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Metabolic Profile of Indapamide Sustained-Release in Patients with Hypertension

Data from Three Randomised Double-Blind Studies

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Abstract

Objective: To evaluate the influence of indapamide sustained-release (SR) 1.5 mg/day, a thiazide-related sulfonamide diuretic, on serum levels of lipids (total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol and triglycerides), glucose and uric acid, and renal function (serum urea and creatinine levels).

Methods: Pooled data from three randomised, double-blind, controlled studies are analysed. Two of these studies were of short duration (2 and 3 months), one of which included a 9-month nonblind extension phase, and the third was a 12-month prospective study. Short- and long-term metabolic effects of the treatment could thus be analysed. All studies were conducted in patients with mild-to-moderate hypertension; the total population randomised in these studies comprised 1195 patients, of whom 505 had left ventricular hypertrophy (LVH).

Results: After 2 to 3 months' treatment with indapamide SR 1.5 mg/day, there was no significant change from baseline in serum lipid levels and glucose levels. This neutral effect was maintained after 9 and 12 months of treatment. Renal function was not affected by short- or long-term indapamide SR 1.5 mg/day therapy. Serum uric acid level was slightly increased after short-term therapy, but was restored to baseline values during long-term therapy with indapamide SR 1.5 mg/day.

Conclusions: Indapamide SR 1.5 mg/day has no deleterious effect on glucose metabolism, serum levels of lipids and uric acid, or renal function. This antihypertensive agent can be considered to be an attractive therapeutic choice for all patients with mild-to-moderate hypertension, including the elderly and patients with increased cardiovascular risks, i.e. those with LVH.

A significant reduction in cardiovascular mortality has been observed over the past two decades. This decreased incidence of cardiovascular death is largely attributable to an improvement in cardiovascular risk factor detection and management based on the stratification of patients at risk of coronary heart disease. Patients are stratified according to a multidimensional model that takes into account the interactions of multiple risk factors and their contribution to overall coronary heart disease.[1,2] The main lesson from the Framingham study is that both risk estimation and preventive

management should be multifactorial if optimal results are to be achieved.[3]

Arterial hypertension is a major contributor to the risk of coronary heart disease, and it is now well established that the effectiveness of an antihypertensive therapy must be evaluated taking into consideration other cardiovascular risk factors, particularly those related to metabolism, such as the renal function parameters, serum lipid and glucose levels. Considering the potential risk of metabolic adverse effects induced by some antihypertensive treatments, the international guidelines recently highlighted the need to select the lowest dosage of antihypertensive agents in order to protect patients from dose-dependent adverse effects, while maintaining the efficacy of higher dosages over the 24-hour dosing interval.[4,5]

Diuretics are recommended and widely used as first-line therapy in essential hypertension. They have proven benefit on cardiovascular morbidity and mortality, particularly with respect to stroke in the elderly,[6-9] despite known deleterious effects on metabolic profile, such as an elevation of lipid parameters[10-12] and an alteration of glucose metabolism.[10,13-15]

Indapamide is an indoline derivative of chlorsulfonamide and, thus, differs chemically from thiazide diuretics. Its actions include a diuretic effect which, like the one of the thiazides, is induced mainly by inhibition of sodium reabsorption in the cortical segment of the distal convoluted tubule. However, the antihypertensive activity of comparatively low dosages of indapamide can be mainly explained by vasorelaxation, demonstrated by correction of vascular hyperreactivity in patients with hypertension.[16,17] This direct vascular effect is much more marked than that of hydrochlorothiazide or other diuretics and is due to selective binding related to the very intense lipophilicity of indapamide.[18,19] Immediate-release (IR) indapamide 2.5 mg/day is an effective antihypertensive agent,[20-28] which improves arterial parameters[20] and reduces left ventricular hypertrophy (LVH),[21,22] while preserving the metabolic profile.[23-26] In accordance with the international guidelines,[4,5] a new sustained-release (SR), low-dose (1.5mg) formulation of indapamide was developed to further improve the efficacy/acceptability ratio.

The diuretic effect of indapamide SR 1.5 mg/day is mild.[18,19,29] Although there is no difference of diuretic pattern between these two formulations, indapamide SR differs pharmacokinetically from indapamide IR: lower maximal blood concentration (58 versus 154 μ g/L) and a longer time over which circulating concentrations exceed 75% of maximal blood concentration (16.4 versus 1.5 hours).[30] In two European, randomised, double-blind, controlled trials with similar design, indapamide SR 1.5 mg/day was shown to effectively lower office[27] and 24-hour blood pressure, [28,31] and concomitantly reduce hypokalaemia by more than 50% compared with indapamide IR 2.5 mg/day. The Left ventricular hypertrophy regression, Indapamide Versus Enalapril (LIVE) study, a 1-year prospective, randomised, double-blind trial, was aimed at investigating how indapamide SR 1.5 mg/day and enalapril 20 mg/day reverse LVH in patients with hypertension. At endpoint, indapamide SR was found to be significantly more effective than enalapril in reducing left ventricular mass index, while both agents lowered blood pressure to a similar extent.[32,33] In this study, there was no significant difference in clinical acceptability between indapamide SR and enalapril.[34]

The present report analyses the effects of short- and long-term treatment with indapamide SR on serum lipid, glucose, and uric acid levels and renal function in these trials.

Populations and Methods

Data on serum levels of lipids, glucose, uric acid, and renal function (serum levels of urea and creatinine) were obtained from a total of 1195 patients randomised in three clinical trials: two European, randomised, controlled, multicentre studies (the dose-ranging study and the equivalence study), and a 1-year prospective, randomised, double-blind study (the LIVE study), all conducted in patients with mild-to-moderate essential hypertension.[27,28,31-33] Patients included in the LIVE study also had

LVH.[32,33] In all participating countries, the studies were approved by each local institutional review board and all patients provided written informed consent prior to randomisation.

Detailed methods for all three studies have been previously reported[27,28,32] and the salient features have been summarised here.

Study Design and Methods

In all studies, after cessation of all current antihypertensive medication, patients underwent a single-blind run-in period with placebo. This run-in period lasted 1 month in the dose-ranging and the equivalence studies, and 2 weeks in the LIVE study.

Following the run-in period, patients in the dose-ranging study were randomised (in five parallel groups) to receive treatment with placebo, indapamide IR 2.5 mg/day, indapamide SR 1.5 mg/day, indapamide SR 2 mg/day, or indapamide SR 2.5 mg/day for 2 months, in a double-blind manner. In the equivalence study, which aimed to demonstrate the equivalent efficacy between indapamide SR 1.5 mg/day and indapamide IR 2.5 mg/day and evaluate their acceptability, two parallel groups received either indapamide IR 2.5 mg/day or indapamide SR 1.5 mg/day for 3 months in a double-blind manner. At the end of this period, patients with a supine diastolic blood pressure (DBP) <95mm Hg could enter a 9-month nonblind follow-up period with indapamide SR 1.5 mg/day.

In the LIVE study, patients were randomised to receive treatment with indapamide SR 1.5 mg/day or enalapril 20mg daily for 12 months in a double-blind manner.

Similar inclusion criteria were used in the dose-ranging and the equivalence studies: ambulatory men and women, aged 18 to 70 years, with mild-to-moderate essential hypertension defined as a clinic supine trough DBP of ≥95mm Hg and ≤114mm Hg, a plasma potassium level >3.5 mmol/L, and a compliance of at least 80%, as assessed by tablet-counting, at the end of the run-in period. Severe or secondary hypertension, type 1 and unstable type 2 diabetes mellitus, or any significant cardiac, renal, hepatic, neurologic, or other serious disease that might interfere with the study were reasons for non-inclusion, as well as a serum potassium level <3.5 mmol/L. Potassium supplements were given to patients in whom the serum potassium fell to a level <3.5 mmol/L at the intermediate visit. During the 9-month nonblind treatment, a supine DBP of ≥95mm Hg was a criterion for stopping the study treatment.

In the LIVE study, men and women were eligible for inclusion provided they were aged ≥20 years, and presented with LVH and mild-to-moderate hypertension. Main criteria for non-inclusion were coronary heart disease, valvular heart disease, dilated cardiomyopathy, symptomatic heart failure, poor echogenic quality of cardiac structures on echocardiography, abnormal myocardial kinetics, diabetes mellitus and obesity.

Biochemical Assessments

In all studies, laboratory tests performed to determine the metabolic parameters required blood samples obtained by venous puncture in the morning after an overnight fast, and prior to intake of any medication. Analyses were performed locally, at each investigators' site. Values were not transformed for the purpose of statistical analysis.

Although some intermediate visits were scheduled for biological assessments, we only report those evaluation times considered for the present analysis, i.e. baseline and end-of-therapy assessments. It should be noted that for the 9-month nonblind indapamide SR period in the equivalence study, the baseline assessment was considered to be that at M3, the end of the double-blind part of the study.

Fasting serum levels of total cholesterol, triglycerides, glucose, uric acid, urea, and creatinine were assessed at baseline (M0), and at M2 for the dose-ranging study, M3 for the equivalence study (i.e., M0 for the nonblind follow-up), and M12 for the LIVE study and the 9-month nonblind follow-up with indapamide SR.

High-density lipoprotein-cholesterol (HDL-C) levels were assessed at baseline, after 3 months in the equivalence study and after 12 months of treat-

ment in both the long term nonblind follow-up and the LIVE study. Low-density lipoprotein-cholesterol (LDL-C) levels were assessed only in the equivalence study, at baseline and M3, and at the end of the long-term follow-up.

Statistical Analysis

Statistical analyses were performed using SAS software (version 6.08, SAS Institute, North Carolina, US). Metabolic parameters were safety evaluation criteria and were thus considered as secondary criteria in both studies. Metabolic parameters, described as mean with standard deviation and a 95% confidence interval of the variation between the last measurement performed under treatment and baseline value, were assessed in randomised patients with at least one evaluation at baseline and one evaluation under active treatment. For the long-term, nonblind follow-up extension of the equivalence study, the baseline value was defined as that at M3, when patients complying with blood pressure criteria entered the 9-month extension and all received indapamide SR.

Results

Population Characteristics

A total of 1195 patients were randomised in the three studies, and the patients were distributed as follows:

285 patients were randomised in the dose-ranging study, of whom 58 received placebo, 57 indapamide SR 1.5 mg/day, and 59 indapamide IR 2.5 mg/day (the remaining 111 patients received other dosages of indapamide SR).

405 patients were randomised in the equivalence study, of whom 205 received indapamide IR 2.5 mg/day and 200 received indapamide SR 1.5 mg/day. From these two groups, a total of 324 patients entered the 9-month nonblind follow-up phase during which they received indapamide SR 1.5 mg/day.

505 patients were randomised in the LIVE study, of whom 255 received indapamide SR 1.5 mg/day and 250 received enalapril 20 mg/day.

The number of indapamide recipients considered for the analysis of the short-term metabolic effects was 521 (264 receiving indapamide IR 2.5 mg/day, and 257 receiving indapamide SR 1.5 mg/day). The analysis of the long-term effects of indapamide SR 1.5 mg/day was conducted in 579 patients.

The clinical characteristics at baseline of all the included patients are presented in table I, according to the study and treatment group.

Effect of Indapamide Sustained-Release on Serum Glucose and Lipid Levels

Mean values at baseline and post-therapy, and changes in fasting glucose and lipid levels are pre-

Table I. Clinical baseline characteristics of the study populations

Study group	Dose-ranging study			Equivalence study		Long-term study[a]	LIVE study
	Placebo	SR 1.5	IR 2.5	SR 1.5	IR 2.5	SR 1.5	SR 1.5
n	58	57	59	200	205	324	255[b]
Age [years (SD)]	53 (8)	55 (11)	55 (10)	53 (10)	57 (10)	55 (11)	54 (11)[b]
Sex [n (% men)]	33 (57)	25 (44)	28 (47)	99 (50)	114 (56)	169 (52)	162 (64)[b]
Weight [kg (SD)]	73 (12)	70 (12)	69 (12)	73 (13)	72 (11)	72 (11)	76 (12)[b]
Previous treatment [n (%)]	41 (71)	34 (60)	38 (64)	135 (68)	156 (76)	220 (68)	168 (66)
Known hypertension duration [years (SD)]	4.4 (4.6)	4.0 (4.9)	4.6 (6.5)	3.9 (4.4)	5.5 (5.8)	4.6 (5.0)	8.6 (8.5)

a Nonblind extension of the equivalence study.

b Patients considered evaluable on the basis of echocardiography criteria.

IR 2.5 = immediate-release indapamide 2.5mg; **LIVE** = Left ventricular hypertrophy regression, Indapamide Versus Enalapril; **n** = number of participants; **SD** = standard deviation; **SR 1.5** = sustained-release indapamide 1.5mg.

Table II. Changes in fasting serum levels of glucose and lipids after short-term (2 to 3 months) treatment with placebo, indapamide sustained-release (SR) 1.5 mg/day, and indapamide immediate-release (IR) 2.5 mg/day

Laboratory variables	Placebo	Indapamide SR 1.5mg		Indapamide IR 2.5mg	
	dose-ranging study[a]	dose-ranging study[a]	equivalence study[b]	dose-ranging study[a]	equivalence study[b]
Glucose (mmol/L)					
n	51	53	193	57	187
Baseline (SD)	5.44 (1.28)	5.26 (0.72)	5.39 (1.33)	5.23 (0.71)	5.57 (2.28)
Endpoint (SD)	5.34 (0.90)	5.25 (1.08)	5.51 (1.40)	5.48 (1.07)	5.72 (2.21)
Change from baseline (SD)	–0.12 (0.92)	–0.01 (0.87)	0.13 (1.03)	0.24 (0.77)	0.15 (1.45)
CI	–0.37; 0.13	–0.25; 0.23	–0.02; 0.27	0.04; 0.44	–0.06; 0.36
Cholesterol (mmol/L)					
n	51	53	192	57	185
Baseline (SD)	6.25 (1.27)	6.01 (1.04)	6.15 (1.09)	6.17 (0.97)	5.93 (1.08)
Endpoint (SD)	5.98 (1.03)	5.99 (1.12)	6.17 (1.11)	6.32 (1.14)	6.12 (1.13)
Change from baseline (SD)	–0.27 (1.97)	–0.02 (0.84)	0.02 (0.87)	0.16 (0.75)	0.19 (0.97)
CI	–0.54; 0.00	–0.25; 0.21	–0.10; 0.14	–0.04; 0.35	0.05; 0.34
HDL-C (mmol/L)					
n			162		156
Baseline (SD)			1.49 (0.52)		1.37 (0.48)
Endpoint (SD)			1.41 (0.40)		1.34 (0.36)
Change from baseline (SD)			–0.08 (0.50)		–0.03 (0.43)
CI			–0.16; –0.01		–0.10; 0.04
LDL-C (mmol/L)					
n			149		140
Baseline (SD)			3.93 (0.99)		3.74 (1.08)
Endpoint (SD)			4.00 (1.10)		3.94 (1.04)
Change from baseline (SD)			0.07 (0.86)		0.20 (0.83)
CI			–0.07; 0.21		0.06; 0.34
Triglycerides (mmol/L)					
n	51	53	193	57	185
Baseline (SD)	1.57 (1.07)	1.47 (0.75)	1.53 (0.93)	1.45 (0.95)	1.58 (1.13)
Endpoint (SD)	1.49 (1.03)	1.60 (0.82)	1.58 (0.92)	1.88 (2.18)	1.77 (1.35)
Change from baseline (SD)	–0.08 (0.78)	0.12 (0.71)	0.05 (0.68)	0.43 (2.03)	0.18 (1.03)
CI	–0.29; 0.14	–0.07; 0.32	–0.04; 0.15	–0.11; 0.97	0.04; 0.33

a 2-month duration.

b 3-month duration.

CI = 95% confidence interval; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **SD** = standard deviation.

sented in table II. Short-term treatment with indapamide SR did not induce any significant modification in serum levels of glucose, total cholesterol or triglycerides. Serum HDL-C and LDL-C levels were not significantly modified after 3 months' treatment with indapamide SR; endpoint values of these parameters remained within the normal limits. In terms of mean value and change observed post-therapy, no significant differences were observed between patients receiving active treatment and those receiving placebo. The very slight differences observed between endpoint values and changes induced by indapamide SR 1.5 mg/day and indapamide IR 2.5 mg/day in fasting glucose and

Table III. Changes in fasting serum levels of glucose and lipids after long-term (9 to 12 months) treatment with indapamide sustained-release (SR) 1.5 mg/day

Laboratory variables	Indapamide SR 1.5mg/day	
	Nonblind study (9 months)	LIVE study (12 months)
Glucose (mmol/L)		
n	260	251
Baseline (SD)[a]	5.58 (1.78)	5.57 (1.68)
Endpoint (SD)	5.56(1.59)	5.48 (1.69)
Change from baseline (SD)	–0.02 (1.14)	–0.09 (0.88)
CI	–0.15; 0.12	–0.20; 0.02
Cholesterol (mmol/L)		
n	258	252
Baseline (SD)[a]	6.17 (1.07)	5.97 (1.17)
Endpoint (SD)	6.14 (1.10)	5.79 (1.11)
Change from baseline (SD)	–0.03 (0.81)	–0.18 (0.88)
CI	–0.13; 0.07	–0.29; –0.07
HDL-C (mmol/L)		
n	226	251
Baseline (SD)[a]	1.38 (0.37)	1.08 (0.37)
Endpoint (SD)	1.41 (0.41)	1.08 (0.30)
Change from baseline (SD)	0.03 (0.39)	0.01(0.40)
CI	–0.02; 0.08	–0.04; 0.06
LDL-C (mmol/L)		
n	210	
Baseline (SD)[a]	3.99 (1.04)	
Endpoint (SD)	3.92 (1.04)	
Change from baseline (SD)	–0.06 (0.92)	
CI	–0.19; 0.06	
Triglycerides (mmol/L)		
n	254	252
Baseline (SD)[a]	1.67 (1.09)	1.81 (1.26)
Endpoint (SD)	1.76 (1.20)	1.89 (1.51)
Change from baseline (SD)	0.09 (0.93)	0.08 (1.24)
CI	–0.03; 0.20	–0.07; 0.24

a The value observed at M3 in the nonblind study, and M0 in the LIVE study.

CI = 95% confidence interval; **HDL-C** = high-density lipoprotein-cholesterol; **LIVE** = Left ventricular hypertrophy regression, Indapamide Versus Enalapril; **LDL-C** = low-density lipoprotein-cholesterol; **n** = number of participants; **SD** = standard deviation.

lipid levels are clinically irrelevant, but suggest a trend toward a better acceptability profile with indapamide SR 1.5 mg/day.

After long-term (9 to 12 months) treatment with indapamide SR 1.5 mg/day, no significant modification was observed in fasting serum levels of glucose, total cholesterol, HDL-C or LDL-C, and post-therapy levels were unchanged compared with baseline (table III).

Effect of Indapamide Sustained-Release on Serum Uric Acid, Urea and Creatinine Levels

Mean values at baseline and post-therapy, and changes in serum levels of uric acid, urea, and creatinine after short-term (2 to 3 months) treatment with placebo, indapamide SR 1.5 mg/day, and indapamide IR 2.5 mg/day are presented in table IV; the effects of long-term (9 to 12 months) treatment

with indapamide SR on these variables are presented in table V.

Compared with baseline values, serum uric acid level was slightly increased after 2 and 3 months treatment with both indapamide dosages, but serum uric acid level appeared to decrease during long-term treatment with indapamide SR.

Renal function, as assessed by the determination of serum urea and creatinine levels, remained unaffected after short- and long-term treatment with indapamide (both formulations): mean levels remained within the normal range and close to those in the placebo group at all evaluation times. A minor short-term increase in serum urea levels was followed by a decrease during long-term therapy, while serum creatinine levels were unchanged throughout the study.

Discussion

Pooled presentation of metabolic data from the dose-ranging study and the equivalence study was possible because several methodological aspects were similar: (i) the study design; (ii) the inclusion/exclusion criteria; and (iii) the evaluation and analysis. Metabolic findings from the LIVE study were also included in this analysis because, despite the presence of LVH in the randomised population, all included patients also presented with mild-to-moderate hypertension, and the LIVE study design and methods were comparable to those of the other two studies.

Potential limitations to the present approach could be the absence of central laboratory assessments and the lack of standardised values for all biochemical parameters. However, despite these

Table IV. Changes in renal function and serum uric acid levels after short-term (2 to 3 months) treatment with placebo, indapamide sustained-release (SR) 1.5 mg/day, and indapamide immediate-release (IR) 2.5 mg/day

Laboratory variables	Placebo	Indapamide SR 1.5 mg/day		Indapamide IR 2.5 mg/day	
	Dose-ranging study	Dose-ranging study[a]	Equivalence study[b]	Dose-ranging study[a]	Equivalence study[b]
Uric acid (μmol/L)					
n	51	53	185	57	178
Baseline (SD)	319.3 (98.0)	291.8 (83.7)	318.0 (86.0)	285.9 (81.2)	313.3 (93.7)
Endpoint (SD)	320.4 (98.5)	334.9 (88.2)	353.3 (94.5)	359.0 (101.1)	370.3 (107.8)
Change from baseline (SD)	1.52 (83.1)	43.2 (48.6)	35.3 (70.2)	73.1 (86.1)	57.0 (68.2)
CI	–21.6; 24.6	29.8; 56.5	25.1; 45.5	50.3; 96.0	46.9; 67.1
Urea (mmol/L)					
n	48	55	200	58	200
Baseline (SD)	5.56 (1.36)	5.63 (1.46)	5.58 (1.74)	5.89 (1.49)	5.76 (1.65)
Endpoint (SD)	5.65 (1.46)	6.14 (1.60)	5.90 (1.75)	6.10 (1.75)	6.22 (1.83)
Change from baseline (SD)	0.18 (1.10)	0.50 (1.49)	0.32 (1.40)	0.21 (1.19)	0.46 (1.56)
CI	–0.11; 0.48	0.10; 0.90	0.12; 0.51	–0.10; 0.53	0.24; 0.68
Creatinine (μmol/L)					
n	50	54	193	57	187
Baseline (SD)	83.6 (17.0)	86.7 (18.1)	88.0 (16.8)	86.0 (18.0)	87.5 (17.3)
Endpoint (SD)	85.2 (16.2)	86.3 (18.9)	86.3 (17.3)	88.2 (18.3)	86.1 (17.6)
Change from baseline (SD)	1.6 (14.4)	–0.4 (13.0)	–1.7 (13.0)	2.2 (13.3)	–1.5 (13.8)
CI	–2.5; 5.6	–4.0; 3.1	–3.5; 0.2	–1.3; 5.7	–3.4; 0.5

a 2-month duration.

b 3-month duration.

CI = 95% confidence interval; **SD** = standard deviation.

Table V. Changes in renal function and serum uric acid levels after long-term (9 to 12 months) treatment with indapamide sustained-release (SR)1.5 mg/day

Laboratory variables	Indapamide SR 1.5 mg/day	
	Nonblind study (9 months)	LIVE study (12 months)
Uric acid (μmol/L)		
n	251	252
Baseline (SD) [a]	364.1 (100.1)	340.8 (78.6)
Endpoint (SD)	344.2 (94.0)	353.5 (101.3)
Change from baseline (SD)	–19.9 (73.0)	12.7 (65.6)
CI	–29.0; –10.8	4.6; 20.8
Urea (mmol/L)		
n	293	252
Baseline (SD)[a]	6.03 (1.82)	5.79 (1.51)
Endpoint (SD)	5.94 (1.87)	5.96 (1.57)
Change from baseline (SD)	–0.09 (1.45)	0.17 (1.54)
CI	–0.25; 0.08	–0.02; 0.36
Creatinine (μmol/L)		
n	260	252
Baseline (SD)[a]	86.1 (17.7)	72.9 (21.4)
Endpoint (SD)	87.4 (16.7)	76.5 (15.5)
Change from baseline (SD)	1.4 (11.5)	3.6 (19.0)
CI	–0.0; 2.8	1.3; 6.0

a The value observed at M3 in the nonblind study, and M0 in the LIVE study.
CI = 95% confidence interval; **SD** = standard deviation.

limitations, all three studies provide concordant evidence that the short- and long-term antihypertensive activity of indapamide, especially the SR formulation, is devoid of the well-known diuretic-associated metabolic adverse effects.

In the studies discussed here, indapamide SR did not adversely affect fasting serum glucose levels, serum lipid levels, or renal function as estimated by serum creatinine, since, despite some slight changes from baseline of several parameters, these effects were clinically irrelevant. In all studies, endpoint values were within the normal ranges whatever the evaluation period. Metabolic parameters in patients receiving active treatment were not significantly different from those in placebo recipients in the dose-ranging study.

Although serum uric acid levels were slightly increased from baseline in all short-term evaluations, this change tended to be smaller with the indapamide SR formulation and serum uric acid levels were lower after 3 months than after 2 months with both indapamide formulations. Moreover, a tendency for decreased serum uric acid levels was observed after 12 months' treatment with indapamide SR 1.5 mg/day. Elevated serum uric acid levels are common with antihypertensive diuretic therapy, and 3 to 5% of patients treated with diuretics develop clinical manifestations of gout.[35] As observed in the Medical Research Council trial, the frequency of withdrawals due to gout was significantly higher among patients receiving diuretics than control patients receiving placebo, and treatment with diuretics led to a >10-fold increase from baseline values in serum uric acid levels compared with placebo (+45 versus +4 μmol/L).[36] In the current studies, increase in serum uric acid levels remained below +45 μmol/L, after short-term treatment with indapamide SR, and serum uric acid level was restored to baseline values during long-term therapy. Gout was not diagnosed in any recipient in any period.

Serum urea levels were increased in the short term only, by both formulations of indapamide, but to a lesser extent with the indapamide SR formula-

tion. However, serum creatinine levels remained unchanged from baseline values indicating that renal function was preserved.

The dose-dependent hyperglycaemia that has often been reported with thiazide diuretics in populations similar to those of the current studies, i.e. nondiabetic patients with essential hypertension[15,37] was not observed in the three studies discussed here. Thus, fasting serum glucose levels were not affected during administration of both formulations of indapamide, confirming that indapamide does not affect glucose metabolism.

All lipid parameters were unaffected by long-term treatment with indapamide SR 1.5 mg/day. This absence of effect on lipid parameters has recently been recognised in international clinical guidelines for the management of hypertension.[4]

The present results corroborate earlier findings in smaller patient groups suggesting time- and dose-dependent metabolic effects of diuretics, i.e. a lower incidence of metabolic adverse effects associated with long-term treatment and lower dosages,[25,37-41] which justify the international recommendations to select lower dosages in order to reduce metabolic adverse effects while maintaining antihypertensive efficacy.[4-6] The problem commonly encountered during treatment with diuretics is the determination of the adequate dosage since most of the time, both efficacy and metabolic adverse effects are dose-dependent.

Effects of the two indapamide formulations on electrolyte parameters and in particular on plasma potassium have previously been reported in detail.[27,28,31,33] It is noteworthy that after short-term administration (4 to 6 weeks), patients treated with indapamide SR 1.5 mg/day had 50% lower incidence of hypokalaemia compared with those treated with indapamide IR 2.5 mg/day. During the 9-month follow-up, 91.3% of the patients treated with indapamide SR 1.5 mg/day maintained normokalaemia, i.e. ≥3.5 mmol/l. Only four patients were withdrawn from treatment due to hypokalaemia on long-term indapamide SR treatment.

A better metabolic tolerance of indapamide over other diuretic agents associated with a comparable antihypertensive efficacy has been already observed with the original indapamide IR 2.5mg formulation.[10,24,25,42-45] Ames' meta-analysis,[25] which included 31 reports on thiazides (430 participants in low-dose studies and 559 in the high-dose regimens) and 13 studies of indapamide comprising 558 participants, concluded that: (i) thiazide effects on serum lipid levels and systolic blood pressure are dose-dependent; (ii) thiazides adversely affect the serum lipid profile even at low dosages; and (iii) indapamide 2.5 mg/day lowers blood pressure by the same amount as thiazide diuretics but with no adverse effects on serum lipid levels, since it causes a significantly smaller increase in serum cholesterol and triglyceride levels than low-dose thiazides. Although the studies included in the present analysis did not comprise groups assigned to receive parallel treatment with hydrochlorothiazide or other conventional diuretics, the findings confirm the metabolic neutrality of both dosages of indapamide. Reasons for the favourable metabolic profile of indapamide as compared with other diuretics probably include dose- as well as drug-related components. Metabolic alterations seem to reflect, at least in part, the magnitude of natriuretic-kaliuretic effects. Since indapamide exerts more potent vascular effects than other diuretics, it is capable of reducing elevated blood pressure at comparatively lower dosages inducing less natriuresis-kaliuresis.[16,17,19] In fact, the SR formulation has facilitated further reduction in indapamide dosage with no reduction in antihypertensive efficacy. Blood pressure remained steadily controlled with indapamide SR throughout these studies,[27,28,31] demonstrating an efficient antihypertensive activity of indapamide, even at the lower dosage, and confirming its optimal efficacy/safety ratio.

Conclusion

Indapamide SR 1.5 mg/day seems to be the only agent of the diuretic class proven in large numbers of patients to provide an efficient blood pressure control without any associated adverse effects on glycaemia, or serum lipid or uric acid levels. It

follows that indapamide SR 1.5 mg/day is well tolerated and may be used for the management of patients with hypertension, including the elderly and patients with increased cardiovascular risks, i.e. those with LVH.

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