THERAPEUTIC UPDATE

THE CURRENT STATUS OF CALCIUM ANTAGONISTS IN CARDIOVASCULAR THERAPY

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SYNOPSIS

The calcium antagonists are a group of pharmacological agents which block the influx of calcium ions into the cells by their specific action on the slow calcium channels which are present on the membrane of myocardial and vascular smooth muscle cells. As a result of this action, all calcium antagonists possess the property of dilating coronary arteries and the peripheral arterioles. Although all calcium antagonists depress myocardial contractility in isolated muscle preparation, this negative inotropic property is minimised in the intact circulation by their afterload reduction property. Verapamil, but not Nifedipine, is highly effective in abolishing attacks of supraventricular tachycardia and is successful in this respect in about 90-100% of instances. The conversion rate for atrial fibrillation and atrial flutter is much lower; but even in those cases which do not convert to sinus rhythm the ventricular rate is considerably reduced. Both Nifedipine and Verapamil are highly effective in Prinzmetal's angina and are specific agents in this condition. They are also effective in Heberden's angina with an efficacy equal to that of the beta blockers. Nifedipine has profound hypotensive effects and Nifedipine given either orally or sublingually will probably emerge as the drug of choice in hypertensive emergencies. Both Nifedipine and Verapamil are potent hypotensive agents for the long term treatment of hypertension. The role of calcium antagonists in the treatment of hypertrophic cardiomyopathy is at present unproven. The side effects of calcium antagonists are few. The commonest side effect of oral Verapamil is constipation. Because of its profound effect on the cardiovascular system it is likely that the calcium antagonists will become a very important group of drugs in the treatment of cardiovascular disorders in this present decade.

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INTRODUCTION

Major advances have taken place in the introduction and development of new drugs for the treatment of the various cardiovascular disorders in the last 2 decades. During this period of time, new important agents such as Lidocaine, Disopyramide and Verapamil for the treatment of cardiac arrhythmias, the beta blockers and vasodilators for the treatment of ischaemic heart disease and hypertension, and dopamine and dobutamine for the treatment of severe pump failure have all found an established place in cardiovascular therapy. With regard to the calcium antagonists, Verapamil was first introduced for the treatment of angina pectoris about 14 years ago but soon became forgotten completely (1). One decade later, in the 1970's, Verapamil was rediscovered to be highly effective for terminating supraventricular tachycardia and has since remained the drug of choice for this condition (2). Recently, due largely to the pioneering work of

Professor A. Maseri, it became apparent that vasospasm of the coronary arteries is a frequent and important phenomenon in the pathogenesis of many of the coronary syndromes. The finding that the calcium antagonists are highly effective for terminating as well as preventing coronary vasospasm has resulted in tremendous interest in their other clinical applications thus leading to their present comeback to cardiovascular therapy (3). Today, the indications for the use of the calcium antagonists are wide ranging, embracing not only coronary vasospasm and cardiac arrhythmias, but also angina of effort, unstable angina, hypertension and hypertrophic cardiomyopathy.

Electrophysiology and Pharmacology

Figure 1 shows the action potential of a myocardial cell. With the onset of depolarization, there is a rapid upstroke of the action potential. In the next phase of the action potential called the plateau phase, calcium ions are transported into the cell across the cell membrane via specific calcium channels. This leads to a whole chain of events leading ultimately to the coupling of excitation-contraction process of the myofibril. An identical event occurs with regard to the vascular smooth muscle. Calcium antagonists act by specifically blocking this influx of calcium ions across the cellular membrane (4).

Many calcium antagonists are today available, but the 3 most commonly used in clinical practice are Verapamil, Nifedipine and Diltiazem. Only Verapamil and Nifedipine are currently available in Singapore and only both these agents will subsequently be discussed.

The pharmacological properties of these 2 agents

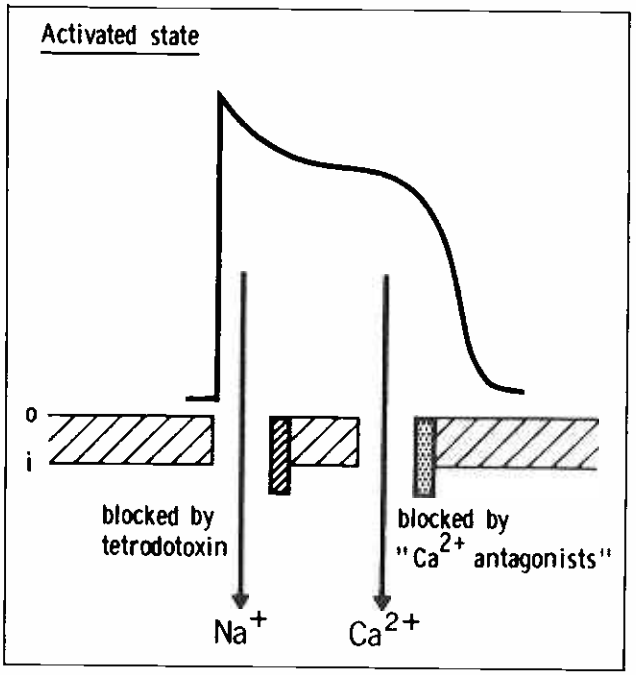

Fig. 1 This diagram shows the action potential of a myocardial cell. At the onset of depolarization there is a rapid influx of Na^+. During the plateau phase Ca^+ travel across the cell membrane into the cell via specific slow calcium channel gates. These gates are blocked by calcium antagonists (Modified from Nayler, W. [4]).

are summarized in Table 1. Although they are both calcium antagonists, there are similarities as well as differences in their pharmacological properties. For example, both agents dilate arterial smooth muscle and therefore are very useful for the treatment of coronary vasospasm and hypertension. In the intact circulation, Verapamil but not Nifedipine significantly reduces A-V nodal conduction (5). Both agents depress myocardial contractility but this is minimised by their effect in reducing afterload in the intact circulation.

TABLE 1

Properties of Calcium Antagonists

	Verapamil (Isoptin)	Nifedipine (Adalat)
Coronary vessels	D	D
Peripheral arterioles	D	D
Inotropic state of the heart	↓	↓
SA node activity	↓	—
AV nodal conduction	↓	—

D = dilate

↓ = depress

Clinical Applications

(1) **Cardiac arrhythmias**

The major clinical application of the calcium antagonists in cardiac arrhythmias is in the area of supraventricular tachyarrhythmias, particularly supraventricular tachycardia (6). Table 2 shows the experience of this department as seen in the past 3 years. The conversion rate of supraventricular tachycardia with I.V. Verapamil reported previously varies from 80% to 100%. In patients where the supraventricular tachycardia is either of the A-V re-entry type or reciprocating type utilizing an anomalous pathway, the conversion rate is very high being around 95 to 100%. In supraventricular tachycardia of the ectopic type, the conversion rate is somewhat lower, being in the region of about 80%. In our experience of 64 episodes of supraventricular tachycardia in 49 patients, the conversion rate with I.V. Verapamil was 91%. (Table 2 and Fig. 2). Because of the uniformly high rate of success, I.V. Verapamil is today the treatment of choice for supraventricular tachycardias which are persistent and which have not responded to simple vagotonic measures.

Unlike supraventricular tachycardia, the conversion rate for atrial fibrillation and atrial flutter as reported in the literature is considerably lower being around 7% and 32% respectively. In

our experience, the conversion rate with I.V. Verapamil for atrial fibrillation was 20% and that for atrial flutter was 34% (Table 2). However, although the arrhythmia infrequently converted to sinus rhythm, the ventricular rate invariably decreased significantly, due to an increase in A-V nodal block. This slowing of the ventricular rate is usually beneficial especially when the initial ventricular rate is particularly rapid. (Fig. 3) Verapamil is generally ineffective for the treatment of ventricular arrhythmias except when they are associated with Prinzmetal's angina.

Complications following I.V. Verapamil are uncommon. However, the injection should be given over approximately 1 min., ideally with continuous electrocardiographic and blood pressure monitoring. Severe hypotension and uncontrolled heart failure, the presence of pre-existing A-V nodal block or sick sinus syndrome and the prior administration of beta blockers are all contraindications to the use of I.V. Verapamil. In our series, the systolic pressure usually decreased by less than 20 mmHg, but severe hypotension was not encountered. In 2 patients with unsuspected sick sinus syndrome, I.V. Verapamil produced asystole prior to termination of the supraventricular tachycardia (Fig. 4). In another patient who had been given 40 mg of oral Propranolol 2 hours earlier, I.V. Verapamil produced transient Wenckebach A-V block (Fig. 5).

TABLE 2

Intravenous Verapamil in Cardiac Arrhythmias (93 Episodes in 62 Patients)

Arrhythmia	No. of Episodes	Conversion Rate
Supraventricular tachycardia	64	58 (91%)
Atrial fibrillation	10	2 (20%)
Atrial fibrillation (with WPW syndrome)	3	0 (0%)
Atrial flutter	14	5 (34%)
Ventricular tachycardia	2	0 (0%)

Side effects (1) Transient sinus arrest - 2 patients
(2) Wenckebach A-V block - 1 patient

(2) **Coronary Artery Disease**

The elegant work of Professor A. Maseri in the past few years has confirmed beyond any doubt that coronary vasospasm is the mechanism in the pathogenesis of Prinzmetal's angina. Coronary vasospasm probably also plays an important role (in varying degrees in different patients and in different situations even for the same patient) in unstable angina, angina of effort, acute myocardial infarction and sudden death. Classical Prinzmetal's angina is uncommon, and we recently reported on 4 patients discovered over a 1 year-period who responded extremely well to oral Nifedipine (7). Since then, we have added another 2 patients to our series. Both oral Nifedipine and Verapamil are effective in abolishing and preventing recurring attacks in Prinzmetal's angina and either should be given on a long-term basis in this condition.

In recent years, both Verapamil and Nifedipine have also been shown to be effective for the treatment of angina of effort (Heberden's angina)(8). The efficacy of either oral Verapamil or Nifedipine in this condition is equal to that of the beta-blockers. The exact mode of action of the calcium antagonists in ameliorating symptoms in Heberden's angina is at present unclear. At this point of time, it is uncertain whether we should start on beta-blockers or calcium antagonists as the first drug of choice

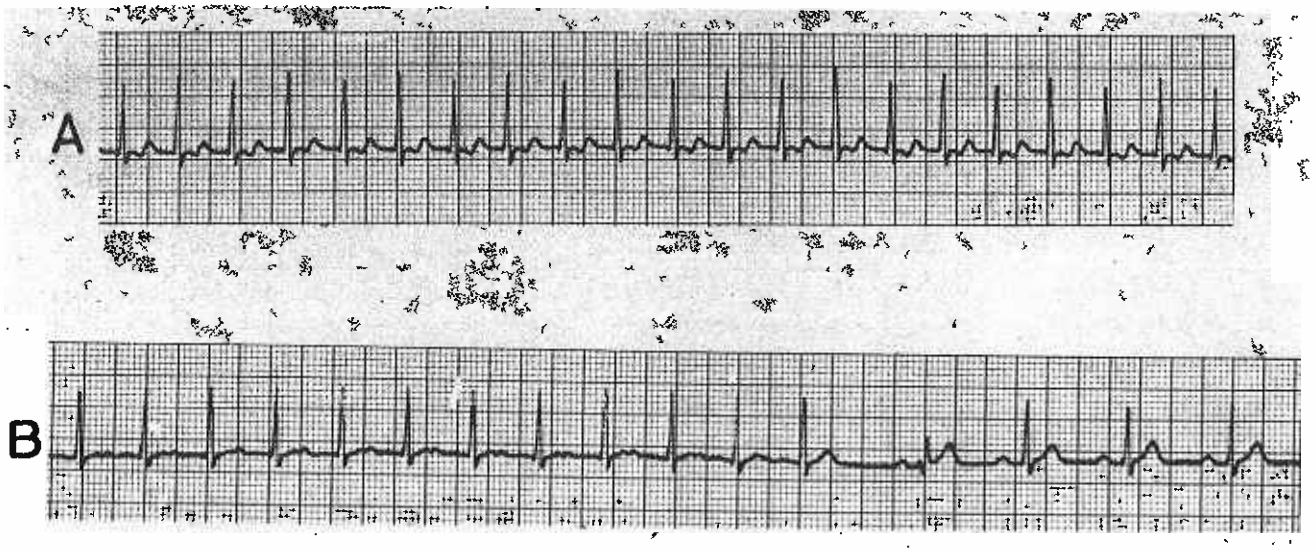

Fig. 2 Panels A and B are not continuous tracings. Panel A shows rapid supraventricular tachycardia before I.V. Verapamil. Panel B shows termination of the tachycardia after 10 mg. intravenous Verapamil.

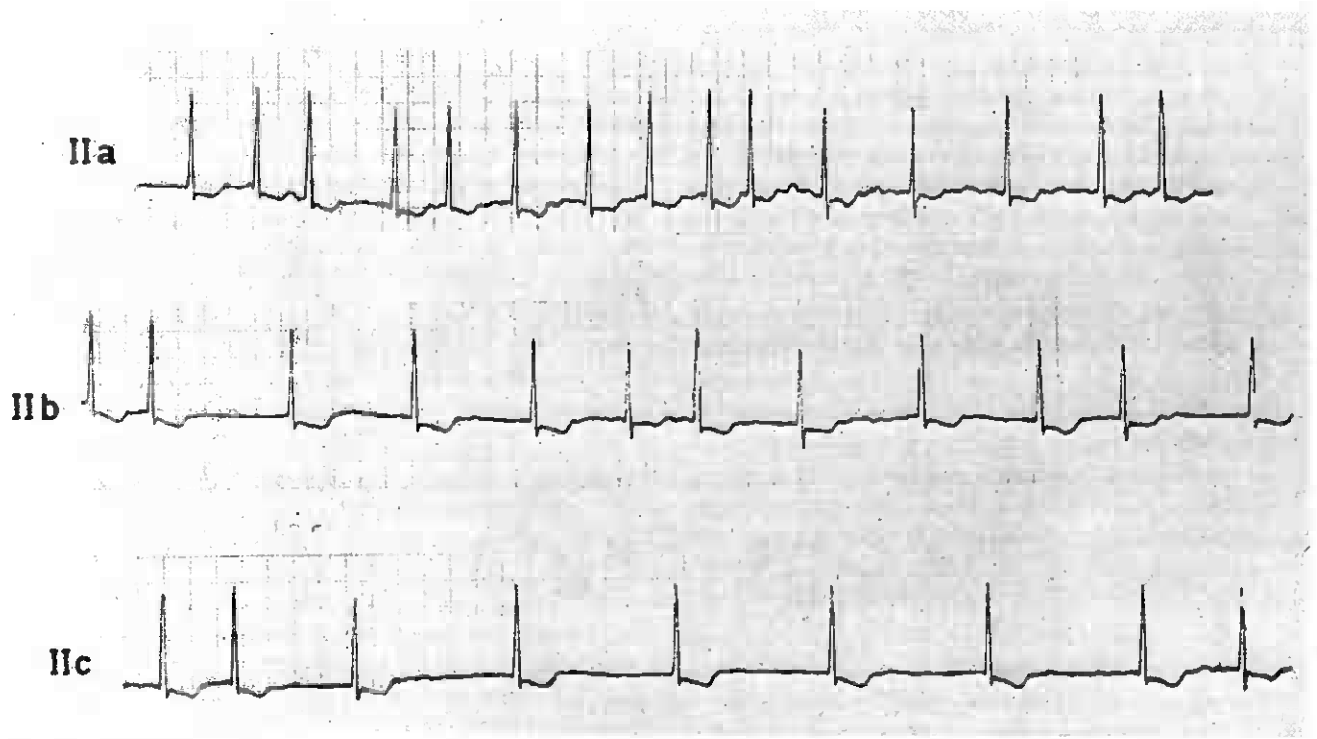

Fig. 3 Panels IIa, IIb and IIc are not continuous tracings. Panel IIa shows rapid atrial fibrillation. Panel IIb shows atrial fibrillation with a slower ventricular rate after 7.5 mg intravenous Verapamil. Panel IIc shows further slowing of the ventricular rate after 15 mg. intravenous Verapamil.

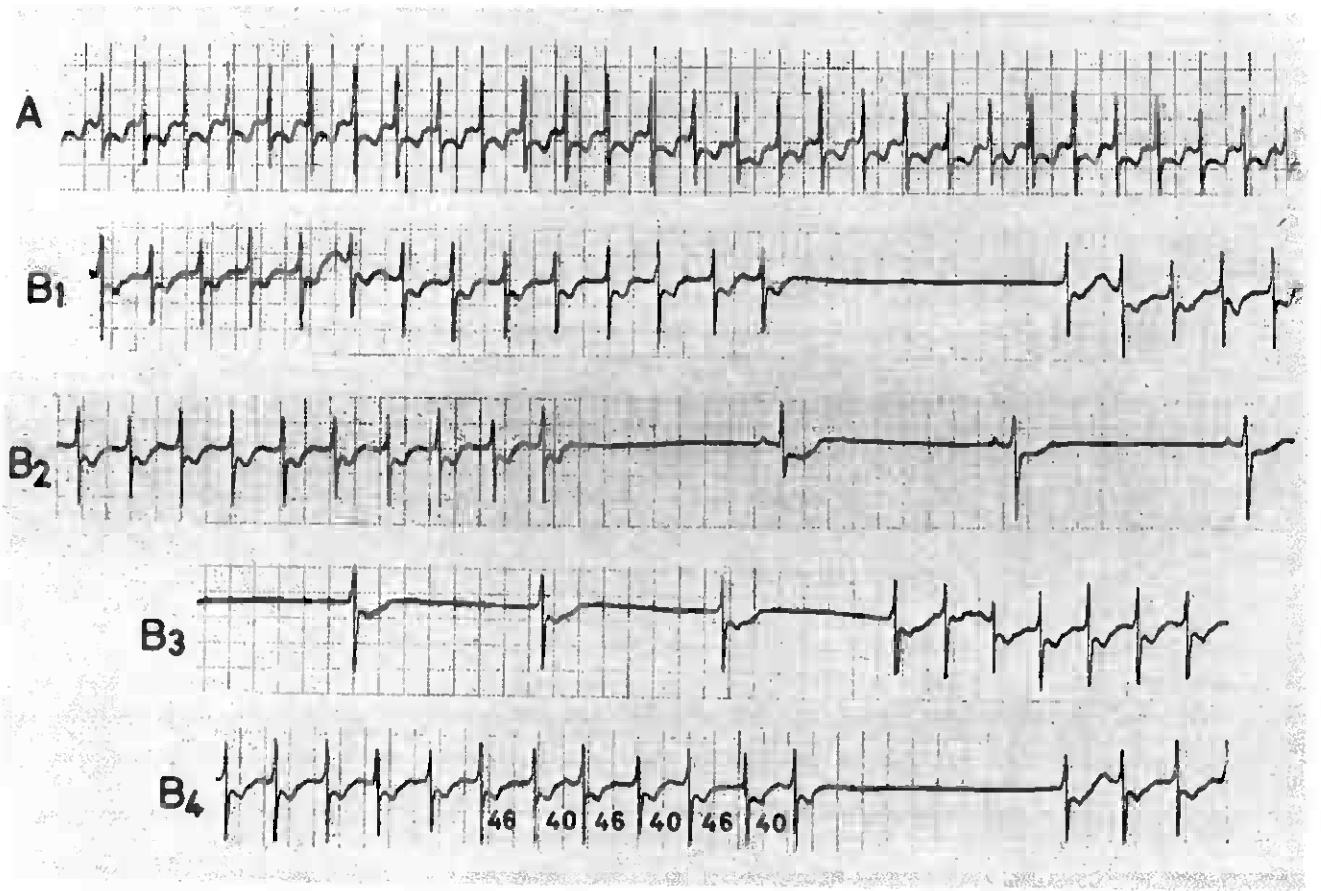

Fig. 4 Panel A shows rapid supraventricular tachycardia. Panels B1 to B4 are continuous and are recorded after 10 mg. of intravenous Verapamil was given. In each panel, periods of sinus arrest can be seen with the termination of the tachycardia. Panel B4 shows the phenomenon of cycle length alternation of the QRS complexes before the termination of tachycardia.

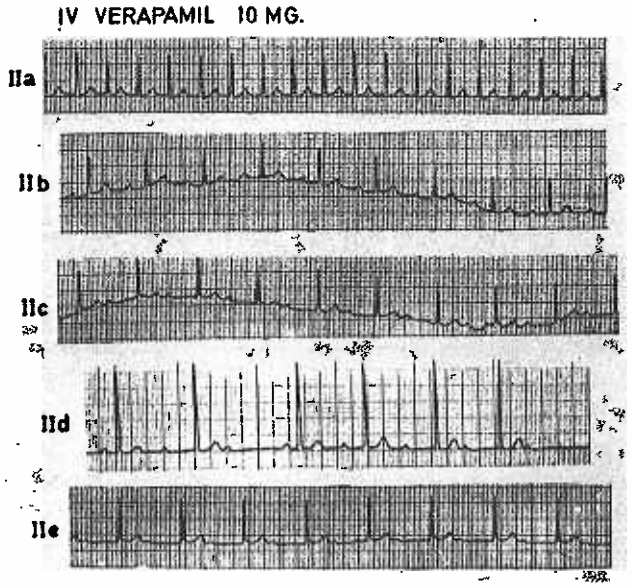

Fig. 5 Panels IIa to IIe are not continuous. Panel IIa shows rapid supraventricular tachycardia. Panel IIb shows conversion to sinus rhythm after 10 mg. of intravenous Verapamil. Panels IIc and IId recorded several minutes after IIb show an increase in A-V block with first degree A-V block in IIc and Wenckebach A-V block in IId. Panel IIe was recorded many hours later and still shows first degree A-V block.

in a patient presenting with significant Heberden's angina. So far beta blockers have been traditionally regarded as the agent of choice in this condition. However, in patients who have contraindications to beta blocker therapy eg bronchospasm or who do not tolerate this drug well, calcium antagonists should be substituted without any reservations. Side effects of oral Verapamil and Nifedipine are few. The possible complications of oral Verapamil are heart failure (usually in those with poor myocardial function) and A-V nodal block or sinus arrest (usually in patients with pre-existing A-V nodal or sino-nodal disease). However, about 30% of patients will complain of constipation which usually is not severe and responds well to laxatives. The main side effects of Nifedipine are flushing, giddiness and a slight increase in sinus rate. In severe angina unresponsive to either beta blockers or calcium antagonists alone, both these drugs could be combined as the anti-anginal effect obtained from combining both these drugs is significantly enhanced. In combining a calcium antagonist with a beta blocker, it is preferrable to use Nifedipine rather than Verapamil because Nifedipine, unlike Verapamil, has no effect on A-V conduction. Oral Verapamil and an oral beta blocker can also be combined, especially in a young patient with no A-V nodal disease or heart failure, but care must be taken to detect the possible complications of A-V block and heart failure.

Because vasospasm is frequently present in patients with unstable angina, calcium antagonists should be added to the therapeutic regime if there is inadequate response to the initial therapy of beta blocker and nitrates. Although calcium antagonists have been given in the early phase of acute myocardial infarction for the purpose of reducing infarct size, the role of such agents in this situation is uncertain and their routine use is not recommended.

(3) **Hypertension**

The hypotensive effect following I.V. Verapamil given for the termination of cardiac arrhythmias was noted more than a decade ago, but specific application of the calcium antagonists for the treatment of hypertension has taken place only recently (9). Both Verapamil and Nifedipine are effective agents for lowering raised blood pressure with an efficacy equal to that of beta blockers. However, it is our clinical impression that Nifedipine is more potent than Verapamil in this respect and this is probably because of its greater effect in relaxing vascular smooth muscle. We assessed the immediate hypotensive effect of I.V. Verapamil and oral Nifedipine in 2 separate groups of patients numbering 15 in each group (10). Intravenous Verapamil was given in a dosage varying from 5 to 15 mg. Oral Nifedipine was given in a fixed dosage of 10 mg. As is seen in Fig. 6 and 7, both these agents significantly lowered both the systolic as well as the diastolic blood pressure without any significant side effects. The hypotensive effect of I.V. Verapamil was immediate and that of Nifedipine was clearly seen when blood pressure was measured 30 minutes after its oral administration. The current commonly used agents for the acute lowering of blood pressure all have some significant disadvantages. Intravenous Nitroprusside has to be titrated very carefully (preferably to be given by an infusion pump and in an intensive care environment) to avoid inadvertent hypotension. Diazoxide has to be given intravenously with frequent careful monitoring of the blood pressure. Nifedipine when used for the lowering of blood pressure has many advantages and may well become the drug of choice when the blood pressure is required to be lowered quickly such as in hypertensive encephalopathy, hypertensive intracerebral haemorrhage, hypertensive heart failure etc. First, it can be given orally; second its onset of action is rapid and its duration of action is reasonably long (approximately 6 hours); third it is a potent hypotensive agent; fourth, there is no postural hypotension; fifth, it does not require as intensive monitoring as when either I.V. Nitroprusside or I.V. Diazoxide is used and sixth it is relatively cheap (10 mg of Nifedipine costs 44 cents).

Both oral Verapamil and Nifedipine have also been shown to be effective antihypertensive agents with a potency equal to the beta blockers when employed on a chronic basis. Before a new drug can be widely advocated for the treatment of hypertension, it is essential to show that it

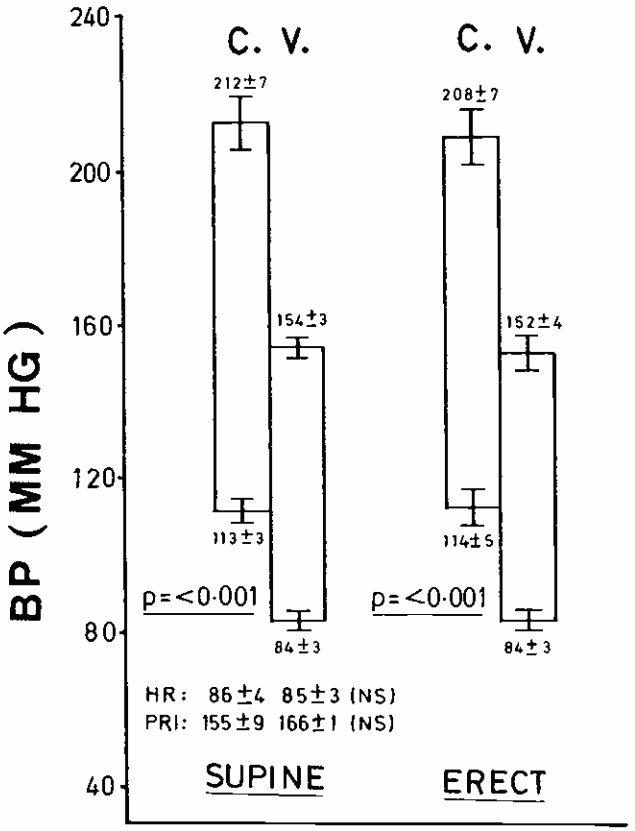

Fig. 6 This figure shows the hypotensive effect of intravenous Verapamil (5 - 15 mg) in both the supine and erect positions together with the supine heart rate and the PR interval before and after intravenous Verapamil in 15 patients. C = control, V = After intravenous Verapamil, HR = Heart rate, PRI = PR interval (Chia et al, 1981[10]).

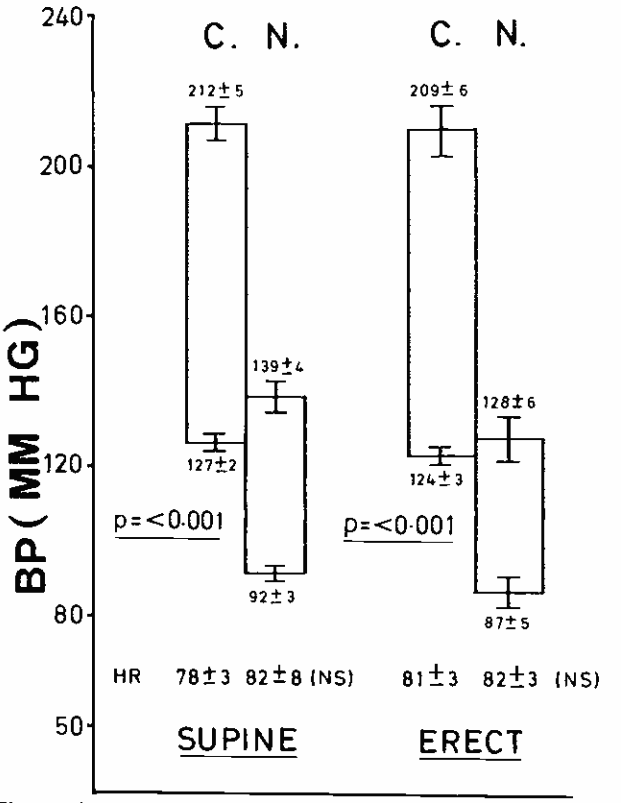

Fig. 7 This figure shows the hypotensive effect of 10 mg. Nifedipine given orally in both the supine and erect positions. The heart rate before and after Nidefipine is also given. C = Control N = After Nifedipine. HR = Heart rate. (Chia et al 1981[10]).

possesses certain special properties, such as efficacy in lowering a raised blood pressure without any significant side effects, not readily available with the other existing antihypertensive agents, because of the already very crowded field. Calcium antagonists possess many desirable properties which may make them suitable for widespread use in hypertension. First, they are potent antihypertensive agents; two, unlike Hydrallazine, they do not produce marked tachycardia although they are also arterial dilators and thus are suitable as monotherapy; three, they normalise the abnormal haemodynamics of hypertension by reducing the raised peripheral arterial resistance and increasing cardiac output and four, side effects are minimal. Currently, the agent employed for Step 1 therapy in hypertension is either a beta blocker or a diuretic. With all the above advantages, it is possible that the calcium antagonists could in the future be indeed seriously considered as a Step 1 agent. In addition, calcium antagonists could be combined with either diuretics, beta blockers or both in the treatment of hypertension.

(4) **Hypertrophic Cardiomyopathy**

This condition is fairly common in Singapore and we have reported on our experience in 35 cases collected over the past few years (11). Traditionally the treatment of hypertrophic cardiomyopathy has involved the use of beta blockers. Two groups have recently reported that in patients treated with Verapamil, the functional status and effort tolerance are significantly improved. In addition, reduction of left ventricular outflow gradient, reduction of left ventricular volume and regression of electrocardiographic evidence of left ventricular hypertrophy have been observed (12, 13). Currently, we have evaluated the effect of Verapamil on 13 patients over a 6 month period. Our preliminary observation is that this drug is unimpressive in causing improvement in the electrocardiogram. The exact efficacy of calcium antagonists in the treatment of hypertrophic cardiomyopathy is still uncertain and must await further studies.

CONCLUSION

In conclusion, it is clear that the calcium antagonists are effective and useful agents in the treatment of supraventricular tachyarrhythmias, Prinzmetal's and Heberden's angina, and hypertension.

Experience has shown that introduction of a new drug is invariably accompanied by glowing reports and promises which frequently cannot be fulfilled. As practising clinicians our attitude towards new pharmacological agents and new methods of treatment should be that "we must not be the first to abandon the old nor the last to embrace the new"(14). It is the popular belief that the last 2 decades was the era of the beta blockers in the pharmacological therapy of cardiovascular disorders. Given the current progress, I

am confident that this present decade will belong to the calcium antagonists.

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