Amlodipine

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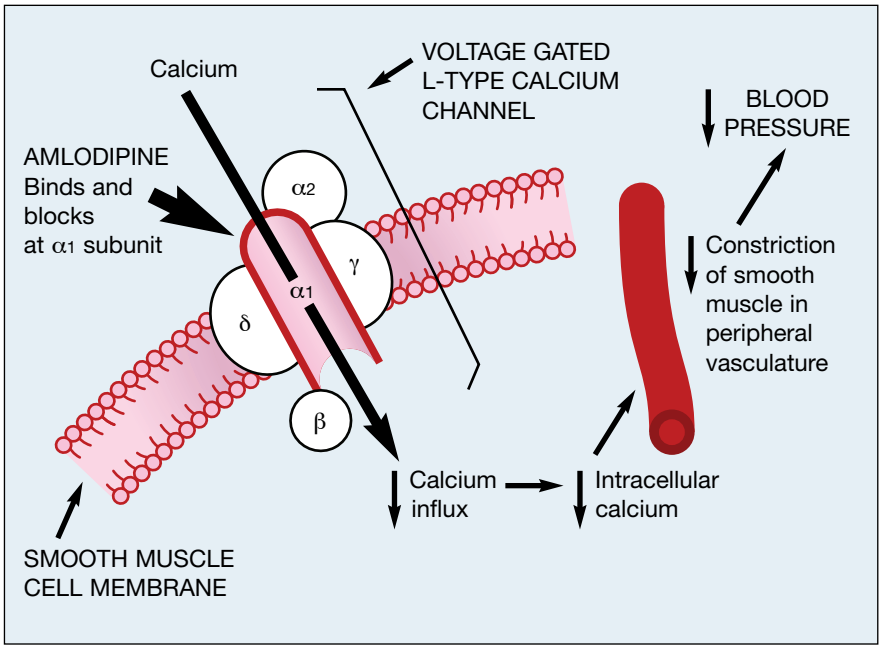
Introduction

Calcium channel blockers are classified as dihydropyridines or non-dihydropyridines depending on their chemical structure. Amlodipine has a dihydropyridine ring as part of its structure and is used both for its antihypertensive and anti-anginal properties. Several studies have sought to determine the efficacy of amlodipine in comparison to other commonly-used antihypertensives including two large studies with pre-defined subpopulations with diabetes.[1,2]

Pharmacology

Figure 1 outlines the pharmacological action of amlodipine. Amlodipine blocks voltage-gated L-type calcium channels by binding to their α_1-subunit and preventing the influx of calcium ions after depolarisation of the cell membrane. In contrast to the non-dihydropyridines it has a predilection for channels in smooth muscle, and most clinical benefit is derived from its vasodilating effects on the coronary and peripheral vasculature – its relative lack of effect on the myocardial calcium channels conferring inotropic stability. It has a long half-life (around 40 hours) and can therefore be given once daily. There has been interest in the potential role of amlodipine as an anti-atherogenic agent with *in vitro* studies suggesting biological effects such as lipid anti-oxidant activity, inhibition of smooth muscle cell proliferation and protection of the cell from cytokine-induced damage by molecules such as TNFα, all of which may be independent of calcium channel modulation.

Figure 1. Pharmacological action of amlodipine



Trials of safety and efficacy

The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) recruited 33 357 participants with hypertension and at least one other coronary heart disease risk factor (including diabetes).[1] Participants were randomised to receive chlorthalidone (12.5–25mg daily), amlodipine (2.5–10mg daily) or lisinopril (10–40mg daily). Target blood pressure was 140/90mmHg and further open-label antihypertensives were added to achieve this. The primary outcome of combined fatal coronary heart disease and non-fatal myocardial infarction occurred in 2956 participants over six years with no difference between treatments (11.5% chlorthalidone *vs* 11.3% amlodipine *vs* 11.4% lisinopril). The secondary outcomes of all-cause mortality did not differ between treatments, but the incidence of combined cardiovascular disease, stroke and heart failure was higher for lisinopril *vs* chlorthalidone and the incidence of heart failure higher for amlodipine *vs* chlorthalidone. The investigators concluded that thiazide-like diuretics should be used as first-line because of improvement in some of the secondary outcomes and the fact that these drugs are more cost effective.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated superiority of an amlodipine based antihypertensive regimen compared with an atenolol based one.[2] In total, 19 257 participants with hypertension and at least three other cardiovascular risk factors were randomised to receive either amlodipine (5/10 mg) ± perindopril (4/8mg) or atenolol (50/100mg) ± bendroflumethiazide (1.25/2.5mg), titrated with further therapy as required to achieve a blood pressure target of <140/90mmHg. The trial was terminated early after 5.5 years' median follow-up with significantly fewer cardiovascular events or procedures,

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stroke or all-cause mortality in the group receiving the amlodipine based regimen (hazard ratios 0.84, 0.77 and 0.89 respectively). The superiority of the amlodipine based regimen can partly be explained by greater efficacy in lowering blood pressure (there was a 2.7mmHg systolic blood pressure difference between the groups throughout the trial), but favourable effects on other metabolic parameters, such as HDL-cholesterol, triglyceride and glucose values, may contribute.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared amlodipine with the angiotensin-II receptor blocker (A2RB) valsartan in 15 245 hypertensive participants with high cardiovascular risk. There were no significant differences seen between the groups in the primary outcome of composite cardiac morbidity and mortality, with an incidence of 10.4% in the amlodipine group and 10.6% in the valsartan group, despite a higher risk of myocardial infarction in the valsartan group (4.8% *vs* 4.1% in the amlodipine group). The secondary outcomes of all-cause mortality and stroke did not differ between the groups.[3]

The main adverse effect reported in clinical trials for amlodipine is peripheral oedema occurring in around 20–40% of study subjects. In ALLHAT, there was evidence of a significantly higher rate of heart failure in the amlodipine group (10.2%) when compared to the chlorthalidone group (7.7%) which may reflect a beneficial effect of the diuretic rather than a deleterious effect of amlodipine, or a misdiagnosis of heart failure in subjects with peripheral oedema. In ASCOT, the rate of heart failure was 1% in the amlodipine based regimen, compared to a rate of 2% in the atenolol based regimen, despite the use of bendroflumethiazide as first 'add-in' therapy in the atenolol arm. In VALUE, the rates of cardiac failure were 5.3% and 4.6% in the amlodipine and valsartan groups respectively.

Specific evidence for use in diabetes

The ALLHAT and ASCOT studies both had pre-defined sub-groups of patients with diabetes. In all, 36% (12 063 participants) of the study population in ALLHAT had type 2 diabetes and results paralleled those of the study population as a whole; there were no significant differences between amlodipine, chlorthalidone and lisinopril in the outcomes of combined fatal coronary heart disease plus non-fatal myocardial infarction, all-cause mortality, stroke or combined coronary heart disease.

Twenty-seven percent (5145 participants) of the study population in ASCOT had type 2 diabetes and had more cardiovascular events and procedures than those without the condition. As in the general study population, the amlodipine based regimen was superior in reducing the number of individuals suffering an event, with a hazard ratio of 0.87.

Although verified diabetes mellitus was one of the qualifying risk factors for inclusion into the VALUE trial, there is no indication what proportion of the study population had diabetes at baseline, or sub-group analysis for participants with diabetes.

Does amlodipine increase new-onset diabetes incidence?

In ALLHAT, new-onset diabetes was significantly more common in the chlorthalidone group than in the amlodipine group and the lisinopril group (11.6% *vs* 9.8% *vs* 8.1%). In ASCOT, the rate of newly-diagnosed diabetes was significantly higher in the atenolol/bendroflumethiazide arm compared to the amlodipine/perindopril arm (8% *vs* 6%). The VALUE trial revealed a significantly lower rate of new-onset diabetes with valsartan compared to amlodipine (13.1% *vs* 16.4%). These results seem to conflict, although the beneficial effects in the amlodipine based regimen in ASCOT may reflect an overall positive effect of the ACE inhibitor.

Discussion

There is good evidence that amlodipine can be safely used as a first-line agent for the treatment of hypertension even in patients with diabetes. Evidence from clinical trials suggests that patients require to be on as many as three different agents for treatment of hypertension with most ending up on a combination of ACE inhibitor (or A2RB), calcium antagonist and diuretic. However, the potential benefits of drugs acting on the renin angiotensin system is reflected in the updated National Institute for Health and Clinical Excellence (NICE) guidelines for the management of patients with type 2 diabetes, which recommend an ACE inhibitor (or A2RB) as first-line in this group, even when there is no evidence of nephropathy.[4]

Key points

- Amlodipine is a dihydropyridine calcium channel blocker used to treat hypertension and angina
- In people with diabetes amlodipine has been proven to be effective in reducing cardiovascular events when used first-line and in combination with an ACE inhibitor
- Updated NICE guidelines recommend that it is used second- or third-line in combination with either an ACE inhibitor or an angiotensin-II receptor blocker

Conflict of interest statement

There are no conflicts of interest.

References

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