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An Update on the Safety of Amlodipine

Ian H. Osterloh

Pfizer Central Research, Sandwich, Kent, England

Summary: A previous article on the safety of amlodipine reviewed data from over 4,000 subjects who participated in clinical trials sponsored by Pfizer Central Research. Once-daily amlodipine was shown to be a well-tolerated treatment of hypertension and myocardial ischemia. Although amlodipine is a potent vasodilator, there was a low incidence of side effects such as headache, flushing, and dizziness. Amlodipine was not associated with adverse effects on hematologic or biochemical safety parameters nor on serum cholesterol or triglyceride levels. Amlodipine did not alter electrical conduction in the heart. Amlodipine had a favorable safety profile in comparative trials vs. β-blockers. The data base of comparative trials vs. other calcium antagonists was small but the toleration of amlodipine was similar to that of verapamil and diltiazem. No data from comparative trials vs. another calcium antagonist of the dihydropyridine class have been available. This article reviews data from recently completed trials vs. nitrendipine and from trials in which amlodipine was used in combination with other agents. Amlodipine was better tolerated than nitrendipine and had a much lower incidence of side effects usually related to vasodilatation. This difference in side-effect profile was especially marked during the first days of treatment. Amlodipine was well tolerated when used in combination with β-blockers, diuretics, ACE inhibitors, and nitrates. The gradual onset of action and relatively long half-life of amlodipine are the probable cause for the improved toleration in comparison with other dihydropyridines. Besides the low incidence of trivial side effects, increasing clinical experience with amlodipine provides no evidence that amlodipine is a cause of rare but serious adverse effects. It is concluded that amlodipine is an antihypertensive and anti-ischemic agent that has the combined advantages of a good safety profile with once-daily dosage and a smooth onset and long duration of action.
Key Words: Amlodipine—Safety.

Calcium antagonists have proved to be effective and well-tolerated agents in the treatment of hypertension and/or myocardial ischemia. Many calcium antagonists, especially agents containing the dihydropyridine ring, are now under development. In a recent review of calcium antagonists, Purcell et al. (1) specified a number of requirements for new, "second-generation" agents. These requirements included increased potency, reduced incidence of side effects, and a long duration of action to increase patient compliance and provide prolonged control of ischemia or elevated blood pressure over a 24-h period.

Amlodipine is a new calcium antagonist of the dihydropyridine class that can be administered in once-daily doses of 5 or 10 mg to patients with hypertension or angina. The pharmacokinetic profile of amlodipine is unique for a calcium antagonist. After oral administration, amlodipine is slowly absorbed (with a time to peak plasma concentration of 6–12 h), and the plasma elimination half-life is relatively long (approximately 35–50 h). The once-daily treatment regimen has been found to produce a smooth, gradual onset of antihypertensive action with prolonged duration (2). These features suggest that amlodipine may have a reduced propensity to cause side effects such as flushing, headache, and dizziness (which can result from rapid onset of vasodilatation) and may therefore enhance patient compliance.

A previous article (3) provided an extensive review of clinical data from 4,227 subjects who had been recruited to clinical trials of amlodipine sponsored by Pfizer Central Research. Figures given for side-effect incidence in this report include all side effects of definite or unknown relationship to the study drug. In the pooled data base of 2,988 subjects treated in double-blind, placebo-controlled studies, amlodipine treatment was associated with a slightly higher incidence of side effects (29.8%) than placebo

Address correspondence and reprint requests to Dr. I. H. Osterloh at Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT19 9NJ, England.

(22.1%). Most of this difference was due to edema (9.8% vs. 2.3%), which was usually well tolerated. There was also a slightly higher incidence of flushing (2.4% vs. 0.5%) and fatigue (4.6% vs. 2.9%) in the amlodipine-treatment group. However, in the patients treated with amlodipine, the incidence of other side effects (which are commonly caused by vasodilators) such as headache (8.1%) and dizziness (3.0%) was no higher than in patients treated with double-blind placebo (8.1% and 3.4%, respectively).

A large number of patients (1,317) were recruited to trials comparing the efficacy and safety of amlodipine with other active antihypertensive or antianginal drugs. The most commonly used comparative agents were β-blockers (atenolol and nadolol). Compared to this class of drugs, amlodipine had a favorable safety profile, the incidence of severe side effects being approximately one-half that reported for patients receiving β-blockers. The data base comparing amlodipine with other calcium antagonists was small; in a study vs. verapamil, edema was more common in patients receiving amlodipine but constipation was more common in patients receiving verapamil. In a study vs. diltiazem, both amlodipine and diltiazem were similarly well tolerated.

Amlodipine was not associated with the deleterious effects on serum creatinine, urate, and fasting glucose that were caused by hydrochlorothiazide, and in contrast to hydrochlorothiazide and nadolol, amlodipine was not associated with unfavorable changes in serum cholesterol and serum triglyceride levels. Amlodipine was shown to be well tolerated by elderly patients, and is not contraindicated in patients with cardiac conduction abnormalities. Dosage modifications are unnecessary in renal impairment, but the dosage regimen for patients with hepatic impairment is not yet established.

Since the previous review article (3) was prepared, further studies have been undertaken to compare the efficacy and safety of amlodipine with a wider range of drugs, and to explore efficacy in new indications. The total number of subjects to have received amlodipine now exceeds 5,000.

This article summarizes the new information on the safety of amlodipine, including an evaluation of the safety of amlodipine in comparison with another dihydropyridine calcium antagonist (nitrendipine), and the safety of amlodipine when used in combination with other commonly prescribed antihypertensive and antianginal agents [β-blockers, diuretics, and angiotensin-converting enzyme (ACE) inhibitors].

METHODS

In all clinical trials, the investigators were asked to determine the occurrence of side effects by indirect questioning. The severity of the side effects (mild, moderate, or severe) and the course (disappeared with continued treatment, tolerated with continued treatment, required symptomatic therapy, required dose reduction or temporary discontinuation, or required permanent discontinuation of the study drug) were recorded on the case record forms. The investigators were also asked to classify the relationship of the side effects to the study drug as definitely related, uncertain causality, or not related.

In the following sections, all side effects of definite or possible relationship to the study drug and all side effects for which no cause was assigned are presented and discussed.

RESULTS

Comparison of amlodipine vs. nitrendipine

Data are available from two open multicenter comparative studies of amlodipine vs. nitrendipine. In study NY-86-003, performed at five centers in West Germany, patients with mild to moderate hypertension entered a 4-week placebo washout phase, and then were randomized to receive 5 mg of amlodipine once daily or 20 mg of nitrendipine once daily. Amlodipine could be adjusted upwards to 10 mg/day and nitrendipine to 40 mg/day after 2 weeks to obtain a supine diastolic blood pressure of ≤ 90 mm Hg. Duration of active treatment lasted for 8 weeks. In study CH-88-004, performed at eight centers in Switzerland, patients with mild to moderate hypertension entered a 2-week placebo washout phase, and were then randomized to receive 5 mg of amlodipine once daily or 20 mg of nitrendipine once daily for 4 weeks. Dosage adjustments were not permitted in this study.

The incidence of side effects in the West German and Swiss studies are summarized in Tables 1 and 2, respectively. The figures for percentage incidence include all recorded side effects except those classified by the investigator as definitely not related to the study drug.

In spite of the longer duration of treatment and greater mean daily dosage employed in the study in West Germany, the results of both trials are very similar. The incidence of amlodipine-treated pa-

TABLE 1. *Incidence of side effects in open study NY-86-003 (West Germany) of amlodipine vs. nitrendipine*

	Amlodipine		Nitrendipine		
No. of patients:	*n*	%	*n*	%	*p* Value[a]
Evaluable	38		36		
With side effects[b]	10	26.3	17	47.2	$p < 0.1$
Flushing	3	7.9	8	22.2	$p < 0.1$
Headache	3	7.9	4	11.1	N.S.
Vertigo	3	7.9	3	8.3	N.S.
Edema	0	0.0	2	5.6	$p < 0.1$
Hot flushes	1	2.6	2	5.6	N.S.
Rhinitis	1	2.6	2	5.6	N.S.

N.S., not significant.

[a] The *p* values based on χ^2 test comparing the incidence of side effects in the two treatment groups; N.S. indicates $p \geq 0.10$.

[b] Includes all side effects of definite or unknown relationship to the study drug with incidence ≥5% in either treatment group.

tients experiencing side effects in the West German study was 26.3%, but there was a somewhat higher incidence of nitrendipine-treated patients with side effects (47.2%). In the Swiss study, the incidence of patients with side effects was 27.5% and 47.4% for the amlodipine and nitrendipine treatment groups, respectively. Close examination of data presented in Tables 1 and 2 shows that most of the side effects experienced by patients in both treatment groups were probably consequent upon the pharmacodynamic actions of the drugs. However, the higher incidence of flushing, headache, and tachycardia in the patients receiving nitrendipine suggests that rapid vasodilatation may have been the cause of the larger number of side effects observed for this treatment group.

Since the two studies employed different durations of treatment and dosage regimens, it may not be appropriate to pool the results for the purpose of statistical testing. However, if the difference in the incidence of side effects is related to the speed of onset of vasodilatation, then it might be expected that the difference would be most apparent at the start of treatment. At the end of the placebo washout phase, both studies employed the same starting dose of amlodipine (5 mg once daily) and nitrendipine (20 mg once daily). It is therefore valid to pool side-effect data collected during the first 3 days after the start of active treatment, and the results are illustrated in Table 3.

The results presented in Table 3 illustrate a marked difference in toleration at the start of therapy with a side-effect incidence of 2.6% on amlodipine compared to 24.3% on nitrendipine. The side effects reported in the nitrendipine group provide further evidence that toleration at the start of drug treatment may be compromised by the unwanted effects of acute vasodilatation.

TABLE 2. *Incidence of side effects in open study CH-88-004 (Switzerland) of amlodipine vs. nitrendipine*

	Amlodipine		Nitrendipine		
No. of patients:	*n*	%	*n*	%	*p* Value[a]
Evaluable	40		38		
With side effects[b]	11	27.5	18	47.4	$p < 0.1$
Headache	3	7.5	9	23.7	$p < 0.05$
Flushing	3	7.5	9	21.1	$p < 0.1$
Edema	2	5.0	2	5.3	N.S.
Fullness	2	5.0	0	0.0	$p < 0.1$
Fatigue	2	5.0	2	5.3	N.S.
Tachycardia	0	0.0	2	5.3	$p < 0.1$

N.S., not significant.

[a] The *p* values based on χ^2 test comparing the incidence of side effects in the two treatment groups; N.S. indicates $p \geq 0.10$.

[b] Includes all side effects of definite or unknown relationship to the study drug with incidence ≥5% in either treatment group.

TABLE 3. *Incidence of side effects during the first 3 days of active treatment in two open studies of amlodipine vs. nitrendipine*

	Amlodipine		Nitrendipine		
No. of patients:	*n*	%	*n*	%	*p* Value[a]
Evaluable	78		74		
With side effects	2	2.6	18	24.3	$p < 0.001$
Headache	1	1.3	8	10.8	$p < 0.01$
Flushing	0	0.0	8	10.8	$p < 0.001$
Fatigue	0	0.0	2	2.7	$p < 0.1$
Tachycardia	0	0.0	2	2.7	$p < 0.1$

Another side effect reported once for the amlodipine treatment group was a feeling of hunger. Other side effects reported once each for the nitrendipine treatment group were vasodilatation, hot body, palpitation, dry mouth, sweating, pollakisuria, hot flushes, rhinitis, and edema.

[a] The *p* values based on χ^2 test comparing the incidence of side effects in the two treatment groups.

Amlodipine as combination therapy

In addition to studies assessing the antihypertensive and antianginal efficacy and safety of amlodipine monotherapy, a number of comparative studies in which both treatment groups received background antihypertensive therapy have been performed. In these studies, the background therapy has included diuretics, β-blockers, or ACE inhibitors. The overall incidence of side effects reported in these studies is summarized in Table 4. The results of these trials indicate that amlodipine is very well tolerated when used in conjunction with other commonly prescribed antihypertensive drugs.

In many trials of angina, short- or long-acting nitrates have been used as background therapy in some patients and the combination of amlodipine with these drugs is well tolerated.

A previous article (3) reported that formal volunteer studies had shown that there was no pharmacokinetic interaction between amlodipine and digoxin or cimetidine. A further volunteer study to investigate a possible interaction with warfarin has been performed (data on file, Pfizer U.K. Ltd. Study Report 011, Phase I study to assess the potential of amlodipine to alter the pharmacodynamics of warfarin). The results showed that 10 mg of amlodipine daily did not enhance or attenuate the anticoagulant effect of warfarin (0.75 mg/kg administered as a single dose).

Other safety issues

As the clinical development of amlodipine progresses from phase III to phase IV trials, the number of patients treated continues to increase. The number of patients treated with amlodipine now exceeds 5,000. Although a number of serious events (myocardial infarctions, strokes, etc.) are inevitable when a large number of predominantly middle-aged or elderly patients with hypertension and/or ischemic heart disease are treated, there is no evidence to suggest that amlodipine treatment has been the cause of death in any patient.

TABLE 4. *Incidence of side effects in studies of amlodipine vs. double-blind placebo in patients receiving background antihypertensive therapy*

Study no.	Background treatment		Background drug plus amlodipine: No. patients evaluable	Background drug plus amlodipine: No. (%) with side effects	Background drug plus double-blind placebo: No. patients evaluable	Background drug plus double-blind placebo: No. (%) with side effects	p Value[c]
104	HCTZ	(50 mg daily)	53	27 (50.9)	53	18 (34.0)	$p < 0.1$
339	Atenolol	(50 mg daily)	75	18 (25.3)	74	13 (17.6)	N.S.
342[a]	Captopril	(25 mg b.i.d.)	29	9 (31.0)	29	5 (17.2)	N.S.
343[b]	Enalapril	(10 mg daily)	20	8 (40.0)	18	6 (33.3)	N.S.

N.S., not significant.
[a] Studies of double-blind, randomized, crossover design.
[b] Studies of double-blind, parallel-group design.
[c] The p values are based on χ^2 test comparing the incidence of side effects in the two treatment groups; N.S. indicates $p \geq 0.10$.

DISCUSSION

A previous article (3) summarized the results of safety testing from a clinical trials data base of over 4,000 subjects, and indicated that amlodipine was well tolerated, with a low incidence of side effects normally attributed to the unwanted effects of acute vasodilatation. However, a direct comparison with another drug of the dihydropyridine class was not available. The two studies of amlodipine vs. nitrendipine are of interest because the latter drug is the only dihydropyridine that has been advocated for use in a once-daily dosage regimen. Unfortunately, both studies were of an open design. Thus, it is possible that the investigators or patients may have introduced some bias into the reporting of side effects during the trial. Nevertheless, the similarity in incidence of side effects in the two trials and the profile of side effects observed more commonly with nitrendipine suggest that the difference in toleration is a true effect.

Caution is also needed in interpreting the results of a comparison of side effects during the first 3 days of treatment (Table 3). Amlodipine has a relatively long plasma half-life (35–50 h) and therefore plasma levels take several days to approach the steady-state concentration. Thus, the very good toleration of amlodipine at the start of treatment may be related to the fact that optimal plasma levels are still to be achieved. Nevertheless, the good toleration of amlodipine throughout the 4-week (Swiss study) and 8-week (West German study) treatment periods suggests that its pharmacokinetic properties (with only a modest difference between peak and trough plasma levels) may still be advantageous during prolonged therapy. A treatment with a low incidence of side effects at the start of therapy is, of course, likely to improve patient compliance.

Although nitrendipine is the only other dihydropyridine currently available for once-daily dosing, slow-release formulations of other dihydropyridines have been developed. Comparative trials of amlodipine vs. these formulations would be of interest and are currently ongoing.

Increasing clinical experience with amlodipine has confirmed that there is no evidence to suggest that the drug has caused any clinically significant drug interactions. The once-daily dosage regimen of amlodipine and the relative lack of adverse events commonly encountered with other classes of cardiovascular agents suggest that amlodipine will be a valuable addition to the range of drugs used to treat hypertension and/or myocardial ischemia.

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REFERENCES

1. Purcell H, Waller DH, Fox K. Therapeutic focus on calcium antagonists in cardiovascular disease. *Br J Clin Pract* 1989;43:369–79.
2. Julius S. Amlodipine in hypertension: an overview of the clinical dossier. *J Cardiovasc Pharmacol* 1988;12(suppl 7):S27–33.
3. Osterloh IH. The safety of amlodipine. *Am Heart J* 1989;118:1114–20.