Specialist Information and Advisory Services

A Summary of Calcium Channel Blocker Preparations With an Update on their Use in the Management of Hypertension and Angina in Elderly Patients

This Information has been prepared for the use of healthcare professionals, and should be used in conjunction with official sources of information such as the BNF and manufacturer's SPCs.

Authors:	Date of Preparation:	Version:	Planned Review Date:
J Kuczynska / G Lewis	November 2000	2	July 2001

South West Medicines Information and Training, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW Tel: 0117 9282867 Fax: 0117 9283818 E-mail:swmi@ubht.swest.nhs.uk

Calcium Channel Blockers

Drug	Half-Life (h)	Comments	Indications	Preparations	Licensed for:		Dose Interval	Approx. Cost Per 28 Days
					Hypertension	Angina		
Amlodipine	36	* Gradual onset & prolonged duration of action * Fewer early vasodilator side-effects i.e. abrupt fall in BP * Lack of clinically important increase in cardiac or peripheral sympathetic activity (reflex tachycardia) * Shown to be safe in patients with moderate to severe heart failure (NYHA II-III) (PRAISE trial) * Dose reduction needed in elderly patients * Third generation calcium channel blocker	Hypertension Angina	**ISTIN** 5, 10mg	Y	Y	24 hrs	£11.85 - 17.70
Diltiazem	4-7	* Slows heart rate but does not completely abolish the increase in heart rate during mild exercise * Depresses cardiac conduction * Avoid in heart failure * Avoid concurrent beta-blockers unless specialist supervision * Interacts with digoxin (increased plasma levels, possible risk of bradycardia)	Hypertension Angina	**GENERIC** 60mg	Y	Y	8 hrs	£6.27 - 12.54
				ADIZEM-SR 90,120,180mg	Y	Y	12 hrs	£10.56 - 17.60
				ADIZEM-XL 120, 180, 240, 300 mg	Y	Y	24 hrs	£12.90 - 10.24
				ANGITIL SR 90,120, 180mg	Y	Y	12hrs	£8.45 - 14.08
				ANGITIL XL 240, 300mg	Y	Y	24 hrs	£10.15 - 9.22
				CALCICARD CR 90, 120mg	Y	Y	12 hrs	£11.06 - 18.43
				DILZEM SR 60, 90, 120mg	Y	Y	12 hrs	£11.23 - 22.46
				DILZEM XL 120, 180, 240mg	Y	Y	24 hrs	£11.40 - 22.80
				SLOZEM 120, 180, 240mg	Y	Y	24 hrs	£8.20 - 15.60
				TILDIEM 60mg	N	Y	8 hrs	£8.28 - 20.61
				TILDIEM LA 200, 300mg	**Y**	Y	24 hrs	£12.80 - 24.41
				TILDIEM RETARD 90, 120mg	Y	Y	12 hrs	£9.95 - 22.12
				VIAZEM XL 120, 180, 240, 300, 360mg	Y	Y	24hrs	£9.22
				ZEMTARD 120XL, 180XL, 240XL, 300XL	Y	Y	24hrs	£18.24 - 40.52

Felodipine	8	*Highly vascular selective *Second generation calcium channel blocker *Fluctuating antihypertensive effects over 24 hours *No clinical benefit in patients with CHF previously receiving enalapril or diuretics	Hypertension Angina	**PLENDIL** 2.5, 5,10mg	Y	Y	24 hrs	£6.09 - 10.92
Isradipine	7-8	*Second generation calcium channel blocker	Hypertension	**PRESCAL** 2.5mg	Y	N	12 hrs	£12.53 - 50.12
Lacidipine	7	* Gradual onset & prolonged duration of action * Fewer early vasodilator side-effects i.e. abrupt fall in BP * Lack of clinically important increase in cardiac or peripheral sympathetic activity (reflex tachycardia) * Shown to be safe in a short term haemodynamic study in patients with mild to moderate heart failure * Third generation calcium channel blocker	Hypertension	**MOTENS** 2, 4mg	Y	N	24 hrs	£10.23 - 25.53
Lercanidipine	2-5h	*Highly lipophilic, binds to cell membranes. This allows prolonged duration of action & once daily dosing * Effects on heart rate reported as minimal * Similar in efficacy to other antihypertensives * Third generation calcium channel blocker	Hypertension	**ZANIDIP** 10mg	Y	N	24hrs	£9.74 - 19.48
Nicardipine	4-8	*Increases plasma digoxin levels *First generation calcium channel blocker	Hypertension Angina	**CARDENE** 20, 30mg **CARDENE SR** 30, 45mg	Y Y	Y N	8 hrs 12 hrs	£12.57 - 19.46 £9.68 - 19.36

Nifedipine	3-4	* May increase plasma digoxin levels * Short-acting preparations should be avoided. * Reflex tachycardia may compromise failing myocardial function - avoid in heart failure. * Avoid post MI	Hypertension Angina	****GENERIC** 5,10mg* **ADALAT** 5, 10mg* **ADALAT LA 20,** 30, 60mg, **ADALAT RETARD** 10,20mg **ADIPINE MR** 10, 20mg **ANGIOPINE MR** 10mg, 20mg **ANGIOPINE 40 LA** **CARDILATE MR** 10mg, 20mg **CORACTEN SR** 10, 20mg **CORACTEN XL** 30, 60mg **FORTIPINE LA** 40mg **HYPOLAR RETARD 20** **NIFEDOTARD 20MR** 20mg **TENSIPINE MR** 10, 20mg **UNIPINE XL 30mg** *also licensed for Raynaud's phenomenon. **Information on licensed indications is based on the licensed indications for Adalat	N N Y Y Y Y Y Y Y Y Y Y Y Y Y Y	Y*** Y*** Y Y Y Y N Y Y Y Y Y Y Y N *** see BNF	8 hrs 8 hrs 24 hrs 12 hrs 12 hrs 12 hrs 24 hrs 12 hrs 12 hrs 24hrs 24 hrs 12 hrs 12hrs 12 hrs 24hrs	£5.13 - 12.72 £5.67 - 14.45 £8.15 - 25.29 £8.50 - 20.40 £8.26 - 16.52 £6.24 - 15.40 £8.65 - 17.30 £6.93 - 20.55 £6.67 - 18.61 £6.73 - 16.74 £7.46 - 14.93 £12.81 - 25.62 £10.62 - 21.24 £7.62 - 19.02 £9.51 - 19.02
Nisoldipine	7-12* see comments	The formulation is designed to provide uniform plasma drug conc. throughout 24 hours. Interacts significantly with grapefruit juice (doubling of AUC of nisoldipine). Short duration comparative studies showed similar efficacy to other antihypertensives but a higher incidence of ADRs leading to discontinuation, compared with amlodipine. Undergoes extensive metabolism by hepatic cytochrome p450 enzymes.	Hypertension Angina	**SYSCOR MR** 10, 20, 30mg	Y	Y	24 hrs	£9.36 -26.21

Verapamil	3-7	* Interacts with digoxin (increased plasma levels & risk of bradycardia and AV block) * Greater effect on cardiac conduction & contractility than diltiazem * Avoid in patients with heart failure, AV block, sinoatrial disease, marked bradycardia * IV verapamil can cause hypotension & asystole when given to patients on beta blockers * Combination of oral verapamil and oral beta blockers should be avoided. May precipitate AV block and cardiac failure. * Causes constipation	Hypertension Angina Supra-Ventricular Tachycardia	**GENERIC** 40, 80, 120, 160mg **CORDILOX** 40, 80, 120mg* **CORDILOX 160** **SECURON*** 40, 80, 120mg **HALF-SECURON SR** 120mg **SECURON SR** 240mg **UNIVER** 120, 180, 240mg **VERAPRESS MR** 240mg **VERTAB SR** 240mg *also licensed for supraventricular arrhythmias	Y Y Y Y Y Y Y Y Y	Y Y N Y Y Y Y Y Y	8-12 hrs 8-12 hrs 12 hrs 8-12 hrs 12-24 hrs 12-24 hrs 24 hrs 12-24 hrs 12-24hrs	£3.87 - 12.51 £7.68 - 15.43 £12.77 £7.67 - 14.32 £6.82 - 13.64 £10.64 - 21.28 £7.51 - 24.48 £13.50 - 27.00 £8.63 - 17.26

Prices are based on MIMS December 1999, BNF No. 38 September 1999 and Drug Tariff January 2000
NB: Check latest Tariff for generic prices “Prices are volatile …..”

Notes

Properties of calcium channel blockers

- The ***dihydropyridines*** - *amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine* - cause vasodilation by reducing calcium influx in vascular smooth muscle. They are relatively selective for the peripheral vasculature and have negligible effect on cardiac contractility & cardiac conduction.

- ***Verapamil*** produces less peripheral vasodilation but causes depression of myocardial contractility and of the cardiac conduction system (especially at the AV node). The actions of ***diltiazem*** are intermediate between verapamil and the dihydropyridines

Adverse effects of calcium channel blockers

- Minor vasodilatory side-effects of all *dihydropyridines* include flushing, headache and dizziness. Short-acting calcium channel blockers (CCB) also produce significant fluctuations in BP and heart rate. The incidence of these important adverse effects is significantly less with long-acting drugs or long-acting formulations.

- All CCB can cause severe ankle and pedal oedema as a late-onset side-effect. This is worse with the dihydropyridines. Dose reduction or changing to another class of CCB may help, but diuretics are of little or no benefit, as this is a localised oedema that does not reflect generalised fluid retention. Reflux oesophagitis is another troublesome side-effect common to all CCB, caused by a reduction in lower oesophageal sphincter pressure

- Recent studies have linked CCB with cancer and gastrointestinal (GI) haemorrhage but the results have been conflicting. The latest analysis of data from the original study of CCB and GI haemorrhage found that the use of CCB does not materially increase the risk of upper GI bleeding. Another recent case control study has confirmed this. Further data are needed before firm conclusions can be reached on the risk of cancer with CCB.

Calcium channel blockers after myocardial infarction

- *Dihydropyridine* CCB should not be given to patients with a recent myocardial infarction (MI). It has been shown that immediate-release formulations of nifedipine may be harmful. Although the new long-acting dihydropyridines cause fewer reflex sympathetic effects eg tachycardia, they should not be used post MI until data are available to prove that they are effective in reducing mortality.

- In the late post myocardial infarction period***, verapamil*** has been shown to protect against reinfarction, in patients without heart failure and no history of heart failure in the acute phase. It can be considered an alternative to beta-blockers for prophylaxis of reinfarction. Whether ***diltiazem*** should be used post-MI is less clear.

Calcium channel blockers in angina

- In the prophylaxis of stable angina *dihydropyridines* can be combined safely with a beta-blocker but short-acting nifedipine is best avoided as it probably increases the risk of reinfarction or death in patients with symptomatic coronary disease .

- Calcium channel blockers are second-line drugs in the management of stable angina. They are indicated when beta-blockers are poorly tolerated, contra-indicated or ineffective.

- Trials in ischaemic heart disease suggest that in the absence of left ventricular dysfunction ***diltiazem*** or ***verapamil*** are preferred choices if a CCB is needed. ***Verapamil*** is contra-indicated in patients with heart failure or on concomitant beta-blockers. ***Diltiazem*** may be combined with beta-blockers under close medical supervision, but is contra-indicated in heart failure.

- Calcium channel blockers are preferred to beta-blockers for the treatment of angina caused by coronary artery spasm.

Calcium channel blockers in hypertension

- The efficacy of CCB (and ACE inhibitors) in preventing MI and stroke and reducing mortality in hypertension has not been studied.

- A recent case-control study in patients with hypertension found an approximately 60% greater risk of MI in patients taking short-acting CCB compared with a control group receiving beta blockers or diuretics. A prospective cohort study of elderly patients on different antihypertensive drugs found a small but significantly higher mortality in the nifedipine-treated group. In a case control study of hypertensive patients, the risk of an adverse cardiovascular event for patients taking short-acting CCB was eight times that for those taking long-acting ones. There is no clear evidence of an association between either intermediate or longer acting CCB and increased mortality.

- In recent studies in hypertensive patients with NIDDM, patients given the long-acting CCB ***nisoldipine*** were five times more likely to have a MI than patients treated with enalapril, and patients receiving fosinopril had a significantly lower risk of the combined outcome of acute MI, stroke or hospitalised angina than those receiving amlodipine. This further supports the use of ACE inhibitors in diabetic patients in preference to CCB.

- In hypertensive patients for whom agents proven to prevent MI and stroke (ie beta blockers and thiazides) are inadequate or inappropriate, an ACE inhibitor (or ***verapamil*** in ischaemic patients) as monotherapy, or added to a diuretic seem the safest current option.

Choice of preparation

- The choice of agent is complex given the large number of drugs and preparations

- For both hypertension and angina, verapamil or diltiazem are reasonable first choice agents in many patients. Diltiazem is often preferred as verapamil can cause constipation. Where these are unsuitable, long-acting dihydropyridines such as amlodipine, lacidipine, or sustained-action formulations of nifedipine eg nifedipine (GITS) are preferred. These can safely be combined with a beta blocker and give 24 hour control of BP in patients with hypertension.

- Amlodipine has been shown to be safe in patients with all grades of heart failure.

A recent review has classified CCB into first, second and third generation.

Group (tissue selectivity)	First generation	Second Generation		Third generation
		Novel Formulations	New Chemical Entities	
Dihydropyridine (artery> cardiac)	**Nifedipine** **Nicardipine**	**Nifedipine SR/ GITS** ***Felodipine ER** **Nicardipine SR**	**Isradipine** **Nimodipine** **Nisoldipine**	**Amlodipine** **Lacidipine** **?Lercanidipine**
Benzothiazepine (artery=cardiac)	**Diltiazem**	**Diltiazem SR**		
Phenylalkylamine(artery ≤cardiac)	**Verapamil**	**Verapamil SR**	**Gallopamil**	
Phenylalkylamine/ benzimidazolyl (artery>cardiac)	**Mibefradil****			
Notes	Rapid onset and short duration of action Negative inotropic and chronotropic effects (diltiazem and verapamil, in particular) Reflex sympathetic activation (fall in BP,tachycardia) (nifedipine)	Improved pharmacokinetic properties through the development of SR preparations(but some formulations may not be 100% bioavailable) New chemical entities(dihydropyridines) with improved pharmacokinetics and increased vascular selectivity Prolonged duration of action Fewer vasodilation-mediated adverse events Less influence on atrio-ventricular conduction Reduced negative inotropic and chronotropic effects		Long half-lives Interaction with specific high affinity binding sites in the calcium channel complex Gradual onset and prolonged duration of action Maintain therapeutic efficacy throughout 24 hours Lack of clinically relevant increase in cardiac or peripheral sympathetic activity Safe in heart failure(proven for amlodipine, some evidence for lacidipine)

(adapted from Ref.15)

* Felodipine may be classed either as a novel formulation or a new chemical entity

**Although the first drug of its chemical class, the pharmacokinetic and pharmacodynamic properties of mibefradil are those of a third generation agent.
NB Mibefradil has now been withdrawn

Calcium Channel Blockers in the Management of Hypertension and Angina in Elderly Patients

This is a controversial topic that is the subject of considerable debate amongst experts. The following review highlights recent clinical studies, guidelines and opinion in this area.

- Current hypertension management guidelines emphasise the need to tailor treatment to individual patients, rather than following a rigid 'stepped-care' approach. According to the latest British Hypertension Society guidelines, hypertension in elderly patients including isolated systolic hypertension (ISH) are compelling indications for thiazides. ISH in the elderly is a compelling indication for dihydropyridine calcium antagonists; elderly patients and angina are listed as possible indications for calcium channel blockers (CCB)[23]

- Trial evidence and expert opinion favour the use of thiazides in the elderly[24,25]

- On the basis of recent evidence ACE inhibitors should be preferred to CCB in patients with diabetes mellitus[26], heart failure or proven or suspected left ventricular dysfunction[27]

- In the management of angina the choice of therapy is more limited, therefore although they are not first line treatment, CCB are widely used in the management of angina and the dihydropyridines especially so if there is a degree of left ventricular dysfunction. Diltiazem or verapamil can be used as an alternative to beta-blockers[28]; diltiazem is more widely used as verapamil can cause constipation

- The results of the new meta-analysis[29] have not yet been published; it would be advisable to await publication before incorporating this information into any decision-making process. (The commentary in ref. 7 on the post hoc analysis of data from the Syst-Eur trial[30] is incorrect. It states that this is one of the studies which showed that CCB are not as effective in selected subgroups, whereas the study found that nitrendipine based antihypertensive treatment caused a greater reduction in overall mortality and mortality from cardiovascular disease in elderly diabetic patients with systolic hypertension, compared with non-diabetic patients[26,30].)

Recent major clinical trials of calcium channel blockers in hypertension which included elderly patients

Trial & reference	Protocol	Outcome measures	Results	Comments
STOP-Hypertension-2 study[31]	RCT in 6614 hypertensive pts aged 70-84 Conventional vs new antihypertensives	CV mortality	No difference in CV death, or stroke, MI + CV death between ACE inhibitors & CCB cf. diuretics & beta blockers	Subgroup analysis showed ACE inhibitors as superior to CCB in reducing risk for CCF [RR 0.78 (95% CI 0.63-0.97), p 0.025] and MI [0.77 (0.61-0.96),p0.02]
NORDIL[32]	Prospective, randomised, open, blinded-endpoint evaluation study, 10 881 hypertensive pts aged 50-74. Diltiazem vs diuretics, beta-blockers or both	Combined primary endpoint of fatal and non-fatal stroke, MI, and other CV death	All regimens equally effective in preventing all stroke, MI and other CV death	Marginally signif lower risk of stroke with diltiazem based therapy, RR 0.8(95% CI 0.65-0.99, p 0.04) Clinical relevance of this is uncertain
INSIGHT [33]	Prospective, randomised, double-blind trial in 6321 hypertensive pts aged 55-80. Nifedipine GITS vs co-amilozide	CV death, MI, HF or stroke	Both regimens equally effective in preventing overall CV or cerebrovascular complications	Marginally signif excess of HF (OR 2.2 (95% CI 1.07-4.49), p 0.028(non-fatal HF) and fatal MI [3.22 (1.18-8.8), p 0.017] with nifedipine-based treatment. Clinical importance uncertain
Syst-Eur [34]	RCT in 4695 pts with ISH aged > 60. Nitrendipine, combined or replaced with enalapril or HCTZ or both, vs placebo	Primary endpoint of fatal and non-fatal stroke	Active treatment decreased total incidence of stroke by 42%	Benefit of active treatment seen soon after randomisation, when most patients were still on monotherapy with nitrendipine

RCT= randomized controlled trial
RR = relative risk
OR = odds ratio
CV = cardiovascular
MI = myocardial infarction
CCF = congestive cardiac failure
HF = heart failure
ISH = isolated systolic hypertension
GITS = gastro-intestinal transport system
HCTZ = hydrochlorothiazide

References

1. Calcium antagonists: overused and inadequately assessed
Prescrire International 1996; 16(161): 304

2. Short-acting calcium channel blockers in hypertension - the debate continues
Pharm. J. 1996; 256: 644 (May 11)

3. Beevers DG & Sleight P
Short acting dihydropyridine (vasodilating) calcium channel blockers for hypertension: is there a risk?
BMJ 1996; 312: 1143 (May 4)

4. Calcium antagonists are not equivalent post - MI
Drugs & Therapy Perspectives 1996; 7(12): 5(Jun 24)

5. Freis ED & Papademetriou V
Current drug treatment and treatment patterns with antihypertensive drugs
Drugs 1996; 52: 1(July)

6. Psaty BM et al
The Risk of Myocardial Infarction Associated with Anthypertensive Therapies
JAMA 1995; 274 (8): 620-25

7. Choosing a Calcium Channel Blocker in Cardiovascular Disease
POM Vol 12 No 1 January 1998
S&W DIS (Southampton)

8. New Medicines on the Market
Information on New Drugs. Stage 4 .
Mibefradil. February 1998 North West DIS(Manchester)

9. Packer M et al
Effect of amlodipine on morbidity & mortality in severe chronic heart failure(PRAISE)
N.Eng.J.Med.1996; 335: 1107-14

10. Estacio RO et al
The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension
N.Eng.J.Med.1998; 338: 645-52

11. Pahor et al
Calcium channel blockade and incidence of cancer in aged populations
Lancet 1996; 348: 493-7

12. Jick H et al
Calcium-channel blockers and risk of cancer
Lancet 1997; 349: 525-8

13. Rosenberg L et al
Calcium channel blockers and the risk of cancer
JAMA 1998; 279: 1000-4

14. Alderman MH et al
Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients
Lancet 1997; 349: 594-8

15. Luscher TF & Cosentino F
The classification of calcium antagonists and their selection in the treatment of hypertension-a reappraisal
Drugs 1998; 55(4): 509-17

16. Nisoldipine modified-release: another long-acting calcium antagonist formulation
Drugs & Therapy Perspectives 1997;9:1-5

17. Safety of calcium-channel blockers
MeReC Bulletin 1998;9(4)::13-16

18. Kelly JP et al
Major upper gastrointestinal bleeding and the use of calcium channel blockers
Lancet 1999;353:559

19. Abascal VM et al
Calcium antagonists and mortality risk in men and women with hypertension in the Framingham Heart Study
Arch.Int.Med. 1998;158:1882-1886

20. Suissa S et al
Antihypertensive drugs and the risk of gastrointestinal bleeding
Am. J-Med. 1998,105:230-235

21. Tatti P et al
Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FALET) in patients with hypertension and NIDDM
Diabetes Care 1998;21:597-603

22. Psaty MB and Furberg CD
British guidelines on managing hypertension
BMJ 1999;319:589-590

23. British Hypertension Society. Guidelines for the Management of Hypertension 2000:
Brief Summary www.hyp.ac.uk/bhs

24. Kendall MJ
Conventional versus newer antihypertensive therapies – a draw
Lancet 1999; 354: 1744

25. Maxwell CJ et al
Nifedipine and mortality risk in the elderly: relevance of drug formulation, dose and duration
Pharmacoepidemiol.Drug Saf. 2000; 9: 11-24

26. Abernerthy DR and Schwarz JB
Drug therapy: Calcium-Antagonist Drugs
NEJM 1999; 341: 1447-57

27. Bronson DL
Conventional and newer antihypertensive drugs had similar efficacy in elderly people with hypertension
EBM 2000; 5: 85

28. North of England Stable Angina Guideline Development Group
North of England evidence based guidelines development project: Summary version of evidence based guideline for the primary care management of stable angina
BMJ 1996; 312: 827-32

29. Josefson D
Calcium channel blockers inferior to cheaper drugs
BMJ 2000; 321: 590

30. Toumilehto J et al
Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension
NEJM 1999; 340; 677-84

31. Hansson L et al
Comparison of effect of old and new antihypertensive drugs on cardiovascular mortality in elderly patients with hypertension: the Swedish Trial in Old Patients with Hypertension-2
Lancet 1999; 354: 1751-6 (commentary in EBM 2000; 5: 85)

32. Hansson L et al
Effects of calcium antagonists compared with diuretics and B-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study
Lancet 2000; 356: 359-65

33. Brown MJ et al
Morbidity and mortality in patients randomised to double-blind treatment with long-acting calcium-channel blocker or diuretic in the
Lancet 2000; 356: 366-72

34. Staessen JA et al
Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension
Lancet 1997; 350: 757-64