REVIEW ARTICLE

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Antihypertensive Effect of Manidipine

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Abstract

Manidipine is a lipophilic, third-generation, highly vasoselective, dihydropyridine (DHP) calcium channel antagonist, which, when given on a once-daily basis, effectively reduces blood pressure (BP) in patients with mild-to-moderate essential hypertension. Manidipine has a gradual onset and a long duration of action, effectively maintaining reduced BP levels throughout the 24-hour dosing period, and is effective in the long term with no evidence of intolerance. The BP-lowering capacity of manidipine is similar to that of other established DHPs and of angiotensin-converting enzyme inhibitors. Diabetic patients and very elderly patients with mild-to-moderate hypertension also respond favourably to treatment with manidipine. Manidipine has neutral effects on glucose and lipid metabolism and is generally well tolerated. Manidipine thus represents a first-line option for lowering BP in patients with mild-to-moderate hypertension.

1. Introduction

Hypertension is associated with an increased risk of major cardiovascular events and end-stage renal disease, which can be significantly lowered by effective blood pressure (BP) control.[1–3] However, BP is not adequately managed in the majority of hypertensive patients.[4,5] In the last National Health and Nutrition Examination Survey (NHANES), conducted in 1999–2000, 68.9% of participants were aware of their hypertension, 58.4% were treated, and hypertension was controlled (BP <140/90mm Hg) in only 31% in the US.[6] These figures were even poorer in many European countries, with the proportion of patients undergoing treatment ranging from 32 to 55%, and 5–27% of hypertensive patients achieving BP control.[7] As lack of adherence to treatment and drug-related side-effects are probably the main variables influencing BP control, new strategies and more effective antihypertensive agents are needed to improve hypertension control in the community.

Manidipine is a lipophilic, highly vasoselective third-generation dihydropyridine (DHP) calcium channel antagonist with strong membrane binding capacity, which effectively and safely controls BP with once-daily dosing.[8,9] Mean maximum plasma concentrations of manidipine are reached 1–4 hours after a single oral dose of 20mg. The drug is highly plasma-protein bound. The extent of manidipine absorption is significantly increased with food, and accumulation does not occur after repeated administration. Oral manidipine undergoes extensive first-pass hepatic metabolism, with 63% of the drug eliminated in the faeces and 31% in the urine. Elimination is significantly delayed in patients with severe hepatic impairment.[8]

In this article the clinical evidence supporting the use of manidipine as a first-line agent in patients

with mild-to-moderate hypertension, including those with diabetes and the elderly, will be reviewed.

2. Antihypertensive Efficacy and Side-Effects

The short-term antihypertensive efficacy and the relative tolerability of different doses of manidipine were evaluated in a double-blind, randomised, placebo-controlled, parallel group study, in 52 patients with mild-to-moderate hypertension.[10] After 4 weeks of treatment, the mean decrease in BP measured 24 hours after dosing was 15/10mm Hg with manidipine 10 mg/day, 24/16mm Hg with 20 mg/day and 27/19mm Hg with 40 mg/day compared with 4/5mm Hg in the placebo group. Similarly, the percentage of patients with normalised diastolic BP ($\geq$90mm Hg) increased with increasing dosages of manidipine (10mg 23%, 20mg 55%, 40mg 61%). The percentage of patients with both systolic and diastolic BP normalisation (140 and $\leq$90mm Hg, respectively) was also dose related (10mg 15%, 20mg 45%, 40mg 54%), whereas 15, 54 and 54%, respectively, had normalised systolic BP.

The success rate figures (normalised diastolic BP or decrease in diastolic BP decrease $\geq$10mm Hg from baseline) were 46% with manidipine 10 mg/day, 90% with manidipine 20 mg/day and 77% with manidipine 40 mg/day. Importantly, 24-hour ambulatory BP performed in these patients showed significant and sustained reductions in systolic and diastolic BP (figure 1) with no significant modification of the normal BP circadian rhythm. The trough : peak ratio of manidipine was >0.5 for all three dosages, as necessary for once-daily administration. As 10 and 20mg schedules showed a satisfactory BP response with only mild adverse drug reactions, these two doses were chosen for further drug development.

The homogeneity of the antihypertensive effect of manidipine over a 24-hour treatment period was also assessed by Mancia et al.[11] These investigators found the smoothness index in hypertensive patients was 0.6 with manidipine, thereby confirming the efficacy of manidipine over a 24-hour treatment period. The effects of manidipine on BP circadian rhythm in patients with essential hypertension were further assessed in two Japanese trials. In the first trial 17 patients received manidipine 10–30 mg/day for at least 2 weeks.[12] BP was monitored every 30 minutes for 48 hours before and after treatment by an ambulatory BP monitoring device. Results showed that manidipine significantly reduced mean systolic and diastolic BP during the entire 24-hour, day-active and night-resting periods. The circadian amplitude of BP, which was abnormally high before treatment, was

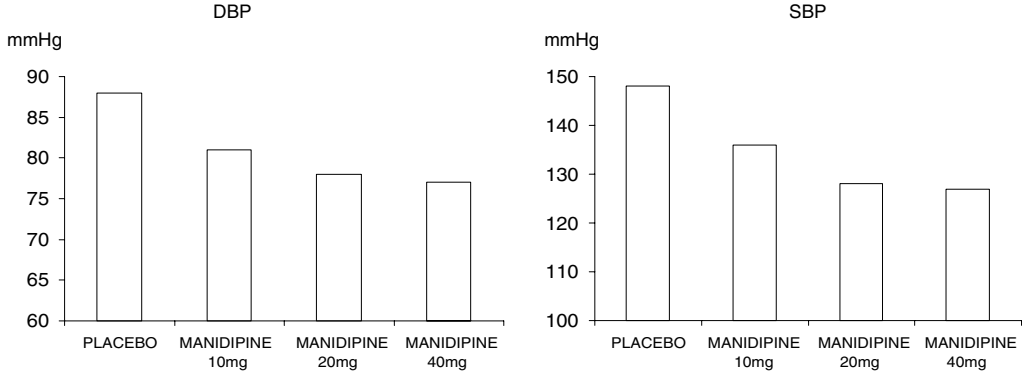

Fig. 1. 24-hour ambulatory blood pressure measurements in patients with mild-to-moderate hypertension receiving manidipine 10, 20 or 40 mg/day or placebo (all comparisons versus placebo: $P < 0.05$).[10] **DBP** = Diastolic blood pressure; **SBP** = systolic blood pressure.

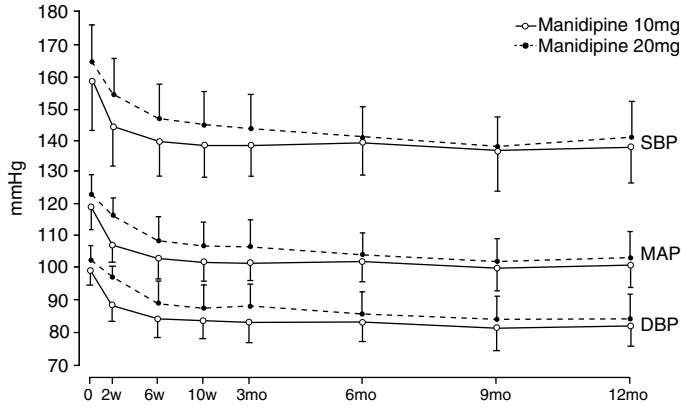

Fig. 2. Effect of manidipine on blood pressure and mean arterial pressure over 12 months of treatment in hypertensive patients. **DBP** = Diastolic blood pressure; **MAP** = mean arterial pressure; **SBP** = systolic blood pressure. Reproduced with permission from Fogari et al.[14]

also reduced to within the reference range after treatment with manidipine. The second trial investigated the effects of manidipine 10–40 mg/day on the diurnal variation of arterial pressure and systemic haemodynamics.[13] Systolic and diastolic BP were significantly reduced by manidipine at almost all measurement points, and BP reductions were not significantly different between daytime and nighttime. It thus appears that patients treated with manidipine can avoid the excessive decrease in BP during nighttime observed with other calcium channel antagonists.

The long-term efficacy and tolerability of manidipine (10–20mg once daily) was evaluated in 183 patients with sitting diastolic BP of 95mm Hg or greater and 115mm Hg or less and systolic BP of 210mm Hg or less.[14] After a 2-week run-in period manidipine 10mg once a day was given. Two weeks later, patients whose diastolic BP remained at 90mm Hg or greater or who had a reduction in diastolic BP of less than 10mm Hg were administered manidipine 20mg once a day. Follow-up visits were performed at 6, 10, 14, 26, 38 and 52 weeks after starting manidipine treatment. Significant reductions in BP were seen after only 2 weeks of treatment (from 162/101 to 149/93mm Hg) and BP was further reduced with continued treatment, reaching 140/83mm Hg after 12 months ($P < 0.001$ versus baseline for all comparisons) (figure 2). At the end of the 52-week treatment period, 95% of patients receiving manidipine 10 mg/day and 86% of patients receiving manidipine 20 mg/day had normalised BP (diastolic BP $\leq$90mm Hg). Overall, 28 patients (17 in the manidipine 20mg and 11 in the manidipine 10mg treated group) complained of adverse events, the most common being ankle oedema (4.9%), headache (3.8%), palpitations (2.7%) and flushing (2.2%). Neither cardiovascular nor cerebrovascular events or other serious adverse events were reported.

3. Comparison with Other Dihydropyridines

The chronic effects of manidipine, amlodipine, felodipine, and lacidipine on BP, heart rate, and plasma norepinephrine levels were evaluated in 60 patients with mild-to-moderate essential hypertension in a double-blind study with a parallel group design.[15] After a 4-week placebo period, patients were randomly administered once daily amlodipine 5–10mg (n = 15); felodipine 5–10mg (n = 15); lacidipine 4–6mg (n = 15); manidipine 10–20mg (n = 15), for 24 weeks. At the end of the treatment period, BP was reduced by 18/14mm Hg with manidipine, 19/14mm Hg with amlodipine, 18/13mm Hg with felodipine and 17/13mm Hg with

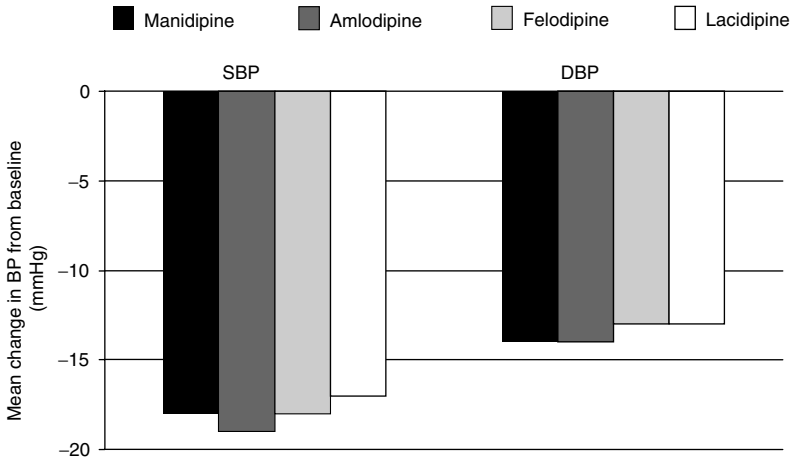

Fig. 3. Blood pressure-lowering effects of manidipine, amlodipine, felodipine and lacidipine after 24 weeks of treatment in hypertensive patients.[15] **BP** = Blood pressure; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure.

lacidipine (figure 3). Heart rate increased only with felodipine (by 3.1 beats/min), whereas plasma norepinephrine levels increased with amlodipine and felodipine but not with manidipine and lacidipine.

In another double-blind, multicentre trial, 489 patients with mild-to-moderate essential hypertension were randomly assigned to 48 weeks of once-daily manidipine, 10–20mg, or amlodipine, 5–10mg.[16] BP was reduced by 18/14mm Hg with manidipine and by 20/14mm Hg with amlodipine (both $P < 0.01$ versus baseline). The efficacy of these two treatments was equivalent after the 8-week titration phase and was maintained throughout the study period (figure 4).

Finally, in a recent trial the antihypertensive effects of manidipine and lercanidipine were compared in 53 patients with mild-to-moderate hypertension.[17] Although overall reductions in BP were not significantly different with manidipine 10 mg/day and lercanidipine 10 mg/day over the 12-week treatment period, almost twice as many manidipine recipients were able to achieve normalised BP of less than 140/90mm Hg compared with lercanidipine recipients despite identical mean BP

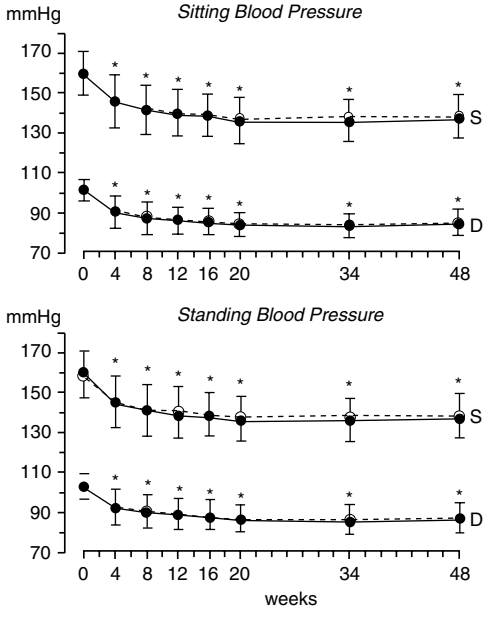

Fig. 4. Change in sitting and standing blood pressure in patients with essential hypertension completing 48 weeks of treatment with manidipine or amlodipine. **D** = Diastolic blood pressure; **S** = systolic blood pressure. —●— Amlodipine; - -○- - manidipine. $^*P < 0.05$ versus baseline. Reproduced with permission from Zanchetti et al.[16]

measurements at baseline (35 versus 18%, respectively; $P < 0.01$).

4. Comparison with Angiotensin-converting Enzyme Inhibitors

In a small, one-year, non-blinded trial patients with mild-to-moderate essential hypertension were randomly assigned to receive manidipine 10–40 mg/day(n = 18) or delapril 15–60 mg/day (n = 22) for 12 months.[18] Significant reductions in BP were observed in both treatment groups. The reduction in diastolic BP was significantly greater in the manidipine than in the delapril group (−20mm Hg versus −10mm Hg, $P < 0.01$), whereas the difference in systolic BP (−18mm Hg versus −10mm Hg) did not reach statistical significance. Further comparative data between manidipine and other angiotensin-converting enzyme (ACE) inhibitors are provided in section 5.

5. Efficacy in Special Patient Populations

5.1. Diabetic Patients

Several landmark studies have illustrated the importance of reducing BP in diabetic hypertensive patients to prevent further diabetes-related cardiovascular complications.[19–21] In these trials ACE inhibitors and calcium channel antagonists have clearly demonstrated favourable antihypertensive effects in this patient population, and have been shown to contribute to the reduction in the incidence of micro and macrovascular complications with no adverse metabolic effects.

In a randomised, double-blind trial, hypertensive patients with type 2 diabetes mellitus were randomly assigned to manidipine 10–20 mg/day or enalapril 10–20 mg/day for 24 weeks.[11] The office systolic and diastolic BP were significantly ($P < 0.01$) and similarly reduced from baseline values with manidipine (16 ± 10 and 13 ± 6mm Hg, respectively) and enalapril (15 ± 10 and 13 ± 6mm Hg, respectively). The proportion of patients in whom office diastolic BP was reduced by 85mm Hg or less was similar in the manidipine and enalapril treatment groups (37% vs 40%). The reduction of 24-hour BP was also similar in the manidipine and enalapril groups for both drugs (systolic BP 6 ± 11 vs 8 ± 10mm Hg; diastolic BP 5 ± 8 vs 5 ± 7mm Hg) (figure 5).

Similar results were seen when manidipine (10–20 mg/day) was compared with another ACE inhibitor, lisinopril (10–20 mg/day) in patients with mild-to-moderate hypertension, type 2 diabetes mellitus and microalbuminuria.[22] BP reductions seen at week 24 were further reduced by the end of the treatment period. At week 48, BP was reduced by 18/14mm Hg in manidipine recipients and by 17/13mm Hg in lisinopril recipients ($P < 0.01$ versus baseline). In this trial, manidipine induced a greater regression of left ventricular mass, whereas lisinopril was more effective in the reduction of microalbuminuria.

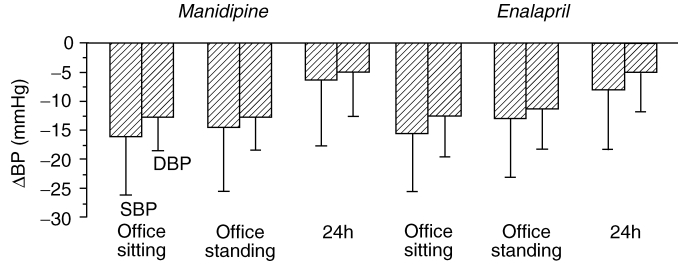

Fig. 5. Change from baseline in systolic and diastolic blood pressure measured in various settings, in diabetic hypertensive patients receiving manidipine or enalapril for 24 weeks. No significant difference was observed between manidipine and enalapril for each of the three assessments. **BP** = Blood pressure; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure. Reproduced with permission from Mancia et al.[11]

5.2. Patients with Renal Impairment

Conventional calcium antagonists elicit predominant vasodilation of the afferent arteriole and this may aggravate glomerular hypertension. In contrast, manidipine acts not only on the afferent, but also on the efferent arteriole and this suggests a renoprotective effect in patients with chronic kidney disease.[23] This issue was addressed in a multicentre, prospective, double-blind study comparing manidipine (20 mg/day) and nifedipine (60 mg/day) in 101 hypertensive patients with chronic renal failure (creatinine clearance <42 ml/min).[24] A significant reduction in systolic ($P < 0.001$) and diastolic ($P < 0.001$) BP compared with the baseline values was reached with both treatments. Proteinuria did not change significantly in the manidipine group but increased in the nifedipine group ($P < 0.05$). The number of patients with severe adverse reactions was significantly greater in the nifedipine group than in the manidipine group (14.5% vs 8.5%, $P < 0.01$).

In a recent prospective randomised, double-blind study the efficacy and tolerability of manidipine (10–20 mg/day) were compared with those of enalapril (10–20 mg/day) in 136 patients with primary renoparenchymal disease.[25] During a 48-week follow-up, mean systolic BP decreased from 155 ± 11.7 to 138.7 ± 13.9mm Hg in the manidipine and from 157.3 ± 11.8 to 134.2 ± 13.9mm Hg in the enalapril group, whereas mean diastolic BP decreased from 100.3 ± 4.2 to 86.1 ± 6.5mm Hg in the manidipine and from 100.3 ± 4.2 to 84.7 ± 6.3mm Hg in the enalapril group ($P < 0.01$ versus baseline for both drugs; $P < 0.05$ for manidipine versus enalapril comparisons). Proteinuria remained unchanged in manidipine recipients (from 1.6 ± 1.59 to 1.62 ± 1.79 g/24h), and decreased significantly in

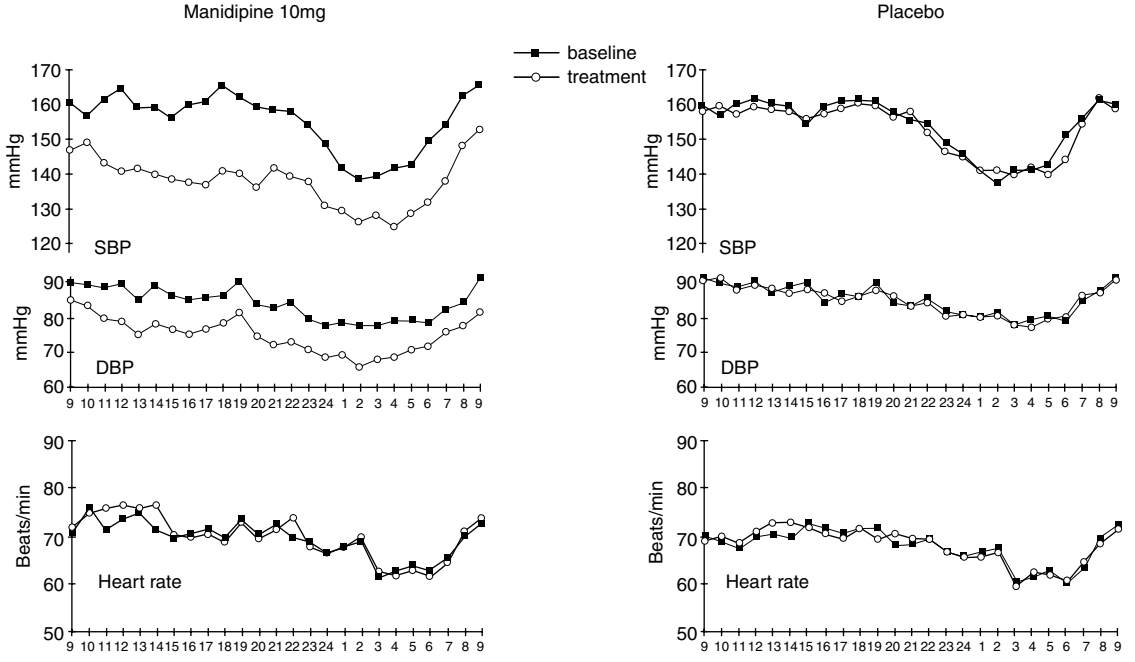

Fig. 6. Effect of low-dose manidipine or placebo on 24-hour blood pressure and heart rate in very elderly hypertensive patients treated for 8 weeks. **DBP** = Diastolic blood pressure; **SBP** = systolic blood pressure. Adapted with permission from Fogari et al.[42]

enalapril recipients (from 1.37 ± 1.45 to 1 ± 1.55 g/24h). However, no significant difference was observed in the rate of renal function decline in the two groups.

5.3. Elderly Patients

Treatment of hypertension in elderly patients results in a significant reduction in cardiovascular morbidity and mortality.[26–32] Calcium channel antagonists may be particularly effective in this patient group as they can lower peripheral resistance[33] and arterial stiffness,[34] reduce left ventricular hypertrophy,[35] and inhibit atherogenesis and calcium deposition in blood vessels.[36,37] In addition, they are not associated with adverse metabolic effects[38,39] and are inactivated by biotransformation in the liver, a process not greatly affected by aging.[40]

The antihypertensive efficacy of manidipine in the elderly was compared with that of delapril in a Japanese study involving 1748 patients aged 60 years of age or greater with essential hypertension.[41] Manidipine 5–20 mg/day and delapril 15–60 mg/day were equally effective in reducing BP after a mean 28.4 months of treatment (from 148/82 to 141/78mm Hg and from 151/84 to 142/80mm Hg, respectively). There were no significant differences in the total incidence of death between the two groups. Cardiovascular events (both fatal and non-fatal) were noted in 34 out of 699 patients (22.5/1000 patient-years) in the delapril group and 50 out of 1049 patients (19.7/1000 patient-years) in the manidipine group, with no significant difference between the two groups.

The effect of manidipine (10 mg/day) in the very elderly was evaluated in a randomised, placebo-controlled trial involving 58 patients aged 76–89 years (mean 82).[42] After 4 weeks of treatment, sitting BP was reduced by 11/5mm Hg with manidipine and standing BP, an important measure in elderly patients, was reduced by 8/5mm Hg (both $P < 0.001$ versus placebo). The trough/peak ratio in the manidipine group was 0.67 for systolic and 0.59 for diastolic BP, which indicates a favourable effect over the 24-hour treatment period and is in accordance with previous findings in younger patient populations.[10] No differences regarding heart rate were observed between the manidipine and placebo groups (figure 6), and no serious side-effects were reported.

6. Conclusion

Manidipine is a third-generation DHP calcium antagonist, which has been shown significantly to lower office and 24-hour BP compared with placebo in patients with essential hypertension. The resulting reduction in BP, which is similar to that of the other calcium antagonists, is maintained over 24 hours and sustained over a long period, with preservation of the circadian BP pattern and no significant changes in heart rate. In elderly patients with mild-to-moderate essential hypertension, manidipine significantly decreases BP compared with placebo. Moreover, the drug significantly lowers BP in patients with hypertension and co-morbidities such as type 2 diabetes mellitus or renal impairment, is devoid of adverse metabolic effects and is well-tolerated. Manidipine thus represents a first-line BP-lowering treatment option in patients with mild-to-moderate hypertension.

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