Amlodipine - a third generation dihydropyridine calcium antagonist

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Amlodipine – a third generation dihydropyridine calcium antagonist

H.-M. Steffen

Amlodipine, a third generation dihydropyridine calcium antagonist, is characterized by a higher vascular selectivity and a smaller negative inotropic effect compared to nifedipine. With its long elimination half-life and low variability in trough-to-peak plasma concentrations, once-daily application is possible without loss of therapeutic efficacy. Placebo-controlled and comparative studies with a variety of antianginal and antihypertensive agents have confirmed the efficacy of amlodipine in patients with arterial hypertension and/or coronary artery disease. As a result of gradual onset of action, amlodipine demonstrates no clinically significant stimulation of neuroendocrine systems and preliminary results have shown that it may be useful in patients with heart failure. Amlodipine is well tolerated and exerts no adverse or unfavourable effects on carbohydrate and lipid metabolism. As a result of these factors, amlodipine represents a therapeutic advance in the treatment of hypertension and coronary artery disease. J Clin Basic Cardiol 1999; 2: 45–52.

**Key words:** amlodipine, dihydropyridine, calcium antagonist, coronary artery disease, arterial hypertension, left ventricular hypertrophy, diabetes mellitus

Calcium antagonists (CAs) were first introduced into pharmacotherapy over 25 years ago as coronary vasodilators for the treatment of coronary heart disease and have since achieved notable recognition in the treatment of arterial hypertension [1]. The initial investigations of the working group with Albrecht Fleckenstein [2] led to the finding that the common effect of this very heterogeneous class of substances can be ascribed to a specific impairment of calcium ion influx through so-called slow-channels embedded in the cell membrane. In accordance with their chemical structure, CAs can be divided into four groups [3, 4], of which only the first three are important for cardiovascular therapy: phenylalkylamines (prototype: verapamil), dihydropyridines (DHPs), prototype: nifedipine), benzothiazepines (prototype: diltiazem), and diphenylalkylamines (prototype: cinnarizine).

On the basis of their biophysical and pharmacological properties, the four types of potential-dependent, calcium selective membrane channels found in many body tissues are differentiated and described as L- (long-term activation), T- (temporary opening), N- (neuronal), and P-type (Purkinje-cells). Conventional calcium antagonists act in this process as selective blockers of the L-type calcium channel which consists of five subdivisions described as α1, α2, β, γ, and δ with a molecular weight of approximately 400 kDa. The α1-subtype is the actual membrane pore and has specific binding sites for phenylalkylamines, DHPs, and benzothiazepines [5]. Mibefradil, a benzimidazolyl-tetraline represented the first T-type calcium channel blocker (CCB), but last year this drug was withdrawn worldwide from the market due to unforeseen drug interactions via the cytochrome P450 system.

Efforts to obtain substances with a higher tissue selectivity, longer duration of action and, compared to the parent substance, a less marked negative inotropy have led to the development of a new generation of CAs, in particular within the class of DHPs (see Table 1). Publications during the last 5 years have initiated a still ongoing debate about the safety of CAs, especially the DHPs [6–8], despite the fact that the efficacy and safety of nitrrendipine has been demonstrated in the high risk group of elderly patients with systolic hypertension [9]. Also, a recent case-control study has shown that patients on long-acting CAs had no increased risk of cardiovascular events compared with those on β-blocker monotherapy [10], probably because of a lack of persistent stimulation of the sympathetic nervous system [11]. A retrospective cohort analysis of more than 1400 newly diagnosed hypertensive patients without coronary heart disease (CHD) also showed no increased relative risk for those treated with predominantly long-acting CCBs compared to β-blockers or diuretics [12]. Amlodipine, due to its unique pharmacokinetic and pharmacodynamic properties, is of major importance among the novel DHPs and will be described in greater detail hereafter.

**Preclinical pharmacology**

As a function of plasma concentration, amlodipine inhibits the contraction of vascular smooth muscle in depolarized rat aorta at a rate about double that of nifedipine; the maximum efficacy is achieved after three hours compared to 30 minutes for nifedipine [13]. In the guinea pig, concentrations required for a 50 % contraction inhibition are 160 times higher for myocardial tissue than for coronary arteries [5]. Amlodipine in a concentration of 100 nMol weakens the maximum contraction of the isolated aorta at a rate about 60% that of nifedipine; the maximum efficacy is achieved after more than 200 min compared to 30 min for nifedipine [14].

**Table 1. Selectivity and pharmacological properties of various calcium antagonists (modified in accordance with [5, 126, 127])**

<table>
<thead>
<tr>
<th>Vascular selectivity</th>
<th>Conduction system</th>
<th>Time to peak plasma levels</th>
<th>Elimination half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>nifedipine</td>
<td>+ + + +</td>
<td>-</td>
<td>20–40 min</td>
</tr>
<tr>
<td>amlodipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>6–12 h</td>
</tr>
<tr>
<td>felodipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>2–8 h</td>
</tr>
<tr>
<td>isradipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
<tr>
<td>lacidipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>3 h</td>
</tr>
<tr>
<td>manidipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
<tr>
<td>nicardipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>1 h</td>
</tr>
<tr>
<td>nilvadipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>2 h</td>
</tr>
<tr>
<td>nimodipine*</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
<tr>
<td>nisoldipine*</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
<tr>
<td>nifedipine*</td>
<td>+ + + + +</td>
<td>-</td>
<td>2 h</td>
</tr>
<tr>
<td>nitrendipine</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
<tr>
<td>diltiazem</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
<tr>
<td>verapamil</td>
<td>+ + + + +</td>
<td>-</td>
<td>1–2 h</td>
</tr>
</tbody>
</table>

* cerebral vessels > peripheral vessels
++ coronary vessels > peripheral vessels

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traction of human papillary muscles by 17% whereas a concentration of 14 nMol already results in a 50% contraction inhibition of isolated human coronary arteries [14]. These findings confirm amlodipine’s tissue selectivity in the human model as well. The guinea pig papillary muscle requires a five-fold higher amlodipine concentration compared to nifedipine to initiate a 50% decrease in muscle contraction, which means that amlodipine has approximately a fivefold weaker negative inotropic action on the heart muscle compared to the parent compound nifedipine [15]. The relative tissue selectivity of amlodipine – mainly a consequence of different membrane potentials of heart and vascular muscles – is comparable to nitrrendipine and is approximately fourfold to that of nifedipine [5]. The coronary dilating action of amlodipine and nifedipine is 3,000-fold stronger than papaverine compared to a factor of 10,000-fold for nisoldipine [15].

Binding studies of membrane preparations have shown that amlodipine binds and dissociates very slowly at the dihydropyridine receptor of the α1-subdivision of the calcium channel. Thus, binding saturation is not achieved until approximately five hours after administration compared to approximately one hour with isradipine [5]. A further special feature of amlodipine is that this substance interacts, to a certain extent, with the binding sites for phenylalkylamines and benzothiazepines. Plasma concentrations twenty- to thirty-fold above that required for vascular dilation are required to retard atrioventricular conduction, as demonstrated in animal models [16]. However, clinically relevant doses do not influence this, with a dose-dependent effect [18]. The survival time of stroke-prone rats was prolonged [5]. Pretreatment with amlodipine also prevented the ischaemic calcium overload of myocytes in normotensive rats after reperfusion [5] and ischaemia-induced endothelial dysfunction [19]. Expansion of infarction zone and ventricular remodeling were not influenced [20]. However, Hoff et al. showed a decrease in the experimental infarction size in a group of canines treated with amlodipine [21]. There was no impairment of left ventricular function in dogs with acute myocardial infarction while on therapy with amlodipine [22]. Dogs pretreated with amlodipine and subjected to several ischaemic episodes with subsequent reperfusion experienced a more rapid recovery of regional wall movement, and a less-pronounced loss of energy rich phosphate in the ischaemic areas [23]. A study in pigs demonstrated beneficial effects in a model of pacing-induced heart failure with either amlodipine or fosinopril and combined amlodipine/angiotensin-converting enzyme inhibition (ACEI) provided greater benefit with respect to vascular resistance and neurohumoral activity compared with either monotherapy [24]. Overall, these findings from animal experiments highlight cardioprotective properties which would be desirable in the treatment of patients with coronary heart disease and/or arterial hypertension and probably heart failure.

Clinical pharmacology – therapeutic relevance

Following once daily oral administration, amlodipine is virtually completely absorbed from the intestinal tract. Peak plasma levels are reached after 6 to 12 hours. It has a relatively high bioavailability of 60 to 80% [5, 25]. Steady state plasma concentrations in healthy volunteers are achieved after the 7th dose, without accumulation since this substance follows linear kinetics [13, 26]. Amlodipine has a very large volume of distribution (21 l/kg) and, similar to other CAs, 95% are bound to plasma proteins. Amlodipine undergoes slow hepatic metabolism. Less than 10% of the orally administered dose is excreted unchanged. The metabolites possess no calcium antagonistic properties and are excreted via urine (60%) and in faeces (20–25%). This drug has a very long elimination half-life of 35–50 hours [5, 25]. While patients with renal insufficiency showed no accumulation, elimination was delayed in patients with hepatic cirrhosis [27] so that monitoring of therapy is recommended in these patients. No adverse interactions were observed for digoxin, cimetidine, and nitroglycerine [5, 13]. Concurrent food intake does not influence amlodipine’s rate of absorption or plasma levels [28].

Studies over the last 10 years have shown that the incidence of myocardial infarction, sudden cardiac death, apoplectic insult and silent myocardial ischaemia show a circadian distribution of incidence with a peak in the early morning hours [29]. Quyyumi et al. have observed in patients with stable CHD using multiple ergometric exercise tests that the ejection fraction was lower in the early morning hours at the time of a significant ST segment depression than at mid-day or in the early evening [30]. Circadian rhythms were demonstrated for various physiological functions; heart rate and BP showed an increase in the early morning hours [31, 32]. Heightened sympathetic alpha-adrenoceptor activity associated with an increase in peripheral resistance was observed in normotensives [33] and hypertensives [34] in the early morning hours. Furthermore, clinical studies have shown that pharmacokinetics and pharmacodynamics of antihypertensive or antiischaemic substances vary markedly with the time of the day, as observed with propranolol, organic nitrates and nifedipine [35]. In this complex situation, substances such as amlodipine are most beneficial because of a low variation of plasma levels, a high oral bioavailability, long elimination half-life and small variations between peak and trough plasma levels [26]. These properties insure a continuous efficacy over 24 hours with once daily dosing and hence improve patient compliance [36].

Clinical studies – coronary heart disease

The anti-anginal efficacy of varying amlodipine doses (1.25–10 mg) was investigated in 136 patients with stable angina pectoris compared to placebo. Exercise ECGs were carried out 24 hours after each dose [37]. Exercise duration was prolonged by 31% with the 10 mg dose. Compared to baseline, a 48% increase in the time to onset of angina was observed. The incidence of ischaemic attacks and use of glyceryl trinitrate decreased significantly for all doses of amlodipine tested. In a study with similar design, once-daily administration of 10 mg amlodipine prolonged the time to onset of angina by 28%; nitrate consumption decreased by 50% and the frequency of anginal attacks dropped by 67% [38]. Invasive measurements after a 20 mg intravenous application of amlodipine showed a reduction of systemic resistance with an increase in stroke volume and a slight increase in heart rate at rest and during
exercise. The maximum filling rate determined by radio-
nuclide ventriculography was increased [39]. The maximum rate of pressure increase in the left ventricle remained un-
changed after intravenous amiodipine administration (10–20
mg) during monotherapy and after pre-treatment with a β-
blocker [17]. Bernink et al. [40] compared amiodipine and
diltiazem in patients with stable exercise-induced angina in
a double-blind study over a period of 8 weeks: 80 patients were
assessed by means of ergometric tests 24 h after amiodipine
and 12 h after diltiazem, respectively. The time to onset of
angina was prolonged by 25% with amiodipine and by 3%
with diltiazem compared to baseline. The decrease in the fre-
quency of attacks and nitrate consumption were comparable
in both groups. Silke et al. found a comparable reduction of
the mean arterial blood pressure after intravenous application
of amlodipine, diltiazem and verapamil in patients with CHD;
the most notable decrease in peripheral resistance at rest and
during exercise was observed with amiodipine, which in turn,
resulted in a significant reduction in pulmonary capillary pres-
sure during exercise [41].

The effects of an add-on therapy with amiodipine were
investigated in a placebo-controlled, double-blind study in 134
patients with stable angina pectoris inadequately controlled
with β-blocker therapy. This study demonstrated that the ad-
ministration of amiodipine led to a decrease in the frequency
of anginal attacks by 52 to 67 %. The total exercise duration
was prolonged significantly after 4 weeks of treatment 24 h
after oral dosing [42]. In patients with exercise-induced ST-
segment depression at rest despite β-blocker therapy, fasting
the ST segment depression decreased 28 % when measured 8 h and 24 h post
oral dosing of 10 mg amiodipine once-daily. The ischaemia-
free exercise interval was increased by 76 % and 81 %, respec-
tively [43]. Administration of amiodipine led to an increase
in ejection fraction and a decrease in regional wall motion
abnormalities as shown during stress echocardiography in
patients with multivessel disease while on therapy with long-
acting nitrates and β-blockers [44]. The anti-anginal efficacy
and prolonged exercise tolerance remained constant even dur-
ing long-term therapy over a period of 2 years [45]. In an-
other study, the frequency of angina was significantly reduced in
a placebo-controlled, double-blind comparison for 4 weeks
in 52 patients with vasospastic angina. Fasting the ST segment
heath rate did not change and the favourable effect of therapy
persisted in the subsequent one-year open treatment phase
[46].

The Circadian Anti-Ischaemia Program in Europe (CAPE
trial) was a 10-week, multi-centre, randomized, double-blind,
placebo-controlled study that enrolled 250 men with stable
angina while on antianginal treatment and a minimum of 4
ischaemic episodes per day (≥ 1 mm ST segment depression
for ≥ 1 minute) documented by Holter monitoring over 48
hours and/or a total ischaemia time of ≥ 20 minutes [47]. In
the control group, the addition of placebo reduced the number
of ischaemic events by 44 % and the integral of all ST depres-
sions (a measure of the total ischaemic burden) by 50 % com-
pared to a decrease of 60 % and 62 %, respectively while on
oral amiodipine therapy (both significant at p ≤ 0.05). Fur-
thermore, acute nitroglycerine consumption and angina at-
tacks were significantly less frequent in the amiodipine group.

The Prospective Randomized Evaluation of the Vascular
Effects of Norvasc Trial (PREVENT) was a multi-centre,
randomized, double-blind, placebo-controlled clinical study
that was initiated to test the antithromogenic effect of amlo-
dipine in patients with angiographically confirmed CHD. Pre-
liminary results from this trial were presented in Dallas in
November 1998 during the 71st Scientific Sessions of the
American Heart Association. 825 patients (43 % with prior
myocardial infarction, 65 % on β-blocker therapy) were
randomized and followed for 3 years. Compared to placebo,
amiodipine as add-on therapy reduced hospitalizations due to
angina by 35 % and revascularization procedures (PTCA or
bypass) by 46 %. For detailed analysis one has to await the
final publication which hopefully will soon appear.

Clinical studies – arterial hypertension

Over 200 patients with mild to moderate arterial hyperten-
sion were treated with amiodipine 1.25–10 mg in a placebo-
controlled double-blind study over a period of 8 weeks [48].
The extent of BP reduction was dose-dependent and averaged
-20/9 mmHg after 8 weeks with no changes in heart
rate. In a similar 4-week study of 210 patients, BP was re-
corded both in the sitting and supine position at hourly inter-
vals during the initial 12 hours and 24 hours post oral dosing.
Diastolic BP was reduced in all patients at amiodipine doses ≥
2.5 mg. Heart rate remained unchanged at all doses both in
the lying and standing position compared to baseline values
[49]. Parallel to amiodipine’s pharmacokinetic, the maximum
BP lowering effect was observed after approx. 6–12 hours with-
out any significant changes in heart rate. After discontinua-
tion of therapy, baseline BP values were not attained even 6
days after cessation of therapy [25]. Ambulatory BP monitor-
ing using intra-arterial [50] and non-invasive [51–54] meas-
urements with observation periods of 4 and 28 weeks showed a
continuous 24-h effect of BP control over a period of time
with preservation of circadian rhythm and no significant
change in heart rate. The trough/peak ratio for the antihyper-
tensive effect ranges from 50–100 % with an average of 63 %
[55]. This represents a major advantage for long-term anti-
hypertensive therapy in view of the aforementioned incidence
of cardiovascular events in the early morning hours [29], a
phase of the day during which short-acting antihypertensives
fail to blunt rapid increases in BP upon waking [32, 34].
Hamada et al. evaluated 24-h ambulatory BP and simultane-
ous Holter monitoring before and after 4 weeks of adminis-
tration of amiodipine, short-acting nifedipine, or its slow-re-
lease formulation [56]. While the mean hourly BP was re-
ceded significantly to similar degrees only during nifedipine-
induced increases in heart rate, especially during the daytime.
Invasive measurements have shown that the initial reduction
of peripheral vascular resistance and the increase in stroke
volume was unchanged one year after initiation of amiodipine
therapy [52]. No loss of efficacy was observed in an open study
of oral amiodipine over a period of 27 months [57].

2.5–10 mg of amiodipine was equivalent to 25–100 mg of
dihydrotlthiazide [58] or 50–100 mg of atenolol with re-
spect to the BP reduction [59]. The BP lowering effect of 5
mg amiodipine in the supine and standing position did not
differ significantly from 2 x 20 mg of nifedipine in a retard
formulation [60]. Waerbel et al. [61] investigated amiodipine
5 mg once-daily and nifedipine 20 mg once-daily over 4
weeks. Conventional measurements showed a similar degree
of BP reduction, while ambulatory BP monitoring revealed a
significant BP reduction only with amiodipine during the fi-
nal 6 hours of the dosage interval compared to the baseline
value. With ambulatory BP monitoring there was no signifi-
cant BP reduction for captorplor compared to amiodipine dur-

ing the final 3 hours of the dosage interval [62]. Omvik et al.
[63] examined amiodipine and enalapril in more than 400
patients with mild to moderate arterial hypertension and ob-
served no differences in the extent of BP reduction; Fowler et
al. [64] found a significantly higher BP reduction, especially

REVIEWS

Amiodipine

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for diastolic values, in patients with moderate to severe hypertension while on amlodipine. Amlodipine (5 mg/day) reduced systolic and diastolic BP to a similar degree as 8 or 16 mg/day of candesartan cilexetil [65]. Enalapril and amlodipine were equally effective in patients with isolated systolic hypertension [66]. While short-acting DHPs should be abandoned due to serious adverse events long-acting DHPs are recommended by JNC VI report [67] as well as the 1999 WHO-ISH guidelines [68] as an alternative to diuretics for the first line therapy of isolated systolic hypertension.

Acebutolol (400 mg/day), amlodipine (5 mg/day), chlorothalidone (15 mg/day), doxazosin (2 mg/day) and enalapril (5 mg/day) were compared in the Treatment of Mild Hypertension Study (TOMHS). The final results showed similar efficacy in reducing systolic and diastolic blood pressure versus placebo for these antihypertensives in approximately 900 patients with mild hypertension [69]. Controversial findings were obtained with regard to concomitant therapy with diuretics. While Glasser et al. were able to achieve an additional BP reduction by adding on amlodipine to pre-existing diuretic therapy [70], bendroflumethiazide had no additional BP lowering effects compared to placebo after four-week pretreatment with amlodipine [71]. The administration of amlodipine in combination with captopril [72] or enalapril [73] resulted in an additional BP reduction of 18/12 mmHg and 19/10 mmHg compared to placebo. Co-administration of amlodipine and candesartan cilexetil resulted in a significantly greater BP reduction than either drug alone [65].

Left ventricular hypertrophy (LVH) has been considered an independent risk factor for sudden cardiac death, ventricular arrhythmias, coronary heart disease and heart failure [74, 75]. The coronary reserve of hypertensive hearts is diminished by 30–50 %. This implies a predisposition to myocardial ischaemia even in the haemodynamically-compensated state with normal coronary arteries [76]. Motz et al. [77] were able to show an increase in the coronary reserve by approx. 30 % in a small group of patients with angiographically normal coronary arteries who were treated over a period of 9–12 months with various antihypertensives. Furthermore, data from several studies indeed suggest a decrease in cardiovascular mortality and morbidity of hypertensive patients after LVH regression [78–80]. Fayyadi et al. [81] observed a significant reduction of left ventricular mass index over a period of 18 months in patients with mild hypertension. The latter finding needs confirmation which is being sought between the amlodipine and placebo groups among patients with LVH [90]. Regression of LV muscle mass after treatment with 5–20 mg amlodipine for 3–12 months [86–88]. In one of our own studies, left ventricular muscular mass was reduced by approx. 9 % following a 28-week amlodipine therapy together with an increase in early-diastolic filling [54]. This is comparable to earlier reports for chronic therapy with nitrates or captopril [89]. Picca et al. showed a comparable decrease in LV muscle mass together with an increase in early-diastolic flow for both enalapril and amlodipine during the course of an 18-months observation period in patients with LVH [90]. Regression of LV muscle mass was similar when amlodipine was compared to enalapril [91], fosinopril [92] or lisinopril [93] for 6–12 months. In addition, amlodipine was superior to lisinopril in previously untreated hypertensive patients in reducing the mean common carotid intima-media thickness [94] which is an established surrogate marker for early atherosclerosis.

**Neurohormonal and metabolic effects**

In vitro tests have shown that amlodipine reduces ADP- or collagen-induced thrombocyte aggregation [95]. The growth of human kidney mesangial cells is inhibited [96], as has been demonstrated for other calcium antagonists of the dihydropyridine group [5, 97]. The vasodilating effect of calcium antagonists in the kidneys predominantly affects afferent vessels. In experiments, the fall of glomerular filtration rate following administration of angiotensin II can be completely nullified with amlodipine [98]. In hypertensives, 4-week amlodipine therapy increased glomerular filtration rate by 11 %, renal blood flow by 16 % and decreased renal vascular resistance by 24 % [99]. While Cappuccio et al. showed a stimulation of plasma renin activity in 6 patients with arterial hypertension and unchanged sodium excretion in 24-h urine during a 2-week treatment [100], Lund-Johansen et al. did not observe an increase in plasma volume or extracellular fluid in a larger group of amlodipine-treated patients [52]. Plasma renin activity, aldosterone and angiotensin II concentrations as well as plasma levels of atrial natriuretic peptide were unchanged in both young and elderly hypertensives [27, 54, 99–103].

In contrast to findings with the DHPs nifedipine [56], felodipine [104] or nitrendipine [105], amlodipine does not lead to a stimulation of noradrenaline and adrenaline secretion at rest or during exercise [27, 54, 56, 102, 103, 106, 107]. The absence of a neurohormonal stimulation is desirable especially during the pharmacotherapy of heart failure patients. In addition to the higher negative inotropic effect of older CAs, the recurrent stimulation of the sympathetic nervous system may explain the unfavourable patient outcomes in post-infarction trials with nifedipine [108]. A randomized, double-blind, placebo-controlled study of more than 100 patients with chronic heart failure in NYHA stages II–III and ejection fractions < 30 % has demonstrated that the treatment with amlodipine in addition to a basis therapy with digoxin, diuretics and/or ACEI improved the exercise duration and heart failure symptoms within 8 weeks [106]. In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) more than 1100 patients with severe chronic heart failure and ejection fractions < 30 % were stratified according to ischaemic or nonischaemic aetiology and randomly assigned to double-blind treatment with either placebo or amlodipine while already on therapy with diuretics, ACEI and digitalis. While there was no difference in cardiovascular morbidity and mortality between the amlodipine and placebo groups among patients with ischaemic heart disease, amlodipine reduced the risk of death by 46 % in patients with nonischaemic cardiomyopathy [109]. The latter finding needs confirmation which is being sought in the PRAISE–II trial. In this context, the cytoprotective activity of amlodipine which appears to be independent of its effects on calcium flux may play an important role by limiting the cytokine-induced damage in dilated cardiomyopathy [110]. In contrast to older DHPs which may have dangerous side effects in heart failure patients amlodipine is listed for the treatment of angina and hypertension in patients already on ACEI, diuretics, and digitalis [67].

After a 3-week amlodipine therapy (5 mg/day), no changes were monitored in insulin sensitivity, insulin secretion, total cholesterol, lipoprotein subfractions or triglycerides in the
healthy subjects tested [111]. Whereas Courten et al. reported [112] unchanged glucose, insulin and lipoprotein plasma concentrations in obese, insulin-resistant hypertensives after 6-month therapy with amlodipine, Beer et al. described a decrease in fasting and glucose-stimulated serum insulin levels in a placebo-controlled study of 7 days duration [113]. An improvement of the initially decreased insulin sensitivity was seen in non-obese hypertensive patients after 2–4 months therapy with amlodipine [114]. No unfavourable metabolic effects were reported for amlodipine from the TOMHS authors with regard to plasma lipid changes [115].

Safety

The evaluation of approximately 40 placebo-controlled studies with roughly 3,000 patients showed a mild side effect profile typical for amlodipine’s peripheral vasodilating action (see Table 2). A placebo-controlled crossover study with a 2-week treatment period showed a significantly higher rate of side effects, in particular headache and flush, while on nifedipine in a retarad preparation (41 %) versus amlodipine (27 %). With amlodipine, only the frequency of ankle edema was significantly higher (9 % vs. 2 %) when compared to placebo [60]. Side effects for once-daily doses of 20 mg nisoldipine were more frequent than for once-daily 5 mg amlodipine not only during the initial 3 days of therapy (39.5 % versus 5 %), but also at the end of the 4-week observation period (47.4 % versus 27.5 %) [61]. Compared to enalapril, both groups produced equally-effective BP reduction with a discontinuation rate of 4 % overall with cough (13 %) in the enalapril group and lower leg edema (22 %) in the amlodipine group as the most frequently reported side effects [63]. In a multicentre study of more than 100 patients, a side effect rate of 27.5 % was observed in out-patients over a period of 3 months with lower leg edema (13.8 %) as the most frequent adverse event [116]. Whereas in the CAPE study side effects occurred during amlodipine treatment in 17.3 % of the patients compared to 13.3 % for placebo [47], the side effect rate in the TOMHS study was higher in the placebo group than in any of the drug treatment groups. Of all antihypertensives tested, amlodipine was best tolerated: 82.5 % of the initially randomized patients in the verum group still received this medication at the end of the 4-year observation period [69]. Clinical trial databases revealed incidence rates for all-cause mortality, myocardial infarction, and new/worsened angina among all amlodipine-treated patients of 3.0, 3.3, and 1.6/1000 patient-years of exposure, respectively [117]. Among those in comparative trials alone the all-cause death rate (3 out of 942 for a rate of 6.7/1000 patient-years) was comparable to that of non-CCB agents (4 out of 4126 for a rate of 4.1/1000 patient-years).

Last year two studies gained much interest in the context of the ongoing CCB controversy since they suggested that CAs probably promote adverse cardiovascular events in diabetic patients with hypertension.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial [118] was a prospective, randomized, blinded comparison of the effect of moderately controlled BP (target diastolic BP 80–89 mmHg) with that of intensively controlled BP (target diastolic BP 75 mmHg) on the incidence and progression of complications in Type 2 diabetes using nisoldipine (10–60 mg/day) or enalapril (5–40 mg/day). After 67 months of the study the Data and Safety Monitoring Committee recommended the discontinuation of the hypertensive cohort since a significant difference in the rate of cardiovascular events was observed for patients on nisoldipine compared to enalapril. Data for the hypertensive subgroup (n = 470) on the incidence of myocardial infarction, a secondary endpoint of the study, were subsequently analyzed and published while the blinded treatment in the normotensive cohort (n = 480) was continued. Control of BP, blood glucose, and lipid concentrations were comparable in both treatment groups, but nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions (25/235 vs. 5/235). Complications at base line were equally distributed between both treatment groups, however, there were significantly more patients on a concomitant β-blocker or diuretic therapy in the enalapril group.

The objective of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) was – somewhat contrary to what the title suggests – to compare the effects of open-label therapy with fosinopril (20 mg/day) and amlodipine (10 mg/day) on serum lipids and diabetes control in 380 Type 2 diabetics with hypertension which were followed for an average of 3.5 years [119]. While both treatments were equally effective in lowering BP with no differences in metabolic effects, the primary endpoint of the study, patients on amlodipine were at a significantly higher risk of acute myocardial infarction, hospitalized angina, and especially stroke. Of particular interest, however, is the fact that the risk of unfavourable cardiac events was lowest among patients (n = 108 or 28 % of the total study population) who were on combination therapy of fosinopril with amlodipine.

A comparison of the 5-year incidence rates for myocardial infarction in the aforementioned studies (amlodipine: 12 %, nisoldipine: 11 %, fosinopril: 9 %) to historical controls (Helsinki Heart Study: 7.5 % [120], Schwabing Study: 12.5 % [121]) or the results of the UK Prospective Diabetes Study Group 39 (captopril: 10 %, atenolol: 8 % [122]) suggests no real difference but rather a need to explain the unusually low incidence (2 %) in the enalapril treated patients in the ABCD trial. Also, subgroup analyses from the Systolic Hypertension in Europe (Syst-Eur) trial [123] revealed an even greater benefit for a DHP-based (nifedipine) antihypertensive treatment in older diabetics with isolated systolic hypertension (all cardiovascular endpoints in diabetics -63 % compared to -21 % in non-diabetics). Finally, in the Hypertension Optimal Treatment (HOT) study [124] major cardiovascular events in the 1501 diabetic patients were halved with aggressive BP control (target diastolic BP ≤ 80 mmHg) which usually was achieved only by combination therapy with felodipine and ACEI and/or β-blocker compared to less intensive therapy (target diastolic BP ≤ 90 mmHg).

The PRAISE study [109] has established the safety of amlodipine for the treatment of angina and/or hypertension in patients with advanced left ventricular dysfunction. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) 40,000 patients have been randomized to compare amlodipine, lisinopril, doxazosin, and

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### Table 2. Side effects of amlodipine versus placebo, summarized from 40 placebo-controlled studies [128]

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Amlodipine (n = 1775)</th>
<th>Placebo (n = 1213)</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ankle edema</td>
<td>9.8 %</td>
<td>2.3 %</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>headache</td>
<td>8.1 %</td>
<td>8.1 %</td>
<td>ns</td>
</tr>
<tr>
<td>tiredness</td>
<td>4.6 %</td>
<td>2.9 %</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>vertigo</td>
<td>3.0 %</td>
<td>3.4 %</td>
<td>ns</td>
</tr>
<tr>
<td>nausea</td>
<td>2.8 %</td>
<td>1.9 %</td>
<td>ns</td>
</tr>
<tr>
<td>flush</td>
<td>2.4 %</td>
<td>0.5 %</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>withdrawn</td>
<td>1.1 %</td>
<td>0.7 %</td>
<td>ns</td>
</tr>
</tbody>
</table>

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chlordiazepoxide for effects on nonfatal myocardial infarction or fatal coronary heart disease in high risk patients who have had previous myocardial infarction. About 1/3 of the patients suffer from diabetes, however, after a separate evaluation of the primary endpoint in this subgroup representing more than 7000 patient-years the Data and Safety Monitoring Board of this study recommended that the trial continues according to the protocol [125]. In summary, once-daily amlopidine provides a favorable side-effects profile without adversely affecting neurohormonal or metabolic parameters, thereby providing safe and reliable 24-hour therapy for patients with coronary heart disease and/or arterial hypertension.

References

Amlodipine


