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Low-dose antihypertensive therapy with 1.5 mg sustained-release indapamide: results of randomised double-blind controlled studies

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Objective **In accordance with international recommendations on the need to decrease doses of antihypertensive drugs, a low-dose (1.5 mg) sustained-release (SR) formulation of indapamide was developed to optimize the drug's efficacy : safety ratio. The aim of this work was to evaluate the benefit of a low-dose diuretic by consolidating the efficacy and safety results of two clinical trials with a similar design.**

Patients and methods **Clinical data were obtained in two European randomized double-blind studies with 690 mild to moderate hypertensive patients (95 mmHg ≤ supine diastolic blood pressure ≤ 114 mmHg using a mercury sphygmomanometer) treated respectively for 2 and 3 months, with a mean age of 53 and 57 years, 44 and 57% males, mean supine diastolic blood pressure of 100.6 and 102.5 mmHg and mean supine systolic blood pressure of 161.0 and 164.5 mmHg.**

Results **The first study, a dose-finding study with indapamide SR at 1.5, 2 and 2.5 mg versus placebo and the immediate-release (IR) formulation of indapamide, showed that the 1.5 mg dosage of the new indapamide formulation had an improved antihypertensive efficacy : safety ratio. The second study confirmed the equivalence of blood pressure reductions with 1.5 mg indapamide SR and 2.5 mg indapamide IR, and better acceptability with 1.5 mg indapamide SR, particularly in the number of patients with serum potassium levels < 3.4 mmol/l, which was reduced by more than 50%. The long-term efficacy of 1.5 mg indapamide SR was observed through a 9-month open-treatment follow-up to the second study.**

Conclusion **The 1.5 mg SR formulation of indapamide has an improved antihypertensive efficacy : safety ratio, which is in accordance with international recommendations for the use of low-dose antihypertensive drugs and diuretics in first-line therapy of hypertension.** *J Hypertens* **1998, 16:1677–1684 © Lippincott Williams & Wilkins.**

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Introduction

In the last 30 years, several classes of antihypertensive drugs have been available, allowing the first-line use of diuretics, β-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers or α-blockers. Recommendations made by all the scientific and regulatory authorities have stressed that low doses of these drugs are needed for the best safety : efficacy ratio [1,2]. Multicenter trials lasting from 2 to 6 years have confirmed the decrease in morbidity and mortality in hypertensive patients treated almost exclusively with diuretics and β-blockers [3–5], and the reduction in cerebrovascular accidents and coronary heart disease, versus placebo, was shown to be greater with diuretics than with β-blockers [5]. Thus, diuretics remain a first-line treatment for essential hypertension because their beneficial effect on morbidity and mortality has been demonstrated in the long term and because of improvements in their use, particularly with a reduction in dosage.

Indapamide is a thiazide-related sulfonamide diuretic developed as an antihypertensive agent in the early 1970s.

Its antihypertensive efficacy at a daily dose of 2.5 mg with an immediate-release (IR) form has been demonstrated in double-blind controlled studies versus placebo or other antihypertensive drugs [6–9]. It is associated with a neutral effect on lipid [10] or carbohydrate [6,11] metabolic parameters. The aim of developing a sustained-release (SR) form of indapamide with a reduced dosage of 1.5 mg was to improve the safety : efficacy ratio and to meet international recommendations urging the use of low doses of antihypertensives. Two European, randomized, double-blind trials, with a similar design, were conducted first to determine the new dose of the SR form and then to compare the effects of this new dose and form with 2.5 mg indapamide IR. Moreover, a 9-month open extension to the equivalence study was designed to provide additional information on long-term clinical and biological acceptability in hypertensive patients treated with 1.5 mg indapamide SR [12,13]. The aim of the present work was to evaluate the benefit of a low-dose diuretic by consolidating the efficacy and safety results of two clinical trials with a similar design.

Patients and methods

Study objective and design

Two European, controlled, multicenter studies were conducted consecutively to achieve the following objectives: (1) a 2-month dose-finding study versus placebo and 2.5 mg indapamide IR to select an appropriate dose of the SR tablet (1.5, 2 or 2.5 mg), looking for no difference in efficacy between indapamide SR and 2.5 mg indapamide IR but a lower incidence of patients with serum potassium level of < 3.4 mmol/l; and (2) a 3-month study to confirm that the selected dose of indapamide SR was equivalent in efficacy to 2.5 mg of the IR form but better acceptability in terms of serum potassium levels as outlined in objective 1.

Identical methods were used in both studies. Following a 1-month single-blind placebo run-in (enrolment visit month –1), hypertensive patients were randomly allocated to parallel groups (inclusion visit month 0) for one of the above treatments on a double-blind basis for 2 months in the dose-finding study and for 3 months in the equivalence study. At the end of the 3 month-equivalence study, a 9-month open treatment period using 1.5 SR with two intermediate visits 3 months apart (months 6 and 9) was proposed to all patients, whatever the initial treatment (1.5 SR or 2.5 IR), with a supine diastolic blood pressure (DBP) of < 95 mmHg, in order to provide additional long-term information. No other antihypertensive treatment was allowed. The studies were approved by ethics committees in the countries concerned (dose-binding study: Broussais Hospital, Paris, France; Medical Ethics Committe of Brussels, Belgium; University of Pavia and University and Hospital of Bologna, Italy; East Berkshire Health Authority, North Birmingham Health Authority, Wexham Park Hospital and Goodhope Hospital, UK; equivalence study: Committee for the Protection of People in Biomedical Research, Saint Germain en Laye, France; Faisanderie Clinic, Brussels, Belgium; Universities of Bologna, Pavia and Sassari, Italy; Alcala de Henares Hospital, Madrid, Spain; PMR Ethical Committee, Eastbourne, UK).

Patients

Inclusion criteria were the same in both studies, comprising male and female outpatients, aged 18–70 years, with mild to moderate essential hypertension, defined as a supine DBP of ≥ 95 and ≤ 114 mmHg after having provided written informed consent. The patients were asked to cease taking all current antihypertensive medications. After 4 weeks of the single-blind placebo run-in period, the patients were included 1 month later (month 0) on the basis of a persistent supine DBP of ≥ 95 and ≤ 114 mmHg and compliance of at least 80% (tablet-counting).

Patients were excluded from the trial for severe or secondary hypertension or any significant cardiac, renal, hepatic, neurologic or other serious disease that might interfere with the study. A further exclusion criterion was a serum potassium level of < 3.5 mmol/l. Potassium supplements were to be given if the serum potassium level was < 3.5 mmol/l at the intermediate visit in each study. During the 9-month open treatment, a supine DBP of ≥ 95 mmHg was a criterion for stopping the study treatment.

Blood pressure measurement

Blood pressure was measured conventionally 24 h after the last drug intake using a calibrated mercury sphygmomanometer, at rest after 10 min in the supine position, and in triplicate at 1 min intervals at each visit in compliance with World Health Organization guidelines; the mean of the triplicate determinations was used for analysis. Standing blood pressure was measured after 1 min of standing.

Statistical analysis

Statistical analyses were performed using SAS software (6.08 version, SAS Institute, Cary, North Carolina, USA). In both studies, the primary efficacy parameter was the supine DBP change between baseline and the last observation. In the equivalence study, an additional primary parameter used was the percentage of patients with a serum potassium level of < 3.4 mmol/l. Secondary efficacy parameters included the change from baseline in supine SBP, standing DBP and SBP, responder rates (supine DBP ≤ 90 mmHg or a reduction in supine DBP of ≥ 10 mmHg) and controlled patients rates (supine DBP ≤ 90 mmHg). In the dose-finding study, a total of 200 patients were required to detect a 10 mmHg difference between the placebo and treated groups in supine DBP reduction. In the equivalence study, a total of 300 patients

were required, defining equivalence as a maximum 2 mmHg difference between groups in supine DBP reduction (with the 95% confidence interval of this difference itself not exceeding ± 5 mmHg). For supine SBP, confidence interval limits were ± 9.5 mmHg. Efficacy and safety were analyzed in both studies on an intention-to-treat basis, the last measurement being carried forward to the last study visit if the patient did not complete the trial (baseline value in some cases).

In the dose-finding study, a one-way analysis of variance was performed, followed by a Newman–Keuls test if significant treatment effects were present. In the equivalence study, a procedure using two one-sided tests was adopted, with $\alpha = 2.5\%$ [14]. The other variables were analyzed for a difference between groups. The incidence of patients with a serum potassium level of < 3.4 mmol/l was also calculated. In the long-term follow-up to the equivalence study, a descriptive analysis for all patients treated was performed. An analysis of time to treatment failure (Kaplan–Meier) was performed in order to study the time to onset of the three following events: (1) the occurrence of uncontrolled blood pressure (supine DBP > 90 mmHg); and (2) the occurrence of a supine DBP of ≥ 95 mmHg (criterion for stopping the treatment); and (3) the occurrence of patients with a serum potassium level of < 3.4 mmol/l for the first time.

Results

Patient characteristics

Of 839 hypertensive patients selected for the two double-blind studies (364 for the dose-finding study, 475 for the equivalence study), 690 were randomized (285 and 405 for the dose-finding and equivalence study, respectively) and none were lost to follow-up. Patients selected but not included dropped out mainly because they were placebo-responders. Baseline characteristics of the patient population are summarized in Table 1.

In the dose-finding study, the 285 randomized patients were randomized in the intention-to-treat analysis. A total of 268 patients completed the study and 17 were withdrawn because of a major protocol deviation (n = 4; placebo, two; 1.5 SR, one; 2 SR, one), severe hypertension (n = 1; placebo), treatment-unrelated causes (n = 3; placebo, one; 1.5 SR, one; 2.5 SR, one) and adverse events (n = 9; placebo, one; 2.5 IR, one; 1.5 SR, one; 2 SR, one; 2.5 SR, five).

In the equivalence study, the 405 randomized patients were all randomized in the intention-to-treat analysis. A total of 381 patients completed the double-blind study and 24 were withdrawn because of a major protocol deviation (n = 2; 2.5 IR, one; 1.5 SR one), treatment-unrelated causes (n = 10; 2.5 IR, six; 1.5 SR, four) and adverse events (n = 12; 2.5 IR, seven; 1.5 SR, five).

Of the 381 patients who completed the study, 67 patients did not enter the long-term period either for inefficacy (n = 44) or for other reasons not related to treatment (n = 23). The other 314 patients entered the long-term treatment period along with 10 new patients (Belgium six, Spain four) not taken into account in the equivalence study because of the delay in setting up the study in these countries. Thus, a total of 324 patients entered the long-term follow-up period and were randomized in the descriptive analysis. Baseline characteristics of these patients are summarized in Table 1. Thirty-three out of these were enrolled with a supine DBP of ≥ 95 mmHg at month 3 (protocol violation), 15 initially treated with 1.5 mg SR and 18 with 2.5 IR. A total of 270 patients completed the long-term study and 54 patients were withdrawn because of a major deviation protocol (n = 2), lack of efficacy (n = 19), treatment-unrelated causes (n = 24) and adverse events (n = 9).

Efficacy

Mean changes in supine DBP and supine SBP from baseline and the rates of responders and patients with controlled blood pressure are shown for both studies in Table 2.

In the dose-finding study, no significant linear dose-trend in the decrease in supine DBP was observed across the three groups treated with SR. The antihypertensive efficacy (supine DBP and supine SBP) of 1.5 mg indapamide SR was significantly greater than that of placebo ($P \leq 0.01$, Newman–Keuls) and similar to the other SR dosages and to 2.5 IR. The rates of responder and controlled patients achieved with 1.5 mg SR did not differ significantly from those of 2.5 IR and were significantly higher than placebo (response rate, $P = 0.028$; control rate, $P = 0.003$). Similar results were obtained with standing DBP (mean reduction of 10.3 ± 8.8 mmHg with 1.5 SR versus 9.8 ± 7.8 mmHg with 2.5 IR) and with standing SBP (mean reduction of 19.2 ± 16.2 mmHg with 1.5 SR versus 18.3 ± 15.4 mmHg with 2.5 IR).

In the equivalence study, a significant reduction from baseline in supine DBP was shown with both treatments; the equivalence was demonstrated by a difference of 0.4 mmHg in supine DBP reduction between 1.5 SR and 2.5 IR, with a 95% confidence interval in the predefined equivalence range. The rates of responders and controlled patients were not statistically different.

The difference in standing DBP between 1.5 SR and 2.5 IR was −0.03 mmHg; the intertreatment differences in supine and standing SBP were 2.3 and 1.2 mmHg, respectively. All the 95% confidence intervals of the differences fell into the predefined equivalence range.

In the long-term treatment study, blood pressure values at each visit and changes from month 3 are presented

Table 1 Baseline demographic characteristics

	Dose-finding study					Equivalence study		Long-term
	Placebo	2.5 IR	1.5 SR	2.0 SR	2.5 SR	1.5 SR	2.5 IR	1.5 SR
n	58	59	57	55	56	200	205	324
Age (years)	53 ± 8	55 ± 10	55 ± 11	54 ± 11	53 ± 10	53 ± 10	57 ± 10	55 ± 11
Sex no. (% male)	33 (57%)	28 (47%)	25 (44%)	26 (47%)	26 (46%)	99 (50%)	114 (56%)	169 (52%)
Body weight (kg)	73 ± 12	69 ± 12	70 ± 12	73 ± 11	72 ± 11	73 ± 13	72 ± 11	72 ± 11
Treated HT no. (%)	41 (71%)	38 (64%)	34 (60%)	35 (64%)	31 (55%)	135 (68%)	156 (76%)	220 (68%)
Duration of HT (years)	4.4 ± 4.6	4.6 ± 6.5	4.0 ± 4.9	4.7 ± 6.4	4.3 ± 4.9	3.9 ± 4.4	5.5 ± 5.8	4.6 ± 5.0
Supine DBP (mmHg)	102.5 ± 5.3	101.2 ± 4.6	101.0 ± 4.4	101.7 ± 5.5	101.5 ± 5.0	100.6 ± 4.0	101.5 ± 4.7	87.7 ± 6.5
Supine SBP (mmHg)	164.4 ± 13.5	164.4 ± 16.2	161.0 ± 16.3	164.5 ± 15.0	161.8 ± 16.7	161.7 ± 16.0	164.4 ± 15.7	142.6 ± 14.0

Values are means ± SD except as stated otherwise. IR, immediate-release formulation of indapamide (2.5 mg); SR, sustained-release formulation of indapamide (1.5, 2.0, 2.5 mg); HT, hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Blood pressure in controlled studies

	Dose-finding study					Equivalence study	
	Placebo	2.5 IR	1.5 SR	2.0 SR	2.5 SR	1.5 SR	2.5 IR
n	58	59	57	55	56	200	205
Supine DBP							
Change from baseline††	−5.3 ± 8.8	−9.9 ± 7.0*	−11.0 ± 9.2**	−8.9 ± 9.4*	−10.2 ± 8.1*	−10.7 ± 7.4	−11.1 ± 7.9
Change from 1.5 SR	5.7	1.1	–	2.1	0.8	0.4	
95% CI	+2.4, +9.0	−1.9, +4.1	–	−1.4, +5.6	−2.5, +4.0	−1.05, +1.93	
Supine SBP							
Change from baseline††	−9.2 ± 17.0	−17.8 ± 14.2*	−18.6 ± 14.3**	−17.9 ± 15.6*	−16.8 ± 14.3*	−15.4 ± 14.1	−17.8 ± 14.9
Change from 1.5 SR	9.4	0.9	–	0.8	1.9	2.3	
95% CI	3.6, 15.2	−4.4, +6.1	–	−4.8, 6.4	−3.5, 7.2	−0.52, +5.16	
Blood pressure control†††	13 (22%)	26 (44%)	32 (56%)*	20 (36%)	30 (54%)	114 (57%)	124 (61%)
Responders††	19 (33%)	31 (53%)	35 (61%) *	28 (51%)	38 (68%)	131 (66%)	142 (69%)

Values are means ± SD or absolute numbers (%) or 95% confidence interval (CI). IR, immediate-release formulation of indapamide (2.5 mg); SR, sustained-release formulation of indapamide (1.5, 2.0, 2.5 mg); DBP, diastolic blood pressure; SBP, systolic blood pressure. Blood pressure control was defined as a supine DBP of ≤ 90 mmHg; responders were defined as those with a supine DBP of ≤ 90 mmHg and/or decrease of ≥ 10 mmHg from baseline. **$P \leq 0.01$, ***$P \leq 0.001$, dose-finding treatment effect tested with analysis of variance or $\chi 2$ test; equivalence study: two one-sided tests, with significant equivalence if 95% confidence interval is included within ±5 mmHg for supine DBP and ±9.5 mmHg for supine SBP. No difference between the 1.5 mg SR and the 2.5 mg IR dose in the dose-finding study was significant (Newman–Keuls); *$P \leq 0.05$, **$P \leq 0.01$, versus placebo (Newman–Keuls).

Table 3 Blood pressure in the long-term study

Visit	Month 3	Month 6	Month 9	Month 12	ITT
n	324	305	292	270	324
Supine DBP (mmHg)	87.7 ± 6.5	86.3 ± 6.0	87.0 ± 6.1	87.6 ± 8.2	88.5 ± 8.3
Change from month 3 (mmHg)	–	−1.2 ± 7.4	−0.3 ± 7.8	+0.5 ± 8.5	+0.8 ± 8.3
Supine SBP (mmHg)	142.6 ± 14.0	141.5 ± 11.9	142.4 ± 12.2	142.6 ± 14.6	143.8 ± 14.8
Change from month 3 (mmHg)	–	−0.8 ± 12.8	+0.4 ± 12.8	+1.1 ± 14.2	+1.3 ± 13.6
Kaplan–Meier analysis (% of patients)					
Supine DBP < 95th mmHg (%)	100	99.6 ± 0.3	96.7 ± 1.1	91.8 ± 1.7	–
Supine DBP ≤ 90 mmHg (%)	100	100	83.4 ± 2.6	71.1 ± 3.2	–

Values are means or % ± SD; n, number of patients evaluable at each visit. Month 3, initial visit of the long-term study (last visit in equivalence study); month 12, last visit in dose-finding study; ITT, intention to treat (end-point value): no. of patients with supine DBP < 95 or ≤ 90 mmHg at the visit (Kaplan–Meier: 100% at month 3, n = 291 or 220, respectively); DBP, diastolic blood pressure; SBP, systolic blood pressure.

in Table 3. A total of 220 patients had a supine DBP of ≤ 90 mmHg at month 3 and 291 had a supine DBP of < 95 mmHg. Of these, 71.1% of patients maintained a supine DBP below 90 mmHg and 91.8% below 95 mmHg at all visits (months 3, 6, 9 and 12; Kaplan–Meier). Conversely, of the 104 patients enrolled in month 3 with a supine DBP of > 90 mmHg, 75 (72%) achieved a supine DBP of ≤ 90 mmHg during the long-term study. Of the 33 patients enrolled in month 3 with a supine DBP of ≥ 95 mmHg, 26 (79%) achieved a supine DBP of < 95 mmHg during the long-term study.

Safety

Clinical and laboratory safety data were evaluated in all patients who took at least one dose of treatment (dose-finding study, n = 285; equivalence study, n = 405). No serious treatment-related adverse event was observed in either study.

In the dose-finding study, seven placebo patients, 10 taking 2.5 IR, eight taking 1.5 SR, six taking 2 SR and 14 taking 2.5 SR reported at least one adverse event (intertreatment, NS). Headaches and dizziness were the

Table 4 Serum potassium after treatment for 4 weeks (dose-finding study) or 6 weeks (equivalence study)

	Dose-finding study		Equivalence study	
	1.5 SR	2.5 IR	1.5 SR	2.5 IR
n	57	59	200	205
$K^+ < 3.0$ mmol/l no. (%)	0 (0%)	1 (2%)	3 (1.5%)	7 (3%)
$K^+ < 3.4$ mmol/l no. (%)	6 (11%)*	17 (29%)*	18 (9%)***	50 (24%)***
Baseline K^+ (mmol/l)	4.28 ± 0.46	4.16 ± 0.38	4.18 ± 0.38	4.20 ± 0.38
Δ K^+ (mmol/l)	−0.43 ± 0.52	−0.42 ± 0.45	−0.25 ± 0.43***	−0.40 ± 0.46***

Values are means ± SD or absolute numbers of patients (%). IR, immediate-release formulation of indapamide (2.5 mg); SR, sustained-release formulation of indapamide (1.5 mg). *$P \leq 0.05$, ***$P \leq 0.001$, 1.5 SR versus 2.5 IR (Fisher's exact test and Student's t test).

Table 5 Laboratory parameters

	Dose-finding study		Equivalence study		Long-term study
	1.5 SR	2.5 IR	1.5 SR	2.5 IR	1.5 SR
n	57	59	200	205	324
Fasting glucose					
Entry	5.2 ± 0.7	5.2 ± 0.7	5.4 ± 1.3	5.6 ± 2.2	5.7 ± 2.0
Change	−0.0 ± 0.8	+0.2 ± 0.8	+0.1 ± 1.0	+0.1 ± 1.4	−0.0 (−0.1,0.1)
Total cholesterol					
Entry	5.9 ± 1.1	6.2 ± 1.0	6.2 ± 1.1	5.9 ± 1.1	6.1 ± 1.1
Change	−0.0 ± 0.8	+0.2 ± 0.7	−0.0 ± 0.8	+0.2 ± 0.9	−0.0 (−0.1,0.1)
HDL cholesterol					
Entry	NA	NA	1.5 ± 0.6	1.4 ± 0.5	1.4 ± 0.4
Change	NA	NA	−0.1 ± 0.5	−0.0 ± 0.4	+0.0 (−0.0,0.1)
Triglycerides					
Entry	1.5 ± 0.7	1.4 ± 0.9	1.5 ± 0.9	1.6 ± 1.1	1.7 ± 1.2
Change	+0.1 ± 0.7	+0.4 ± 2.0	+0.0 ± 0.7	+0.2 ± 1.0	+0.1 (−0.0,0.2)
Uric acid					
Entry	287.5 ± 82.7	284.1 ± 80.5	311.2 ± 83.1	316.3 ± 93.8	363.1 ± 100.9
Change	+40.1 ± 48.1	+70.7 ± 85.7	+33.7 ± 66.5	+51.2 ± 67.0	−16.0 (−23.4, −8.7)
Urea					
Entry	5.6 ± 1.5	5.9 ± 1.5	5.6 ± 1.8	5.8 ± 1.7	6.1 ± 1.8
Change	+0.5 ± 1.5	+0.2 ± 1.2	+0.3 ± 1.4	+0.5 ± 1.5	−0.1 (−0.23,0.07)
Creatinine					
Entry	85.8 ± 18.4	85.3 ± 18.1	87.2 ± 17.1	88.2 ± 17.3	85.9 ± 18.0
Change	−0.4 ± 12.6	+2.1 ± 13.1	+1.8 ± 12.7	−1.4 ± 13.2	+1.1 (−0.0,2.3)
Sodium					
Entry	141.3 ± 4.3	141.7 ± 3.0	140.8 ± 2.6	141.1 ± 2.8	140.4 ± 3.0
Change	−0.4 ± 2.3	−0.4 ± 4.2	−0.3 ± 2.7	−0.7 ± 3.2	−0.0 (−0.4,0.3)
Chloride					
Entry	103.3 ± 4.3	102.7 ± 4.3	103.2 ± 3.2	103.3 ± 3.3	101.1 ± 4.0
Change	−2.4 ± 4.5	−3.3 ± 4.8	−1.16 ± 4.1	−2.9 ± 4.7	+0.3 (−0.1,0.8)

Values are means ± SD or means (95% confidence intervals), and are expressed as mmol/l, except uric acid and creatinine (μmol/l). IR, immediate-release formulation of indapamide (2.5 mg); SR, sustained-release formulation of indapamide (1.5, 2.5 mg); HDL, high-density lipoprotein; NA, not applicable. Entry was month 0 for the dose-finding study and equivalence study and month 3 for the long-term follow-up of the equivalence study.

Table 6 Serum potassium in the long-term study

	Month 3	Month 6	Month 9	Month 12
n	321	287	276	261
Baseline K^+ (mmol/l)	3.92 ± 0.54	4.05 ± 0.60	4.04 ± 0.56	3.88 ± 0.46
Δ K^+ (mmol/l)	-	+0.14 ± 0.57	+0.14 ± 0.57	−0.04 ± 0.46
Kaplan–Meier analysis				
$K^+ \geq 3.4$ mmol/l	284 (100%)	99.3 ± 0.5%	94.2 ± 1.5%	91.3 ± 1.8%

Values are means ± SD, except Kaplan–Meier analysis (no. or % of patients ± SD); n, number of evaluable patients. Month 3 was the initial visit of the long-term study and last visit of the equivalence study; month 12 was the last visit of the long-term study.

most frequently reported events. Nine patients dropped out due to an adverse event (headache, n = 1, placebo; serum potassium of 2.8 mmol/l, n = 2, 2.5 IR and 2.5 SR; skin allergy, n = 2, 1.5 SR and 2 SR; dizziness, n = 2, 2.5 SR; asthenia, n = 1, 2.5 SR; gout, n = 1, 2.5 SR).

In the equivalence study, 46 patients taking 1.5 SR reported at least one adverse event versus 50 patients taking 2.5 IR (NS). There were 12 dropouts due to adverse events, five patients in the 1.5 SR group (one each with dizziness and headache, tachycardia, dry mouth and serum potassium levels of 2.7 and 2.9 mmol/l) and seven in the 2.5 IR group (one each with dizziness, palpitations and dyspnea, cough, serum potassium levels of 2.5, 2.6 and 2.8 mmol/l, and lack of efficacy). In the dose-finding study, the incidence of patients with a serum potassium level of < 3.4 mmol/l at week 4, before the administration of potassium supplements, was significantly reduced with 1.5 SR (by more than 50%). This reduction was also observed in the equivalence study at the intermediate visit in which it was a primary safety parameter (Table 4); in this study, the mean decrease in serum potassium levels was significantly lower with 1.5 SR than with 2.5 IR (0.25 ± 0.43 versus 0.40 ± 0.46 mmol/l, respectively; $P = 0.001$). The remaining biochemistry, in particular lipid and carbohydrate parameters, was not significantly affected by 1.5 SR, except for a moderate effect on serum uric acid (Table 5).

In the long-term study, among the 324 enrolled patients in the long-term extension, there were nine dropouts due to adverse events including increased diabetes (n = 1), atrial fibrillation (n = 1), gynecomastia (n = 1), angina pectoris (n = 2), palpitation (n = 1), fatigue and polyuria (n = 1) and cerebrovascular accidents (n = 2), one of them leading to death 2 months later, after neurosurgical intervention for haemorrhage. A total of 284 patients had a serum potassium level of ≥ 3.4 mmol/l at the initial visit (month 3) and 91.3% of these maintained normokalemia at all visits (months 3, 6, 9 and 12; Kaplan–Meier, Table 6). In the subgroup of patients treated for a complete year (3 month double-blind period followed by 9 month open period) with 1.5 SR, 2.3% of patients had kalemia of < 3.4 mmol/l at the month 12 visit (three out of 128 patients present at the visit). The other main biochemistry parameter changes are presented in Table 5. Of the 690 patients in the two studies, 1% (three out of 257) of the patients treated with 1.5 SR and 3% (eight out of 264) of those treated with 2.5 IR had serum potassium levels of < 3 mmol/l; no patient with a serum potassium level of < 2.5 mmol/l was observed; only two out of 257 patients on 1.5 SR and four out of 264 on 2.5 IR withdrew because of a low serum potassium level. The mean decrease in serum potassium on 1.5 SR was 0.3 mmol/l. A number of withdrawals because of adverse events (6%) were observed in the 690 patients in the two studies (17 out of 285 patients in the first study, and 24 out of 405 in the second). However, a pooled analysis showed that only 2.3% (six out of 257) of the patients treated with 1.5 SR and 2.6 % (seven out of 264) of those treated with 2.5 IR withdrew from treatment because of adverse events. The analysis of long-term safety showed few dropouts (3%) due to adverse events.

Discussion

Controlled studies

Indapamide SR at 1.5 mg was selected in the dose-finding study for its antihypertensive efficacy, which was similar to the other dosages and formulations of indapamide, in particular 2.5 IR (likely efficacy plateau), and significantly greater than placebo. From the safety point of view, 1.5 mg indapamide SR reduced the incidence of patients with serum potassium levels of < 3.4 mmol/l by more than 50% (62%) compared with 2.5 IR, thereby optimizing the efficacy : safety ratio of indapamide and meeting the target of the development program.

The equivalence study validated this choice in a larger sample-size population by demonstrating statistical equivalence in antihypertensive efficacy between 1.5 SR and 2.5 IR and by confirming the benefit in terms of kalemia. The results of the two studies were compared in a pooled presentation on the basis of shared methodology: matching design, same inclusion and noninclusion criteria, same outcome measures, intention-to-treat analysis and compliance with European Good Clinical Practice guidelines.

The doses of indapamide SR were chosen according to an arithmetic progression of 0.5 mg after discarding the 1 mg dose because this had been considered ineffective in previous studies [15–18]. Since no dose lower than 1.5 SR was tested (no blank dose), it cannot be claimed that this is the lowest dose equivalent to 2.5 IR. This difficulty is frequently encountered in dose-finding studies. However, 1.25 mg indapamide IR, independently developed in the United States at the same time as an effective low dose, has not demonstrated equivalent efficacy to 2.5 mg IR but has shown a significant difference versus placebo. Published data [19–21] indicate that 1.25 mg indapamide IR could be clinically less effective than 1.5 mg SR, showing a mean decrease in DBP of −8 mmHg (1.5 SR, −11 mmHg), in SBP of −11 mmHg (1.5 SR, −17 mmHg) and a mean responder rate of 51% (1.5 SR, 64%). The duration of treatment exposure differed in the two studies (8 and 12 weeks), but was sufficient for a full evaluation of antihypertensive efficacy since this is generally achieved after treatment for 4–6 weeks [22–24]. The selection of patients was based on conventional blood pressure measurement and not ambulatory blood pressure monitoring, since current knowledge is based on blood pressure measurement by mercury sphygmomanometer which remains the reference method, having been prognostically validated. Ambulatory blood pressure monitoring, performed in these two studies to

provide descriptive efficacy parameters, confirmed the conventional measurement results [13,25].

An important finding is that the results in the dose-finding and equivalence studies were coherent and complementary; the efficacy of 1.5 SR was very similar in degree in both studies, as well as compared with 2.5 IR (reduction in supine DBP of 11 mmHg, reduction in supine SBP of 15–18 mmHg, responder and controlled patient rates of 61–66 and 57%, respectively). The equivalence study clearly stated the statistical and clinical equivalence in efficacy between indapamide 1.5 SR and 2.5 mg IR despite the reduction in the dose. The latter point is important since 2.5 IR is used as a reference antihypertensive diuretic, and has extensively demonstrated its efficacy in many comparative studies versus other antihypertensive drugs, including hydrochlorothiazide, chlorothiazide, cyclopenthiazide, chlorthalidone, bendrofluazide and meticrane [7]. The safety data from the equivalence study confirmed, with a controlled statistical power, the significant reduction in patients with a serum potassium level of < 3.4 mmol/l with 1.5 SR versus 2.5 IR. Compared with other diuretics such as chlorthalidone or hydrochlorothiazide, indapamide seems to present a lower incidence [26,27]. The absence of any adverse effect on lipid and carbohydrate profiles is in agreement with the results of the meta-analysis by Ames [10], who compared the lipid effects of indapamide versus those of the thiazides, and the known data with 2.5 IR [11].

The antihypertensive efficacy of 1.5 SR was maintained in the long term (12 months), proving the absence of therapeutic escape, since 71 and 92% of patients exposed to the risk still had a supine DBP of ≤ 90 mmHg or < 95 mmHg, respectively, at the end of the long-term treatment. At month 12, 91.3% of patients still had a potassium level of at least 3.4 mmol/l. Other laboratory parameters were metabolically neutral, including both lipid and carbohydrate metabolism, as observed in the short-term controlled studies.

Conclusions

The development of a low-dose presentation of indapamide in a new SR coated tablet formulation optimized the safety : efficacy ratio while providing short- and long-term antihypertensive efficacy throughout the 24 h after the dose. Indapamide SR at 1.5 mg complies with the requirements laid down by international scientific and regulatory authorities both for low-dose antihypertensive therapy and for the preferential use of a diuretic as first-line treatment for hypertension.

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