

ORIGINAL ARTICLE

Efficacy of indapamide 1.5 mg, sustained release, in the lowering of systolic blood pressure

GM London

Service de néphrologie, Hôpital Manhès, Ste Geneviève des Bois, France

The relationship between the increase in blood pressure and the incidence of cardiovascular disease is well recognized today. Studies have shown that more attention should be paid to systolic blood pressure (SBP) in relation to cardiovascular risk and that therapeutic interventions should preferably focus on reducing SBP. The antihypertensive efficacy of indapamide 1.5 mg sustained release (indapamide SR), a low-dose thiazide-type diuretic, was assessed on SBP. Three randomized, double-blind, controlled studies were conducted with indapamide SR, over a period of 3 to 12 months. Elderly patients or patients with target-organ damage, hypertension and left ventricular hypertrophy (LVH) (LIVE study) or with type II diabetes with microalbuminuria (NESTOR study) showed a decrease in SBP varying from 22.7 to 31.8 mmHg. The treatment with

indapamide SR resulted in a better or equivalent control of SBP than treatment with a standard dose of a true thiazide diuretic (hydrochlorothiazide), a calcium channel blocker (amlodipine), and an angiotensin-converting enzyme inhibitor (enalapril). No therapeutic escape was observed. All treatments showed good acceptability with no unexpected adverse event. In conclusion, indapamide SR is very effective in lowering SBP—a major independent cardiovascular risk factor—notably in hypertensive high-risk patients with LVH, the elderly and diabetics, when compared to major antihypertensive treatments. This SBP-lowering effect is maintained over the long term.

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Introduction

The aim of this review is to assess the efficacy of indapamide 1.5 mg sustained release (indapamide SR; brand names: Natrilix SR, Natrilix LP, Natrilix Retard, Natrilix AP, Fludex LP, Fludex retard, Fludex SR, Fludex 1.5 mg, Tertensif SR, Tertensif retard, Arifon retard, Pretanix) on the reduction in systolic blood pressure (SBP) and to highlight its effect in hypertensive patients with diabetes, the elderly and patients with target-organ damage.

Increasing importance of SBP

Epidemiological studies have emphasized the close relationship existing between the increase in blood pressure (BP) and the incidence and prevalence of cardiovascular disease.¹ In the past, the severity of hypertension was classified principally on the basis of diastolic blood pressure (DBP).² This was related

to the haemodynamic characteristics of the disease, which was attributed to a reduction in the calibre or number of small arteries, with a resulting increase in peripheral vascular resistance and the fact that increases in peripheral resistance was the principal haemodynamic cause of high BP. Peripheral resistance is a determinant of mean blood pressure (MBP) close to the level of DBP. Nevertheless, many cross-sectional studies have shown that end-organ damage in hypertensive people is more strongly associated to SBP. Furthermore, recent prospective epidemiological studies^{3,4} have directed attention to SBP as a better guide than DBP to evaluate cardiovascular and all-cause mortality. A meta-analysis of outcome trials has confirmed the overwhelming importance of SBP as a determinant of risk.⁵ Studies have shown that drug treatment of hypertension frequently results in an adequate control of DBP (≤ 90 mmHg), whereas the ability to control SBP (≤ 140 mmHg) is achieved to a significantly smaller extent.^{4–7} Such studies have focused attention on the factors that determine the level of SBP and cardiovascular risk in hypertensive individuals, and on therapeutic interventions preferably reducing SBP. Several therapeutic trials have

Correspondence: Dr GM London, Service de néphrologie, hôpital Manhès, 8 rue Roger Clavier, Fleury Merogis, 91712 Ste Geneviève des Bois, France.

confirmed that SBP increases markedly with age while DBP^{8–10} becomes stable and even tends to fall spontaneously after the age of 50–60 years. In the Systolic Hypertension in the Elderly Program study¹¹ involving elderly subjects with isolated systolic hypertension (ISH), the reduction in cardiovascular risk was associated with a decrease in SBP, whereas, in contrast, a decrease in DBP was associated with an increase in cardiovascular risk.¹² In the past few years, several authors^{13–15} have clearly shown that brachial pulse pressure was also a strong cardiovascular risk factor for myocardial infarction in populations of individuals with hypertension. Furthermore, some studies¹⁶ have clearly indicated that cardiovascular risk is related not only to an increase in SBP but also to a decrease in DBP. Cardiovascular mortality was indeed substantially reduced but, at the end of the trial, the population was still characterized by a low DBP contrasting with an elevated SBP. Taken together, these findings indicate that, in elderly subjects treated for hypertension, the classic haemodynamic pattern of ISH is still present despite adequate drug treatment.¹¹

Pathophysiological approach to reduction in SBP

Medical treatment of hypertension usually results in parallel decline of SBP as well as DBP. Nevertheless, as already stated previously, an adequate control is frequently achieved on DBP and to a significantly smaller extent on SBP.^{4–7} In the case of ISH, the therapeutic goal is to obtain a preferential decrease in SBP while maintaining unchanged DBP. In patients with essential hypertension, the International guidelines recommend the use of thiazide-type diuretics in monotherapy or in combination; they also highlight the need to select the lowest dosages.^{17,18} Other recommended pharmacological classes of antihypertensive agents include beta-blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and calcium antagonists.¹⁹

While diuretics are still regarded as the treatment of choice in elderly patients and those with systolic hypertension, not all drugs in this class have the same efficacy.¹⁹ Indapamide SR, a thiazide-type diuretic, has shown activity in the elderly, as well as in patients with left ventricular hypertrophy (LVH) or type II diabetes mellitus.^{20,21}

Indapamide SR and SBP

Three large double-blind clinical trials assessing the effect of indapamide SR on SBP are reviewed. These studies have all been published and their methodology has already been thoroughly detailed. This review, therefore, mainly focuses on the results reported in various groups of hypertensive patients with major cardiovascular risk factors.

SBP lowering in elderly patients

After a 4-week, single-blind, placebo run-in period, 524 patients with a mean age of 72.4 years and a mean supine SBP/DBP of 174.5/97.9 mmHg (hypertension criteria defined as 161 to 209 mmHg and below 110 mmHg for supine SBP and DBP, respectively) were included in this study. Of these, 128 patients had an ISH defined as 160 < SBP < 210 mmHg and DBP < 95 mmHg. All patients were randomized for a 12-week treatment period with one of the three following active drugs: indapamide SR, the calcium channel blocker amlodipine 5 mg or a standard dose of the true thiazide diuretic hydrochlorothiazide 25 mg.²² An additional 12 months follow-up open period with indapamide SR was performed in the responder patients.²³

Results showed an equivalent antihypertensive effect for the three treatment arms (equivalence $P < 0.001$); the mean decreases in SBP/DBP were $-22.7/-11.8$ mmHg with indapamide SR; $-22.2/-10.7$ mmHg with amlodipine 5 mg and $-19.4/-10.8$ mmHg with hydrochlorothiazide 25 mg, Figure 1. During the follow-up period, the efficacy of indapamide SR was maintained for a year. A decrease in SBP/DBP of $-26.3/-14.3$ mmHg was observed in the 356 patients treated with indapamide SR, Figure 1. In the ISH subgroup, indapamide SR is significantly more effective than hydrochlorothiazide 25 mg at reducing SBP (-24.7 vs -18.5 mmHg, respectively; equivalence $P = 0.117$), while similar results were obtained with amlodipine 5 mg (-23 mmHg, equivalence $P < 0.001$). The normalization rate was relatively high for indapamide SR (75.3%), when compared with amlodipine (66.9%) and hydrochlorothiazide (67.3%). Moreover, in the subgroup of ISH patients, the normalization rate was as high as 84.2% in the indapamide SR groups vs 80.0% for amlodipine and 71.4% for hydrochlorothiazide.

The most frequently reported clinical adverse effect was peripheral oedema with amlodipine (7.4%) and back pain with either hydrochlorothiazide (5.8%) or indapamide SR (1.5%).

SBP lowering in hypertensive patients with type II diabetes—the NESTOR study

Following a 4-week placebo run-in period, 570 type II diabetic hypertensive patients with microalbuminuria were randomly allocated to receive either indapamide SR ($n = 284$) or enalapril 10 mg ($n = 286$) once a day for a 1-year treatment period. An additional label treatment by amlodipine 5–10 mg (first step) and atenolol 50–100 mg (second step)/day was allowed after 6 weeks of treatment.²⁴

Results showed that the decrease in SBP was significantly ($P = 0.02$) more important with indapamide SR (-23.8 mmHg) than with enalapril (-21.0 mmHg), Figure 2. The noninferiority of indapamide SR vs enalapril was achieved for

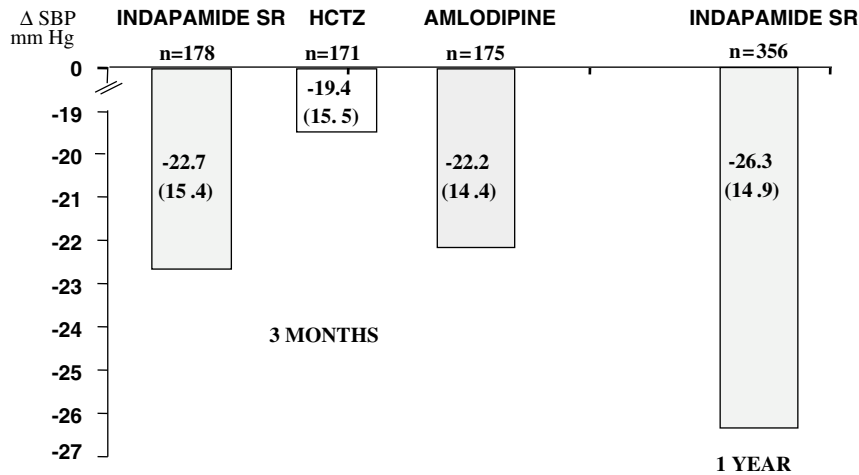


Figure 1 SBP lowering in the elderly hypertensive patients. Comparison between indapamide SR, hydrochlorothiazide (HCTZ) and amlodipine after 3 months, and change obtained in patients followed up for 1 year on indapamide SR therapy (mean change from baseline, data from Emeriau *et al*²²).

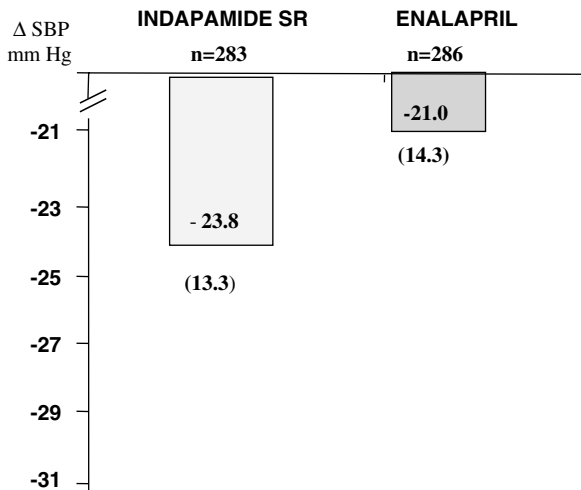


Figure 2 SBP lowering in type II diabetic hypertensive patients: the NESTOR study. Comparison between indapamide SR and enalapril after 1 year of treatment (mean change from baseline, data from Marre *et al*²⁴).

microalbuminuria reduction. A significant decrease in the urinary albumin/creatinine ratio (UACR) was observed, 35% with indapamide SR and 39% with enalapril with a similar decrease in MBP (-16.6 mmHg with indapamide SR and -15.0 mmHg with enalapril). Moreover, 49 and 43% of the patients were treated with monotherapy with indapamide SR and enalapril, respectively.

A subgroup of 187 patients aged over 65 years old was assessed.²⁵ Indapamide SR reduced microalbuminuria by 46%. This effect was equivalent to enalapril (47%) with a similar decrease in MBP (-17.6 ± 9.4 mmHg with indapamide SR and -15.3 ± 9.5 mmHg with enalapril). Additionally, 43% of the patients treated with indapamide SR and 37% treated with enalapril had UACR normal-

ization (<2.5 mg/mmol for men and <3.5 mg/mmol for women) at the end point.

Both in the main and in the elderly subgroup of the Natrilix SR vs enalapril study on hypertensive type II diabetes with microalbuminuria (NESTOR), indapamide SR and enalapril showed a similar reduction in microalbuminuria. The metabolic profile and renal function were unimpaired by the two treatments.

These results support the use of indapamide SR as a first-line therapy in type II diabetic hypertensive patients with microalbuminuria.

SBP lowering in hypertensive patients with left ventricular hypertrophy—the LIVE study

The left ventricular hypertrophy: Indapamide vs enalapril (LIVE) study, a 1-year, multinational, prospective, randomized, double-blind study, compared the efficacy of indapamide SR and enalapril 20 mg in reducing left ventricular mass index (LVMI) in hypertensive patients with left ventricular hypertrophy (LVH).²⁶

Patients, 20 years old or more and with LVH (LVMI in men >120 g/m²; LVMI in women >100 g/m²) and mild to moderate hypertension were included. Two successive selections of echocardiograms were performed per patient. A committee validated LVH before inclusion, provided centralized ongoing quality control during the study, and performed an end-of-study reading of all echocardiograms blinded to sequence.²⁷ This rigorous methodology was pointed out as a gold standard study for assessing LVH in hypertensive patients by ESC/ESH 2003 guidelines.¹⁸

A total of 411 patients were analysed for LVMI variation in the population treated with monotherapy, 205 patients were treated with indapamide SR

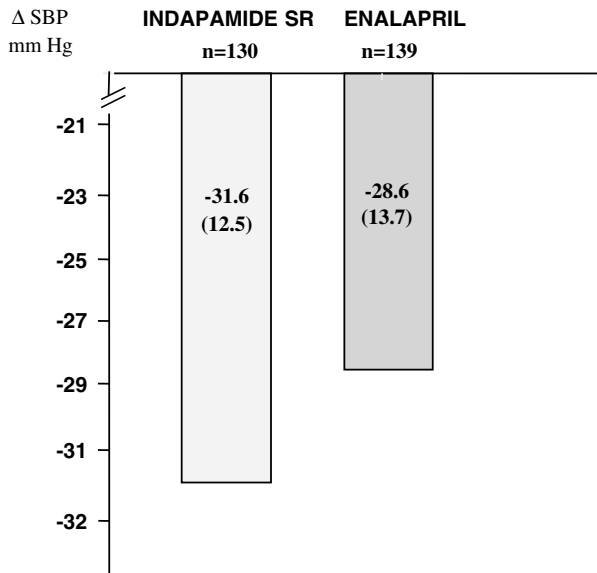


Figure 3 SBP lowering in hypertensive patients with LVH: the LIVE study. Comparison between indapamide SR and enalapril (mean change from baseline after 1-year monotherapy, data from Gosse *et al*²⁶).

and 206 patients received enalapril 20 mg; their mean age was 54 years.

Results showed that both indapamide SR and enalapril 20 mg significantly reduced SBP from baseline ($P < 0.001$). The decrease in SBP was -25.2 mmHg with indapamide SR and -24.5 mmHg enalapril. Statistical equivalence of the two treatments was confirmed. In the population who completed 1 year of monotherapy, the decrease in SBP was greater with indapamide SR (-31.6 mmHg, $n = 130$) than with enalapril (-28.6 mmHg, $n = 139$), Figure 3.

Moreover, indapamide SR reduced LVMI significantly more than enalapril 20 mg: -6.5 g/m², $P = 0.013$ (-4.3 g/m² when adjusted for baseline values; $P = 0.049$). The effect was not correlated to BP reduction. Indapamide SR progressively reduced wall thicknesses throughout the 1-year treatment period. In contrast, the effect of enalapril observed at 6 months was not maintained at 12 months.

Discussion

The study of the effects of diuretics has shown that they increase arterial distensibility.¹⁹ Whether this effect is the 'passive consequence' of BP decrease or the result of altered sodium balance remains uncertain. An MBP-independent association between sodium intake and pulse pressure was observed in younger subjects suggesting that dietary sodium may exert some non-pressure-dependent effects on structure and function of large arteries.²⁸ Several studies indicate that sodium could exert

such a pressure-independent contribution. Avolio *et al*²⁹ reported that the slope of the positive relationship between age and arterial stiffness was steeper in Chinese urban subjects in whom the sodium intake was higher compared with rural people. In an experimental study, Et-Taouil *et al*³⁰ demonstrated that a high-sodium diet decreased aortic compliance independently of blood pressure and in association with changes in aortic hyaluronan content.

For similar natriuretic effect, the higher efficacy of indapamide SR could be due to decreased wave reflections observed with indapamide but not with other diuretics. Indeed, Benetos *et al*³¹ have shown that the combination of hydrochlorothiazide and amiloride had no significant effect on the wave reflection while a recent controlled study demonstrated that indapamide SR reduced arterial wave reflections.³² This effect of indapamide suggests the possibility of a direct nondiuretic-dependent effect on arterial function and structure.^{30,33}

Clinically, SBP should be at the heart of BP management; it is an easily assessable parameter which allows a thorough evaluation of treatment efficacy. The three randomized comparative studies reviewed in this paper provided concordant evidence that the short- and long-term antihypertensive activity of indapamide SR is active on lowering SBP. The treatment with indapamide SR resulted in a better or equivalent control of SBP than treatment with a standard dose of a true thiazide diuretics (hydrochlorothiazide), a calcium channel blocker (amlodipine) and an ACE inhibitor (enalapril). BP remained steadily controlled with indapamide SR throughout these studies. Beyond the SBP effect, indapamide SR displayed an important impact on microalbuminuria in patients with type II diabetes, as shown in the NESTOR study. In addition, the LIVE study clearly demonstrated the superiority of indapamide SR over enalapril 20 mg in reducing the LVMI in hypertensive subjects with LVH.³⁴

Moreover, indapamide SR is devoid of the well-known diuretic-associated metabolic adverse events. Renal function, as assessed by the determination of urea and creatininaemia, remained unaffected after short- and long-term therapy with indapamide SR. Mean levels remained within the normal range and close to those in the placebo group at all evaluation times.

Indapamide SR has been proven to have a neutral effect both on lipid and glucose profiles.³⁵ It is well tolerated and may be used for the management of patients with hypertension including those with type II diabetes, increased cardiovascular risks (LVH) and the elderly.

These results confirm the efficacy of indapamide SR in hypertension, target-organ damage, LVH and in the elderly with or without ISH. They provide valuable information on the management of hypertensive patients with major independent risk factors for cardiovascular disease.

In summary, more attention should be paid to the level of SBP in relation to cardiovascular risk. These observations suggest that the decrease in SBP is a strong predictive factor of the occurrence of cardiovascular risk induced by the haemodynamic factors influencing SBP. Moreover, controlled clinical trials have shown that indapamide SR represents an appropriate choice as a first-line drug in many hypertensive patients, and also in at-risk patients including the elderly, subjects with other cardiovascular risk factors, target-organ damage, diabetes or impaired renal function.

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