Review Article

Calcium-channel blockers and anaesthesia

Pierre-Georges Durand MD,* Jean-Jacques Lehot MD,*
Pierre Foëx D DPh†

Verapamil was the first calcium-channel blocker (CCB). It has been used since 1962 in Europe then in Japan for its anti-arrhythmic and coronary vasodilator effects.¹ The CCB have become prominent cardiovascular drugs during the last 15 years. Many experimental and clinical studies have defined their mechanism of action, the effects of new drugs in this therapeutic class, and their indications and interactions with other drugs. Due to the large number of patients treated with CCB it is important for the anaesthetist to know the general and specific problems involved during the perioperative period, the interactions with anaesthetics and the practical use of these drugs.

Le verapamil a été initialement utilisé comme un bloqueur des canaux calciques (CCB). Il a été utilisé depuis 1962 en Europe puis au Japon pour ses propriétés anti-arythmiques et ses effets vaso-dilatateurs coronariens.¹ Les CCB sont devenus des drogues cardiovasculaires de choix depuis les 15 dernières années. Plusieurs études cliniques et expérimentales ont défini leurs mécanismes d'action, leurs effets et leurs indications ainsi que leurs interactions avec les autres médicaments. Aussi, étant donné le grand nombre de patients traités avec les CCB, il est d'une importance majeure que l'anesthésiste sache les problèmes généraux et spécifiques qu'emmène ce groupe de médicaments durant la période pré-opératoire, les interactions avec les anesthésiques et l'utilisation pratique de ces médicaments.

Key words

PHARMACOLOGY: calcium channel blockers.

From the Anaesthesia and Intensive Care Department, Hôpital Cardio-vasculaire et Pneumologique, Lyon (France)* and the Nuffield Department of Anaesthetics, The Radcliffe Infirmary, Oxford (U.K.).†

Address correspondence to: Dr. P-G. Durand, Department of Anaesthesia and Intensive Care, Hôpital Cardio-vasculaire et Pneumologique – 69394 Lyon Cedex 03 – France.

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Comparative pharmacology of CCB

Classification and chemical characteristics

The classification proposed by the World Health Organization² (Table I) divides the CCB into two groups: Group A consists of CCB selective for slow calcium Ca^{++} channels (verapamil and derivatives; dihydropyridines (DHP): nifedipine, nicardipine, nimodipine, nitrendipine, diltiazem); Group B consists of CCB non-selective for slow Ca^{++} channels (diphenylpiperazines, prenylamine derivatives, bepridil, perhexiline).

Spedding's classification^{3,7} divides CCB into three groups according to their mechanism of action: Group I is made up of DHP which act through a membrane site; Group II (verapamil, diltiazem) is an heterogeneous group made up of hydrophobic molecules acting through two different sites on the calcium channels; Group III (flunar-

TABLE I Classification of calcium-channel blockers ording to their degree of specificity for calcium channels

	CCB	Specificity for slow calcium-channel
Group A	Verapamil	+++
	Diltiazem	
	Dihydropyridines	
	– nifedipine	
	– nicardipine	
	– nimodipine	
	– nitrendipine	
Group B	Diphenyl piperazines	+++
	Prrenylamine	
	Bepridil	
	Perhexiline	

zine, perhexiline, bepridil) possesses a structural homogeneity and is made up of lipophilic molecules which exhibit less selective mechanisms of action.

Calcium-channel blockers are mixtures of isomers possessing different levels of activity. For example, the nicardipine positive isomer is more powerful than its negative isomer. The verapamil negative isomer is more powerful than its positive isomer with regards to vascular and myocardial effects.³

Mechanism of action

Calcium plays a fundamental role in the excitation-contraction coupling in myocardial cells and smooth muscle. Its penetration into the cell allows the Ca^{++} release from the sarcoplasmic reticulum which is responsible for muscle contraction. Contraction takes place in the myocardial cell because of the actin-myosin interaction facilitated by the troponin Ca^{++} complex. In the vascular smooth muscle calmodulin plays the same role as troponin in the cardiac muscle and allows the actin-myosin interaction.^{4,5}

Calcium enters into the cell through two types of channels: receptor-operated channels (ROC) and voltage-operated channels (VOC). Calcium-channel blockers decrease Ca^{++} entry through the VOC during phase 2 of the action potential of the fast response cells (slow calcium channel) and during phase O of the action potential of the slow response cells contained in the sino-atrial and atrio-ventricular nodes.

Voltage-operated channels are a hundred-fold more selective for Ca^{++} than for Na^{+} and have been divided into sub-types.^{6,7} Hess⁸ recognised three sub-types ("L" long-lasting inward calcium current; "T" transient inward calcium current "N" found in sensory neurones) according to their kinetics, size, conductance, voltage dependence, preferential localisation (i.e., myocardial cell and

vascular smooth muscle for T and L) and their CCB selectivity. The L channels are inhibited by DHP but DHP seemed to have little effect on T and N channels.⁸

Voltage-operated channels are made up of sub-units. Some sub-units allow the CCB to link to the channels,⁹ others allow phosphorylation and activation of VOC through indirect stimulation by H_2 -agonists and beta-agonists¹⁰ leading to Ca^{++} entry into the cell.

Calcium-channel blockers prevent activation of VOC, block Ca^{++} entry into the cell and inhibit the excitation-contraction coupling. Verapamil decreases allosterically the fixation of DHP to the cell whereas diltiazem increases this fixation.¹¹ Additionally, bepridil can attach to smooth muscle calmodulin.¹² The blockade of VOC takes place at rest with DHP but is frequency-dependent with verapamil and diltiazem.^{13,14} In addition CCB may have a VOC independent action through blockade of α_2 post-synaptic vascular receptors.¹⁵

Pharmacokinetic variables (Table II)¹⁶

Calcium-channel blockers exhibit relatively similar pharmacokinetic properties.^{17–19} The bioavailability of diltiazem shows important individual variations.²⁰ Calcium-channel blocker metabolism is essentially hepatic through demethylation and dealkylation, leading to several possibly biologically active metabolites. Thus hepatic failure or decreased hepatic blood flow due to cardiac failure slows the metabolism of CCB.²¹ The elimination of the inactivated compounds takes place mainly in the kidneys. However, chronic treatment prolongs the half-life because of saturation of hepatic first-pass effect, i.e., verapamil elimination half-life is extended to 6–9 hr.¹⁷

Interactions

Interactions with other drugs have been frequently reported.²² Serum digoxin concentrations increase with CCB treatment, probably through diminution of renal clearance.²³ Cimetidine increases bioavailability and serum levels of verapamil, diltiazem and DHP.²⁴ Conversely verapamil increases serum theophyllin levels in some patients.²⁵

Pharmacodynamic effects (Figure)

Cardiovascular effects differ according to the CCB considered and result from direct effects and effects elicited by stimulation of the baroreflex.²⁶ Calcium-channel blockers act on nodal tissue. In an *in vitro* study with rat isolated atrial cells, Kawai *et al.*²⁷ found a similar dose-dependent inhibitory effect of nifedipine, verapamil and diltiazem characterized by increases in sinus recovery time, effective refractory period, and functional refractory period of the atrio-ventricular node. However, in clinical studies, inhibitory effects were observed only

TABLE II

Pharmacological properties of CCB	Verapamil	Diltiazem	Bepridil	Nifedipine	Nicardipine	Nimodipine
Dose						
- Oral	80–160 mg · 8 hr ⁻¹	30–120 mg · 8 hr ⁻¹	200–300 mg · 24 hr ⁻¹	10–40 mg · 8 hr ⁻¹ intranasal 10 mg · 4 hr ⁻¹	20 mg · 8 hr ⁻¹	240 mg · 24 hr ⁻¹
- IV	15–45 mg · 24 hr ⁻¹	75–150 mg · 24 hr ⁻¹	4 mg · kg ⁻¹ · 24 hr ⁻¹	5–15 µg · kg ⁻¹	2–5 mg · hr ⁻¹	2 mg · hr ⁻¹
Oral absorption (%)	>90	>90	90	>90	99	>90
Onset of action (min)	<30	15	48–72 hr	intranasal 3, oral 20	20–60	30–90
First pass extraction by liver after oral administration (%)	75–90	70–80	30–40	40–60	20–40	90
Bioavailability (%)	20	25–50	60	50	30	5–10
Protein binding (%)	90	80	99	90	98	99
Elimination half-time (hr)	4–10	2–6	33	3–5	3–5	2
Therapeutic plasma concentration (ng · ml ⁻¹)	50–250	100–250	300–1100	10–100	5–100	10–30
Excretion (%)						
- Renal	85	40	1	80	55	20
- Hepatic	15	60	99	20	45	80

FIGURE Differential effects of the available calcium-entry blockers on the major determinants of left ventricular function. D = diltiazem; N = nifedipine, V = verapamil; NC = no change. (Reproduced, with permission, from McCall *et al.*)

with verapamil and diltiazem but opposite effects were observed with nifedipine²⁷ and nicardipine.²⁸

All CCB cause a dose-dependent decrease in mean arterial pressure and systemic vascular resistance (SVR).²⁹ The baroreflex-induced increase in heart rate is greater with nifedipine than with verapamil or diltiazem²⁶ due to a more potent vasodilator effect of DHP.³⁰

The effects of CCB on cardiac performance are complex. *In vitro*, all CCB demonstrate potent negative inotropic effects³¹ but clinical studies have shown variations of heart rate and afterload.²⁹ However, verapamil

seems to be the most,³⁰ and nicardipine the least cardiac depressant after intracoronary injection.³²

These decreases in contractility, heart rate and afterload reduce myocardial oxygen consumption (MVO₂).

In the normal and in the ischaemic myocardium intracoronary administration of CCB impaired left ventricular relaxation but conversely, because of decreased afterload and sympathetic response, intravenous administration enhanced ventricular relaxation.³⁰ Calcium-channel blockers have spasmolytic and vasodilator properties on the coronary circulation. Spasmolytic effects have been demonstrated in pharmacologically induced spasm³³ and clinical studies have confirmed functional improvement.³⁴ A dose-dependent increase in coronary blood flow (CBF) has been demonstrated with all CCB both in normal and constricted coronary arteries.^{35,36}

Dihydropyridines have spasmolytic effects on the cerebral circulation and increase carotid blood flow.^{37,38} Calcium-channel blockers reverse the decrease in renal blood flow caused by angiotensin II³⁹ and diltiazem and nicardipine may increase glomerular blood flow in human nephropathies.^{39,40} Calcium-channel blockers may also protect kidneys against ischaemia. In sheep, verapamil 50 µg · kg⁻¹ was injected into the renal artery prior to one hour ischaemia and this improved postischaemic creatinine excretion.⁴¹ Conversely, nifedipine may induce acute renal failure in a few situations.⁴² Thus further data are needed to define the renal effects of CCB.

Calcium-channel blockers may also dilate pulmonary arteries, especially in the presence of hypoxaemic vasoconstriction⁴³ or at an early stage of primary pulmonary hypertension.^{44,45} A subsequent increase in venous admixture has been found by some authors⁴⁶ but not by all.⁴⁷ Anti-atherogenic properties of CCB such as isradipine

ine have been demonstrated experimentally⁴⁸ but not confirmed in man. Endocrine effects have been shown; calcium-channel blockers increased plasma angiotensin II concentrations without changes in plasma aldosterone and renin activity.³⁹ Verapamil has been shown to inhibit atrial natriuretic factor secretion induced by rapid ventricular pacing.⁴⁹

Indications not related to anaesthesia

Confirmed indications

The efficacy of CCB has been confirmed in coronary artery disease (CAD),⁵⁰ especially coronary spasm³⁴ in which most CCB have demonstrated similar effects: CCB reduced the number of episodes by 50 per cent in more than 60 per cent of patients. Diltiazem and nifedipine had additive effects but induced more untoward effects.⁵¹

The action of CCB in angina pectoris results from an increase in CBF in the ischaemic area⁵² and from a reduction of $\dot{M}\dot{V}O_2$. The $\dot{M}\dot{V}O_2$ decreases due to a reduction of afterload which is more pronounced with DHP, and to negative chronotropic and inotropic effects induced by verapamil and diltiazem. A dose-dependent improvement of performance during exercise and a decrease in the number of angina pectoris crises has been demonstrated.^{53,54} The combination of diltiazem and nifedipine was more effective in stable angina pectoris than diltiazem or nifedipine alone.⁵⁵ In patients with moderately depressed left ventricular (LV) function, the combination of diltiazem with propranolol increased LV ejection fraction during exercise compared with propranolol alone;⁵⁰ this could have been due to the afterload reduction caused by diltiazem. Dihydropyridines seem better tolerated than diltiazem or verapamil when LV failure was present.⁵⁶

Calcium-channel blockers have been used in acute hypertension. Bauer *et al.*⁵⁷ observed a ten per cent decrease in systolic blood pressure in five patients given diltiazem $0.3 \text{ mg} \cdot \text{kg}^{-1}$ administered over three minutes. Nifedipine $5\text{--}30 \text{ mg PO}$ or verapamil $5\text{--}10 \text{ mg IV}$ also have been used in acute hypertension.⁵⁷

Calcium-channel blockers are also utilized in mild to moderate hypertension⁵⁸ though most studies involved a relatively small number of patients observed for less than three months.⁵⁸ Oral verapamil 240 mg daily in adults was as efficient as atenolol or propranolol.⁵⁹ Dihydropyridines such as nicardipine or nitrendipine have also been utilized.⁶⁰ However, hypotension may occur, leading to myocardial ischaemia, especially with DHP such as nifedipine at usual dosages.^{61–63}

Whilst DHP do not possess antiarrhythmic properties, verapamil has been used for many years in the manage-

ment of paroxysmal supraventricular tachycardias.⁶⁴ The success rate of conversion to sinus rhythm was more than 80 per cent after 10 mg IV in adults, and approached 100 when combined with carotid sinus massage.⁶⁵ Diltiazem $0.15 \text{ mg} \cdot \text{kg}^{-1} \text{ IV}$ or bepridil $2\text{--}4 \text{ mg} \cdot \text{kg}^{-1} \text{ IV}$ produced similar results.^{65,66} Calcium-channel blockers administered orally preventively have been less successful.⁶⁷ Verapamil slowed the ventricular response during atrial fibrillation.⁶⁸ Verapamil, diltiazem or bepridil have been successful in treating ventricular arrhythmias during acute myocardial infarction (AMI) and idiopathic ventricular tachycardias with right bundle branch block and left axis deviation.^{69,70}

Possible indications

Due to the role of Ca^{++} in ischaemic myocardial cell injury⁷¹ CCB have been proposed for use in AMI. Several multicentre studies have shown no effect on mortality^{72,73} but diltiazem decreased the incidence of cardiac events in AMI without Q wave⁷⁴ and AMI without LV failure.⁷⁵

The role of CCB in the treatment of cardiac failure remains to be defined.⁷⁶ The reduction of SVR induced by DHP might increase cardiac output in acute or chronic cardiac failure in the short term. However, this effect seems to disappear in the longer term⁷⁷ and the negative inotropic effect of DHP might have occurred, as reflex sympathetic compensation was less effective in these patients.⁷⁸ Therefore, CCB seem to be less effective than converting enzyme inhibitors or nitrates in the treatment of cardiac failure.^{77,79}

Verapamil improved function in 50 per cent of patients who presented with obstructive cardiomyopathy.⁸⁰ This improvement occurred at rest and during exercise, was greater with verapamil than with nifedipine⁸¹ and coincided with an improvement of LV diastolic function. The LV intraventricular outflow pressure gradient decreased when the verapamil-induced cardiac depression was more pronounced than the fall of SVR.

Calcium-channel blockers have been included in cold crystalloid cardioplegic solutions during cardiac surgery. Nifedipine $200 \mu\text{g} \cdot \text{L}^{-1}$ decreased the effects of myocardial ischaemia but led to difficulties in weaning from cardiopulmonary bypass.^{82,83} Diltiazem $150 \mu\text{g} \cdot \text{kg}^{-1}$ improved myocardial protection but elicited myocardial depression and conduction disturbances.⁸⁴ Verapamil 50 mg added to the priming of cardiopulmonary bypass during coronary artery bypass graft (CABG) surgery prevented coronary vasospasm.⁸⁵ More studies are needed to define the place of CCB in cardioplegia.^{83,84}

Cerebral artery spasms are usually associated with sub-arachnoidal haemorrhage due to rupture of cerebral aneurysm. Nimodipine administered through a nasogas-

tric tube every four hours for three weeks decreased the incidence of severe neurological deficits due to spasm in man⁸⁶ and reduced the subsequent morbidity and mortality.⁸⁷ After clipping of intracranial aneurysm, IV nicardipine induced an increase in cerebral blood flow in the hypoperfused areas and a decrease in the hyperperfused areas.⁸⁸ However, this was accompanied by worsening of the neurological status in patients with cerebral oedema.⁸⁸ Nimodipine seems to present vasoregulator properties⁸⁹ but further studies of cerebral blood flow and outcome are needed.

In monkeys nimodipine $10 \mu\text{g} \cdot \text{kg}^{-1}$ administered five minutes after cerebral ischaemia improved the outcome and the histological score.⁹⁰ In man, after cardiac arrest IV nimodipine decreased the coma duration but did not change the final outcome.⁹¹ Gelmers *et al.*⁹² found a decrease in mortality when nimodipine was started orally within 24 hr of acute ischaemic stroke, possibly because this treatment decreased the incidence of cardiovascular complications. The beneficial effects of nimodipine could be attributed to increased cerebral blood flow^{93,94} without significant change in post-ischaemic cerebral metabolism⁹⁵ but these effects are disputed.^{96,97}

Dihydropyridines may be beneficial in Raynaud's syndrome,^{98,99} and nifedipine or verapamil in oesophageal spasm.¹⁰⁰

Pharmacological interactions during anaesthesia

Halogenated anaesthetics

Experimental studies have determined the interactions between CCB and halogenated anaesthetics on the cardiovascular system. The negative inotropic effect of these combinations has been shown on isolated myocardial cells^{101–103} and in experimental studies with open^{104–106} or closed^{107–109} chests. Enflurane combined with CCB caused more myocardial depression than halothane or isoflurane. This has been demonstrated with verapamil in closed-chest animals during acute^{108,109} and chronic¹¹⁰ experiments, with diltiazem on isolated myocardial cells¹⁰¹ and with bepridil in open-chest dogs.¹⁰⁵ Diltiazem or verapamil in combination with halothane decreased cardiac performance more than nifedipine¹⁰⁶ or nicardipine.¹¹¹

The combination of CCB with halogenated anaesthetics also decreased mean arterial pressure.^{104–108} At equianaesthetic potency, enflurane combined with verapamil¹⁰⁸ or bepridil¹⁰⁵ decreased arterial pressure more than halothane or isoflurane. This was accompanied by increased SVR and decreased cardiac output with both enflurane^{105,108} and halothane.¹¹² Isoflurane in combination with CCB either increased,¹¹³ did not change¹¹⁴ or decreased¹⁰⁴ SVR. In swine, anaesthetized with halo-

thane for a similar decrease in arterial pressure, SVR was reduced only by nifedipine.¹⁰⁶

Calcium-channel blockers and halogenated anaesthetics may modify CBF through two possible mechanisms: (1) decrease in coronary perfusion pressure, and (2) coronary artery vasodilatation. Most studies found no change in CBF in spite of a decrease in coronary perfusion pressure;^{107,109,113,114} one study in open-chest sheep found a 66 per cent decrease in CBF with halothane (inspired concentration = 1.2 per cent and after a verapamil cumulative dose of $0.16 \text{ mg} \cdot \text{kg}^{-1}$).¹¹² The combination of nicardipine and isoflurane (at 1 MAC and 2 MAC) caused a substantial decrease in arterial pressure and an increase in CBF.¹¹¹ In open-chest animals asynchronism of LV wall motion was observed with¹¹⁶ or without^{112,113,115} critical coronary constriction.

Verapamil and diltiazem slow AH conduction;²⁷ as halothane and enflurane similarly slow AH conduction and the three halogenated anaesthetics slow HV conduction and intra-ventricular conduction,¹¹⁷ CCB and halogenated anaesthetics may exert additive effects on the conduction system. In dogs, enflurane (1.2 MAC with diltiazem $40 \text{ mg} \cdot \text{kg}^{-1} \text{ min}^{-1}$ IV administered over a 40-min period¹¹⁸ led to a sinus arrest. Hantler *et al.*¹¹⁹ reported two cases of sinus bradycardia in patients treated preoperatively with diltiazem and anaesthetized with enflurane and fentanyl.

In dogs anaesthetized with halothane, enflurane or isoflurane (1.2 and 1.5 MAC), verapamil increased the AH interval more than did diltiazem.¹¹⁷ Atlee *et al.*¹¹⁷ in their experimental study with verapamil or diltiazem reported three cases of auriculo-ventricular block with enflurane and one complete heart block with halothane or isoflurane. Bepridil $5 \text{ mg} \cdot \text{kg}^{-1}$ IV increased the AH interval in dogs anaesthetized with enflurane but not with halothane or isoflurane.¹²⁰ However, nifedipine, in combination with halogenated anaesthetics, did not modify auriculo-ventricular conduction.¹¹⁷ One of the patients described by Hantler *et al.*¹¹⁹ presented with a Mobitz I auriculo-ventricular block associated with sinus bradycardia.

Calcium-channel blockers did not increase the depressant effects of halogenated anaesthetics on His-Purkinje and intraventricular conduction.¹¹⁷ On the other hand, verapamil and diltiazem exhibited protective effects against epinephrine induced arrhythmias in dogs anaesthetized with halothane.^{121,122}

Experimentally CCB enhanced the reduction of renal and carotid blood flows induced by halogenated anaesthetics. This has been shown with several combinations: nicardipine and isoflurane;¹¹¹ verapamil and either halothane, enflurane or isoflurane.^{107,109} In rats, verapamil

and halothane or isoflurane inhibited hypoxaemic pulmonary vasoconstriction.¹²³

Pharmacodynamic and pharmacokinetic reasons explain these interactions. Pharmacodynamic interactions can occur at the cellular level and in the autonomic nervous system. Lynch *et al.*^{124,125} showed that halothane and enflurane had similar effects on the slow calcium channels in myocardial cells but the effects of isoflurane were different.¹²⁶ Durrett *et al.*¹²⁷ found that the negative inotropic effects of halothane depended upon intracellular mechanisms. Wheeler *et al.*¹²⁸ showed that halothane decreased Ca^{++} release from the sarcoplasmic reticulum. Terrar and Victory¹²⁹ showed that isoflurane depressed the inward calcium current and the amplitude of contraction in myocytes isolated from guinea-pig ventricle. Thus halogenates and CCB have additive effects on myocytes. Recently, Nakao *et al.*¹³⁰ and Blanck *et al.*¹³¹ observed that nitrendipine could be displaced from its membrane sites by halogenated anaesthetics in proportion of their anaesthetic potency. Maze *et al.*¹³² showed that verapamil decreased the MAC of halothane. Halogenated anaesthetics impair the baroreflex responses¹³³ and hence decrease the sympathetic response to CCB. In dogs anaesthetized with halothane one per cent (inspired concentration), the administration of nifedipine $10 \mu\text{g} \cdot \text{kg}^{-1}$ IV was accompanied by a reduction of arterial pressure and SVR together with a rise in heart rate and cardiac output; with halothane two per cent nifedipine decreased arterial pressure to a greater extent but did not increase heart rate and cardiac output.¹³³

Pharmacokinetic interactions have also been demonstrated. Serum verapamil levels were increased by halothane, enflurane or isoflurane.¹³⁴ This increase was explained by either a reduction of hepatic blood flow¹³⁵ or a dysfunction of the autonomic nervous system.¹³⁴

The negative inotropic effects induced by the combination of CCB and halogenated anaesthetics may be reversed by calcium chloride^{103,112} but is potentiated by magnesium.¹⁰³ However, calcium is ineffective in conduction disturbances which may respond to isoprenaline, glucagon and electrostimulation.¹¹⁸

Few clinical studies have assessed the effects of the combination of CCB and halogenated anaesthetics. Schulte-Sasse *et al.*¹³⁶ showed that verapamil $0.15 \text{ mg} \cdot \text{kg}^{-1}$ IV was well tolerated during anaesthesia with low inspired concentrations of halothane (0.35 per cent) in CAD patients. The IV administration of verapamil may be hazardous in some circumstances. For example, Moller *et al.*¹³⁷ reported cardiac arrest when verapamil 5 mg was injected IV to reduce tachycardia in a 56-yr-old patient during halothane anaesthesia who had presented with haemorrhagic shock. However, the combination of IV

nicardipine and halothane seemed to be safe.¹³⁸ For Merin,¹³⁹ and in our experience, preoperative CCB treatment allows the use of halogenated anaesthetics. However, IV verapamil or diltiazem is not recommended in halothane or enflurane anaesthetized patients, especially when these patients present with cardiac failure or conduction disturbances.

Other anaesthetics

During high-dose narcotic anaesthesia IV, CCB are usually well tolerated. In dogs given fentanyl $150 \mu\text{g} \cdot \text{kg}^{-1}$ ¹⁴⁰ or $500 \mu\text{g} \cdot \text{kg}^{-1}$,¹⁴¹ or alfentanil $160 \mu\text{g} \cdot \text{kg}^{-1}$,¹⁴² injection of CCB caused no deleterious effects but serum diltiazem levels greater than $1000 \text{ ng} \cdot \text{ml}^{-1}$ induced auriculo-ventricular blocks. In dogs receiving fentanyl $150 \mu\text{g} \cdot \text{kg}^{-1}$, IV nifedipine $20 \mu\text{g} \cdot \text{kg}^{-1}$ caused a decrease in arterial pressure and a tachycardia which led to myocardial ischaemia.¹⁴³ In dogs with critical coronary constriction, receiving similar fentanyl anaesthesia, verapamil decreased coronary perfusion pressure and increased heart rate leading to a reduction in systolic function and to early diastolic dysfunction.¹⁴⁴ In CAD patients with good LV function during high-dose fentanyl anaesthesia, verapamil $75\text{--}150 \mu\text{g} \cdot \text{kg}^{-1}$ IV was well tolerated.¹⁴⁵ No pharmacokinetic interaction has been reported with narcotics.¹⁴¹

Barbiturates decreased the calcium uptake from sarcoplasmic reticulum,¹⁴⁶ and most general anaesthetics inhibited Na-Ca exchange at the sarcolemma.¹⁴⁷ However, Pierrot *et al.*¹⁴⁸ injected diltiazem $0.15 \text{ mg} \cdot \text{kg}^{-1}$ IV in swine anaesthetized with thiopentone $100 \text{ mg} \cdot \text{kg}^{-1}$ and observed only a transient decrease in arterial pressure without any change in cardiac output.

The combination of CCB and local anaesthetics can enhance their cardiac toxicity. This was demonstrated in dogs with diltiazem or verapamil associated with lidocaine,¹⁴⁹ and with nifedipine associated with bupivacaine.¹⁵⁰ Though verapamil did not modify lidocaine kinetics,¹⁵¹ lidocaine decreased serum verapamil levels by increasing the initial volume of distribution and verapamil total clearance.¹⁵²

Neuromuscular relaxants

Potential of succinylcholine or pancuronium muscle relaxation by CCB has been observed in cats¹⁵³ and rats.¹⁵⁴ Calcium-channel blockers decreased the magnitude of the twitch or the vecuronium dosage necessary to obtain a 50 per cent reduction of twitch.¹⁵⁵ In a rat phrenic-hemidiaphragm preparation, Salvador *et al.*¹⁵⁶ showed substantial potentiation of succinylcholine by diltiazem or verapamil, and a potentiation of pancuronium by nicardipine. The interaction site may be the

cholinergic post synaptic membrane.¹⁵⁴ These interactions were not found in man^{157,158} possibly because smaller concentrations were used.

Perioperative use

Myocardial ischaemia

While a large number of studies reported the value of prescribing beta-blockers before anaesthesia to prevent myocardial ischaemia¹⁵⁹ the answer is still unclear for CCB. The recurrence of angina pectoris 24 hr after discontinuing CCB has been reported.¹⁶⁰ The administration of nifedipine until the day of CABG surgery was accompanied by the need for more inotropic support but less vasodilatation therapy after cardiopulmonary bypass compared with patients who had received their last dose of nifedipine the day before surgery.¹⁶¹ Conversely, the continuation of diltiazem until anaesthesia did not introduce haemodynamic differences compared with a control group.¹⁶² In spite of continuing verapamil and nifedipine until surgery, tachycardia occurred during laryngoscopy in CAD patients.¹⁶³ Three prospective studies attempted to define the role of CCB administered until surgery to prevent myocardial ischaemia during CABG surgery.^{164–166} Slogoff and Keats¹⁶⁴ in 444 patients observed significantly more ischaemic episodes in patients administered no treatment or only CCB prior to surgery than in patients administered beta-blockers associated or not with CCB. Chung *et al.*¹⁶⁵ confirmed these findings in 92 patients. Tuman *et al.*¹⁶⁶ studied 803 patients given either beta-blocker, CCB or no treatment prior to surgery. Although the CCB patients presented with greater LV dysfunction before surgery, the incidence of perioperative myocardial infarction and ischaemia was significantly greater in the control group than in the CCB group, and in the CCB group than in the beta-blocker group. The mortality rate, however, was similar between the groups. In these three studies, CCB seemed to prevent ischaemia less than beta-blockers. However, these studies were not randomized and the groups' sizes were unequal. As tachycardia was correlated with ischaemic episodes¹⁶⁴ the inclusion of patients administered different CCB in the CCB groups could have led to methodological bias. Henling *et al.*¹⁶⁷ showed that the preoperative administration of beta-blocker with CCB was not accompanied by a greater incidence of conduction disturbances.

In two randomized studies,^{168,169} diltiazem $0.15 \text{ mg} \cdot \text{kg}^{-1}$ IV followed by a continuous infusion of $3\text{--}5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ started before induction of anaesthesia and continued till 3–12 hr after tracheal extubation in CAD patients undergoing non-cardiac surgery decreased the incidence of ischaemic episodes and was accompanied by

few cardiovascular side-effects. Intravenous bepridil or sublingual nifedipine resolved coronary artery spasm, especially during CABG surgery,^{170,171} and sublingual nifedipine 10 mg reduced the vascular resistance of venous coronary graft.¹⁷²

Hypertension

The efficacy of CCB to prevent or to treat perioperative hypertensive episodes has been widely reported. Verapamil $0.1 \text{ mg} \cdot \text{kg}^{-1}$ IV¹⁷³ or sublingual nifedipine 10 mg^{174,175} prevented the laryngoscopy pressor response without effect on heart rate. Calcium-channel blockers have been used to induce controlled hypotension during surgery. Zimpfer *et al.*¹⁷⁶ administered verapamil $0.07 \text{ mg} \cdot \text{kg}^{-1}$ IV during neuroleptanalgesia; arterial pressure decreased by 10–20 per cent during the first ten minutes due mainly to a decrease in SVR. Nicardipine IV decreased arterial pressure to 50–60 mmHg in hip surgery. This was accompanied by a decrease in SVR and an increase in cardiac output.¹⁷⁷ Kishi *et al.*¹⁷⁸ administered nicardipine (1–2 mg IV) to control hypertensive episodes in vascular surgery and observed no change in right and left filling pressures and in heart rate. Nifedipine seemed effective but its light sensitivity complicates its use.¹⁷⁹ Van Wezel *et al.*¹⁸⁰ compared verapamil, nifedipine and nitroglycerine IV to maintain arterial pressure less than 120 per cent of control in CABG surgery. Nifedipine and nitroglycerine were well tolerated but verapamil increased the PQ interval, pulmonary artery, and pulmonary capillary wedge pressures. Intravenous nicardipine was used in the management of pheochromocytoma.¹⁸¹ Its effects seemed due to α_2 post synaptic blockade and inhibition of catecholamine release from the tumour.¹⁸² Also, CCB have been used to control postoperative hypertension. Intranasal nifedipine 10 mg controlled hypertension after carotid endarterectomy in 13 of 14 patients, a second administration being effective in the last patient. This was accompanied by an increase in cardiac index and mixed venous oxygen saturation and a decrease in pulmonary capillary wedge pressure.¹⁸³ Mullen *et al.*¹⁸⁴ compared IV diltiazem, intranasal nifedipine and IV sodium nitroprusside to treat hypertension after CABG surgery. The dosages necessary to obtain equivalent effects on arterial pressure were respectively $150\text{--}300 \mu\text{g} \cdot \text{kg}^{-1}$, 20–50 mg and $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Heart rate and MVO_2 decreased only with diltiazem. Indices of LV systolic function were reduced by diltiazem or nifedipine but not by sodium nitroprusside. Only sodium nitroprusside decreased myocardial lactate uptake. Intravenous nicardipine $12.5 \text{ mg} \cdot \text{hr}^{-1}$ was efficient in 44 out of 47 patients in less than 15 min followed by a $3 \text{ mg} \cdot \text{hr}^{-1}$ infusion.¹⁸⁵ In our experience, nicardipine

appears easier to administer than sodium nitroprusside. Nicardipine did not change heart rate and did not elicit rebound hypertension at discontinuation, presumably due to stable plasma norepinephrine levels and longer biological half-life.^{186,187} The efficacy of nicardipine in reducing blood pressure was similar to that of nitroglycerine but unlike nitroglycerine, nicardipine did not reduce the preload, thus it increased cardiac index.¹⁸⁸

Arrhythmias

Intravenous verapamil or diltiazem has been used to treat supraventricular tachyarrhythmias during¹⁸⁹ or after¹⁹⁰ surgery, with few cardiovascular untoward effects. However, cardiac depression or auriculo-ventricular conduction disturbances may occur when CCB are associated with beta-blockers.^{191,192}

Malignant hyperthermia

Experimental data suggested that CCB could prevent malignant hyperthermia.¹⁹³ Unfortunately, the combination of dantrolene with verapamil caused cardiovascular collapses in swine¹⁹⁴ and man.¹⁹⁵

Conclusion

Like beta-blockers, CCB were initially used exclusively by cardiologists. They are now at the disposal of anaesthetists and intensive care physicians, especially since the development of IV preparations. As these drugs have profound effects on the cardiovascular system, extensive knowledge and understanding of their effects, including their interactions with anaesthetic agents, must lead to a more efficient and safer use.

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