REVIEW OF THE AVAILABLE EVIDENCE ABOUT NIFEDIPINE IN THE TREATMENT OF HYPERTENSION

Introduction

The aims of the present review were to make an evidence-based recommendation regarding inclusion/exclusion of long-acting nifedipine (LAN) in the WHO Model List of Essential Medicines (EML) and to consider possible alternatives.

Findings from a meta-analysis published in 1995 suggested that in the secondary prevention of myocardial infarction, short-acting nifedipine in moderate to high doses causes an increase in total mortality.\(^1\) Several plausible explanations for this adverse outcome have been suggested, including a proischaemic effect, a negative inotropic effect, marked hypotension, and proarrhythmic effects. A prohemorrhagic effect attributed to antiplatelet and vasodilatory actions of calcium channel blockers has also been reported.\(^1\) More recently, in two case-control studies an increased risk of cardiovascular events in hypertensive patients treated with short-acting calcium channel blockers was found.\(^2,3\) As a result, in 1997 the VI Report of the Joint National US Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended avoiding the use of short-acting calcium channel blockers in patients with hypertension and angina pectoris.\(^4\) At that time, data for long-acting calcium channel blockers were scarce, but in 1996-2004 several trials have been published which deserve attention.

Specific objectives:

- To assess the efficacy and safety of LAN for the treatment of different types of hypertension (essential, isolated systolic, hypertensive emergencies and hypertension in pregnancy).
- To evaluate the existing evidence on the role of LAN in patients with common comorbidities (heart failure, coronary heart disease, diabetes, and chronic kidney disease) and in certain subgroups (advanced age and particular ethnic origins).
- To assess the efficacy and safety of LAN as a tocolytic agent for preterm labour.
- To evaluate the patent status of the existing LAN formulations.

For all these conditions, the efficacy and safety of possible alternatives was assessed and was taken into consideration.

Methods

We made a bibliographic search through the computerised databases Medline and Cochrane reviews, looking for the main clinical trials and meta-analyses on nifedipine and on possible alternatives for the treatment of the different types of hypertension (essential, isolated systolic, emergency and hypertension during pregnancy). The available evidence on the treatment of patients with the commonest comorbidities (heart failure, coronary heart disease, diabetes, and chronic kidney disease), and in patients with common demographic characteristics (by age and by various ethnic groups) was also reviewed. As nifedipine is also used as a tocolytic for preterm labour, its efficacy in this condition was also evaluated.
Evaluation of the efficacy and safety of nifedipine and possible alternatives in each type of hypertension was based on total mortality and on the main cardiovascular end points (myocardial infarction, stroke and heart failure) from studies. Other assessed variables were doubling in serum creatinine concentration and development of end-stage renal disease for diabetic patients and those with chronic kidney disease, and length of pregnancy prolongation and perinatal mortality and morbidity in the presentation of preterm labour.

The patent status of different formulations of nifedipine and their potential alternatives was obtained from the FDA webpage (‘Orange Book’).

The following were the main clinical questions addressed in the present review:

- Is LAN effective and safe for the treatment of hypertension?
- Should an alternative or an additional dihydropyridine or other long-acting calcium channel blocker be included in the EDL?
- Is there a dihydropyridine which is more effective and safe than nifedipine for the treatment of essential hypertension?
- What is the efficacy and safety of nifedipine in other indications as hypertension of pregnancy and as a tocolytic for preterm labour? Are there other medicines or other dihydropyridines which can be preferable for the treatment of these conditions?

**Essential (systolic-diastolic) hypertension**

The results of several randomised clinical trials showed that in comparison with placebo, in patients with hypertension treatment with thiazide diuretics and/or β-blockers reduce the risk of some major cardiovascular events (stroke, myocardial infarction).5-7 Both groups of drugs (thiazide diuretics and β-blocker agents) are generally regarded as first line treatment for patients with essential hypertension.4,8

For other antihypertensive drugs, namely new antihypertensive drugs (i.e., ACE inhibitors, calcium channel blockers, α-blockers and angiotensin antagonists), results of clinical trials have been available more recently. In general, these “new drugs” have been compared in clinical trials to “old drugs”.

The Chinese trial STONE (Shanghai Trial Of Nifedipine in the Elderly) compared a long-acting formulation of nifedipine to placebo in patients with hypertension.9 The results were favourable to nifedipine (see table 1) but the allocation of patients to the treatment groups was alternative (not randomised), the distribution of certain baseline clinical characteristics of patients to both groups of treatment was not symmetrical, no blood pressure endpoint in the placebo group was set, and there was no available pharmacokinetic information on the long-acting formulation of nifedipine used in this study.

In a meta-analysis of four published trials (two with amlodipine, one with nisoldipine, and one with nitrendipine) comparing a dihydropyridine with placebo in hypertensive patients, the relative risks of total major cardiovascular events (stroke, coronary heart disease, heart failure, or cardiovascular death) and of stroke were reduced by the
calcium channel blockers (RR=0.82 [95%CI 0.71-0.95], and RR=0.62 [95%CI 0.47-0.82], respectively), although the effect of drugs on heart failure was not clear (RR=1.21 [95%CI 0.93-1.58]).

In the INSIGHT (INtervention as a Goal in Hypertension Treatment) trial, a long-acting formulation of nifedipine (GITS) was similarly effective to hydrochlorothiazide plus amiloride in reducing a composite variable of cardiovascular events (see table 1). However, the results were also compatible with a 36% increase of the overall cardiovascular end-points with nifedipine compared to the diuretic combination. More patients died of myocardial infarction and were admitted for heart failure in the nifedipine group, but the number of events was small in both groups (see table 1).

Nifedipine retard was also compared with ACE inhibitors in a smaller clinical trial in Japanese hypertensive patients (JMIC-B). No differences were observed between both groups of treatment in reducing major cardiovascular end-points (see table 1).

The ALLHAT (the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) study is the largest trial up to now on the treatment of hypertension. The primary outcome was CHD or non-fatal myocardial infarction. No difference between amlodipine and chlortalidone was seen in the primary variable and in secondary outcomes (stroke and total mortality) (see table 2). However, a higher rate of heart failure was seen with amlodipine (RR=1.38 [95%CI 1.25-1.52]).

Recently in the VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation) no difference was seen between valsartan and amlodipine in the primary end-point (a composite variable of cardiac mortality and morbidity). The relative risk was 1.04 (95%CI 0.94-1.15) (see table 2).

The incidence of myocardial infarction and stroke was higher with valsartan and that of heart failure was higher with amlodipine. However, it has been suggested that the inequalities in blood pressure in favour of amlopidine, specially in the early period (blood pressure $4.0/2.1$ mm Hg lower with amlodipine compared to valsartan after one month), hinder the comparison of cardiovascular outcomes.

The HOT study (Hypertension Optimal Treatment) assessed the effects of intensive lowering of blood pressure in patients with hypertension. Felodipine was given to all patients, who were allocated to a target diastolic blood pressure of $\leq 90$ mm Hg, $\leq 85$, or $\leq 80$ mm Hg. The lowest incidence of major cardiovascular events occurred with felodipine at a mean achieved diastolic blood pressure of 82.6 mm Hg. However, 41% and 28% of randomized patients received concomitant treatment with an ACE inhibitor or a $\beta$-blocker, respectively. As felodipine was not compared to any other antihypertensive class of drug, the results do not provide any evidence on the relative benefits of this agent as an antihypertensive, and hence on their place in the treatment of hypertension.

In the STOP-2 trial (Swedish Trial in Old Patients with hypertension-2), two dihydropyridines (felodipine or isradipine) were compared to ACE inhibitors (enalapril or lisinopril) and to “conventional antihypertensives” (atenolol, metoprolol, pindolol or hydrochlorothiazide plus amiloride). No differences in mortality were seen between the different groups of treatment. However, the trial was powered only to compared
“conventional” versus “newer antihypertensive drugs” (ie, ACE inhibitors plus calcium channel blockers) (see table 2).

In two other large clinical trials, one with diltiazem and the other with a controlled-onset extended-release formulation of verapamil, similar results were obtained with the calcium channel blockers compared with a thiazide or a \( \beta \)-blocker.\(^{18,19}\)

Finally, in a meta-analysis of clinical trials with more than 1,000 patients where a calcium channel blocker was compared with a thiazide diuretic and/or a \( \beta \)-blocker, no major differences were found between both groups of treatment in all variables (stroke, coronary heart disease, cardiovascular death and total mortality), except a higher rate of heart failure in patients randomized to calcium channel blockers (RR=1.33 [95%CI 1.21-1.47]).\(^{10}\)

**Isolated systolic hypertension**

Two major trials on the treatment of isolated systolic hypertension have been published.

In the SHEP trial (*Systolic Hypertension in the Elderly Program*),\(^5\) treatment with chlorthalidone reduced the risk of fatal and non-fatal stroke (RR=0.64 [95%CI, 0.50-0.82]) and of major cardiovascular events (RR=0.68 [95%CI, 0.58-0.79]) in comparison to matching placebo.

The Syst-Eur trial (*Systolic hypertension in Europe*) was the largest study where a dihydropyridine was compared with placebo, in patients with isolated systolic hypertension.\(^{20}\) In this trial, nitrendipine reduced the risk of stroke (RR=0.58 [95%CI, 0.40-0.83]) and of a composite variable of cardiac end-points (heart failure and myocardial infarction) (RR=0.74 [95%CI, 0.56-0.97]) in comparison to placebo. However, 36.5% of patients assigned to the active treatment concomitantly received other antihypertensive drugs (enalapril and/or hydrochlorothiazide), while patients assigned to placebo received more placebo as second step, and a third placebo as a third step if blood pressure was not controlled. On the other hand, the decision of investigators to continue with a placebo group despite the publication of the positive SHEP results was also of concern.\(^{21}\)

Favourable results to the nitrendipine treatment compared with placebo were also observed in the Syst-China (*Systolic Hypertension in China*) trial, but the less orthodox method of allocation (alternative) used in this study, limited the interpretation of results.\(^{22}\)

Recently in a substudy of the LIFE trial (*Losartan Intervention For End-point reduction*), in elderly patients with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy, losartan, an angiotensin receptor blocker (ARB), was superior to atenolol in reducing a composite end point of cardiovascular death, stroke or myocardial infarction (RR=0.71 [95%CI, 0.53-0.95]).\(^{23}\) The main limitations in this trial were that more than 60% of patients in each group received concomitant treatment with hydrochlorothiazide, and \( \beta \)-blockers were a suboptimal control group, because they are not first choice in the elderly and because their efficacy in isolated systolic hypertension is not proven.\(^{24}\)
Hypertensive crises

In a **hypertensive emergency**, immediate blood pressure control to limit or to prevent target organ damage (hypertensive encephalopathy, intracranial haemorrhage, unstable angina, acute myocardial infarction, etc.) is required. Treatment with certain parenteral antihypertensive agents (sodium nitroprusside, labetalol, nitroglycerin or enalaprilat) is generally recommended for most of these situations. In a **hypertensive urgency** (hypertension with optic disc edema, severe perioperative hypertension...) it is desirable to achieve a blood pressure reduction within a few hours. Treatment with oral doses of drugs with relatively fast onset of action (i.e., loop diuretics, β-blockers, ACE inhibitors) is recommended for these situations and for isolated elevated blood pressure, in the absence of symptoms, although results from randomised clinical studies are lacking. Sublingual administration of short-acting nifedipine has been used for this purpose, but there is no evidence of its benefit and several serious adverse effects (including myocardial ischaemia) have been reported. In addition, the inability to control the degree of fall in blood pressure make this agent unacceptable.

**Special populations and situations**

*Ethnic variability in the natural history of hypertension*

The prevalence, severity and individual impact of hypertension are increased in black people. In clinical trials, black patients have shown reduced blood pressure responses to monotherapy with β-blockers and ACE inhibitors, compared with diuretics or calcium channel blockers. Renin concentrations tend to be lower in black people compared to white people. Antihypertensive agents that inhibit the renin-angiotensin system (RAS) have been less effective as initial treatment in reducing blood pressure values than other alternatives. In some studies, this less marked response has been overcome by using increased doses of thiazide diuretics.

The results of the AASK (African American Study of Kidney Disease) trial have shown that RAS blockade can provide significant clinical benefits in Afro-American patients with hypertensive renal disease. On the other hand, the greater differences observed in the ALLHAT study in black versus nonblack patients for combined CVD and stroke, along with a similar trend for heart failure and lesser blood pressure lowering with lisinopril, are in accord with the reports of poorer blood pressure response with ACE inhibitors in black patients. In the ALLHAT study, ACE inhibitors-induced angioedema occurred 2 to 4 times more frequently in black patients with hypertension than in other groups.

*Diabetes*

No major clinical trial has been performed to assess the effect of blood pressure lowering on cardiovascular morbidity and mortality in hypertensive patients with diabetes. Most comparisons have been made in relatively small studies, or in substudies or subgroups analyses of larger trials. ACE inhibitors have a favourable effect on cardiovascular outcomes as demonstrated in the MICRO-HOPE (Heart Outcomes Prevention Evaluation) study.
In the UKPDS (UK Prospective Diabetes Study), no differences between an ACE inhibitor and a β-blocker were found. In the subgroup of diabetic patients included in the LIFE trial, losartan reduced the composite endpoint of cardiovascular death, stroke or myocardial infarction compared to atenolol (RR=0.76 [95% CI, 0.58-0.98]). The same limitations quoted above regarding the LIFE study apply to the interpretation of these results, plus the fact that β-blockers are not of choice in diabetic patients.

In the ALLHAT trial, no differences in cardiovascular outcomes in the 12,063 patients with type 2 diabetes included were seen between chlortalidone, amlodipine, and lisinopril.

On the other hand, there are a number of studies showing that ACE inhibitors and, more recently, some angiotensin receptor blockers, retard the development and progression of diabetic nephropathy. In albuminuric patients with type I diabetes, captopril reduced the risk of doubling serum creatinine concentration in comparison to placebo (RR=0.57 [95% CI, 0.35-0.94]). More recently, in hypertensive patients with nephropathy due to type 2 diabetes, losartan reduced the risk of the composite variable (doubling serum creatinine concentration, development of end-stage renal disease or death) in comparison to placebo (RR=0.84 [95% CI, 0.72-0.98]), and irbesartan reduced the same composite variable in comparison to placebo (RR=0.81 [95% CI, 0.67-0.99]) and to amlodipine (RR=0.76 [95% CI, 0.63-0.92]).

**Chronic kidney disease**

ACE inhibitors have also shown a favourable effect on the progression of nondiabetic renal disease in patients with hypertension. A recent meta-analysis of 11 trials comparing the efficacy of antihypertensive regimens including ACE inhibitors to the efficacy of regimens without ACE inhibitors in predominantly nondiabetic renal disease, showed a greater mean decrease of urinary protein excretion (of 0.46g/L; 95% CI, 0.33-0.59), end-stage renal disease (RR=0.69 [95% CI, 0.51-0.94]) and the combined outcome of doubling the baseline serum creatinine concentration or end-stage renal disease (RR=0.70 [95% CI, 0.55-0.88]) with antihypertensive regimens including ACE inhibitors. Finally, the results of the AASK trial suggest that an ACE inhibitor (ramipril) is more effective than a β-blocker (atenolol) or a dihydropriidine calcium channel blocker (amlodipine) in slowing the decline of glomerular filtration rate in Afro-American hypertensive patients with nephrosclerosis.

**Heart failure**

ACE inhibitors (at doses higher than those used in hypertension), β-blockers, and anti-aldosterone compounds have well established efficacy for prevention of cardiovascular events and mortality in patients with heart failure when added to furosemide. ARBs may be a sound alternative for patients who are intolerant to ACE inhibitors.

On the contrary, in the PRAISE trial (Prospective Randomized Amlodipine Survival Evaluation study), the larger published study with a dihydropriidine-type calcium antagonist in patients with heart failure, amlodipine did not differ from placebo in
cardiovascular morbidity or mortality. More recently, in the ALLHAT trial, amlodipine was associated with a higher rate of heart failure than chlortalidone or lisinopril.

Similar results were reported from a meta-analysis of the main clinical trials comparing dihydropyridine or non-dihydropyridine-type calcium channel blockers versus diuretics/β-blockers (RR=1.33 [95%CI, 1.21-1.47]) or versus ACE inhibitors in patients with hypertension (RR=1.18 [95%CI, 1.8-1.27]).

**Coronary heart disease**

In patients who have suffered myocardial infarction, β-blockers, ACE inhibitors, and recently aldosterone antagonists have proven to be the most beneficial drugs. In patients with hypertension and stable angina pectoris, the first drug of choice is usually a β-blocker. Short-acting calcium channel blockers are not recommended and long-acting calcium antagonists are usually recommended as second or third line therapy in combination with a β-blocker. The results of more recently published trials seem to confirm this recommendation.

In the ALLHAT study, amlodipine had the same efficacy as other antihypertensive agents in preventing coronary events in hypertensive patients.

In the INVEST trial (*The International Verapamil-Trandolapril study*), treatment with sustained release verapamil and trandolapril showed an efficacy similar to atenolol or hydrochlorothiazide in reducing a composite variable of death, non-fatal myocardial infarction and non-fatal stroke in patients with hypertension and coronary artery disease.

Recently, in the ACTION trial (*A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system*), the addition of nifedipine GITS to the conventional treatment of angina pectoris showed no effect on major cardiovascular events in comparison to placebo, but reduced the need for coronary angiography and interventions (see table 1).

It has been suggested that these results are less convincing than those obtained with ACE inhibitors in the HOPE and EUROPA (*EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease*) trials. However, compared with these two other studies, in the ACTION trial a higher percentage of patients were concomitantly treated with β-blockers (80%, 39% and 62%, respectively) and with lipid-lowering drugs (68%, 28% and 57%).

**Hypertension in pregnancy**

It is generally agreed that for the treatment of mild-to-moderate pregnancy hypertension which started before pregnancy, if taken before pregnancy, diuretics and most other antihypertensive agents, except ACE inhibitors and angiotensin II receptor blockers, may be continued. Methyldopa is the most extensively evaluated antihypertensive agent in pregnancy. It is recommended as first choice when hypertension is diagnosed for the first time during pregnancy. β-blockers are considered safe in the later part of pregnancy; however, their use in early pregnancy may be associated with fetal growth retardation.
The results of a recently published meta-analysis suggest that treatment-induced falls in maternal blood pressure may adversely affect fetal growth. Given the small maternal benefit derived from therapy, the authors have suggested that in order to evaluate benefits and risks of oral antihypertensive drug treatment of mild-to-moderate pregnancy hypertension, data from new clinical trials are needed.55

For the treatment of severe pregnancy hypertension, hydralazine, labetalol, and nifedipine have been evaluated in clinical trials. However, the results of a recent meta-analysis indicate that, compared to other antihypertensive drugs, hydralazine is associated with a higher incidence of adverse effects on the mother and on the fetus.56 Labetalol has consequently been suggested as a more favourable alternative, although adequately powered clinical trials are needed.57

**Combination therapy**

In most hypertensive patients, therapy should be started gradually and target blood pressure values should be achieved progressively, but to reach such target blood pressures a large proportion of patients will require combination therapy with more than one agent.58 The results of several clinical trials indicate that monotherapy is successful in only 25-40% of patients,59 and in some groups (such as diabetics) an average of 2.5 to 3 drugs will be required in order to achieve adequate blood pressure control.35,36

On the other hand, only a limited number of two-drug combinations are safe and effective in reducing blood pressure values and are therefore recommended. In general, a dihydropyridine-type calcium antagonist can be combined with almost all the other antihypertensive drugs, even with a β-blocker.

**Tocolytic treatment for preterm labour**

In most countries, β-agonists are the reference tocolytic drugs. Their efficacy in prolonging pregnancy in threatened premature labour compared to placebo is proven, but no benefit on neonatal morbidity or mortality has been demonstrated.60,61 Despite this weak evidence on their efficacy, some clinicians remain convinced that, in selected pregnancies the fetus will benefit by being enabled to remain in utero a bit longer by use of a tocolytic agent. β-agonists have some contraindications, and serious adverse effects such as pulmonary edema have been reported. Ritodrine is the drug with more evidence of efficacy in this indication, but salbutamol and terbutaline may be equally effective.

Calcium channel blockers (especially nifedipine)62 have been compared with ritodrine in randomised trials. In a meta-analysis of randomised clinical trials, nifedipine was associated with longer pregnancy and fewer maternal side-effects that ritodrine.63 However, nifedipine has not been compared with placebo in any randomised trial.

Atosiban, an oxytocin antagonist which can only be given by infusion, was associated with a higher percentage of withdrawals from some studies, due to lack of efficacy in comparison to ritodrine.64,65 Atosiban is expensive, patent-protected and difficult to use, and its marginal efficacy is uncertain.
Patent status of LAN formulations and other dihydropyridines

Several generic preparations of LAN, amlodipine and nitrendipine are available in certain countries. The patent of the LAN formulation used in the two biggest trials with nifedipine (nifedipine GITS) will expire during the first trimester of 2005 and that of felodipine has not yet expired (see table 3).

Discussion

1. Is long-acting nifedipine effective and safe for the treatment of hypertension?

The available evidence on long-acting nifedipine (LAN) for the treatment of hypertension is limited, but the results of a few studies suggest that it can be quite safe, especially if administered in combination and/or as a second or third line therapy.

In hypertensive patients nifedipine has been compared to diuretics in a large clinical trial, to ACE inhibitors in a smaller one, and to placebo in a less orthodox study. In the first clinical trial, more patients died of myocardial infarction or were admitted for heart failure with nifedipine than with diuretics. However, the numbers of events in each group were small, and the incidence of overall cardiovascular events was similarly reduced with nifedipine and diuretics. A recently published clinical trial showed that the addition of LAN to the standard treatment of angina pectoris (β-blockers, statins, aspirin) did not reduce major cardiovascular events in comparison to placebo, although less coronary angiographies and interventions were needed in the dihydropyridine group. On the other hand, the positive results obtained with other long-acting dihydropyridines in their respective large clinical trials (with nitrendipine and, especially, with amlodipine) and in the meta-analyses of clinical trials comparing calcium channel blockers with diuretics/β-blockers or with ACE inhibitors, suggest that in patients with hypertension treatment with calcium channel blockers is reasonably safe, except in those with heart failure.

2) Should some dihydropyridine or other long-acting calcium channel blocker be included in the EDL?

Several reasons suggest that a dihydropyridine calcium channel blocker should be kept in the in the EDL:

1) A high percentage of patients with hypertension need treatment with a combination of two or three different classes of antihypertensive drugs to achieve the target blood pressure values. As hypertension affects at least 25% of the adult population, patients in need of three antihypertensive agents are common, and thus combined antihypertensive treatment should be seen as “essential”.

2) Only a few two-drug combinations are safe and effective. The dihydropyridine-type calcium channel blockers can be combined with almost all the other antihypertensive classes of drugs, even with a β-blocker.
3) In black people, calcium channel blockers can be more effective than some other antihypertensive drugs in lowering blood pressure.

3) Is there more effective and safer dihydropyridine than nifedipine for the treatment of essential hypertension?

Three dihydropyridine-type calcium channel blockers have been evaluated in large clinical trials. In the Sys-Eur trial, nitrendipine showed favourable results on cardiovascular end-points but it was only compared to placebo, and only in patients with isolated systolic hypertension. In the HOT trial, treatment with felodipine showed the benefits of lowering diastolic blood pressure down to 90 mm Hg. However, felodipine was not compared to any other antihypertensive agent. The STOP-2 trial was not powered to compare felodipine alone with “conventional antihypertensive drugs” (diuretics or β-blockers). Finally, in the ALLHAT study, the efficacy of amlodipine was similar to that of chlortalidone in reducing total mortality and the incidence of coronary heart disease, although the incidence of heart failure was marginally higher with amlodipine. It has been suggested that amlodipine is now the best evaluated dihydropyridine in the treatment of essential hypertension and it is recommended as third or four line therapy (after diuretics, β-blockers and ACE inhibitors). However, no information is available on amlodipine for treatment of hypertension during pregnancy or as a tocolytic.

4) What is the efficacy and safety of nifedipine in other indications such as hypertension of pregnancy and as a tocolytic for preterm labour? Should other medicines or other dihydropyridines be preferred for the treatment of these indications?

In a recent overview of comparative trials on the treatment of severe hypertension in pregnancy, hydralazine has been associated with a higher percentage of adverse reactions to the mother and the fetus than other antihypertensive drugs. Labetalol and nifedipine are possibly safer alternatives, but nifedipine can be preferable for patients with contraindications or who can not tolerate treatment with a β-blocker. On the other hand, the beneficial effect of tocolytic agents in preterm labour seems scarce. New data from clinical trials with a placebo control group in selected patients at risk of preterm labour are needed. Meanwhile, nifedipine can be an alternative for patients with contraindications or in those intolerant to ritodrine treatment (e.g., with asthma).

Several generic preparations of LAN, amlodipine and nitrendipine are available in certain markets and the patent of nifedipine GITS (used in the two biggest published trials with nifedipine) will expire during the first trimester of 2005. The patent of felodipine has not yet expired.

Conclusions

1. Results from a limited number of studies suggests that treatment with long-acting nifedipine formulations can be quite safe, especially in combination with other antihypertensives and/or as a second or third line therapy.
2. Other quite safe long-acting dihydropyridines are nitrendipine and amlodipine. At present amlodipine should be considered as the dihydropyridine calcium channel blocker with the most extensive experience from a clinical trial (the ALLHAT study). However, nitrendipine has only been evaluated against placebo in isolated systolic hypertension, and amlodipine showed a marginally lower benefit/risk ratio with respect to diuretics in the ALLHAT trial.

3. It seems necessary to keep a long-acting dihydropyridine channel blocker as an antihypertensive agent in the EML, because a significant proportion of hypertensive patients need treatment with a combination of two or more antihypertensives, and because the dihydropyridine-type calcium channel blockers can be combined with almost all other classes of antihypertensives (even β-blockers). Finally, in black people calcium channel blockers can lower blood pressure values more effectively than some other antihypertensives.

4. Nifedipine has been extensively evaluated as a tocolytic agent and for the treatment of severe hypertension in pregnancy.

5. There are several generic preparations of LAN and of amlodipine in certain countries, and the patent of nifedipine GITS (the formulation used in the biggest published trials with nifedipine) will expire in a few months.

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* nitrendipine is not available in the United States. Its patent has expired in some European countries.