Role of calcium antagonists in cardiovascular therapy

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SUMMARY The development of drugs which selectively block the "slow" channels by which calcium enters the cell (calcium antagonists) has provided valuable information about the role of transmembrane calcium exchange in man and has offered new therapeutic approaches. The principal effect on the cardiovascular system is relaxation of vascular smooth muscle but some of these drugs also have electrophysiological effects, especially slowing of conduction in the atrioventricular node; verapamil is the agent of choice in supraventricular tachycardia. Significant myocardial depression does not usually occur with doses used clinically. The calcium antagonists have specific value in variant angina. By causing peripheral vasodilatation they are also effective hypotensive agents and do not cause reflex tachycardia in chronic use. Their value in hypertrophic cardiomyopathy and in the protection of ischaemic myocardium remains to be proven.

The term "calcium antagonist" was introduced by Fleckenstein in 1969 to describe the actions of compounds which had both coronary vasodilator and negative inotropic properties^{1,2}; the effects of these compounds on the myocardium were identical to those of calcium deficiency, which had been recognised by Ringer in 1882.³ In recent years the pivotal role of calcium in connecting the dual processes of excitation of the cell membrane and contraction of the muscle fibres has been well documented.⁴ Though transmembrane exchange of sodium and potassium is the basis of cell membrane electrical activity, it has become clear that calcium ions are also important in the generation of normal and abnormal pacemaker activity and in the conduction of these impulses through the specialised tissues of the heart.⁵

We propose to describe and explain the effects of several calcium antagonists on the cardiovascular system based on current knowledge of transmembrane calcium exchange.

Excitation-contraction coupling

(a) EXCITATION

Excitation of mammalian myocardium depends on the operation of channels in the cell membrane through which ions may move inward from the extracellular space.⁶ Three such inward channels are recognised on the basis of ionic selectivity, specificity of inhibition by chemical agents, and time constant of activation.^{7,8} The

sodium or fast inward channel, which is blocked by tetrodotoxin, has a very short activation time, during which influx of sodium is rapid. The slow inward channel can be blocked by manganese and nickel and has a longer period of activation, during which there is less rapid influx of calcium (and some sodium). A third inward channel, carrying magnesium, which has an intermediate activation time, and which can be blocked by catecholamines, has recently been described.⁹

The action potentials found in different anatomical (and functional) areas of the heart can be explained in terms of different components of slow and fast channel activity. In cardiac muscle fibres the initial rapid upstroke of the action potential (phase 0) results from a rapid influx of sodium through the fast channels upon depolarisation of the cell membrane. Rapid repolarisation (phase 1) occurs when the sodium channels close and is then delayed by the continuing slow influx of calcium which causes the plateau of the action potential (phase 2). Repolarisation continues with the closure of these channels (phase 3).

In the sinus node and in the central part of the atrioventricular node¹⁰ activation is largely calcium-dependent and phase 0 there is slower than in the muscle fibres. Furthermore, after repolarisation the pacemaking and conducting tissues undergo spontaneous diastolic depolarisation associated with calcium influx (phase 4).

(b) CONTRACTION

When the intracellular concentration of calcium reaches 10^{-6} molar the contractile proteins actin and myosin interact.¹¹ This is highly dependent on the slow

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channel influx which triggers release of calcium from intracellular storage sites, including the sarcoplasmic reticulum¹²; the rapid rise in free intracellular calcium initiates the hydrolysis of adenosine triphosphate to adenosine diphosphate by myofibrillar adenosine triphosphatase, releasing energy which is used to slide the actin filaments along the myosin filaments, thus generating tension.²

Calcium antagonism

The prototype of the new family of drugs, which Fleckenstein called calcium antagonists, was verapamil.¹³ Since then a number of compounds have been found to have similar properties; among the most important of these are the methoxy derivative of verapamil, D600; the 1,4 dihydropyridine, nifedipine, and its congener niludipine; the diphenylamines, prenylamine and fendiline; perhexiline; and diltiazem.¹⁴⁻¹⁸ Unlike other groups of drugs with a common action, for example the beta-adrenoceptor antagonists, the calcium antagonists share no common molecular configuration. Differences have been observed in the way these compounds act; verapamil delays recovery of the slow channel, while nifedipine impairs its activation¹⁹; in addition, the binding of verapamil to muscarinic receptors may be relevant to its specific antiarrhythmic properties.²⁰ This has led to difficulty with the classification of calcium antagonists.²¹ At the present time Fleckenstein restricts this term to those drugs whose outstanding property is completely and reversibly to inhibit the effects of calcium on excitation-contraction coupling in the heart or smooth muscle, or both²²; he prefers this to an alternative, slow-inward-channel inhibition, but the semantic debate continues.

The main actions of the calcium antagonists in man may be inferred from the calcium-dependent processes described *in vitro*; thus verapamil inhibits myocardial excitation-contraction coupling with resultant myocardial depression, relaxes vascular smooth muscle, and depresses pacemaker activity: all these effects are reversed by calcium or isoprenaline.^{1 2 13}

(a) MYOCARDIAL EFFECTS

Calcium influx leads to activation of myofibrillar adenosine triphosphatase which converts phosphate-bound energy into mechanical work: thus calcium influx is an important determinant of myocardial oxygen consumption. Calcium antagonists, therefore, by limiting calcium influx, reduce calcium-dependent splitting of adenosine triphosphate, which in turn reduces myocardial oxygen demand; together with these events the force of myocardial contraction is reduced.^{2 13 23} While this action could potentially be hazardous, it must be viewed in the context of

myocardial function *in vivo*. Firstly, a fall in arterial pressure produces a reflex increase in sympathetic activity²; secondly, by relaxing vascular smooth muscle calcium antagonists decrease left ventricular afterload.²⁴ As the effect on peripheral vascular smooth muscle is seen at 10 to 30% of the dose required to produce excitation-contraction uncoupling,²³ the vascular effects outweigh and offset the central cardiac effects in man, and in practice verapamil or nifedipine usually increase the cardiac output slightly.^{24 25}

(b) VASCULAR EFFECTS

Relaxation of vascular smooth muscle has been most extensively studied in spiral strips of the large calibre extramural coronary arteries.^{5 26} These strips lose their contractile tone in a calcium-free medium but recover it completely on restoration of calcium to the medium. Calcium antagonists counter the effects of vasoconstrictors like histamine, serotonin, ergotamine, acetylcholine, and cardiac glycosides²⁷ by blocking excitation-contraction coupling. Systematic vascular resistance declines,²⁴ indicating an effect on the peripheral vasculature.

(c) PACEMAKER ACTIVITY AND IMPULSE TRANSMISSION

The reduction of cardiac contractility in a calcium-free medium is paralleled by a decrease in heart rate, and verapamil, diltiazem, and nifedipine also suppress sinoatrial and atrioventricular pacemaker activity *in vitro*,²⁸⁻³⁰ effects that are reversed by isoprenaline and by extra calcium.² But in man not all calcium antagonists affect sinus node or atrioventricular nodal function as they do in other species *in vitro*; at doses used clinically nifedipine appears to lack electrophysiological effects in man.³¹ Verapamil has been shown to exert a chronotropic effect on sinus node activity by a baroreceptor mediated increase in sympathetic activity,³² and the similarity in the degree of acceleration of sinus node discharge after both drugs suggests that their peripheral effects are similar.³¹

The therapeutic potential for calcium antagonists is thus considerable. Definite indications include angina, hypertension, and arrhythmias; there may well be a place in hypertrophic cardiomyopathy; a more speculative possibility is the protection of ischaemic myocardium.

Angina

THEORETICAL CONSIDERATIONS

Angina pectoris is usually associated with obstructive coronary artery disease which restricts the extent to which myocardial blood flow can be augmented when the demand for oxygen is increased as, for example, during exercise. While drugs which reduce myocardial

work, such as nitrates and beta-blockers, are effective in angina, so too potentially are calcium antagonists; they could act in this way not only by decreasing myocardial work but also by increasing perfusion through coronary vasodilatation. In several animal species calcium antagonists increase myocardial blood flow³³⁻³⁵ and they can reduce coronary vascular resistance and increase coronary blood flow in patients with normal coronary arteries; but when there is coronary artery disease, even though coronary arteriolar resistance may be decreased at rest, evidence for an increase in coronary blood flow, though conflicting, does exist.³⁶⁻³⁸ Calcium antagonists undoubtedly reverse or inhibit coronary vasospasm: this can be observed directly during coronary arteriography or inferred from haemodynamic or non-invasive monitoring of patients with variant (Prinzmetal's) angina.^{39 40}

CLINICAL STUDIES IN ANGINA

(a) *Variant angina*

Angina at rest associated with ST segment elevation (or depression) is believed to be caused by a temporary increase in coronary arterial tone leading to occlusion of the vessel.^{41 42} While controlled trials in this syndrome are lacking, complete remission of ischaemic events seen in most patients with documented spasm^{39 40 43-45} suggests a major role for calcium antagonists; indeed their withdrawal may lead to prompt recurrence of symptoms.^{39 44} In 12 patients with unstable angina and frequent episodes of ST segment deviation at rest, verapamil (480 mg/day) was compared with placebo in a double-blind study conducted in the coronary care unit⁴⁶; nine of these patients showed direct evidence of coronary spasm either at angiography or with myocardial scintigraphy. During the two treatment periods transient ischaemic attacks were reduced from 123 and 130 episodes during placebo to 31 and 23 episodes, respectively. A similar response was seen with nifedipine in eight patients with variant angina with normal or mildly abnormal coronary arteriograms⁴⁴; this was further confirmed in a study of 127 patients with coronary spasm in which it decreased anginal frequency from an average of 16 attacks a week to two: in 63% control was complete.⁴⁷

(b) *Chronic stable angina*

There are few properly controlled clinical trials on the efficacy of calcium antagonists in chronic stable angina, compared with other standard treatment.

In a single-blind controlled trial on 10 patients nifedipine (60 mg/day) reduced anginal frequency from 11 episodes a patient a week to six and glyceryl trinitrate consumption from nine tablets a week to four; this was associated with a moderate increase in exercise duration.⁴⁸ In our own double-blind studies⁴⁹ in 16 patients, nifedipine (60 mg/day) reduced anginal

frequency and glyceryl trinitrate consumption from 22 to 12 episodes a week and from 18 to 11 tablets a week. We also showed that nifedipine reduced the area of exercise-induced myocardial ischaemia by 35%, as assessed by 16 point praecordial mapping, and the total number of episodes of ST depression on ambulatory monitoring fell by 51%. Sixty per cent of these episodes were asymptomatic and these responded in exactly the same way to nifedipine as the episodes associated with chest pain.

Early studies of verapamil at lower doses gave equivocal results⁵⁰ but during double-blind clinical trials, doses of 360 mg/day^{51 52} reduced anginal frequency and glyceryl trinitrate consumption by approximately 50%, and significantly increased exercise duration.

Few comparative data are available for verapamil and nifedipine but in a single-blind placebo-controlled acute study 10 mg nifedipine and 160 mg verapamil given orally increased exercise duration similarly when compared with placebo⁵³; if the same criteria are examined nifedipine and verapamil in appropriate doses are probably equipotent in chronic stable angina.

Several studies of the combination of nifedipine and beta-blockers uniformly show it to have a distinct beneficial effect approximately equivalent to the additive effects of each drug.^{49 54 55} Our studies showed that the area of exercised-induced ischaemia and the frequency of ischaemic events detected by ambulatory monitoring were reduced by 90 and 95%, respectively⁴⁹; in another study the total work performed increased by 41% with the combination of 30 mg nifedipine per day and metoprolol or alprenolol.⁵⁴ Neither cardiac failure^{49 55} nor change in atrioventricular conduction time occurred on the combination.⁵⁴ Studies with oral verapamil and beta-blockers are now in progress.

MECHANISM OF ANTIANGINAL EFFECT

The mechanisms of antianginal action are complex. The rate-pressure product in exercise duration studies is similar to that on placebo and even for a given workload no significant difference occurs, unlike the situation with beta-blockers.^{36 37 49} Intracoronary injection of small (0.1 mg) doses of nifedipine had the same effect on exercise duration as 1 mg given intravenously despite the absence of peripheral effects with the former and the return of an initially slightly increased coronary flow with both doses to pre-treatment values.³⁵ But increased flow to areas of ischaemia induced by pacing has been described³⁷ and the rate pressure product may not detect small reductions in myocardial oxygen consumption during exercise. Thus in variant angina, calcium antagonists are almost specific, while in pure exercise-induced angina they are moderately effective, and less so than beta-blockers.⁴⁸ The pronounced benefit, however, of combining a beta-

blocker with a calcium antagonist has conspicuously improved the therapy of chronic stable angina, but the precise mode of action and role of calcium antagonists remain to be clarified.

Protection against acute ischaemic damage

Ischaemia leads to a high cytosolic calcium concentration partly by impairing the mechanism by which calcium is pumped out of the cell.^{56,57} This leads to increased use of adenosine triphosphate and impairment of mitochondrial function with decreased production of adenosine triphosphate.⁵⁶ Limitation of calcium influx is therefore a logical approach to myocardial protection against ischaemia. Beta-blockers probably owe part of their protective effect to antagonism to catecholamine-stimulated calcium influx,⁵⁸ and calcium antagonists offer an alternative approach.

In experimental animals numerous methods of assessment of ischaemic damage have indicated a protective effect of several calcium antagonists.⁵⁹⁻⁶² Decreased functional impairment in terms of resting tension, contractility, and systolic function have also been shown with verapamil, nifedipine, and diltiazem.⁶³⁻⁶⁵ In rabbit hearts the increased cellular fragility produced by ischaemia can be prevented by pretreatment with nifedipine.⁶⁶ Caution is however necessary before extrapolating this to the use of calcium-free cardioplegic solutions in cardiopulmonary bypass, as verapamil does not protect heart muscle against the deleterious effects of restoring the calcium concentration after a period of calcium-free perfusion (the calcium paradox).⁶⁷

Protective effects may be dose related. Myocardial perfusion, epicardial electrocardiographic wave forms, and creatine kinase activity yielded beneficial results with lower doses of nifedipine: but in high doses a distinct fall in blood pressure occurred, resulting in decreased coronary perfusion.⁶⁸ Evidence of protection against ischaemia in man is as yet lacking and in clinical use care must be taken to avoid sudden large falls in blood pressure which might lead to a situation similar to that reported in experimental studies. Anecdotal reports of cardiac pain precipitated by nifedipine are difficult to evaluate.⁶⁹

Arrhythmias

(a) SUPRAVENTRICULAR

Of all the calcium antagonists verapamil is the most effective antiarrhythmic agent, and it is almost universally successful when given intravenously (0.15 mg/kg body weight) in reciprocating atrioventricular tachycardia, whether intranodal or in association with an

accessory atrioventricular connection, for example as in the Wolff-Parkinson-White syndrome.^{70,71} Its potent action may be diminished by postural or reflex increases in autonomic tone, which may explain the slightly lower incidence of immediate response when the tachycardia is induced during intracardiac electrophysiological study.⁷² In a formal comparison, success was achieved in 19 out of 20 patients with verapamil as compared with eight out of 20 with practolol.⁷³ While verapamil lengthens atrioventricular nodal conduction time, nifedipine, given in equivalent dose, lacks this property and does not terminate tachycardia.³¹

In atrial fibrillation, the usual response to intravenous verapamil is slowing and a greater degree of regularity in the ventricular response, reversion to sinus rhythm being rare; it is seen in occasional cases of atrial flutter, but here again the major influence is an increase in the degree of atrioventricular block.⁷⁴ In both atrial fibrillation and flutter, this transient intravenous response can be clinically helpful: some studies have shown that oral verapamil can be used to control the ventricular response satisfactorily in atrial fibrillation.⁷⁵ A proportion of patients whose atrioventricular tachycardia is terminated by intravenous verapamil have further attacks successfully prevented by oral administration, but we lack a firm basis for the prediction of such a response: the best results were seen (10 of 12 cases) with intranodal tachycardia, response being less good with verapamil alone in pre-excitation, though combined therapy may work.⁷⁶ Especially with intravenous use, there is a risk of sinuatrial depression in patients with sinuatrial disease or on beta-blockers^{70,73,77}; these situations contraindicate the administration of verapamil. Oral verapamil and digitalis can, however, safely be combined.⁷⁸ While hypotension may occur, this is usually mild and transient; indeed verapamil can be given without ill-effect in patients with myocardial infarction.⁷⁹

(b) VENTRICULAR ARRHYTHMIAS

Though electrophysiological studies⁸⁰ suggest that some ventricular arrhythmias arise because ischaemic cells become depolarised by the slow as opposed to the fast inward channel, and that this is blocked by verapamil, this drug has not proved effective under experimental conditions.⁸¹ Indeed, verapamil given during electrophysiological testing failed to inhibit chronic recurrent ventricular tachycardia.⁸² Some ventricular extrasystoles, whether or not associated with acute myocardial infarction, are suppressed by intravenous verapamil,^{74,83} but clinical value against more serious ventricular arrhythmias has not been demonstrated.⁸⁴ There is one clear exception: where coronary spasm induces ventricular arrhythmias, reversal of the spasm by a calcium antagonist has

secondary but significant antiarrhythmic value.⁸⁵ Though there is good evidence that verapamil protects against the ventricular fibrillation in dogs caused either by coronary artery occlusion^{86,87} or by release of occlusion, its clinical value under these circumstances would be difficult to demonstrate, and such evidence is lacking.

Hypertension

Acute haemodynamic studies have shown the characteristic effects of peripheral vasodilatation in that arterial pressure falls because of reduction in peripheral resistance and is accompanied by a baroreflex mediated increase in heart rate.^{88,89} Since the principal haemodynamic abnormality in essential hypertension is an increase in peripheral vascular resistance, use of drugs which lower peripheral vascular resistance by a direct action on arteriolar smooth muscle is rational. The observation of increased calcium transport in arteriolar smooth muscle of rats with experimental hypertension⁹⁰ provides a further stimulus to investigate its possible role in essential hypertension.

A fall of approximately 28% in both systolic and diastolic pressure occurred in hypertensive patients after 30 mg nifedipine sublingually; this was accompanied by an increase in heart rate of 17% and an increase in plasma renin activity. Both effects were blocked by propranolol, which also caused a further slight reduction in blood pressure.⁹¹ In our own double-blind studies, nifedipine (60 mg/day for one month) reduced supine and standing systolic and diastolic blood pressure by 15 and 20% and by 21 and 23%, respectively.⁹² In another placebo-controlled double-blind study, nifedipine in a dose of only 30 mg/day produced no further fall in blood pressure in patients incompletely controlled on other drugs.⁹³ No increase in heart rate was found in chronic studies during treatment.⁹²

In a double-blind placebo-controlled crossover study, verapamil produced dose-dependent reductions in diastolic blood pressure of 18 mmHg with 240 mg/day and 22 mmHg with 360 mg/day.⁹⁴ In a further study, when verapamil was substituted for existing drugs better control was obtained, and the reductions of blood pressure from baseline values were similar to those obtained in the original placebo-controlled study.⁹⁵ Despite these impressive reductions in blood pressure there was no significant increase in heart rate like that shown in acute studies. This difference in the acute and chronic effects of calcium antagonists is now well documented: it may reflect either an intrinsic effect of the drug, evident only on chronic administration, or a true physiological adjustment such as resetting of the baroreflex.

With oral treatment it is also important to know

whether calcium antagonists may be safely combined with other drugs, especially beta-blockers. Both classes of drugs can depress myocardial contractility, and beta-blockers share, at least with verapamil, a depressant effect on atrioventricular conduction. Nifedipine and propranolol have, however, been usefully and safely combined,^{91,92} but the long-term effects of other calcium antagonist/beta-blocker combinations remain to be documented.

Hypertrophic cardiomyopathy

Whether or not this disorder reflects an abnormally avid transmembrane calcium flux, as is thought to explain the hereditary cardiomyopathy of Syrian hamsters,⁹⁶ the potential benefits of verapamil are currently being appraised. Patients with hypertrophic cardiomyopathy whose left ventricular hypertrophy had remained unchanged or indeed become more severe while receiving propranolol showed substantial regression of hypertrophy on oral verapamil.⁹⁷ This work has been further extended in a study of 22 patients who received a mean oral dose of verapamil of 480 mg/day over an average of 15 months of treatment. Echocardiographic assessment was carried out in some cases and 10 patients underwent repeat cardiac catheterisation: in seven of these the left ventricular muscle mass was decreased and in the remaining three it was slightly increased; in a total of 39 patients observed over a mean follow-up period of 26.4 months the favourable results previously noted have been confirmed.⁹⁸ Indeed, in another study of 28 patients a conspicuous reduction in septal (but not posterior) wall thickness was found in all patients with asymmetric septal hypertrophy⁹⁹; all also showed clinical and electrocardiographic improvement. Given intravenously to patients with left ventricular outflow obstruction, the gradient may be moderately reduced without detrimental effects on the cardiac output, pulmonary artery wedge or left ventricular end-diastolic pressures.¹⁰⁰ In a double-blind placebo-controlled trial verapamil (up to 480 mg/day) and propranolol (up to 320 mg/day) increased exercise duration by 15% in 12 and 11 patients, respectively, out of 19.¹⁰¹ There was no correlation between the haemodynamic improvement noted acutely and exercise capacity or symptoms during the chronic study; neither drug relieved symptoms conspicuously more than placebo.

A potential benefit is the control of supraventricular arrhythmias that may complicate the disorder,¹⁰² but preliminary trials showed no benefit in these or ventricular arrhythmias when the drug was given orally to 30 patients.¹⁰³ Thus any true benefit that may accrue will be long term and dependent on reduction in ventricular mass: the reports await corroboration.

Conclusions

Calcium antagonists (a useful term to describe a diverse group of compounds with similar actions in isolated tissues) share the ability to counteract cardiac ischaemia and hypertension, but have varying actions on cardiac arrhythmias. The spectrum of therapeutic actions resembles that of the beta-blockers, to which calcium antagonists should be regarded as complementary. Thus in variant angina and supraventricular arrhythmias calcium antagonists are the drugs of choice, while in exertional angina beta-blockers are better, though here their efficacy can be enhanced by a calcium antagonist. The relative roles of these two groups of drugs in hypertension, hypertrophic cardiomyopathy, and protection of the ischaemic myocardium are currently being evaluated. As more is learned about their therapeutic efficacy, and their value recognised, calcium antagonists are beginning to assume their proper place, just as beta-blockers did more than a decade ago.

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