Calcium-channel blockers

Important information
This article provides a general summary about the actions and uses of calcium channel blockers. Always check the British National Formulary, particularly for indications, dosages, side effects and contraindications. [1]

What are calcium-channel blockers? [1]

Calcium-channel blockers (CCBs) were developed in the 1970s and are now widely used.

Mode of action

CCBs all inhibit inward movement of calcium ions through the slow channels of active membranes, especially in:

- **Cells of the myocardium** (negative inotropic effect/myocardial depression).
- **Cells within the His-Purkinje system of the heart** (impairment of atrioventricular conduction).
- **Cells of vascular smooth muscle** (dilatation of coronary and peripheral arteries).
- **Cells of the myometrium** (reduce uterine contractile activity)

There are important differences between verapamil hydrochloride, diltiazem hydrochloride, and the dihydropyridine calcium-channel blockers (amlodipine, felodipine, lacidipine, lercanidipine hydrochloride, nicardipine hydrochloride, nifedipine, and nimodipine). Calcium channel blockers (except amlodipine), should be avoided in heart failure as they can further depress cardiac function and exacerbate symptoms. There are three subclasses of CCB:

Dihydropyridine CCBs

- **Nifedipine** - relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than verapamil, and, unlike verapamil, has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work. Nifedipine can be used for Raynaud's syndrome, angina, hypertension, postponement of premature labour, hiccup in palliative care, and for chronic anal fissure (topical ointment). Longer-acting preparations should only be used for hypertension and angina (rarely).
- **Nicardipine** - has similar effects to nifedipine and may produce less reduction of myocardial contractility. Nifedipine, nicardipine hydrochloride, amlodipine, and felodipine are used for angina or hypertension. All are valuable in forms of angina associated with coronary vasospasm.
- **Intravenous nicardipine** is licensed for the treatment of acute life-threatening hypertension (eg, malignant hypertension or hypertensive encephalopathy), aortic dissection (when a short-acting beta-blocker is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective), severe pre-eclampsia, when other intravenous anti-hypertensives are not recommended or are contra-indicated, and for postoperative hypertension.
- **Amlodipine** and **felodipine** - are also similar to nifedipine and do not adversely affect myocardial contractility (with the risk of heart failure). They have a longer duration of action than nifedipine, making them useful in hypertension and angina. All are valuable in angina associated with coronary vasospasm. Side-effects relate to vasodilatation and may improve after a few days (headache, flushing).
- **Lacidipine**, **lercanidipine,** and **isradipine** - again, are similar in effect to nifedipine but are only indicated for hypertension.
- **Nimodipine** - is similar to nifedipine but has an enhanced, selective effect on the cerebral arteries. This makes it useful for cerebral artery spasm and it is used solely for this purpose after subarachnoid haemorrhage (to prevent ischaemic deficit).

Side-effects of all dihydropyridine CCBs relate to vasodilatation and may improve after a few days (headache, flushing). Ankle swelling, which may only partly respond to diuretics, is also common.

Phenylalkylamine CCBs

These are used in angina and effects include reduced myocardial oxygen demand and reversal of coronary vasospasm with minimal peripheral vasodilation. Examples include:

- **Verapamil** - is very negatively inotropic. However, it also impairs atrioventricular conduction, so slowing heart rate and lowering blood pressure. It is a 'rate-limiting' CCB. Verapamil is used for angina, hypertension, and arrhythmias. It is highly negatively inotropic and reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with beta-blockers. Verapamil may also be considered for prophylaxis of cluster headaches (unlicensed use)

Benzothiazepine CCBs

These are intermediate between the above two and have both cardio-depressant and vasodilatory effects. Examples include:

- **Diltiazem** - effective in most forms of angina. The longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. However, because of the risk of bradycardia it should be used with caution in association with beta-blockers.

Efficacy

Angina

- CCBs, along with beta-blockers, are first-line treatment for stable angina.[2]
- Consensus that CCBs are effective in reducing symptoms in stable angina.[3]

- No significant differences, compared with beta-blockers, in frequency of angina, exercise duration, mortality and quality of life.[3]

- Exercise-induced angina is more effectively reduced with amlodipine than atenolol, and the combination is even better.[3]

Hypertension

- Lowering blood pressure prevents strokes and coronary heart disease.[4] CCBs are a key therapeutic choice in the major guidelines for the treatment of hypertension.

Raynaud's disease

- Nifedipine is the mainstay of medical treatment.

- Nifedipine has been shown to reduce frequency and severity of attacks in primary Raynaud's disease but is associated with expected adverse effects (see 'Common adverse effects', below).[5]

- The evidence base for amlodipine and diltiazem is not strong.

Supraventricular arrhythmias

- Intravenous verapamil and diltiazem have been found equally effective at reducing heart rate at 10 or 30 minutes compared with placebo in atrial flutter and atrial fibrillation but use of verapamil could be limited by hypotension.[6] [7]

Tocolysis

- Most experience of CCBs to prevent premature labour has been with nifedipine.[8]

- Compared with betamimetics, CCBs are more effective at postponing birth, with fewer side-effects for women and some short-term benefits for the baby.[9] CCBs may have benefits over oxytocin receptor antagonists and magnesium sulphate but further research is required.

- No CCB is licensed for tocolysis.

Cluster headache

- Verapamil is used (unlicensed indication) to help reduce the severity of cluster attacks and there seems consensus from patient groups and clinicians that it is useful. It has been reported to cause bradycardia and atrioventricular block so further research is needed. [10]

Common adverse effects of calcium-channel blockers

These can be predicted from the type of CCB and mode of action, as already illustrated. Examples include:

Myocardial effects

- Hypotension.
- Heart failure.

Conduction effects

- Heart block.
- Arrhythmias.

Vascular smooth muscle

- Flushing.
- Oedema.
- Headaches.
- Rashes.

Other effects

- Constipation.
- Rashes.
- Gynaecomastia.
- Photosensitivity.

Cautions and contra-indications

Again, these can be predicted from the type of CCB and mode of action. Individual drug monographs need to be reviewed. Some examples include:

- Cardiovascular: shock, unstable angina, significant aortic stenosis, bradycardia, heart failure, etc.
- Avoidance of grapefruit juice with felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil. This may affect metabolism.
- Sudden withdrawal of CCBs may exacerbate angina.

These are best considered under each individual drug.

Monitoring and follow-up

This will be determined largely by the condition being treated. Blood pressure and electrocardiography monitoring may be warranted but are best decided upon an individual basis.

Further reading

- Angina; NICE CKS, October 2022 (UK access only)
- CKS Hypertension; NICE CKS, March 2023 (UK access only)
- Raynaud's phenomenon; NICE CKS, November 2022 (UK access only)

References

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