drug continued for a total of 3 hours.

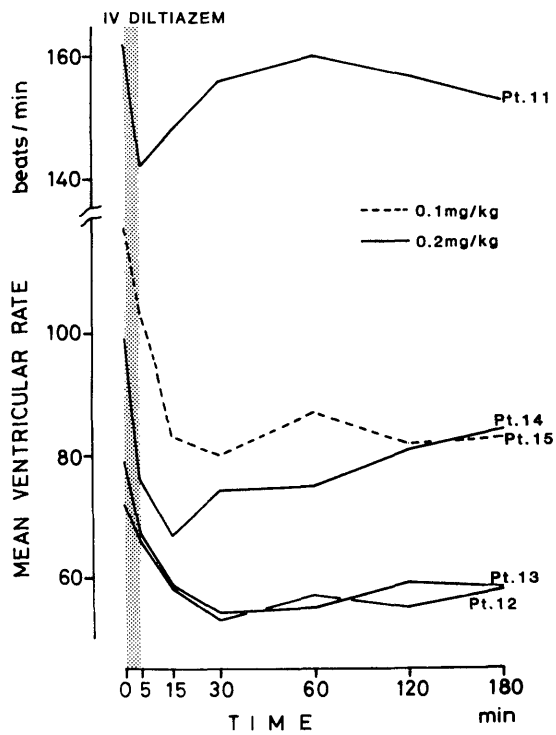

Fig. 4. The change in mean ventricular rate of atrial fibrillation after injection of diltiazem. The mean ventricular rate decreased makedly 15 to 30 minutes after the injection and the effect of the drug continued for up to 3 hours in four of five cases.

change in the F-F rate. The ventricular rate began to increase gradually one hour after the injection, taking a mean of 3 hours to return to the pretreatment value (**Fig. 3**).

None of the cases with atrial flutter was converted to sinus rhythm.

Intravenous lanatoside C, 0.4 mg, was ineffective in Patient 10. Diltiazem (0.1 mg/kg) given 3 hours after the lanatoside C slowed the ventricular rate from 146/min to 81/min 15 minutes after the injection and thereafter atrial flutter converted to atrial fibrillation. The ventricular rate was controlled at about 80/min despite atrial fibrillation for a duration of 60 minutes following the injection.

Group D — Atrial Fibrillation.

Five patients had paroxysmal atrial fibrillation and one was in chronic atrial fibrillation. The drug was given intravenously at 0.1 mg/kg to one patient and at 0.2 mg/kg to the remaining 5 patients (**Table 2 and Fig. 4**).

The ventricular rate of Patient 11 decreased from 162/min to 142/min just after the injection of 0.2 mg/kg, but it began to increase thereafter. In Patients 12, 13 and 14 the ventricular rate also decreased from 83±14/min to 61±5/min 15 minutes after the injection of 0.2 mg/kg and this ventricular rate was maintained for 60 minutes. Three hours after the injection the mean ventricular rate was still slowed at 66±15/min. In Patient 11 the ventricular rate did not decrease satisfactorily. Diltiazem was administered 30 minutes after the onset of atrial fibrillation in Patient 11 and 2 days after the onset in Patients 13 and 14.

Patient 15 had hypertrophic obstructive cardiomyopathy complicated by atrial fibrillation. Diltiazem, 0.1 mg/kg, was injected intravenously over 10 minutes in this case 24 hours after the onset of atrial fibrillation. The ventricular rate decreased from 117/min to 80/min 30 minutes after the injection. The effect of the drug could still be seen after 3 hours.

Group D — Atrial Fibrillation Associated with Wolff-Parkinson-White Syndrome.

Patient 16 suffered from paroxysmal atrial fibrillation associated with Wolff-Parkinson-White syndrome (**Figs. 5 and 6**). The QRS

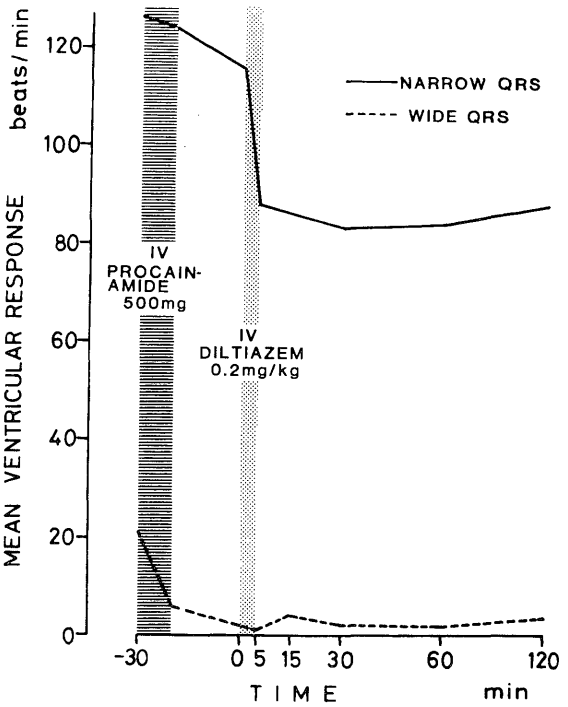

Fig. 5. (A)

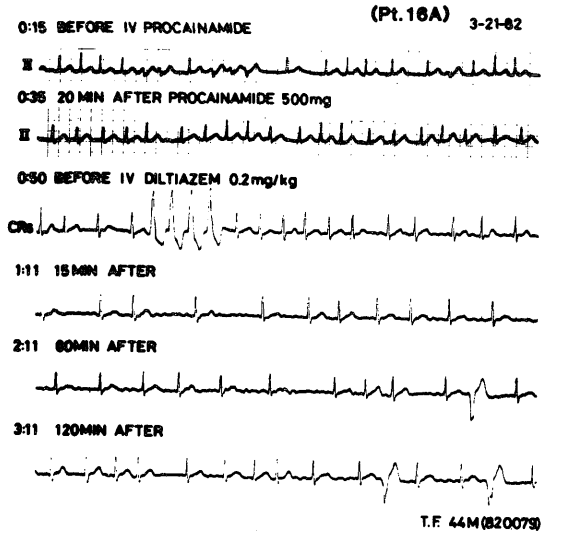

Fig. 5. (B)

Fig. 5. Case 16-A. (A) Ventricular response in atrial fibrillation associated with Wolff-Parkinson-White syndrome after the injection of procainamide plus diltiazem. (B) Tracings were recorded before and 20 minutes after procainamide administration and before and 15, 60, and 120 minutes after diltiazem administration. See text for details.

during atrial fibrillation in this case was mostly narrow (mainly conducted through the atrioventricular node) and occasionally wide (exclusively conducted through the accessory pathway). Procainamide was given prior to diltiazem at the onset of atrial fibrillation (**Fig. 5A and B**). The systolic pressure fell from 125 mmHg to 92 mmHg after the injection of procainamide (500 mg) given over 10 minutes. The injection of procainamide was therefore discontinued. The rate of narrow QRS complexes slightly decreased and the incidence of wide QRS complexes decreased from 20/min to 2-4/min after the injection of procainamide. With intravenous diltiazem (0.2 mg/kg) administered about 20 minutes later, the rate of narrow QRS complexes decreased from 118/min to 83/min over 15 minutes. However, the incidence of wide QRS complexes remained unchanged.

The response of atrial fibrillation to diltiazem (0.2 mg/kg) without prior administration of procainamide was observed on another day (**Fig. 6A and B**). The narrow QRS complex rate decreased from 104/min to 68/min 15 minutes after the injection of diltiazem. However, the incidence of wide QRS complexes began to increase gradually 15 minutes after the injection, resulting in frequent responses of 40 to 50 complexes/min 2 hours later. After 3 hours the incidence of wide QRS complexes had returned to baseline. Supraventricular tachycardia of 4 minutes' duration occurred transiently 4 hours later, but it reverted to sinus rhythm spontaneously.

Blood pressure: After the injection of 0.2 mg/kg in 9 patients without paroxysmal supraventricular tachycardia, the systolic blood pressure fell from 108±16 to 97±12 mmHg, and the

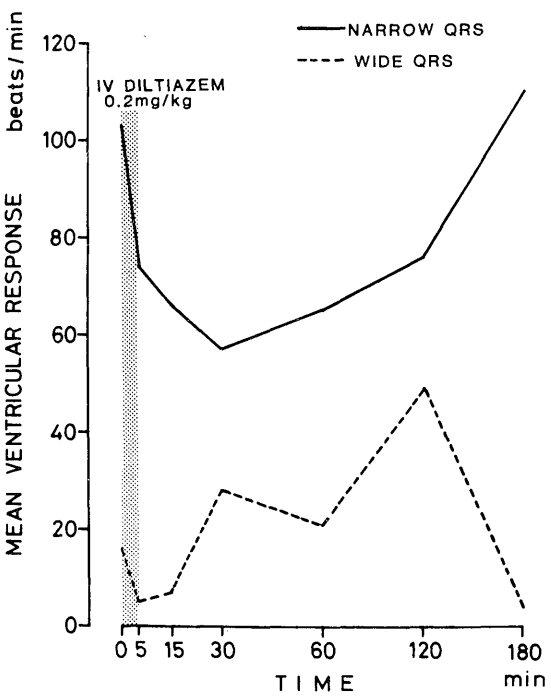

Fig. 6. (A)

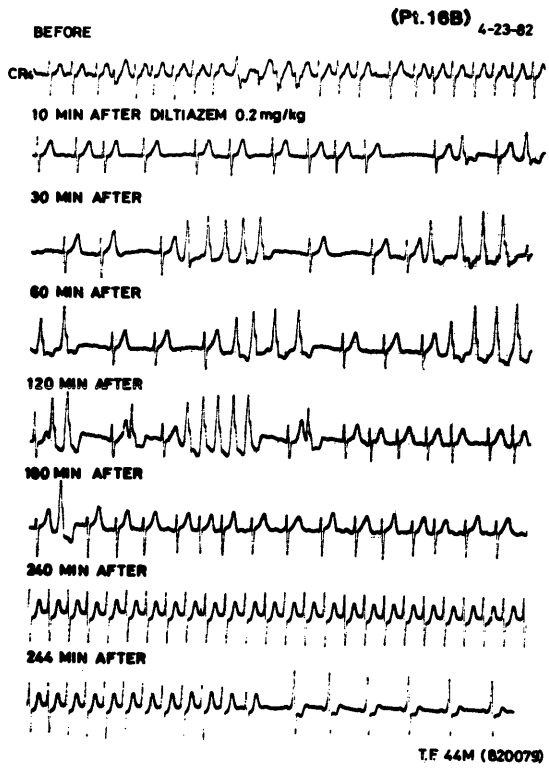

Fig. 6. (B)

Fig. 6. Case 16-B. (A) Ventricular response in atrial fibrillation associated with Wolff-Parkinson-White syndrome after the injection of diltiazem without the preinjection of procainamide. (B) Tracings were recorded before and 10, 30, 60, 120, 180, 240 and 244 minutes after the injection of diltiazem. See text for details.

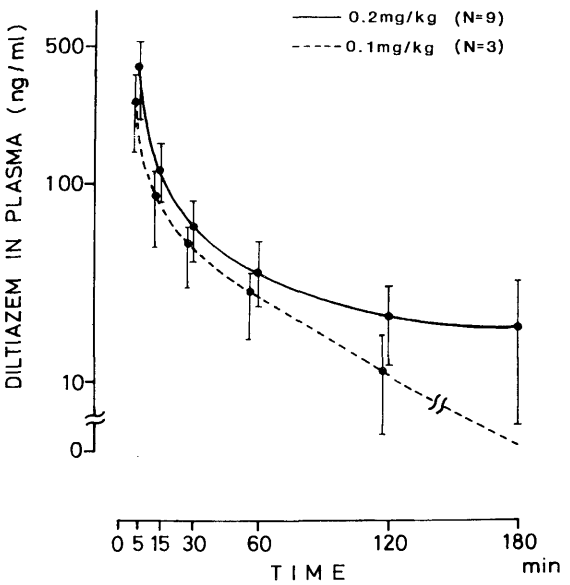

Fig. 7. The time course of the plasma concentration of diltiazem after the injection of 0.1 mg/kg (shown broken line) in 3 and of 0.2 mg/kg (shown solid line) in 9 patients. See text for details.

diastolic blood pressure fell from 68±18 to 62±9 mmHg. This reduction in blood pressure did not reach statistical significance.

Diltiazem Plasma Concentration : **Fig. 7** shows the time course of the mean plasma concentration of diltiazem after the injection of 0.1 mg/kg (5.3±0.2 mg in total) in 3 and of 0.2 mg/kg (10.8±1.7 mg in total) in 9 patients. The mean plasma concentration following 0.2 mg/kg decreased rapidly from 377±160 to 62±22 ng/ml within 30 minutes of the injection. Thereafter it decreased slowly reaching a mean value of 18±12 ng/ml afer 3 hours. The elimination half-life of intravenous diltiazem (0.2 mg/kg) calculated from this curve by a 2 compartment open model was 1.93 hours.

No complications or unwanted effects were observed after the injection of diltiazem.

DISCUSSION

Animal experimental observations suggest: (1) that atrioventricular nodal cells are slow-channel-dependent, (2) that atrioventricular nodal conduction can be slowed or blocked by agents that interfere with slow inward current and (3) that the refractory period is also prolonged by such agents[13, 14]. Verapamil exerts such an action and is used extensively as an antiarrhythmic agent for supraventricular tachyarrhythmias[14~17].

Diltiazem is a widely used antianginal drug in Japan[18, 19] and is finding a place in antianginal treatment in Europe[20, 21]. Recent electrophysiological studies indicate that diltiazem inhibits atrioventricular conduction and is effective against supraventricular arrhythmias[2, 3]. However, few detailed prospective studies of intravenous diltiazem on supraventricular tachyarrhythmias have ever been reported[6~8].

In this study we prospectively studied the effect of intravenous diltiazem on various types of supraventricular arrhythmias and also observed the safety of this drug in patients with underlying cardiac disease. The drug was well tolerated on all occasions by all subjects.

Effects on Paroxysmal Supraventricular Tachycardia Associated with Wolff-Parkinson-White Syndrome.

Diltiazem, 0.2mg/kg, was administered intravenouly in 6 patients with 9 episodes of paroxysmal supraventricular tachycardia. Supraventricular tachycardia terminated in 3 patients (6 episodes). The ventricular rate slowed in the remaining 3 patients without termination of supraventricular tachycardia. It seems likely that these effects of diltiazem are due to inhibition of antegrade atrioventricular nodal conduction[2~5].

Effects on Atrial Flutter and Atrial Fibrillation.

The atrioventricular conduction in atrial flutter was depressed by diltiazem with alteration from 2 : 1 to 4 : 1 conduction, resulting in reduction of ventricular rate. However, no change in F-F rate occurred.

The ventricular rate of atrial fibrillation was slowed maximally at 15-30 minutes after the injection of diltiazem. The effect of diltiazem persisted for 3 hours. In Patient 11, there was only a slight decrease in the ventricular rate. Diltiazem had been administered only 30 minutes after the onset of atrial fibrillation in this case, unlike the other cases. It may be that the effect of diltiazem was weakened by increased

sympathetic tone due to the acute onset of atrial fibrillation.

Atrial fibrillation and atrial flutter did not convert to sinus rhythm after intravenous injection of 0.2 mg/kg of diltiazem, but the drug was found to be effective for controlling the ventricular rate.

Effect of Atrial Fibrillation Associated with Wolff-Parkinson-White Syndrome.

Patient 16 was in atrial fibrillation associated with Wolff-Parkinson-White syndrome. Following intravenous diltiazem the ventricular response through the atrioventricular node decreased, but there was a marked increase in conduction via the accessory pathway. When procainamide was administered prior to diltiazem, the ventricular response through the accessory pathway did not increase after the injection of diltiazem. An increase in the ventricular response through the accessory pathway is also seen after the injection of verapamil or digitalis[17, 22, 23].

The increase in ventricular response during atrial fibrillation through an accessory pathway in this patient may have the following explanations. First, diltiazem may have shortened the conduction time and refractory period of the accessory pathway, an alternative favoured by the effect of previous procainamide which prevented this phenomenon. Secondly, diltiazem, by blocking atrioventricular nodal conduction, may have prevented atrial fibrillation impulses travelling antegradely through the atrioventricular node with preferential use of the accessory pathway. Further detailed electrophysiological studies are needed to elucidate this case. Any drug which blocks at the atrioventricular node and shortens the refractory period of the accessory pathway is potentially dangerous and contraindicated in the Wolff-Parkinson-White syndrome.

In conclusion our results suggest that intravenous diltiazem acts in a way similar to verapamil and shows the electrophysiological properties of a calcium antagonist and was well tolerated. Diltiazem may be useful for the acute treatment of paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation. However, diltiazem may be contraindicated in atrial fibrillation associated with the Wolff-Parkinson-White syndrome.

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