British Heart Journal, 1979, **42**, 124–127

Effect of nifedipine on atrioventricular conduction as compared with verapamil

Intracardiac electrophysiological study[1]

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SUMMARY Intravenous nifedipine, a powerful calcium antagonist, had no obvious effect on atrioventricular conduction when administered to 11 patients during routine intracardiac electrophysiological studies. Verapamil on the other hand showed potent antiarrhythmic properties, depressing atrioventricular nodal conduction. Nifedipine thus appears safe in patients with angina pectoris who have disorders of atrioventricular nodal conduction, and in those receiving beta-adrenergic blocking drugs.

There appear to be differential effects on the slow inward channels of cardiac cells with different 'calcium antagonists'.

Nifedipine, a powerful antagonist of transmembrane calcium influx in cardiac cells (Fleckenstein *et al.*, 1972), has been found to be useful in the treatment of angina pectoris (Camerini *et al.*, 1975). In vitro studies have suggested that nifedipine has effects on atrioventricular nodal tissue similar to those of the other calcium antagonists, as exemplified by verapamil (Taira and Narimatsu, 1975), though its action was more pronounced on coronary artery smooth muscle. However, work in the intact dog heart and observations of the surface electrocardiogram in patients receiving nifedipine have failed to show any significant depression of atrioventricular conduction (Ekelund and Oro, 1975; Taira *et al.*, 1975). If nifedipine does not depress intracardiac conduction, it may provide a useful alternative to the beta-blockers, particularly for patients with angina pectoris and pre-existing conduction abnormalities. The present study was undertaken to assess the effects of nifedipine administered intravenously during routine intracardiac electrophysiological studies and to compare these effects with those seen with verapamil during the same study.

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Received for publication 6 March 1979

Subjects and methods

Eleven patients, the details of whom are shown in Table 1, were studied during routine intracardiac electrophysiological investigations following the procedure previously described (Curry, 1975). In 5 patients paroxysmal reciprocating atrioventricular tachycardia was shown to be associated with an accessory pathway (Wolff-Parkinson-White syndrome) which was overt in 4 patients and concealed in the other. Two further patients who also had paroxysmal reciprocating atrioventricular tachycardia were shown to have re-entry circuits confined close to or within the atrioventricular node (cases 6 and 7). The remaining 4 patients had paroxysmal atrial fibrillation or flutter conducted to the

Table 1 *Age, sex, and clinical diagnosis in 11 patients*

Case	*Age*	*Sex*	*Diagnosis*
1	27	F	WPW 'B'
2	24	F	WPW 'A'
3	33	M	Concealed left accessory pathway
4	39	M	WPW 'A'
5	40	F	WPW 'A'
6	18	M	Intranodal reciprocating tachycardia
7	41	F	Intranodal reciprocating tachycardia
8	24	M	Paroxysmal atrial flutter (1:1 AV conduction)
9	56	M	Paroxysmal atrial flutter
10	52	M	Paroxysmal atrial fibrillation
11	62	M	Paroxysmal atrial fibrillation

ventricles via the atrioventricular node.

In all patients nifedipine (7·5 μg/kg body weight) was injected intravenously over 3 minutes. The drug was drawn up under sodium light in a specially designed light-proof syringe. With one exception (case 6), the drug was given to the patients with paroxysmal reciprocating atrioventricular tachycardia during an established arrhythmia. Case 6 and the remaining 4 patients received the drug during continuous rapid atrial pacing. The method of atrial pacing was such that each paced atrial beat followed the previous QRS complex by a preset delay (60 to 80 ms) in a fashion that simulated re-entry tachycardia. Resting sinus cycle length and intracardiac conduction times (AH and HV intervals) were measured immediately before tachycardia was induced or atrial pacing started, and 5 minutes after the administration of nifedipine. During reciprocating tachycardia or atrial pacing the cycle length and the component regional conduction times (AH, HV, and VA intervals) were measured before and 3 minutes after nifedipine. Verapamil (0·15 mg/kg body weight) was administered to 10 of the 11 patients 45 minutes after nifedipine, as an intravenous bolus and under the same circumstances as nifedipine had been given. The results after verapamil were then compared with those obtained after nifedipine.

Results

Table 2 shows the effect of nifedipine on sinus rate and atrioventricular nodal and His-Purkinje conduction times 5 minutes after administration. In all but 1 patient (case 7) there was a shortening in sinus cycle length but in no patient was there a significant change in atrioventricular nodal conduction. When given during paroxysmal reciprocating atrioventricular tachycardia the arrhythmia was terminated in none (Table 3). There was no important change in cycle length or component conduction times except for 1 patient (case 4) in whom slowing occurred because of prolongation of atrioventricular nodal conduction. In this patient

Table 2 *Cycle length, atrioventricular nodal conduction time (AH interval), and His-Purkinje conduction time (HV interval) during sinus rhythm before and 5 minutes after administration of nifedipine 7·5 μg/kg i.v.**

Case	Sinus cycle length(s)		AH		HV	
	Before	After	Before	After	Before	After
1	550	430	80	75	0	0
2	710	540	75	80	20	20
3	740	650	100	100	40	40
4	590	495	85	85	20	20
5	590	515	90	85	0	0
6	660	540	75	75	35	35
7	600	610	110	110	35	35
8	710	640	120	120	40	40
9	575	525	50	50	50	50
10	650	560	75	75	40	40
11	980	840	65	65	35	35

* All measurements in this and subsequent tables are given in ms.

Table 3 *Change in cycle length (CL), atrioventricular nodal conduction time (AH), His-Purkinje conduction time (HV) and retrograde pathway conduction time to earliest atrial depolarisation (VA) before and 3 minutes after nifedipine in 6 patients with re-entry tachycardia*

Case	CL		AH		HV		VA	
	Before	After	Before	After	Before	After	Before	After
1*	270	280	← antidromic tachycardia →					
2	295	295	145	145	35	35	90	90
3	450	430	205	185	50	50	160	160
4	280	330	100	150	45	45	80	80
5	255	255	110	110	30	30	90	90
6	290	285	115	120	35	35	140	130

* Case 1 had antidromic tachycardia and the relevant measurements could thus not be made.

Table 4 *Response, change in cycle length (CL), and atrioventricular nodal conduction time (AH) in 6 patients with re-entry tachycardia before and 3 minutes after nifedipine and 3 minutes after verapamil*

	Nifedipine				Verapamil			
	CL		AH		CL		AH	
	Before	After	Before	After	Before	After	Before	After
1	270	280			275	T		
2	295	295	145	145	300	T	155	T
3	450	430	205	185	420	T	175	T
4	280	330	100	150	280	T	100	T
5	255	255	110	110	280	T	135	T
6	290	285	115	120	295	T	120	T

T = termination of tachycardia.

Table 5 *Sinus cycle length and atrioventricular nodal conduction time (AH) before and 5 minutes after nifedipine and 5 minutes after verapamil*

Case	Nifedipine				Verapamil			
	Sinus cycle length(s)		AH		Sinus cycle length(s)		AH	
	Before	After	Before	After	Before	After	Before	After
1	550	430	80	75	530	490	80	90
2	710	540	75	80	740	650	75	80
3	740	650	100	100	800	740	100	135
4	590	495	85	85	630	550	85	95
5	590	515	90	85	520	505	90	100
6	660	540	75	75	620	590	75	140
7	600	610	110	110	680	610	110	155
8	710	640	120	120	630	530	120	125
9	575	525	50	50	Not given			
10	650	560	75	75	650	630	75	90
11	980	840	65	65	920	835	65	85

the tachycardia circuit showed considerable spontaneous variation and this change was within the range of previous and subsequent observations made while not receiving any medication. Similarly there was no effect in those patients in whom atrial pacing simulated re-entry tachycardia. Second degree atrioventricular block did not develop nor did the duration of atrioventricular conduction lengthen.

However, verapamil terminated proxysmal re-entry tachycardia in all 6 patients (Table 4); in the other 4 it lengthened atrioventricular nodal conduction time and refractoriness (Table 5), in keeping with its known antiarrhythmic properties (Krikler and Spurrell, 1974). Shortening of sinus cycle length after verapamil and nifedipine was of similar degree.

Discussion

The calcium-ion antagonist verapamil has a powerful depressant effect on conduction through the atrioventricular node (Cranefield *et al.*, 1974; Zipes and Fischer, 1974). Fleckenstein *et al.* (1972) showed in vitro that nifedipine was a considerably more potent calcium-ion antagonist than verapamil on a weight-for-weight basis. However, Taira and Narimatsu (1975), using an isolated dog atrioventricular node preparation, showed that the rate of blood flow through the atrioventricular nodal artery was about 10 times more sensitive to nifedipine than was the atrioventricular conduction time. This suggests that as coronary artery smooth muscle appeared to be far more susceptible to nifedipine than the cells that produce delay in atrioventricular nodal conduction, sufficient nifedipine to increase coronary blood flow might not slow atrioventricular nodal conduction. Furthermore, in the in situ paced hearts of open chest dogs nifedipine in a dose of 3 μg/kg intravenously facilitated atrioventricular nodal conduction if the heart had intact innervation, and also did not have a detrimental effect in the heart deprived of compensatory sympathetic drive by bilateral stellate ganglionectomy (Taira *et al.*, 1975). This facilitating effect of nifedipine was therefore ascribed to a sympathetic mechanism triggered by peripheral vasodilatation and hypotension. At a higher dose level (30 μg/kg) atrioventricular conduction was scarcely affected as long as the sympathetic nerve supply to the heart was intact, but after interruption of the sympathetic nerves both atrioventricular conduction time and the atrioventricular nodal functional refractory period were somewhat increased.

In clinical trials in man there have been no reports of adverse affects on atrioventricular conduction (Camerini *et al.*, 1975; Ekelund and Oro, 1975).

The present investigation was designed to assess the effect of intravenous nifedipine on atrioventricular conduction in patients undergoing routine intracardiac studies. Previous work (Curry *et al.*, 1978) has demonstrated the relation that exists between the electrophysiological properties of atrioventricular conduction and alteration in autonomic balance. The dose of nifedipine was 7·5 μg/kg body weight rather than 15 μg in order to avoid the increased sympathetic drive that accompanies the greater negative inotropic action of the larger dose (Lydtin *et al.*, 1976). Verapamil has been shown to exert a chronotropic action on sinus node activity by a baroreceptor-mediated increase in sympathetic tone (Breithardt *et al.*, 1978) and the similarity in the degree of acceleration of sinus node discharge after both drugs suggests that their peripheral effects are similar. Thus in this dose it is unlikely that an electrophysiological action on atrioventricular conduction is cancelled by an increase in sympathetic tone secondary to a fall in arterial pressure. Comparing the resting basic cycle length and the AH and HV intervals measured during sinus rhythm before and 5 minutes after nifedipine the only change was an acceleration of the heart rate (Table 2).

The administration of a nodal depressant drug during re-entrant atrioventricular tachycardia when the circulating impulse continually depolarises the nodal cells when they are in a state of partial recovery may exaggerate effects not apparent during sinus rhythm. However, tachycardia was never terminated by nifedipine, and in only 1 patient did atrioventricular nodal conduction time lengthen, even then no more than had been seen spontaneously. A similar lack of effect was found during atrial pacing. However, as previously recognised, verapamil exerted a potent antiarrhythmic action in all patients (Schamroth *et al.*, 1972; Krikler and Spurrell, 1974). The action of nifedipine given intravenously, as judged by haemodynamic changes in healthy volunteers and patients with ischaemic heart disease, does not appear to exceed 15 minutes (Lydtin *et al.*, 1975). Our results with verapamil are in keeping with other observations and do not suggest summation with a persisting action of nifedipine.

From the theoretical point of view, the fact that two slow channel inhibitors, verapamil and nifedipine, have such different effects on the atrioventricular node raises important considerations and perhaps warrants a reappraisal of the nature of the slow inward channel or channels. Our

results show that verapamil exerts parallel haemodynamic effects and significant actions on the atrioventricular node while nifedipine exerts haemodynamic effects without depressing atrioventricular nodal function. Both agents have been shown to be potent inhibitors of the slow inward (calcium-dependent) channel and there appears to be either a qualitative or quantitative difference in the nature of the slow channel in smooth muscle and atrioventricular nodal cells.

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