Review Paper

Calcium Antagonists — A Brief Review

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The development of tension in cardiac and vascular smooth muscle is a function of the free ionised intracellular calcium ion (Ca^{++}) Concentration. The Ca^{++} responsible for muscle contraction comes from both intracellular and extracellular sources. The movement of extracellular Ca^{++} into the cell occurs through specific transmembrane ionic channels. Calcium antagonists inhibit this transmembrane influx of Ca^{++} through these channels and the Ca available for muscle contraction is decreased.

In cardiac tissue two types of action potentials have been recognized. The contracting fibres show the fast response action potentials which are mediated by two discrete currents. In these fibres the Phase 0 of the action potential is mediated by the fast Na^{+} current and Phase 2 is mediated by the slow Ca^{++} current. In the nodal tissue (sinoatrial and atrioventricular nodes) the slow response action potentials are seen. Unlike in the fast response fibres, these action potentials are mediated predominantly by Ca^{++} ions. Hence, calcium antagonists have important effects on sinoatrial and atrioventricular nodal function.[1] In the myocardium the effects of these drugs manifest as depression of generation and propagation of action potentials and a decrease in contractility. Due to the effects on the vascular smooth muscle, vasodilatation is produced. Due to these effects myocardial oxygen demand is reduced. In addition, the supply of oxgen to the myocardium is increased due to coronary vasodilatation and relief of vasospasm. Hence, these drugs have wide applications in cardiovascular pharmacology.[2] There is controversy about the exact nomenclature of these drugs.[3] These are referred to as calcium channel blockers and calcium entry blockers also.

The commonly available calcium antagonists differ in their chemical structure as well as their effects on cardiovascular function. For example verapamil (a phenylalkylamine derivative) has more pronounced effects on cardiac contractility and atrioventricular conduction than on the peripheral vascular tone, whereas nifedipine (a dihydropyridine derivative) has more marked vasodilator effects and lesser effects on contractility and conduction of impulses. These differences have led to the classification of these drugs into the following classes.

Class 1 — Phenylalkylamines (eg., verapamil)

Class 2 — Dihydropyridines (eg., nifedipine, nicardipine)

Class 3 — Benzothiazepines (eg., diltiazem)

The effects on the important haemodynamic parameters are shown in Table 1.[4]

Clinical Value

These drugs are used in the management of several cardiovascular disorders.[5]

1. Treatment and prevention of angina

Immaterial of the underlying pathophysiology, calcuim antagonists have been found to be effective in all forms of angina. They can be used where nitrates and beta adrenoceptor

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Table 1

Haemodynamic Effects of Calcium Antagonists

Haemodynamic Effect on:	*Verapamil*	*Nifedipine*	*Diltiazem*
Heart rate	decrease or no change	moderate increase	moderate decrease
Contractility	small decrease	moderate increase	small decrease
Preload	unchanged	unchanged	unchanged
Afterload	moderate decrease	large decrease	moderate decrease
Coronary blood flow	unchanged	moderate increase	moderate increase

blockers have been ineffective. In uncontrolled angina, these agents may be added to a combination of nitrates and beta adrenoceptor blockers. When angina is due to coronary artery spasm, calcium antagonists can be used as drugs of first choice.

The beneficial effects of calcium antagonists in angina pectoris are due to the following reasons.

i. Increase in blood supply to cardiac muscle

   a. decreased coronary artery tone
   b. prevention of coronary artery spasm
   c. redistribution of regional blood flow to ischaemic areas.

ii. Decrease in oxygen demand

   a. vasodilatation and reduced after load
   b. bradycardia
   c. negative inotropic effect

2. Treatment of hypertension

Ability of calcium antagonists to relax vascular smooth resistance muscle and, therefore, to decrease peripheral vascular resistance makes them useful antihypertensive agents. The antihypertensive effect has been found to be greater in patients with higher peripheral vascular resistance. Blood pressure returns to pretreatment values on withdrawal of these drugs. Nifedipine has been found to be extremely useful in rapid lowering of blood pressure.

3. Management of superventricular arrhythmias

Verapamil has been found to be useful in the long term management of patients with supraventricular tachycardia, and in patients with atrial fibrillation and flutter with rapid ventricular responses. It is also frequently used in the emergency termination of attacks of paroxysmal supraventricular tachycardia.

4. Management of patients with hypertrophic cardiomyopathy

Calcium antagonists are used in the management of patients with hypertrophic cardiomyopathy. In this regard verapamil has been used more frequently compared to the other agents.

5. Due to the vasodilator properties, calcium antagonists have been tried in the management of a variety of clinical conditions. In some of these (eg., nifedipine in the management of Raynaud's phenomenon) the benefits have been clearly documented. In others, further clinical evaluation is awaited. Certain agents of the dihydropyridine group of drugs (eg., nimodipine) is also used in treatment and prevention of ischaemic neurological deficits following sub arachnoid haemorrhage.

Adverse Effects

There are adverse effects common to all three classes of drugs and these may be due to peripheral vasodilatation and hypotension. These include dependent oedema, flushing, sensation of heat, dizzyness, giddiness, lightheadedness, fatigue and headache. Nausea, vomiting, constipation and rashes are also not uncommon. In some patients angina and cardiac failure may be precipitated.

Precautions

1. Frequency, duration and severity of anginal attacks may be increased in some patients. The worsening of angina sometimes seen during withdrawal of beta adrenoceptor blockers is not prevented by administration of calcium antagonists.

2. When used in the management of hypertension, careful adjustment of the dose with the blood pressure is needed. The hypotensive effect may be marked in elderly subjects, subjects with poor left ventricular function and those on other medications (especially beta adrenoceptor blockers).

3. Because of the negative inotropic effects, cardiac failure may be precipitated. This is more applicable for verapamil and diltiazem.

4. Negative chronotropic effects may give rise to sinus bradycardia, second and third degree atrioventricular block, sinus arrest or short periods of asystole. Bradyarrhythmias are also seen more frequently with verapamil and diltiazem. These effects are precipitated when used in combination with digoxin or beta adrenoceptor blockers.

5. Calcium antagonists can precipitate cardiac failure or syncope in patients with severe aortic stenosis.

6. Severe myocardial depression may occur, especially when used in combination with other drugs with similar properties (eg., lignocaine).

7. Unlike verapamil and diltiazem (which tend to slow the heart), nifedipine causes tachycardia. Hence, an existing tachycardia may be worsened after administration of nifedipine.

8. Severe hypotension may occur following intravenous administration of verapamil and rarely this may be followed by loss of consciousness. If this occurs therapy should be promptly discontinued. The possibility of undiagnosed sick sinus syndrome has to be considered in the elderly patients. Those with an underlying accessory pathway between the atria and ventricles (eg., Wolff-Parkinson-White syndrome) may following administration of intravenous verapamil, develop antegrade conduction through the accessory pathway producing ventricular tachycardia and fibrillation. If this occurs the patients will need cardioversion or defibrillation. In these subjects the safety of verapamil has to be established by electrophysiological testing before its use.[6]

Contraindications

1. Known hypersensitivity to a specific calcium antagonist (verapamil, nifedipine or diltiazem)

2. States of low blood pressure (< 90 mmHg).

3. Acute myocardial infarction with cardiogenic shock

4. Second and third degree atrioventricular block and marked bradycardia

5. Sick sinus syndrome, unless in the presence of a ventricular pacemaker.

6. Severe cardiac failure, unless secondary to supraventricular arrhythmia which is amenble to treatment with verapamil

7. Information about the use of calcium antagonists in pregnancy is insufficient. Foetal malformations have been reported in animals. They are not recommended in the first trimester.

8. Concomitant use of parenteral beta adrenoceptor blockers and parenteral verapamil is contraindicated.

Drug Interactions

1. Administration of calcium antagonists (verapamil, nifedipine or diltiazem) to patients on digoxin may lead to precipitation of digoxin toxicity.

2. A greater hypotensive effect may be seen when used with other antihypertensive drugs.

3. Slowing of the heart may be greater when used along with digoxin, beta adrenoceptor blockers, quinidine or procainamide.

4. Concurrent administration of cimetidine may lead to an enhanced hypotensive effect in patients already on nifedipine.

Implications in Anaesthesia

Because of the expanding indications for use and the increasing use of calcium antagonists, patients on these drugs may come for anaesthesia. Hence, it is important to be aware of some of the possible complications.[7]

Use of halothane in patients treated with verapamil may result in significant myocardial depression. This is especially important in those with pre-existing myocardial impairment. Animal experiments indicate that the effect of neuromuscular blocking agents to be potentiated by calcium antagonists. Hence, these drugs have to be used cautiously or avoided in patients with neuromuscular problems. A patient with Duchenne muscular dystrophy had developed respiratory arrest after 6 mg of verapamil. Preoperative discontinuation of calcium antagonists in patients presenting for anaesthesia is not recommended. However, awareness of the potential problems and monitoring of cardiovascular and neuromuscular function is essential.

Certain pathophysiological changes produced by calcium antagonists may also have implications of importance to the anaesthetist. The lower oesophageal sphincter pressure is decreased by these drugs and, hence, the risk of regurgitation of gastric contents during induction and mask ventillation techniques is increased. Verapamil (5 mg intravenously) has produced increases in intracranial pressure in hypertensive patients with supratentorial space occupying lesions during general anaesthesia. Hence, calcium antagonists are best avoided in these patients unless intracranial pressure can be monitored and facilities for urgent treatment are available.

Some brief notes on verapamil, nifedipine and diltiazem are given below.

Verapamil

When administered orally, verapamil undergoes first-pass metabolism and bioavailability is low. Peak plasma concentrations are reached in 1-2 hours. It is carried bound to plasma proteins, metabolised in the liver and a major portion is excreted in urine as inactive amines.

Adverse effects: apart from those mentioned earlier, atrioventricular block and ventricular arrhythmias may occur. Its potent negative inotropic effects may precipitate cardiac failure.

Preparations available:

1. Verapamil Hydrochloride tablets, 40 mg and 80 mg

In the management of patients with angina, hypertension and long term management of arrhythmias, verapamil can be commenced in doses of 40 - 80 mg three to four times daily. The dose may be increased until optimum response is achieved. A maximum dose of about 480 mg/day can be used. In the medical management of hypertrophic cardiomyopathy this maximum recommended dose can be increased upto 600 to 720 mg/day.

2. Verapamil Hydrochloride injection for intravenous use 5 mg/ 2 ml

Intravenous verapamil should be administered only with continuous electrocardiographic monitoring and frequent blood pressure monitoring. Verapamil (5 mg) is given over one minute until the therapeutic effect is seen. In the elderly, it is recommended to give this dose over three minutes. If the arrhythmia persists or recurs a second dose of 5 mg can be given after 5-10 minutes.

Use in Children:

0-2 year age group: 0.75 to 2 mg given over 2 minutes.

2-15 years: 2-5 mg given over 2 minutes.

A second dose may be repeated after 30 minutes. Protocols different from above, including low dose intravenous infusions may be used.

Nifedipine

After oral administration, nifedipine is well absorbed from the gastrointestinal tract. It is detected in plasma within 20 minutes and peak concentrations seen in 1-2 hours. Nifedipine is metabolised in the liver and inactive metabolites are excreted in the urine. It has been difficult to establish a direct relationship between the plasma concentration of nifedipine and its effects.

Adverse effects: apart from those mentioned previously some uncommon adverse effects have been reported with nifedipine. these include joint stiffness, pruritus, fever, gingival hyperplasia and hypersensitivity leading to allergic hepatitis.

Preparations available:

1. Nefedipine 10 mg capsules

Dosage should be individualized. In patients with angina a dose of 10 mg thrice daily is commenced. Sometimes more frequent administration of higher doses may be needed to control the symptoms. Nifedipine is also used in rapid lowering of blood pressure. A hard gelatin capsule of nifedipine can be punctured and its contents kept in the mouth for sublingual and intrabuccal absorption. Alternatively, a soft gelatin capsule can be chewed and kept in the mouth enabling absorption to occur. Hypotensive effect is seen within 10 minutes.

2. Nifedipine sustained release tablets, 20 mg

This preparation is useful in the management of patients with hypertension.

Diltiazem

Diltiazem is well absorbed from the bowel after oral administration and peak plasma concentrations are reached in 2-3 hours. It is metabolised in the liver and metabolites, which are predominantly inactive, excreted in the urine.

Adverse effects: in addition to those mentioned previously bradycardia, atrioventricular block and sinus arrest may occur.

Preparations available:

1. Diltiazem Hydrochloride tablets 30 mg and 60 mg

   It is commenced in doses of 30 mg thrice daily. This dose is increased at one or two day intervals to a maximum of about 360 mg/day, given as three or four divided doses.

The generic names, trade names, recommended daily doses and the prices (as at June 1991) 0f the common calcium antagonists registered in Sri Lanka are given in Table 2.

Table 2

The Generic and Trade Names, Dose and Prices (as at June, 1991) of Common Calcium Antagonists Registered in Sri Lanka

Generic name	*Trade names*	*Total daily dose*	*Price/Tablet Rs.cts (tablet size)*
Verapamil	Cordilox	120 - 360 mg	1.57 (40 mg)
	Cordilox		3.35 (40 mg)
	generic		0.93 (40 mg)
	generic		2.35 (80 mg)
	Isoptin		1.30 (40 mg)
	Vasopten		0.44 (40 mg)
	Vasopten		0.86 (80 mg)
Nifedipine	Calcigard	30 - 60 mg	0.82 (10 mg)
	Coracten sustained release cap		9.00 (20 mg)
	Depin-E		1.13 (10 mg)
	Nificard		1.40 (10 mg)
	Nifidil		1.44 (10 mg)
	Fenamon capsules		4.02 (10 mg)
	Fenamon tablets		2.10 (10 mg)
	Vasadalat		1.74 (10 mg)
Diltiazem	Angizem	90 - 180 mg	2.14 (30 mg)
	Angizem		3.32 (60 mg)
	generic		2.35 (30 mg)
	generic		4.35 (80 mg)
	Herbesser		3.55 (30 mg)
	Herbesser		5.70 (60 mg)

REFERENCES

1. Singh B N, Nademanee K, Baky S H. Calcium Antagonists. Clinical Use in Treatment of Arrhythmias., *Drugs*, 1983: 25: 125-153.

2. Calcium antagonists and cardiovascular disease., Ed Opie L H New York, Raven Press 1984.

3. Vanhoutte P M, The Expert Committee of the World Health Organization on Classification of Calcium Antagonists. The Viewpoint of the Raporteur. A symposium: The Calcium ion, Cardiac myosite and vascular smooth muscle in hypertension and its treatment., *American Journal of Cardiology* 1987: 59 3A - 8A.

4. Avery's Drugs Treatment. Principles and Practice of Clinical Pharmacology and Therapeutics, Ed Speight TM, Auckland, ADIS Press, 1987.

5. Ellrodt A G, Singh B N. The role of slow-channel blockers in cardiovascular disease, In: Recent Advances in Cardiology, Ed Rowlands D J, London, Churchill Livingston, 1984.

6. Compendium of Pharmaceuticals and Specialities, Ed Gillis M C Edition 24, Ottawa, Canadian Pharmaceutical Association, 1989.

7. Jenkins L C, Scoates P J. Anaesthetic implications of calcium channel blockers, *Canadian Anaesthesia Society Journal*, 1985: 32; 436-447.