The effect of Verapamil on the cardiac conduction system in man

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Summary

Using His bundle electrograms the effect of Verapamil on the specialized conduction system in eleven patients was studied during routine cardiac catheterization.

In five patients, the absolute and relative refractory periods of the A-V node, and retrograde conduction through the A-V node was studied using programmed electrical stimulation techniques.

Verapamil caused prolongation of anterograde and retrograde A-V nodal conduction times. The effect on anterograde conduction was only partly reversible with Atropine. No significant effect on the remainder of the conduction system was observed.

It is concluded that Verapamil has a direct effect on A-V nodal conduction independent of any vagotonic effect.

Introduction

Clinical trials using Verapamil as an antidysrhythmic agent have shown it to be an effective drug in the control of supraventricular tachycardias (Schamroth, Krikler and Garrett, 1972).

It has previously been shown in cats (Ross and Jorgensen, 1967) that Verapamil produced bradycardia after vagotomy and after beta-adrenergic blockage produced by intravenous propranolol.

Dog experiments injecting Verapamil directly into the arteries supplying the sinus and A-V node have suggested that the mechanism of action of Verapamil on the sinus and A-V node involves a direct cardiac effect as well as an effect mediated by vagal mechanisms (Garvey, 1969).

Singh and Vaughan Williams (1972) reported on Atropine resistant bradycardia caused by Verapamil.

Using His bundle electrograms we have recorded the effects of intravenous Verapamil on the conduction system in eleven patients undergoing routine cardiac catheterization. In five of these patients the effect of Verapamil on the relative and absolute refractory periods of the A-V node and on retrograde

conduction was determined. Informed consent was obtained from all patients.

Subjects and methods

Eight male and three female patients were studied, none of whom were taking Digoxin or diuretics. Details of the patients and their electrocardiograms are shown in Table 1. All were in sinus rhythm and their conduction systems were normal, as judged from their surface electrocardiograms, except for patient D.C. who had right bundle branch block and patients M.B. and K.H. who had rSR' patterns lead V1.

In each patient a His bundle recording was obtained, using the technique described by Sherlag *et al.* (1969). A bipolar electrode catheter was introduced into a femoral vein by direct puncture and passed to the right ventricle under fluoroscopic control. The signal from this catheter was fed into an Elema Mingograf (five patients) and into a Cambridge Multichannel physiological monitor and recorder (six patients). Records were taken with the frequency response set at 80-500 Hz and at a paper speed of 100 mm/sec. An external electrocardiogram was recorded simultaneously. The catheter in the right ventricle was withdrawn across the tricuspid valve until the bi- or triphasic spike of the His potential was seen between the P wave and the QRS complex of the external electrocardiogram. Recordings were taken at rest and continuously for 10-20 min following the slow (over 30 sec) intravenous injection of 10 mg of Verapamil.

Atrial pacing up to a rate of 160/min, or until some degree of A-V block occurred, was performed in six patients before and after Verapamil. In these patients an additional bipolar electrode catheter was introduced percutaneously into an antecubital vein and fluoroscopically positioned against the lateral wall of the right atrium. Right atrial pacing was carried out using a Devices 4270* stimulator. Impulses of 2 msec pulse width were delivered with the output

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TABLE 1. Clinical details of the patients given Verapamil

Patient	Age	Sex	Diagnosis	Rhythm	QRS Axis	PR Interval (S)	QRS Duration (S)	Other
S.D.	15	M	Innocent systolic murmur	sinus	+20°	0.12	0.16	—
M.B.	15	F	Secundum atrial septal defect	sinus	-10°	0.16	0.08	rSR' pattern V1
T.K.	14	M	Pectus excavatum	sinus	+75°	0.16	0.08	—
F.W.	52	M	Mild aortic stenosis	sinus	+10°	0.15	0.10	LVH
K.H.	19	M	Aortic stenosis	sinus	+45°	0.16	0.09	rSR' pattern V1
R.M.	52	M	Hypertrophic obstructive cardiomyopathy	sinus	+20°	0.16	0.08	occasional ventricular ectopic beats
S.M.	16	M	Prolapse of mitral valve cusp	sinus	+20°	0.12	0.08	—
G.W.	19	F	Innocent systolic murmur	sinus	+80°	0.12	0.07	—
M.D.	35	F	Small ventricular septal defect	sinus	+70°	0.16	0.08	RVH
D.C.	64	M	Pulmonary valve stenosis	sinus	-25°	0.16	0.14	RBBB
G.H.	48	M	Ischaemic heart disease	sinus	-25°	0.14	0.10	—
			Ischaemic heart disease	sinus	-25°	0.14	0.10	—

voltage set at twice diastolic threshold. This stimulator was also used for ventricular pacing and for inducing atrial and ventricular premature beats at known parts of the cardiac cycle for the determination of refractory periods.

In patients seven to eleven, an intravenous injection of 1 mg of Atropine was given 10 min after Verapamil. His bundle recordings were repeated after Atropine. Atrial pacing was repeated in patient G.H. after Atropine.

In five of the six patients who were paced from the atrium, the atrial pacing catheter was advanced into the right ventricle for ventricular pacing. Retrograde conduction times (V-A) were measured following the induction of ventricular premature beats at progressively earlier intervals in the cardiac cycle.

The relative and absolute refractory periods of the A-V node were determined in five patients. During regular pacing of the right atrium, premature atrial beats were fired into the cardiac cycle at preset intervals following the preceding atrially paced beat. The interval between the basic paced beat and the premature beat was gradually shortened until the A-H interval began to lengthen. The relative refractory period of the A-V node was determined by measuring the interval between the stimulus artefact of the basic paced beat and the stimulus artefact of the atrial premature beat at the point when the A-H time began to lengthen.

As the atrial premature beat is brought closer to the preceding atrially paced beat, the A-H time prolongs until conduction to the His bundle is blocked. At this point the total refractory period of the A-V node can be determined by measuring the interval

between the stimulus artefact of the atrially paced beat and the stimulus artefact of the atrial premature beat.

The following measurements were made from the records obtained.

P-A, the time in milliseconds from the earliest onset of the P wave, as seen on the surface electrocardiogram, to the onset of atrial activity in the area of the A-V junction as seen on the His bundle electrogram (Scherlag, Samet and Helfant, 1972).

A-His, the time in milliseconds between the onset of the A wave and the intrinsic deflection of the His bundle depolarization on the intracardiac recording.

His-V, the time in milliseconds between the intrinsic deflection of the His bundle depolarization to the earliest onset of ventricular activation as recorded on either the His bundle electrogram or surface electrocardiogram.

V-A, retrograde conduction in milliseconds as measured from the onset of ventricular activation to the intrinsic deflection of the atrial electrogram recorded in the low right atrium.

QRS width, the time in milliseconds from the initial q wave deflection to the terminal S wave deflection.

Heart rate, calculated from the time between two successive R waves on the external electrocardiogram.

The normal A-His interval was taken as 50-120 msec for heart rates below 80/min. The normal His-V interval was taken as 35-55 msec (Narula, Scherlag and Samet, 1970). The normal values are in accordance with normal values obtained in our own laboratory.

TABLE 2. Duration of P-A, A-His, His-V, QRS width (in milliseconds) and sinus rate at rest and after intravenous Verapamil

Patient	Sinus Rate		P-A		A-His		His-V		QRS Width	
	Before	After	Before	After	Before	After	Before	After	Before	After
S.D.	100	85	30	35	65	125	40	40	90	90
M.B.	100	100	35	35	90	140	45	45	80	80
T.K.	120	110	40	40	65	120	50	50	110	110
F.W.	110	80	30	30	70	120	40	40	90	90
K.H.	105	90	40	40	70	90	35	35	80	80
R.M.	70	66	30	25	85	115	45	45	80	80
S.M.	75	75	25	30	115	175	45	45	80	80
G.W.	85	85	35	35	60	80	50	50	90	90
M.D.	85	75	25	25	55	70	50	50	90	90
D.C.	65	65	35	35	80	120	50	50	140	140
G.H.	65	60	—	—	70	120	40	40	100	100

Results

The P-A, A-His, His-V and QRS width (except in the patient with right bundle branch block), in sinus rhythm were normal in all ten patients, indicating normal conduction times through the atria, A-V node, His-Purkinje system and ventricular myocardium (Table 2).

Following intravenous Verapamil, the P-A interval, His-V interval, and QRS width remained unchanged in all patients. The sinus rate was unchanged in five patients but showed significant slowing in six. The mean sinus rate at rest was 91.5/min; following Verapamil the rate fell to 83.1/min. Prolongation of the A-His interval (unpaced) was observed in all eleven patients (Table 2). Maximum prolongation of the A-His interval was observed within 2-3 min following Verapamil injection. The effect of Verapamil was observed to be present for 15-20 min after injection.

The A-His interval showed an average prolongation of 41 msec. Following administration of Atropine in seven patients (five to eleven), the effect of Verapamil on prolongation of the A-His interval was partly reversed. The average prolongation of A-His in these seven patients was 45 msec. The average reversion towards the normal interval after Atropine was 27 msec. In none of the seven patients given Atropine was the effect of Verapamil completely reversed (Fig. 1).

Atrial pacing was performed in eight patients before and after Verapamil. The stimulus-A and H-V times remained constant at all pacing rates both before and after Verapamil. In normal patients, with increasing rates of atrial pacing there is a gradual prolongation of the A-V nodal conduction time, as evidenced by a lengthening of the A-His interval (Damato *et al.*, 1969). Verapamil accentuates this normal effect.

In patient G.W. (Fig. 2) with atrial pacing at a fixed rate of 140/min the A-H interval was 80 msec. Following administration of Verapamil the

FIG. 1. The effect of intravenous Atropine on prolonged conduction times caused by Verapamil, showing a partial reversion of A-His interval towards normal. The upper recording was obtained from an electrode positioned across the tricuspid valve to record the His bundle potential. The two lower recordings are leads I and II of the external electrocardiogram. (a) Recordings at rest—time zero A-His interval 65 msec; (b) recordings after intravenous Verapamil—time 6 min A-His interval 125 msec; (c) recordings after intravenous Atropine—time 9 min A-His interval 105 msec.

A-H interval increased to 125 msec, the atrial pacing rate remaining constant. This prolongation of the A-H interval caused by Verapamil can be observed at any pacing rate but becomes more obvious with higher pacing rates.

Before Verapamil four patients developed 2:1 block at atrial pacing rates of 160/min. Following intravenous Verapamil all four patients developed 2:1 A-V block at much lower (120-130) atrial pacing rates. With the exception of K.H. some degree of A-V block occurred in all patients after Verapamil before an atrial pacing rate of 160/min was reached.

FIG. 2. Prolongation of A-His time after intravenous Verapamil at rest and during atrial pacing at 140/min. The top line is the record obtained from an atrial electrode. The third line is the record from an electrode positioned across the tricuspid valve to record the His bundle potential. The bottom line is a recording of lead III of an external electrocardiogram. (a) Recordings at rest before intravenous Verapamil A-His interval 60 msec; (b) recordings at rest after intravenous Verapamil A-His interval 80 msec; (c) recordings during atrial pacing at 140/min A-His interval 80 msec; (d) recordings during atrial pacing at 140/min after intravenous Verapamil A-His interval 125 msec.

Atrial pacing at a constant rate of 120/min was performed in patient G.H. At this pacing rate there was some degree of prolongation of the A-H time (from 70 msec at rest to 80 msec). Following administration of Verapamil 2 : 1 atrio-ventricular block developed. Twenty minutes later intravenous Atropine was given and normal conduction was restored with an A-H time of 85 msec. Part of the effect of Verapamil may have worn off by the time the second recording (after Atropine) was made.

TABLE 3. The effect of intravenous Atropine (1 mg) on conduction times 10 min after intravenous Verapamil (sinus rate in brackets)

Patient	P-His time (msec)		
	At rest (SR)	After Verapamil	After Atropine
S.D.	65 (100)	125 (85)	105 (115)
M.B.	90 (100)	140 (100)	100 (130)
T.K.	65 (120)	120 (110)	110 (110)
F.W.	70 (110)	120 (80)	85 (100)
K.H.	70 (105)	90 (90)	75 (90)
R.M.	85 (70)	115 (66)	90 (100)
G.H.	70 (60)	120 (60)	80 (85)

Patient	His-V time (msec)		
	At rest (SR)	After Verapamil	After Atropine
S.D.	40	40	40
M.B.	45	45	45
T.K.	50	50	50
F.W.	40	40	40
K.H.	35	35	35
R.M.	45	45	45
G.H.	40	40	40

In the patients in whom retrograde conduction following ventricular premature stimulation was studied it was shown that with earlier premature beats (shorter R-R intervals) the retrograde conduction time (V-A) prolonged and following the administration of Verapamil this prolongation became more marked (Table 5).

In the five patients in whom the relative and absolute refractory periods of the A-V node were determined it was found that both these measurements were prolonged following the administration of Verapamil (Table 4).

Discussion

Verapamil has been shown to be an effective anti-dysrhythmic drug in man (Schamroth *et al.*, 1972). Its exact mechanism of action has been disputed. It does not modify the effect of sympathetic stimulation on either cardiac function or oxygen uptake (Nayler, 1972) and is therefore not considered to be a beta-blocker.

Fleckenstein *et al.* (1967) and Singh and Vaughan Williams (1972) have suggested that its mechanism

TABLE 4. The effect of intravenous Verapamil (10 mg) on the relative and absolute refractory periods of the A-V node measured in milliseconds

Name	R-R Interval	Relative refractory period of the A-V node		Absolute refractory period of the A-V node	
		Before	After	Before	After
G.W.	600	400	500	200	280
R.M.	600	450	500	250	350
D.C.	600	450	550	280	350
J.S.	600	420	480	270	320
L.J.	600	460	520	300	375

TABLE 5. The effect of intravenous Verapamil on retrograde conduction times (in milliseconds) at different R-R intervals

Name		Before			After		
G.W.	V-A	200	245	—	220	310	—
	R-R	550	340	—	550	340	—
R.M.	V-A	135	140	310	155	180	400
	R-R	670	320	260	670	320	260
D.C.	V-A	140	150	180	170	220	—
	R-R	650	490	310	490	310	—
J.S.	V-A	180	210	—	200	270	—
	R-R	600	400	—	600	400	—
L.J.	V-A	200	220	—	210	250	—
	R-R	520	380	—	520	380	—

of action may be via interference with calcium conductance and not via either a beta-blocking action or a quinidine-like effect on the cell membrane. The two most striking effects observed by Singh and Vaughan Williams (1972) were: (1) an Atropine-resistant bradycardia, and (2) a very potent depression of myocardial contractility. Ross and Jorgensen (1967) have shown that Verapamil given to cats produced bradycardia after vagotomy.

We have observed a significant slowing of sinus rate as well as a prolongation of A-H conduction following intravenous Verapamil. This effect on prolongation of A-H conduction is not related to the slowing of sinus rate and was shown to be present during atrial pacing at fixed rates before and after Verapamil.

In seven cases in which Atropine was given following Verapamil the prolongation of A-H conduction was partly reversed. This partial reversion of A-H conduction time towards normal following Atropine was observed when the heart rate was held constant by atrial pacing, indicating that the effect of Atropine was not simply due to change in the sinus rate. This reversion towards the normal A-His interval was not marked and may in fact be due to the initial Atropine effect on vagal tone, independent of Verapamil.

Oram *et al.* (1971) have recorded a reversion of an Atropine-induced tachycardia with Verapamil. Our results suggest that any vagal effect is minor and that its principal mode of action is via an intrinsic effect on the atrio-ventricular node.

The P-A time is taken as a measure of a representative portion of intra-atrial conduction (Scherlag *et al.*, 1972). A normal P-A time following Verapamil suggests that Verapamil has no depressant effect on intra-atrial conduction. This is supported by the work of Singh and Vaughan Williams (1972) who found that increasing concentrations of Verapamil actually increased the conduction velocity through the atria.

Durrer, Schuilenberg and Wellens (1969) have shown that during ventricular pacing retrograde

conduction times increase with progressively earlier ventricular premature beats. Similar findings were obtained in this study and further prolongation in retrograde conduction occurred after Verapamil administration. This delay in retrograde conduction is thought to be occurring within the A-V node but without recordings of retrograde His bundle activity the site of delay cannot be determined with certainty.

This study also demonstrated that both the relative and absolute refractory periods of the A-V node were prolonged following the administration of Verapamil.

Many cases of paroxysmal supraventricular tachycardia are thought to be due to a re-entry mechanism within the A-V node (Goldreyer and Bigger, 1971; Goldreyer and Damato, 1971). This finding, therefore, of prolongation of anterograde and retrograde conduction within the A-V node and prolongation of A-V nodal refractory periods following Verapamil explains why this drug is an effective agent in terminating supraventricular tachycardias which are due to A-V nodal re-entry. Spurrell, Krikler and Sowton (1974) have shown prolongation of both anterograde and retrograde conduction within the A-V node during the termination of supraventricular tachycardia in eight patients by Verapamil in whom a re-entry mechanism within the A-V node was thought to be responsible for the dysrhythmias.

The effect of Verapamil in delaying conduction within the A-V node also explains its mode of action in slowing the ventricular rate in atrial flutter and atrial fibrillation.

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