

role of **CALCIUM CHANNEL BLOCKERS** in **HYPERTENSION**

KEY POINTS

- Thiazides are appropriate initial therapy for most people with hypertension.
- Choice of other antihypertensives is decided by individual patient factors.
- Factors which potentially favour use of calcium channel blockers include arrhythmia (verapamil only), angina, older age and high risk of stroke.
- Factors which may weigh against the use of calcium channel blockers include potential drug interactions, and diltiazem and verapamil are contraindicated in heart block and heart failure.
- Choice between the different calcium channel blockers depends on patient tolerability, co-morbidity and drug interactions.

Factors favouring use of calcium channel blockers:

- Hypertension with co-morbid angina
- Hypertension with co-morbid arrhythmia (verapamil only)
- Elderly people
- People with an increased risk of stroke
- Verapamil and diltiazem may be alternatives to beta blockers for secondary prevention post myocardial infarction if beta blockers are contraindicated or not tolerated.²

THIAZIDES ARE APPROPRIATE INITIAL THERAPY FOR MOST PEOPLE WITH HYPERTENSION

There is limited evidence of superiority of one antihypertensive over another but evidence suggests that for most patients, diuretics can be considered first, based on their effectiveness, safety and low cost.

CHOICE OF ADDITIONAL ANTIHYPERTENSIVES IS DECIDED BY INDIVIDUAL PATIENT FACTORS

Other agents may be chosen for individual patients based on concurrent medical conditions, patient tolerability and drug interactions. Indications for treatment with different antihypertensive agents are discussed in BPJ 6 (June 2007).

FACTORS FOR AND AGAINST THE USE OF CALCIUM CHANNEL BLOCKERS

Factors that potentially favour the use of calcium channel blockers include arrhythmia (verapamil only), angina, or high risk of stroke. Verapamil can also be used post myocardial infarction if beta blockers are contraindicated or not tolerated. In addition, calcium channel blockers may be more suitable than other agents for elderly people and those of African descent.¹

There is some evidence of a superior protective effect of calcium channel blockers in people with a high risk of stroke when compared with other antihypertensives.²

Calcium channel blockers have a favourable effect for treating hypertension with co-existing angina. Verapamil may have a favourable effect when co-existing arrhythmia is present.



Age and ethnicity have less influence on the antihypertensive effect of calcium channel blockers compared with other agents (e.g. ACE inhibitors) and this may present a benefit for calcium channel blocker use in elderly patients.² The National Institute for Health and Clinical Excellence (NICE) issued an updated hypertension guideline in June 2006 which states that calcium channel blockers are a first line alternative to thiazide diuretics in hypertensive patients over 55 years.³

Factors, which may weigh against the use of calcium channel blockers include potential drug interactions, and diltiazem and verapamil are contraindicated in heart block and heart failure.

CHOICE BETWEEN CALCIUM CHANNEL BLOCKERS

Few studies have directly compared calcium channel blockers and choice may be largely based on patient tolerability, comorbidity and interaction profile.

Calcium channel blockers vary in their site of action and therapeutic effect

All calcium channel blockers block the inward flow of calcium ions into cells in vascular smooth muscle, myocardial cells, and cells within the sino-atrial (SA) and atrioventricular (AV) nodes.

Dihydropyridines (amlodipine, felodipine, isradipine, and nifedipine) act mainly on vascular smooth muscle and have minimal effect on normal myocardial cells; therefore their main effect is vasodilation. Their minimal effect on the SA or AV nodes means they are not rate-limiting agents.

Isradipine and MIDAS study concerns.

The MIDAS study published in 1996 was designed to compare the effects of normal release (short acting) isradipine with hydrochlorothiazide on atherosclerosis progression in patients with hypertension. An incidental finding was the higher rate of major cardiovascular events in the isradipine group compared with the hydrochlorothiazide group (25/442 vs 14/441; $P=0.07$). Apart from not reaching statistical significance other factors mitigate against concerns about the use of Dynacirc SRO for hypertension. Firstly, MIDAS was not designed to detect differences in clinical events or outcomes and these findings were incidental. Secondly in MIDAS, normal release isradipine (short acting) was given twice daily and in general short acting dihydropyridines (including nifedipine) have been associated with increased cardiovascular events in several trials and meta-analyses. Dynacirc SRO is formulated to provide a long duration of action similar to felodipine. Subsequent studies using longer-acting calcium channel blockers have shown better cardiovascular outcomes compared with shorter-acting agents.

The dihydropyridines are mainly used for hypertension and angina and common side effects are associated with vasodilatation, such as flushing, headache, and ankle swelling.

Benzothiazepines (diltiazem) and phenylalkylamines (verapamil) have less selective effect on vascular smooth muscle and have greater cardiac effects. They act on the myocardium to reduce contractility and heart rate and are used in angina and hypertension, but should not be used in heart failure. Verapamil has greater selectivity for cardiac tissue than diltiazem and therefore has more cardiac effects and is also used for arrhythmias.^{4, 5, 6}

Choice of dihydropyridine may depend on patient preference

The dihydropyridines are similar in therapeutic effect and the choice between them may depend on patient preference. Long-acting preparations are preferred to short-acting agents which can cause reflex tachycardia and are not suitable for long term treatment of hypertension. Dihydropyridines are either formulated as long-acting preparations such as felodipine, isradipine or nifedipine or inherently long acting such as amlodipine.

Rate-limiting calcium channel blockers may be chosen based on co-morbid conditions

Verapamil and diltiazem are also indicated for use in hypertension and can be considered in patients who have co-existing conditions that would benefit from these agents such as verapamil in patients with co-existing arrhythmias. They are not appropriate in heart failure or heart block, although dihydropyridines can be used with these conditions.

Verapamil and diltiazem are also associated with a number of drug interactions. Co-administration with simvastatin may significantly increase the plasma concentration of simvastatin and potentiate the risk of statin-induced myopathy. Verapamil also significantly increases the plasma concentration of atorvastatin when used in combination. These reactions are less likely with the dihydropyridine group of calcium channel blockers and this should be considered when selecting a calcium channel blocker.

Review concurrent drug therapy when implementing any of the calcium channel blockers.

References

1. Grossman E, Messerli F. Calcium Antagonists. *Prog Cardiovasc Dis* 2004; 47 (1): 34-47
2. Epstein B, Vogel K, Palmer B. Dihydropyridine Calcium Channel Antagonists in the Management of Hypertension. *Drugs* 2007; 67 (9): 1309-1327
3. National Institute for Health and Clinical Excellence. Clinical Guideline: Hypertension: Management of hypertension in adults in primary care. June 2006. <http://www.nice.org.uk/nicemedia/pdf/HypertensionGuide.pdf> Accessed October 2007.
4. Australian Medicines Handbook. Australian Medicines Handbook Pty Ltd. July 2006
5. British National Formulary (BNF). BMJ Publishing Group and Royal Pharmaceutical Society of Great Britain. September 2007
6. Sweetman SC (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, (Edition 2007).
7. Luscher T, Cosentino F. The Classification of Calcium Antagonists and their Selection in the Treatment of Hypertension. *Drugs* 2006; 55 (4): 509-517
8. Thomas S. Hypertension. In: Walker R, Whittlesea C, editors. *Clinical Pharmacy and Therapeutics* (4th Ed.) Edinburgh: Churchill Livingstone Elsevier, 2007: 265-279

COMPARISON OF CALCIUM CHANNEL BLOCKERS

Adapted from Lusher⁷ and Thomas.⁸

Drugs	Group	Indications	Special considerations	Major adverse effects	Comments
Amlodipine Felodipine Isradipine Nifedipine	Dihydropyridines <i>Greater vascular than cardiac tissue selectivity</i>	Hypertension Angina (except isradipine which is only indicated for hypertension)	Less drug interactions with this group but some are significant including the interaction with grapefruit juice	Flushing Oedema Postural hypotension Headache	Similar efficacy to thiazides Recent studies suggest favourable effect in reducing stroke May be beneficial for elderly
Diltiazem	Benzothiazepine <i>Equal vascular and cardiac tissue selectivity</i>	Angina Hypertension	Contraindicated in heart block & heart failure	Bradycardia Heart block	Caution required when used in combination with beta-blocker
Verapamil	Phenylalkylamine <i>Vascular tissue selectivity less or equal to cardiac</i>	Angina Hypertension Arrhythmias Post MI if beta-blockers are unsuitable	Contraindicated in combination with a beta-blocker and in heart block & heart failure	Bradycardia Heart block Constipation	May be suitable for patients with ischaemic heart disease who are unable to tolerate beta-blockers