Drugs 1999; 57 Suppl. 1: 27-29
0012-6667/99/0001-0027/$01.50/0



# Safety Profile of Lacidipine
## Update from a Clinical Trials Database†

*Lars H. Lindholm,*[1] *Philippe Tcherdakoff*[2] and *Alberto Zanchetti*[3]

1 Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
2 Rue Eugéne Labiche, Paris, France
3 Centro di Fisiologia Clinica e Ipertensione, Università di Milano, Ospedale Maggiore and Istituto Auxologico Italiano, Milan, Italy

Although clear benefits of lowering elevated blood pressure with antihypertensive drugs have been demonstrated in numerous intervention trials,[1,2] several community-based studies have reported that a high risk of cardiovascular disease remains in hypertensive patients, despite a reduction in their blood pressure to reasonable levels. Possible reasons for this include irreversible cardiovascular changes and atherosclerosis in those with long-standing hypertension, inadequate lowering of blood pressure (through fear of lowering it too far), the role of other risk factors such as smoking, alcohol and stress, and adverse effects of the antihypertensive drugs themselves. Earlier intervention studies used diuretics and β-adrenoceptor blockers, but more modern approaches include calcium antagonists, ACE inhibitors and angiotensin-II antagonists, and studies are ongoing to determine whether these drugs are as good as, better than, or not as good as, diuretics and/or β-adrenoceptor blockers in preventing cardiovascular disease.[3-5] Recently, retrospective and observational studies have pointed to possible safety concerns with some older, short-acting calcium antagonists, particularly nifedipine,[6,7] although the design of these studies has been criticised and their findings debated.

While awaiting the outcome of prospective, randomised cardiovascular morbidity and mortality studies with calcium antagonists, we utilised a comprehensive datafile of the manufacturer to evaluate the clinical safety profile of the long-acting calcium antagonist lacidipine.

### 1. Patients and Methods

Safety data from 50 phase III or IV trials of the antihypertensive efficacy of lacidipine (2 to 6mg daily) conducted between January 1985 and January 1995 were analysed; these trials included 18 open studies and 32 controlled, double-blind comparisons with placebo or other antihypertensive drugs (including other calcium antagonists, diuretics, β-adrenoceptor blockers and ACE inhibitors). A total of 16 590 hypertensive patients received lacidipine, 13 419 in open studies and 3171 in controlled comparative trials. Most patients (60%) were treated for 12 to 26 weeks and were aged between 45 and 64 years, although 32.3% were elderly (aged ≥65 years). Hypertension had been diagnosed in most patients (57.8%) one year or more prior to the study; however, concomitant cardiovascular diseases were present in a total of only 8.8%. Altogether, the patients studied contributed 5124 person-years of treatment with lacidipine.

All adverse events (including both fatal and nonfatal cardiovascular events) recorded in the 50 studies were classified according to the International Classification of Diseases code (ICD-9), and the times to their occurrence and their duration were analysed. The incidence of adverse events and

† The data in this Short Communication (except for the data on malignant events) have been previously presented in full in *Blood Pressure 1996; 5: 241-9*. This article is published with the permission of the Scandinavian University Press.

dropout rates during treatment with lacidipine were also compared with those of the other antihypertensive drugs studied.

## 2. Results

Of the 16 590 patients who received lacidipine in the 50 clinical trials analysed, 31.9% (females 35.2%, males 28.9%) experienced adverse events (the most common are shown in figure 1). The median day of onset of these events ranged from day 4 for flushing to day 28 for pedal oedema, and their median duration ranged from 3 days (nausea and cutaneous events) to 6 days (pedal oedema). Analyses of adverse events occurring in the 32 controlled comparative trials showed that the overall incidence with lacidipine (30.3%) was lower than with other calcium antagonists (43.8%) and β-adrenoceptor blockers (48.7%), but higher than with diuretics (18.7%), ACE inhibitors (10.4%), and placebo (15.7%). In comparison with other calcium antagonists, the incidences of headache and pedal oedema were both lower with lacidipine (9.0 and 4.4%, respectively, with lacidipine *vs* 16.5 and 14.4% with other calcium antagonists).

### 2.1 Cardiovascular Events

A myocardial infarction led to lacidipine treatment being stopped in 13 patients. This corresponds to an estimated event rate for myocardial infarction of 2.54 per 1000 person-years of treatment. Subgroup analyses of adverse cardiovascular events in patients both with and without concomitant cardiovascular diseases or diabetes mellitus indicated an elevated risk in those who had cardiac symptoms at baseline in comparison with those who had hypertension only; however, there were very few endpoints (1 myocardial infarction, 12 attacks of angina pectoris) on which to base these risk comparisons. The risk of dropout from lacidipine treatment seemed to be highest in those with ischaemic heart disease at baseline.

### 2.2 Malignant Events

In all studies, a total of 21 malignant events occurred during lacidipine treatment, which corresponds to an estimated event rate of 4.10 per 1000 person-years of treatment. The age-standardised (according to the world population) incidences in patients treated with lacidipine were 1.49 (men) and 0.79 (women), whereas those in the European Community in 1990 were 2.74 (men) and 2.09 (women) per 1000 person-years. All but 2 of the malignant events were considered by the investigators to be non–drug-related.[8]

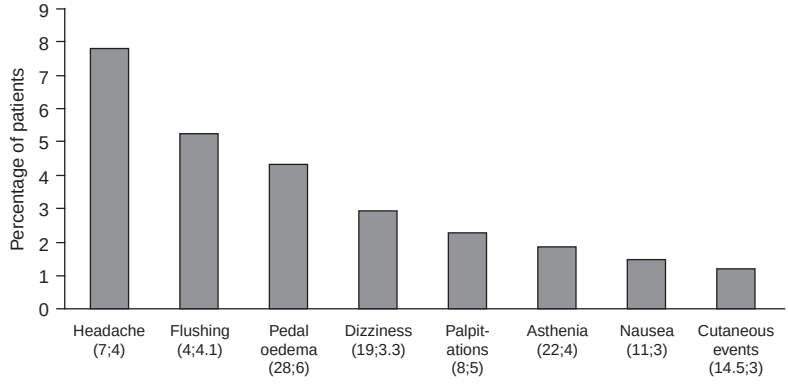


**Fig. 1.** Adverse events (% of patients) experienced during treatment with lacidipine in all 50 clinical studies analysed (n = 16 590). The median day of onset and duration (in days) of each adverse event, respectively, are shown in parentheses (data from Lindholm LH, et al. *Blood Pressure 1996; 5: 241-9*).

### 2.3 Fatal Events

During all studies with lacidipine, 27 fatal events were observed (corresponding to an estimated all-cause fatal event rate of 5.27 per 1000 person-years), and all occurred in patients aged >50 years. A cerebro-cardiovascular cause was considered likely in at least 15 cases, yielding an estimated fatal cardiovascular event rate of 2.93 per 1000 person-years of lacidipine treatment.

## 3. Discussion and Conclusions

Although the data reviewed are characterised by a number of well known limitations (e.g. a small number of events, retrospective analysis, variations in study protocols), the findings indicate that lacidipine is an effective and well tolerated agent with an adverse event profile typical of dihydropyridine-type calcium antagonists. The most common adverse events with lacidipine (fig. 1) are attributable to vasodilatation, e.g. headache, flushing and palpitations, and generally occur within the first week of therapy and last for 4 to 6 days. Dizziness, which is most probably related to the blood pressure-lowering effect, occurs after 2 to 3 weeks and has a median duration of less than one week.

The estimated all-cause fatal event rate with lacidipine treatment in our analysis was 5.27 per 1000 person-years, which is lower than the average levels reported in meta-analyses of antihypertensive drug therapy by Collins et al.[1,2] and Cutler et al.[9] However, the latter analyses comprised much greater person-years of treatment. In our analysis of lacidipine treatment, the very few high risk patients who had signs of cardiac disease at baseline seemed to be at an excess cardiovascular risk compared with those who had hypertension only, but comparisons with other antihypertensive drugs in this regard are not yet possible.

In terms of malignant events, the incidence of which was lower than the age-standardised incidence in the European Community in 1990, our results are in accordance with those of the recent European SYST-EUR trial,[10] which indicated that the risk of cancer was 31% (95% CI –31 to 41%) lower in those receiving a calcium antagonist than in those receiving placebo.

## References

1. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-74
2. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990; 335: 827-38
3. Lindholm LH, Hansson L, Dahlöf B, et al. The Swedish Trial in Old Patients with Hypertension-2 (STOP-Hypertension-2): a progress report. Blood Press 1996; 5: 300-4
4. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study: 24-month data on blood pressure and tolerability. Blood Press 1997; 6 (5): 313-7
5. Zanchetti A. Evaluating the benefits of an antihypertensive agent using trials based on event and organ damage: the Systolic Hypertension in The Elderly Long-term Lacidipine (SHELL) trial and the European Lacidipine Study on Atherosclerosis (ELSA). J Hypertens 1995; 13 Suppl. 13: 535-9
6. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995; 274: 620-5
7. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation 1995; 92: 1326-31
8. Lindholm LH, Tcherdakoff P, Zanchetti A. Safety of the calcium antagonist lacidipine evaluated from a phase III-IV trial database. J Hypertens 1996; 14 Suppl. 2: S15-20
9. Cutler J, Psaty BM, MacMahon S, et al. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management, 2nd ed. New York: Raven Press, 1995: 253-70
10. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350: 757-64

Correspondence and reprints: Prof. *Lars H. Lindholm,* Department of Public Health and Clinical Medicine, Umeå University, SE 901 85 Umeå, Sweden.