Lercanidipine, a new third generation Ca-antagonist in the treatment of hypertension

Gasser R, Klein W, Köppel H

Homepage:

www.kup.at/jcbc

**Online Data Base Search
for Authors and Keywords**

Lercanidipine, a new third generation Ca-antagonist in the treatment of hypertension

R. Gasser, H. Köppel, W. Klein

Recently several large endpoint studies have clearly established the importance of antihypertensive treatment in the prevention of cardiovascular death. Calcium antagonists clearly have their place within the therapeutic efforts aimed at cardiovascular risk control. Despite former debates on side effects and safety problems calcium channel blockers thus still hold an important position in the treatment of systemic hypertension. While earlier developments have focused on increasing potency and selectivity of calcium channel blockers, the most recent developments have brought about drugs with a particularly slow onset and long duration of action. The latest designer-drug in this context is lercanidipine. This particular calcium channel blocker combines practically all desired effects. Pharmacologically the drug has a high lipophilicity which enables a long duration and a single-dose use. It has a unique binding profile which guarantees constant calcium antagonistic action independent of serum concentration changes. The proportion of responding patients lies between 70 and 90 %. The ideal dosage is 10 to 20 mg per day. Adverse effects are few and elderly patients profit from the drug. Thousands of patients throughout Europe have so far been treated with lercanidipine successfully. In particular, the cardiovascular side effects seen with earlier dihydropyridines such as nifedipine are virtually absent with lercanidipine. *J Clin Basic Cardiol 1999; 2: 169–74.*

Key words: lercanidipine, calcium antagonists, hypertension

The second half of the 20th century has seen a constant decrease in cardiovascular mortality in the Western industrialised nations [1]. This decrease has occurred concomitantly with an improved control of hypertension. In the United States, for example, health examination surveys have indicated that adequate blood pressure control in hypertensives has tripled from the late seventies to the early nineties. However, more than 70 % of hypertensive patients are still not subject to proper treatment and will suffer from secondary organ damage, such as stroke, coronary heart disease, heart failure, renal disease, ophthalmic disorders, dementia and others [2]. It is also noteworthy that we are confronted currently with the rapid development of a "second wave" epidemic of cardiovascular disease that is hitting the developing countries and the former socialist republics. There is evidence that death and disability from coronary heart disease and cerebrovascular disease subsequent to hypertension are rising massively in these countries and will outnumber the Western industrial countries by the year 2020 if drastic measures do not occur early enough [3].

Effects of blood pressure on risk of cardiovascular disease
Coronary heart disease
Elevated blood pressure has been related to the risks of major coronary events, such as myocardial infarction and coronary death [4]. It also relates to the amount by which blood pressure is elevated. Patients with a history of previous cerebrovascular disease or myocardial infarction show a direct association between blood pressure levels and risk of recurrent events. Studies which have attempted to distinguish between the effect of hypertension and other factors influencing the risk of recurrence have clearly demonstrated continuous positive associations between blood pressure levels and the longer term risks of stroke and coronary heart disease occurrence.

Cerebrovascular disease
Blood pressure levels have also been positively and continuously related to the risk of stroke [4, 5]. The association to a change of only a few millimetres Hg of blood pressure can be clearly seen from the fact that a prolonged reduction of diastolic blood pressure by only five millimetres Hg is associated by a 35 to 40% reduction of stroke risk [6]. Blood pressure levels are also positively related to cerebral haemorrhage, cerebral infarction and dementia [5].

Other relationships
For example, heart failure and renal disease have been related to elevated blood pressure – while these are not as well established as for stroke and CHD, hypertension related left ventricular hypertrophy has been well described as an independent risk factor for cardiac events. It has, for example, been shown that lowering diastolic blood pressure by 5 mmHg is associated with a 25 % lower risk of end-stage renal disease [7].

Elevated blood pressure in conjunction with other cardiovascular risk factors
In particular, in patients with mild hypertension, the presence of other cardiovascular risk factors determine the course of the patient's cardiovascular events. Age, gender, pre-existing cardiovascular disease, renal disease, diabetes, hyperinsulinaemia and hyperglycaemia, active and passive smoking, obesity, hyperfibrinogenaemia, low socio-economic status, ethnic factors, blood type, LDL particle size, apolipoproteins, plasma renin activity, blood homocysteine levels, blood uric acid levels, certain gene polymorphisms, infective agents, psychological factors etc. are just a few of the factors, which appear in the symphony that determines the tragedy of cardiovascular disease. Hypertension severely aggravates such pre-existing risk factors – differences in the absolute level of cardiovascular risk between patients at risk will often be determined to a greater extent by other risk factors than by the levels of blood pressure. Alternatively, UKPDS has taught us that, in diabetic patients, it is more important to reduce blood pressure than blood glucose in order to prevent cardiovascular events [8]. Syst-Eur has also pushed forward the issue of dementia, which has been diminished in patients with adequate blood pressure control [9]. The facts which we have briefly

outlined above corroborate the rationale for adequate blood pressure control.

Drug treatment for lowering blood pressure

Basically, there are six main drug classes used in the treatment of blood pressure. Diuretics, beta-blockers, calcium antagonists, ACE-inhibitors, angiotensin II-antagonists and alpha adrenergic blockers. While there is no reliable or consistent evidence that reveals substantive differences between drug classes on the effect on blood pressure, there are important differences in the side-effect profiles of each class [10]. Furthermore, we do find important differences between classes in the amount of evidence available from randomised controlled trials on the effect on morbidity and mortality. There are more data demonstrating the benefits of the older agents, such as diuretics, beta-blockers and calcium-antagonists, while there are fewer data available on ACE-inhibitors, angiotensin II-antagonists and alpha-blockers.

Calcium-antagonists in the treatment of hypertension

"All subgroups of calcium-antagonists are effective and well tolerated in lowering blood pressure" (quote from 1999 WHO-International Society of Hypertension Guidelines for the Management of Hypertension [10]). The same guidelines suggest that long acting calcium antagonists are preferred over rapid-onset, short acting calcium-antagonists. The latter should be avoided. Long acting calcium-antagonists are particularly recommended for elderly patients with systolic hypertension and for coloured patients. While several studies have cast an unfavourable light on the use of calcium channel blockers as first-line antihypertensive agents [11–14], morbidity and mortality results of other trials such as Syst-Eur [9], Stone [15] and others have evidenced that calcium-antagonists are definitely useful in the treatment of hypertension.

Lercanidipine – a long acting lipophilic dihydropyridine

The search for new designs of calcium-antagonists with extended properties has superseded the earlier search for new clinical indications for these drugs [16]. Such improved qualities of new dihydropyridines would be prolonged action, less side effects, single dosing (improved compliance) and less negative inotropic and chronotropic action. A second generation of calcium antagonists has addressed this problem with variable success. While drugs like nitrendipine [17] or amlodipine [18] have done reasonably well, others such as mibefradil [19] or isradipine in the MIDAS-trial [20] have not shown such a favourable outcome.

The third generation of dihydropyridines has added an additional property to this class of drugs: high lipophilicity. Currently one of these drugs commercially available is lercanidipine. As a result of the lipophilic character this compound is relatively quickly cleared from plasma building up within the phospholipide bilayer of cell membranes. The dihydropyridine thus accumulated can interact with its target, the DHP site of the target, the L-type calcium channel which lies within the double layer of the cell membrane as well. This phenomenon explains on the one hand the slow onset, on the other hand the long duration of action. Hence, reflex tachycardia is practically absent and the gentle and slow onset of the antihypertensive effect allows a good control of therapy. The enhanced membrane interactions at the arterial wall and smooth muscle cell provide lercanidipine's strong attraction to cell membranes at the molecular level – a vaso-functional tropism at the tissue site of action [21].

Chemistry of lercanidipine

Lercanidipine is derived from a group of new 4-aryl-2,6-dimethyl-1,4 dihydropyridine-3,5-dicarboxylic acids dialkyl esters with different lipophilic amino-alkyl groups in one of the two ester-groups [22, 23]. The aim was to improve the duration of action by increasing the overall lipophilicity. In order to do so, structural variations at the aryl group at position 4 of the 1,4-dihydropyridine and at the non-basic alkyl-ester were introduced. Furthermore, structural variations in the length and branching of the alkyl group linking the amino group to the dihydropyridine nucleus have been introduced. The presence of a 3,3-diphenylpropylmethylamino-2-methyl-2-propyl chain improves the lipophilic properties and membrane adherence of this drug.

Pharmacology of lercanidipine

Calcium antagonists with a long clinical half life

Several different agents with calcium antagonistic activity, dihydropyridine-derivatives, have emerged on the market during the recent years. The first of these drugs, which I remember working on in Albrecht Fleckenstein's laboratories in Freiburg, was amlodipine, a DHP with 30 to 50 hours clinical half life [16, 24]. While in the early days such an extremly long half life appeared useless, in particular when aiming at coronary spasm and angina pectoris, the situation has changed and long acting calcium channel blockers have become an important tool for the treatment of systemic hypertension [25]. Further drugs of this kind which have entered the market are lacidipine and lercanidipine [26]. Distinct molecular properties form the basis of a long plasma half life like amlodipine or a long action via a membrane kinetic control mechanism derived from high lipophilicity. Amlodipine possesses a rate limiting transport across membranes which is much slower than that of the earlier DHP compounds [27]. This drug shows a slow and gradual onset of action. However, the exact pharmacological reasons for this have not been elucidated as yet. In this context, it should be noted that it equilibrates to relatively high levels in membranes as measured by the membrane partition coefficient (log $Kb_{(min)}$ = 4.3). While amlodipine has proven to be a useful antihypertensive drug (note that there are no large endpoint studies) in hypertensive patients with normal renal function, in the older patient, in contrast, who suffers from end-organ damage as a result of long persistent systemic hypertension (in particular, with renal impairment), the half life of amlodipine can increase up to sixty and more hours. This may result, of course, in an accumulation of the drug in the plasma, a drawback well known for amlodipine.

The pharmacokinetics of lercanidipine are clearly distinct from those of amlodipine: it is primarily controlled by the tissue cell compartment via a membrane kinetic control mechanism. Its in vitro calcium antagonistic activity is clearly related to a gradual block of calcium entry into smooth muscle cells via L-type calcium channels. The antihypertensive effect was tested experimentally in several models: it was effective in two-kidney, two-clip model of Goldblatt hypertension in dogs [28] and in spontaneously hypertensive rats [29]. The effect of lercanidipine in animals is gradual in onset and persists for many hours. Displacement binding studies on different membrane preparations showed that lercanidipine was

more potent than both nifedipine and amlodipine [30, 31]. The affinity of lercanidipine for the L-type calcium channel labelled by the tritiated ligands translates into a functional calcium antagonistic activity. Furthermore, lercanidipine promptly and lastingly inhibited guinea-pig ileal longitudinal smooth muscle when precontracted in high K^+ solution [31]. It has also been shown that lercanidipine selectively inhibits the influx of extracellular calcium through voltage-gated calcium channels, but not through receptor-operated calcium channels [30]. The increase of calcium-antagonistic action of lercanidipine is gradual over a period of 3 hours, more slowly than with any DHP ever studied [30, 31]. The smooth onset of lercanidipine's action plays an important role in the prevention of potentially lethal side effects seen with fast acting DHPs [13, 14].

In chronically catheterised dogs with experimental renovascular hypertension lercanidipine decreased diastolic blood pressure in a dose-dependent manner ($ED_{25} = 0.9$ mg/kg p.o; [32]). In the same animals, long term application of lercanidipine showed permanent decrease of diastolic blood pressure indicating no tolerance of the antihypertensive effect.

Gradual onset and selectivity

Lercanidipine is, in comparison to other DHPs characterised by a peculiarly gradual onset and long-lasting duration despite decreasing plasma levels. In chronically catheterised animals, the time to the maximal effect of lercanidipine was significantly longer than that for nicardipine, felodipine and nitrendipine [32, 33]. The antihypertensive effects persisted up to nine hours after oral administration of 3 mg/kg. Sironi and co-workers [34] demonstrated this slow onset of antihypertensive action by intravenous administration of lercanidipine and showed that the peak effects of this drug occurred up to 30 times later than those of, eg, nitrendipine. These *in-vivo* findings seen in animals confirm the *in-vitro* data related in the previous section [30, 31]. The most striking observation with lercanidipine is that the recovery of isolated rat aorta contractile response to high K^+ solution after incubation with lercanidipine was null, most remarkably, even at six hours after removal of the drug from the bath [35]. This has not been seen with any other DHP. The mechanism underlying these observations involves binding properties and drug partitioning in the bilayer matrix of the cell membrane, followed by lateral diffusion to its specific receptor site. Prolonged storage in membrane compartments may contribute to the long duration of action. It has been shown that lercanidipine is endowed with the highest membrane partition coefficient of DHPs. Furthermore, its release from its vesicle membrane is very slow, ie, long permanence in the phospholipidic bilayer [36].

Therapeutic use in essential hypertension

The unique profile of lercanidipine enables the drug to control systemically elevated blood pressure over a long time-window. The time to peak-hypertensive effect ranges from 5 to 7 hours after administration of lercanidipine [35]. The trough-to-peak ratio for the drug is high, above 0.80 for 10 mg lercanidipine – once corrected for placebo, the ratio is further increased, indicating a smooth antihypertensive activity of doses between 10 and 20 mg [37]. In elderly patients, the trough-to-peak-ratio was 0.77 [38]. Testa et al. [35] also report that a dose as low as 5 mg does not suffice for the treatment of even mild to moderate hypertensive patients. Doses of 10, 20 and 30 mg have been tested, given as single and once daily repeated doses, administered for one to four weeks in various randomised, double-blinded [35] studies.

Response to the drug

The rate of responding patients hovers between 66 and almost 90 % – on a dose range going from 10 mg/day up to 20 mg/day [37]. In 8 different controlled trials the drug consistently showed response rates over 60 % [35]. In a randomised, double-blind and placebo-controlled trial on 132 patients lercanidipine was tested with placebo in 10 and 20 mg single-doses a day. Concerning tolerability the drug was excellent and adverse effects reported in the study were minimal [37] (Figure 1).

The study lasted four weeks and the changes in the heart rate observed were negligible. The authors concluded that a dose of 10 mg is the most appropriate for the majority of patients and is associated with no reflex cardiostimulation and with a side-effect profile not significantly different from that of placebo. In another study [39], lercanidipine was compared with atenolol and a combination of atenolol and lercanidipine in 217 patients with moderate hypertension. The authors could show that lercanidipine lowered systolic and diastolic blood pressure by 12 mmHg and 10 mmHg respectively, atenolol by 12 and 15 mmHg. There were no significant differences between atenolol and lercanidipine on systolic and diastolic blood pressure within a time frame of four weeks. Doses have been titrated up from 10 to 20 mg of lercanidipine and from 50 mg to 100 mg atenolol and the response rate was between 80 and 90 %. The combination of the two drugs in non-responders after 8 weeks of treatment elicited only a modest increase in the overall percentage of responders. This means that in both groups, the number of patients who required a combination of the drugs was very small. Heart rate changes were absent with lercanidipine. The same study also tested the effectiveness of once daily administration of lercanidipine by comparing the blood pressure values after 24 hours and 4 hours after the last administration. These two were similar, demonstrating the long duration of antihypertensive effect. Similarly, Policicchio [40] tested the efficacy and tolerability of lercanidipine in patients, comparing it with slow-release nifedipine in a 3 week placebo run-in study. 130 patients were randomised receiving either 10 mg of lercanidipine or 20 mg of slow-release nifedipine twice-daily for four weeks. Dose-doubling and addition of 12.5 mg hydrochlorothiazide were allowed in non-responding patients or when diastolic blood pressure persisted higher than 90 mmHg. In this study both drugs significantly reduced blood pressure in patients with mild to moderate hypertension and it has been demonstrated
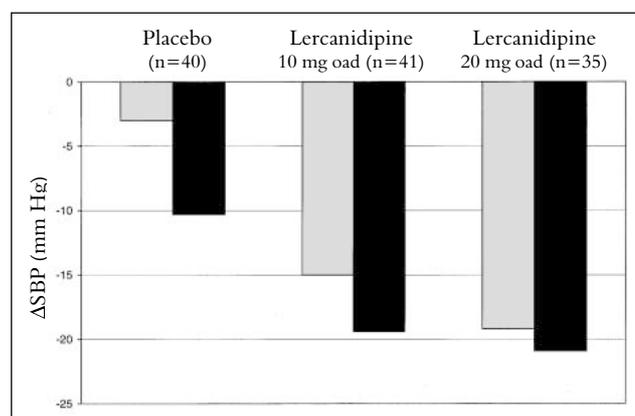

Figure 1. Mean decrease in systolic blood pressure (SBP) after 4 weeks of treatment as seen by Circo in 132 patients (redrawn according to [37]; grey: 24 ± 2 hours post-dose; black: 4–5 hours post-dose)

that the efficacy of 10 mg lercanidipine is comparable to 20 mg of slow-release nifedipine. The efficacy of both drugs was equally improved when they were combined with 12.5 or 25 mg of hydrochlorothiazide. At the end of the treatment-period almost all patients were normalised in both treatment groups. Finally, the study demonstrates that a single dose of lercanidipine per day is as effective as the twice-daily dose of slow-release nifedipine, indicating an important advantage of the drug (single-dose-compliance!). Placebo-controlled studies showed that a single 10 or 20 mg of lercanidipine was more effective than placebo. In comparison with other antihypertensive agents also nitrendipine and amlodipine have been studied effectively [35]. Barbagallo and co-workers [41] showed that 10 mg of lercanidipine is effective in lowering blood-pressure in patients with mild and moderate hypertension as a single dose whereas captopril 50 mg achieved a similar reduction in blood pressure only in two divided doses. Captopril was demonstrated as equally effective in reducing blood pressure and in the percentage of normalised and responding patients. The tolerability of the two doses was also similar. Neither drug significantly altered heart rate. They also showed a very low incidence of adverse effects. Ninci and co-workers [42] showed in a multicenter randomised double-blind and placebo-controlled trial in elderly patients (60 to 85 years) that a single dose of 10, 20 or 30 mg of lercanidipine had a 24 hour lasting effect and was well tolerated. The trough-to-peak ratio referred to diastolic blood pressure measurements taken 24 + 2 (trough) and 4 to 5 (peak) hours of lercanidipine and was 0.77 (see above) which is one of the highest observed amongst calcium-antagonists [43] and reflects a balanced and durable antihypertensive effect [44].

In a particular situation of increased systolic blood pressure typical of the elderly lercanidipine proved to be effective namely "In a double blind randomized controlled study versus placebo in patients with isolated systolic hypertension Lercanidipine was efficacious in lowering systolic blood pressure from mean initial values of 172.6 ± 5.6 mmHg to 140.2 ± 8.7 mmHg." [45]

Lercanidipine was also tested in the treatment of severe hypertension. Several studies are devoted to this question and lercanidipine in doses of 20 mg were administered once or twice daily with an increase up to a maximum of 40 mg daily in 50 patients with severe hypertension (diastolic blood pressure above 110 mmHg). For ethical reasons there was no placebo-comparison. The full course of treatment lasted 90 days with follow-up visits performed every 5 days. Lercanidipine administered once or twice daily led to a significant decrease in diastolic blood pressure within 60 days (Figure 2). The efficacy was confirmed with a high percentage of response (over 90 %). The authors show that the once daily regimen is also very effective in patients with severe hypertension both from the point of view of patient's compliance and from the point of view of detectable blood pressure drop [46]. In another controlled, randomised, double-blind study in 80 patients with uncontrolled severe hypertension, lercanidipine was administered over 12 weeks in doses between 10 and 30 mg once daily and compared to nitrendipine 10 to 30 mg once daily in association with a preexisting antihypertensive therapy (diuretics, ACE-inhibitor or beta-blocker). Lercanidipine reduced diastolic blood pressure by 13 mmHg after 4 weeks, similar to nitrendipine (12 mmHg). In this study lercanidipine showed less side effects than nitrendipine [47]. In over 400 patients, lercanidipine has been tested for a long period of time (12 months; [48]). The patients did not develop any tolerance for lercanidipine. The antihypertensive effect could be maintained throughout the study. In the same study, it was been demonstrated that 10 mg as a single dose was a good choice, only 48 of 355 patients treated with this dose needed an increase of the dose to 30 mg a day.

Other beneficial effects of lercanidipine

Myocardial protection during ischaemia
a.) Antagonism to the vasopressor activity of endothelin-1:
Rossoni and co-workers have shown that Lercanidipine infused for 5 min before flow rate reduction in isolated rabbit hearts prevented in a dose-dependent manner the increase of ischaemic resting tension (ventricular contracture) and favoured a graded recovery of cardiac contractility with regular pacing at reperfusion. Lercanidipine also shifted to the right the dose-dependent curve of endothelin-1 on coronary perfusion pressure and the N^g-mono-methyl-L-arginine induced hyper-responsiveness of the coronary arteries to ET-1 was markedly reduced by Lercanidipine [49]. The data indicate a potent antiischaemic protection by lercanidipine.

b.) Effects of Lercanidipine on mitochondrial lipid-peroxydation:
Bernocchi and co-workers, using myocardial mitochondria from New Zealand white rabbits, showed that 10^{-7} M Lercanidipine exerted a significant protection against Fe^{2+}-induced lipid-oxidation, improving all indices of mitochondrial function and prevented Fe^{2+}-mediated changes in mitochondrial calcium accumulation [50].
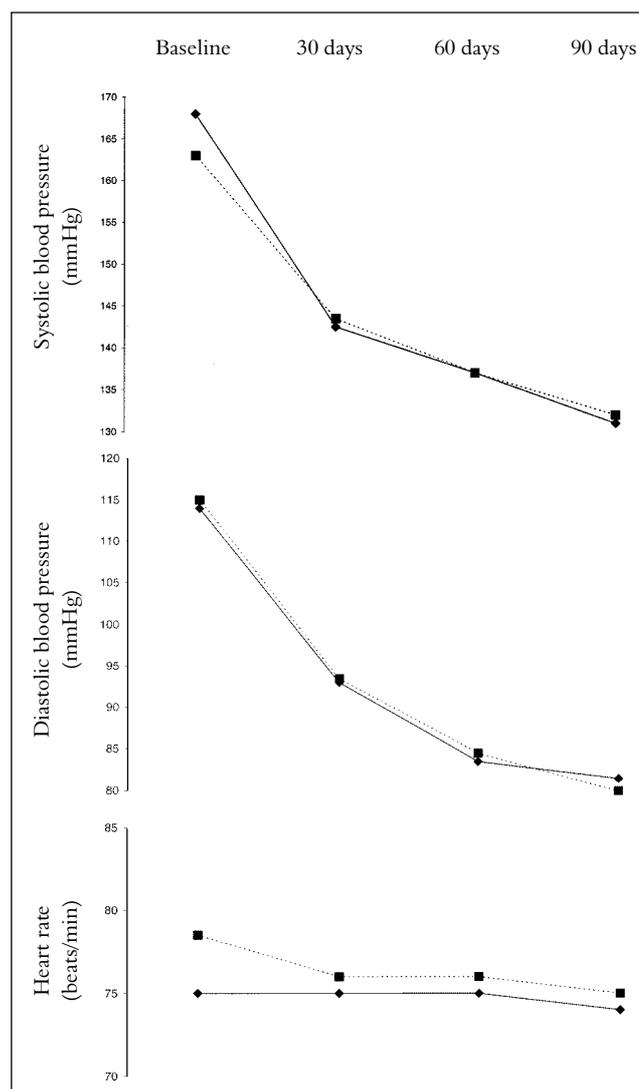

Figure 2. Mean supine systolic and diastolic blood pressure and heart rate at baseline and after 30, 60 and 90 days treatment with lercanidipine 20–40 mg once (n = 16; ◆) or twice daily (n = 20; ■)(redrawn according to [46])

Unusual effects of Lercanidipine

In a study in hypertensive patients with non-insulin dependent diabetes mellitus, the drug showed a slight decrease in fasting blood-glucose, glycosylate-haemoglobin, fructosamin, and improved oral glucose tolerance [35]. Lercanidipine was also effective in inducing proliferation and migration of rat arterial myocytes [51], thus exhibiting a potent antiarteriosclerotic action.

Clinical safety

Practically no vasodilation related adverse effects such as ankle oedema, headache, flush or dizziness could be reported. Data derived from double-blind studies in which lercanidipine was compared to other calcium channel blockers, beta-blockers, ACE-inhibitors and diuretics also showed that lercanidipine had equal or less adverse effects than the others [47]. The cardiovascular safety of lercanidipine is guaranteed by the stable blood-pressure control over 24 h without marked hypotension during the night-time. These may be linked to coronary events and strokes [52]. The overall side-effects are minimal and mostly less than with other drugs.

Conclusion

The recently published large endpoint-trials on antihypertensive treatment have clearly established the importance of a proper control of blood pressure. Calcium channel blockers, despite former debates on side-effects and safety-problems, still hold an important position in the treatment of systemic hypertension.

While earlier developments have focused on increasing potency and selectivity of calcium channel blockers the most recent developments have brought about drugs which are particularly slow in onset and have a long duration of action. The latest "designer-drug" in this context is lercanidipine. This calcium channel blocker combines practically all desired effects through its high lipophilicity. It has, furthermore, an unique binding profile, which guarantees constant calcium antagonistic action independent of serum concentration changes. The available literature shows a brilliant antihypertensive effect of the drug tested in many thousands of patients. A further important advantage of the drug is the single-dose daily application which improves the compliance and therefore control of blood pressure.

References

1. Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialised countries since 1950. World Health Stat Q 1988; 41:155–68.
2. Marques-Vidal P, Tuomilehto J. Hypertension awareness, treatment and control in the community: is the "rule of halves" still valid? J Hum Hypertens 1997; 11: 213–20.
3. Murray CJL, Lopez AD. The global burden of disease. a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. World Health Organisation, Geneva, 1996.
4. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765–74.
5. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol and stroke in Eastern Asia. Lancet 1998; 352: 1801–7.
6. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 45,000 people in 45 prospective cohorts. Lancet 1995; 346: 1647–53.
7. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996; 334: 13–8.
8. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703–13.
9. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350: 757–64.
10. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens 1999; 17: 151–83.
11. Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik RJ. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. Lancet 1996; 347: 1061–5.
12. Pahor M, Guralnik JM, Ferrucci L, et al. Calcium-channel blockade and incidence of cancer in aged populations. Lancet 1996; 348: 493–7.
13. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. Circulation 1995; 92: 1326–31.
14. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995; 274: 620–5.
15. Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Page V, et al. Shanghai Trial of Nifedipine in the Elderly (STONE). J Hypertens 1996; 14: 1237–45.
16. Gasser R. Calcium antagonists: pharmacological agents in search of new clinical indications. Angiology 1990; 41: 36–41.
17. Goa KL, Sorkin EM. Nitrendipine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of hypertension. Drugs 1987; 33: 123–55.
18. Meredith PA, Elliott HL. Amlodipine: clincial relevance of a unique pharmacokinetic profile. J Cardiovasc Pharmacol 1993; 22 (Suppl A): S6–S8.
19. Triggle DJ. Pharmacologic and therapeutic differences among calcium channel antagonists: profile of mibefradil, a new calcium antagonist. Am J Cardiol 1996; 78 (Suppl 9A): 7–12.
20. Brohani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Rerris M, Carr AA, Kappagoda T, Rocco MV, Schnaper HW, Sowers JR, Bond MG. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. JAMA 1996; 276: 785–91.
21. Herbette L. Lipophilic design of dihydropyridine calcium channel blockers: enhanced membrane properties. 3rd European Meeting on Calcium Antagonists. Symposium Lipophilic dihydropyridines: a new generation of calcium channel blockers. Amsterdam, October 31, 1997 (Abstract).
22. Leonardi A, Nardi D, Pennini R, et al. New 1,4-dihydropyridines with antihypertensive activity. IX International Symposium on Medical Chemistry, Berlin, September 14–18, 1986.
23. Nardi D, Leonardi A, Cerri A, et al. Asymmetric N-(3,3 diphenylpropyl)aminoalkyl esters of 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids with antihypertensive activity. J Mol Cell Cardiol 1995; 27: A385.
24. Fleckenstein A, Frey M, Zorn J, Fleckenstein-Grun G. Amlodipine, a new 1,4-dihydropyridine calcium antagonist with a particularly strong antihypertensive profile. Am J Cardiol 1989; 64: 21I–34I.
25. Abernethy DR, Gutkowaka J, Winterbottom LM. Effects of amlodipine, a long acting dihydropyridine calcium antagonist in aging hypertension: pharmacodynamics in relation to disposition. Clin Pharmacol Ther 1990; 48; 76–86.
26. Herbette LG, Vecchiarelli M, Sartani A, Leonardi A. Lercanidipine: short plasma half-life, long duration of action and high cholesterol tolerance. Updated molecular model to rationalize its pharmacokinetic properties. Blood Pressure 1998; 7 (Suppl 2): 10–17.
27. Mason RP, Campbell S, Wang S, Herbette LG. A comparison of bilayer location and binding for the charged 1,4-dihydropyridine Ca^{2+} channel antagonist amlodipine with uncharged drugs of this class in cardiac and model membranes. Mol Pharmacol 1989; 36: 634–40.
28. Zimmerman BG. Peripheral neurogenic factors in acute and chronic alterations of arterial pressure. Circ Res 1983; 53: 121–30.
29. Ganten D. Role of animal models in hypertension research. Hypertension 1987; 9: I2–I4.
30. Guarneri L, Angelico P, Ibba M, et al. Pharmacological in vitro studies of the new 1,4-dihydropyridine calcium antagonist lercanidipine. Arzneim Forsch/ Drug Res 1996; 46: 15–24.
31. Leonardi A, Poggesi E, Taddei C, et al. In vitro calcium-antagonistic activity of lercanidipine and its enantiomers. J Cardiovasc Pharmacol 1997; 29 (Suppl 1): S10–S18.
32. Sironi G, Montagna E, Greto L, Bianchi G, Leonardi A, Testa R. Antihypertensive effects of lercanidipine in experimental hypertensive rats and dogs. Arzneim Forsch/Drug Res 1996; 46: 145–52.
33. Sironi G, Colombo D, Greto L, Testa R, Leonardi A. Antihypertensive activity of lercanidipine and its enantiomers in animal models. J Cardiovasc Pharmacol 1997; 29 (Suppl 1): S33–S40.
34. Sironi G, Montagna E, Greto L, Leonardi A, Testa R. Hemodynamic effects of lercanidipine in anaesthetized open-chest dogs. Arzneim Forsch/Drug Res 1996; 46: 256–61.
35. Testa R, Leonardi A, Tajana A, Riscassi E, Magliocca R, Sartani A. Lercanidipine (Rec 15/2375): a novel 1,4-dihydropyridine calcium antagonist for hypertension. Cardiovasc Drug Rev 1997; 15: 187–219.
36. Herbette LG, Vecchiarelli M, Leonardi A. Lercanidipine: short plasma half-life, long duration of action "A molecular model to rationalize its pharmacokinetic properties". J Cardiovasc Pharmacol 1997; 29 (Suppl 1): S19–S24.
37. Circo A. Active dose findings for lercanidipine in a double-blind, placebo-controlled design in patients with mild to moderate hypertension. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S22–S26.
38. Ninci MA, Magliocca R, Malliani A. Efficacy and tolerability of lercanidipine in elderly patients with mild to moderate hypertension in a placebo-controlled, double-blind study. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S41–S45.

39. Morisco C, Trimarco B. Efficacy and tolerability of lercanidipine in comparison to and in combination with atenolol in patients with mild to moderate hypertension in a double-blind controlled study. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S26–S30.

40. Policicchio D, Magliocca R, Malliani A. Efficacy and tolerability of lercanidipine in patients with mild to moderate essential hypertension: a comparative study with slow-release nifedipine. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S31–S35.

41. Barbagallo Sangiorgi G, Putignano E, Calcara L, Barbagallo M. Efficacy and tolerability of lercanidipine vs. captopril in patients with mild to moderate hypertension in a double-blind controlled study. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S36–S39.

42. Ninci MA, Magliocca R, Malliani A. Efficacy and tolerability of lercanidipine in elderly patients with mild to moderate hypertension in a placebo-controlled, double-blind study. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S40–S44.

43. Meredith PA, Reid L. Differences between calcium antagonists: duration of action and trough to peak ratio. J Hypertens 1993: 11 (Suppl 1): S21–S26.

44. Lipicky RS. Trough/peak ratio: the rationale behind the United States Food and Drug Administration recommendations. J Hypertens 1994; 12 (Suppl 8): S17–S19.

45. Barbagallo Sangiorgi G. A study of the efficacy and tolerability of Lercanidipine as sole treatment in elderly patients with isolated systolic hypertension. A multicenter double blind comparison with placebo. (Data on file)

46. Paterna S, Licata A, Arnone S, Cottone C, Corrao S, Licata G. Lercanidipine in two different dosage regimens as a sole treatment for severe essential hypertension. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S50–S53.

47. Rengo F, Romis L. Activity of lercanidipine in double-blind comparison with nitrendipine in combination treatment of patients with resistant essential hypertension. J Cardiovasc Pharmacol 1997; 29 (Suppl 2): S54–S58.

48. Cafiero M, Giasi M. Long-term (12 month) treatment with lercanidipine in patients with mild to moderate hypertension. J Cardiovasc Pharmacol 1987; 9 (Suppl 2): S46–S50.

49. Rossoni G, Bernareggi M, De Gennaro Colonna V, Polvani G, Berti F. Lercanidipine protects the heart from low flow ischemia damage and antagonizes the vasopressor activity of endothelin-1. J Cardiovasc Pharmacol 1997; 29 (Suppl 1): S41–S47.

50. Bernocchi P, Ceconi C, Cargnoni A, Pedersini P, Boraso A, Curello S, Ferrari R. Effects of lercanidipine on Fe^{2+}-induced mitochondrial lipid peroxidation.J Cardiovasc Pharmacol 1997; 29 (Suppl 1): S63–S68.

51. Corsini A, Bonifatti M, Quarato P, et al. Effect of the new calcium antagonist lercanidipine and its enantiomers on the migration and proliferation of arterial myocytes. J Cardiovasc Pharmacol 1996; 28: 687–94.

52. Floras JS. Antihypertensive treatment, myocardial infarction and nocturnal myocardial ischaemia. Lancet 1988; 2: 994–6.

Mitteilungen aus der Redaktion

Besuchen Sie unsere
zeitschriftenübergreifende Datenbank

☑ **Bilddatenbank**   ☑ **Artikeldatenbank**   ☑ **Fallberichte**

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☑ **Bestellung e-Journal-Abo**