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Efficacy and tolerance of indapamide sustained release 1·5 mg on 24-h blood pressure in essential hypertension

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A new 1·5 mg sustained-release (SR) formulations of indapamide has been developed in accordance with the international guidelines recommending low doses of antihypertensive agents. In order to evaluate its antihypertensive effect over 24 h and its benefit in terms of the efficacy/tolerance ratio, the results of two European double-blind randomized studies, conducted in patients with essential moderate hypertension, are reviewed. Antihypertensive efficacy was assessed using clinic blood pressure (BP) measurements at trough, 24 h after dosing, (primary criteria) and ambulatory BP monitoring; the main safety criterion was the percentage of patients with serum potassium <3·4 mmol . l^{-1}. The results of the dose-ranging study established the antihypertensive efficacy of 1·5 mg of indapamide SR. The equivalence study confirmed the equivalent antihypertensive effect, within the predefined equivalence interval for diastolic blood pressure of ± 5 mmHg, between two formulations of indapamide, the SR at 1·5 mg . day^{-1} and the immediate release (IR) at 2·5 mg . day^{-1}. This effect, observed after 2–3 months of treatment, was long-term and maintained in patients followed over 12 months. Tolerance data showed no effects of indapamide on carbohydrate and lipid metabolisms, a slight increase in the uric acid level, and 50% fewer patients with serum potassium <3·4 mmol . l^{-1} with the SR than with the IR formulation. Pooled data showed that the new formulation of indapamide decreases BP over 24 h, with a trough to peak ratio meeting the FDA standard requirements and improves the efficacy/tolerance ratio of indapamide in essential hypertension.

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Key Words: Diuretic, indapamide, 24-h blood pressure monitoring, antihypertensive, trough/peak ratio, efficacy/tolerance.

Introduction

Because of their proven efficacy in decreasing cardiovascular morbidity and mortality, diuretics have been widely recommended by medical associations as first-line therapy in essential hypertension[1–3]. However, international guidelines have highlighted the need for selecting the lowest dosage of antihypertensive agent in order to protect patients from dose-dependent adverse effects[4,5]. In order to improve the compliance with treatment, most of these agents are usually prescribed once daily. Assessment of the antihypertensive effect over the 24-h dosing interval has been required[6,7]. Since 1988, the U.S.A. Food and Drug Administration (FDA) has recommended calculating the trough/peak antihypertensive effect. This arithmetic index is used to identify an adverse excessive peak effect due to the administration of an unnecessarily high dose, and/or to identify an inappropriate dosing interval[8,9].

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Indapamide, a thiazide-related sulfonamide diuretic, is widely used as an antihypertensive diuretic. Numerous placebo-controlled randomized studies have shown its antihypertensive efficacy in an immediate release formulation at a dosage of 2·5 mg . day^{-1} (IR 2·5 mg)[10]. It has been reported to decrease vascular resistance[11], to improve arterial compliance, and to reduce left ventricular hypertrophy[12,13], without adverse effects on carbohydrate[14] and lipid[15] metabolism. In accordance with international guidelines, a new sustained release and low-dose formulation (SR 1·5 mg) has been developed so as to improve its efficacy/tolerance ratio. Data on the pharmacokinetics of the SR 1·5 mg formulation, and results from two international double-blind randomized studies to assess its antihypertensive efficacy and safety have been reviewed[16–20].

Pharmacokinetic data

The SR 1·5 mg is based on a new pharmaceutical galenic formulation in a hydrophilic high viscosity methylhydroxypropyl cellulose matrix tablet which allows

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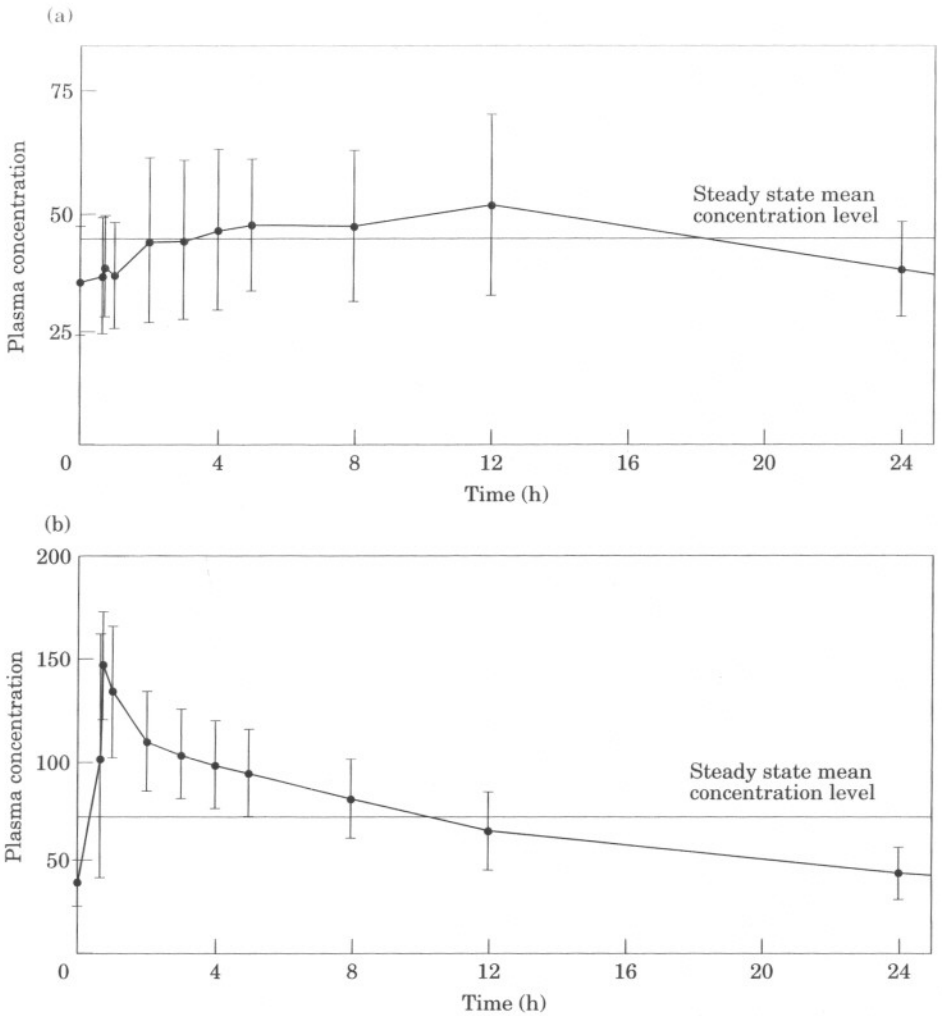

Figure 1 **Pharmacokinetic profile of (a) indapamide sustained release 1·5 mg (SR 1·5 mg) and (b) immediate release 2·5 mg (IR 2·5 mg) formulations. Plasma concentration of indapamide observed at day 7 in 12 healthy volunteers after one tablet intake per day.**

gradual and sustained release of indapamide over 24 h. Pharmacokinetic studies performed in healthy volunteers[21] showed that SR 1·5 mg has limited fluctuation in its plasma concentration around a mean value with a fluctuation coefficient, after repeated indapamide administration, that was four times less than that with 2·5 mg (39·6 ± 27·2% vs 161·1 ± 34·2%). Hence, the SR formulation gives a smooth pharmacokinetic profile with a stable plasma level between two consecutive administrations, and the elimination of useless plasma peak concentration. Figure 1 shows the plasma concentration observed for indapamide SR 1·5 mg and IR 2·5 mg . day^{-1} after repeated administration in healthy volunteers. Compared with IR 2·5 mg, the SR 1·5 mg profile shows a significant reduction in the area under the curve (1089 ± 310 ng . ml^{-1} . h^{-1} vs 1726 ± 458 ng . ml^{-1} . h^{-1}) and the maximal plasma concentration (C_{max} = 58·1 ± 20·2 ng . ml^{-1} vs 153·8 ± 35·1 ng . ml^{-1}). No difference has been found between the two indapamide formulations in the minimal plasma concentration (C_{min} nearly 40 ng . ml^{-1}). In addition, the new SR 1·5 mg maintains the plasma concentration of indapamide near its maximum concentration over a long period of time: $t_{75\%} \approx 16$ h (i.e. 16 h is the time during which the level of drug is at least 75% of C_{max}).

The pharmacokinetic results of indapamide SR 1·5 mg may be considered positive in terms of efficacy [(C_{min}), duration of action ($t_{75\%}$ = 16 h)] and tolerance (less plasma level fluctuation and lower C_{max}). Such a pharmacokinetic profile may provide a blood pressure reduction with sustained antihypertensive efficacy over 24 h, using once daily administration. In addition, the daily dosage reduction and elimination of useless plasma concentration peaks may reduce some dose-dependent adverse effects and thus improve the efficacy/safety ratio.

Table 1 Clinical characteristics

Group (Number of patients)	Dose-finding study					Equivalence study		Long-term study
	Placebo (58)	IR 2·5 (59)	SR 1·5 (57)	SR 2 (55)	SR 2·5 (56)	SR 1·5 (200)	IR 2·5 (205)	SR 1·5 (324)
Age (years ± SD)	53·3 ± 8·4	55·3 ± 10·0	55·2 ± 11·3	53·5 ± 11·1	53·3 ± 9·7	53·4 ± 9·9	56·6 ± 10·0	55·0 ± 11·0
Sex [n (% men)]	33 (57)	28 (47)	25 (44)	26 (47)	26 (46)	99 (50)	114 (56)	169 (52)
Weight (kg ± SD)	72·8 ± 12·2	69·1 ± 12·3	70·0 ± 12·1	73·2 ± 11·9	71·6 ± 11·2	72·8 ± 0·9	72·1 ± 0·8	72·0 ± 11·0
Previous treatment [n (%)]	41 (71)	38 (64)	34 (60)	35 (64)	31 (55)	135 (68)	156 (76)	220 (68)
Hypertension history (years ± SD)	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

IR 2·5=indapamide 2·5 mg immediate release, SR 1·5=indapamide 1·5 mg sustained release, SR 2=indapamide 2 mg sustained release, SR 2·5=indapamide 2·5 mg sustained release, n=number of patients; SD=standard deviation.

Antihypertensive efficacy

The antihypertensive efficacy of the new SR low-dose formulation of indapamide has been evaluated in two major large European studies — a dose-finding study and an equivalence study[16–20] — which are reviewed here.

Patients and methods

Study design

Two European multicentre studies were conducted using similar protocols approved by ethics committees in each of the participating countries: Belgium (4 centres), France (16 centres), Great Britain (4 centres), Italy (3 centres) and Spain (1 centre).

Dose-finding study. After a single-blind 1-month placebo run-in period, patients with mild-to-moderate essential hypertension were randomized into five parallel groups to receive, in a double-blind manner over 2 months, either placebo or indapamide. The dosages of indapamide were IR 2·5 mg or SR 1·5 mg, or SR 2 mg or SR 2·5 mg.

Equivalence study. After a single-blind 1-month placebo run-in period, patients with mild-to-moderate essential hypertension were randomized into parallel groups to receive, in a double-blind manner over 3 months, either IR 2·5 mg or SR 1·5 mg. At the end of this period, patients with a supine diastolic blood pressure <95 mmHg could receive SR 1·5 mg on an open basis for 9 months. The objectives of this study were to demonstrate the efficacy equivalence of these two indapamide formulations, to evaluate the safety of SR 1·5 mg in comparison with IR 2·5 mg, and to assess the long-term efficacy and safety of SR 1·5 mg.

Patients

Ambulatory patients of both genders, aged 18–70 years, were eligible for inclusion after written informed consent, provided they had mild-to-moderate essential hypertension, defined as a clinic supine diastolic blood pressure ≥ 95 mmHg and ≤ 114 mmHg, a plasma potassium $>3{\cdot}5$ mmol $.l^{-1}$, and met a treatment compliance >80%.

Blood pressure measurements

Clinic blood pressure measurement. Arterial blood pressure was measured in the clinic using a mercury sphygmomanometer after 10 min rest, according to World Health Organization recommendations. The mean of three consecutive measurements was considered for analysis. Measurements at the different visits were performed at trough, 24 h after the last tablet intake.

Ambulatory blood pressure monitoring. In addition to clinic blood pressure measurement, some patients (secondary criteria) underwent 24 h ambulatory blood pressure monitoring on the last day of the placebo run-in period and on the last day of the active treatment period. In the long-term follow-up (equivalence study), ambulatory blood pressure monitoring was also performed at the last visit (M12). Monitors (SpaceLabs 90207, Novacor Diasys 200R) were fitted between 0800 h and 1000 h on a regular weekday and were programmed to record blood pressure and heart rate at 15 min intervals during the daytime (0600 h–2200 h) and at 30-min intervals during the night (2200 h–0600 h). Recordings were quality controlled for compliance with fitting times, 24 h recording duration, elimination of aberrant values, number of validated measurements $\geq 80\%$, and isolated missing 1-h time interval data. Trough/peak ratios were calculated for diastolic and systolic blood pressures by averaging values at 2-h intervals. Ratios were then calculated from group and individual data after placebo subtraction.

Results

Results of these two studies have been published in detail elsewhere[16–20]. In this review, we wish to highlight some major points relating to efficacy and safety.

Table 2 Clinic blood pressure measurements: short-term antihypertensive efficacy

Group (Number of patients)	Dose-finding study						Equivalence Study		
	Placebo (58)	IR 2·5 (59)	SR 1·5 (57)	SR 2 (55)	SR 2·5 (56)	*P*	SR 1·5 (200)	IR 2·5 (205)	ΔSR 1·5–IR 2·5 95% CI
DBP at M0 (mmHg ± SD)	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	—
Changes (mmHg)	− 5·3 (8·8)	− 9·9 (7·0)*	− 11·0 (9·2)§†	− 8·9 (9·4)*	− 10·2 (8·1)*	0·004	− 10·7 (7·4)	− 11·1 (7·9)	0·4 [− 1·05; +1·9]
SBP at M0 (mmHg ± SD)	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	—
Changes (mmHg ± SD)	− 9·2 ± 17·0	− 17·8 ± 14·2*	− 18·6 ± 14·3§†	− 17·9 ± 15·6	− 16·8 ± 14·3*	0·005	− 15·4 ± 14·1	− 17·8 ± 14·9	2·3 [− 0·52; +5·16]
Normalized [n (%)]	13 (22)	26 (44)	32 (56)*†	20 (36)	30 (54)*	0·001	114 (57)	124 (61)	− 4% [− 13; +5]
Responders [n (%)]	19 (33)	31 (53)	35 (61)*†	28 (51)	38 (68)*	0·003	131 (66)	142 (69)	− 4% [− 13; +6]
HR at M0 (beats . min^{-1} ± SD)	74·9 ± 10·8	76·3 ± 10·6	74·8 ± 11·0	73·3 ± 9·0	75·5 ± 12·6	—	77·1 ± 9·4	78·2 ± 10·3	—
Changes (beats . min^{-1} ± SD)	− 0·6 ± 9·8	− 0·9 ± 8·8	− 0·1 ± 8·2	− 1·9 ± 6·8	− 2·2 ± 7·8	—	− 0·2 ± 8·9	+1·6 ± 9·6	

IR 2·5 = indapamide 2·5 mg immediate release, SR 1·5 = indapamide 1·5 mg sustained release, SR 2 = indapamide 2 mg sustained release, SR 2·5 = indapamide 2·5 mg sustained release. n = number of patients, MO = inclusion visit, normalized = DBP ⩽ 90 mmHg; Responders: DBP ⩽ 90 mm Hg and/or decrease in DBP ⩾ 10 mm Hg; SD = standard deviation, HR = heart rate beats . minute^{-1}; 95% CI: 95% confidence interval.

Treatment effect analysis: analysis of variance or chi-squared test, † = $P > 0{\cdot}05$ vs IR 2·5 (Newman-Keuls); * = $P \leq 0{\cdot}05$ vs placebo (Newman-Keuls); § = $P \leq 0{\cdot}01$ vs placebo (Newman-Keuls)

Table 3 Clinic blood pressure measurements: long-term antihypertensive efficacy

Visit (Number of patients)	M3 (324)	M6 (305)	M9 (292)	M12 (270)
DBP (mmHg ± SD)	87·7 ± 6·5	86·3 ± 6·0	87·0 ± 6·1	87·6 ± 8·2
Changes/M3	—	− 1·2 ± 7·4	− 0·3 ± 7·8	+0·5 ± 8·5
SBP (mmHg ± SD)	142·6 ± 14·0	141·5 ± 11·9	142·4 ± 12·2	142·6 ± 14·6
Changes/M3	—	− 0·8 ± 12·8	+0·4 ± 12·8	+1·1 ± 14·2

M3=initial visit for the long-term study. M6, M9, M12=visits at 6, 9 and 12 months, respectively. SD=standard deviation.

Analysed population

A total of 690 patients were randomized in the two studies; 285 were randomized in the dose-finding study and 405 in the equivalence study. From the equivalence study, 324 patients entered the long-term follow-up, their clinical characteristics are shown in Table 1.

Efficacy assessed by clinic blood pressure measurement

Short-term efficacy

Table 2 shows the baseline values and changes in systolic blood pressure, diastolic blood pressure and heart rate observed in the different treatment groups, as well as the numbers of responding and normalized patients.

In the dose-finding study, the antihypertensive effect observed in the SR 1·5 mg group was significantly different from that in the placebo group ($P \leqslant 0{\cdot}01$, Newman-Keuls test). No further benefit was noted with increasing doses of indapamide.

In the equivalence study, the results showed a significant reduction in diastolic blood pressure after 3 months treatment with both SR 1·5 mg (− 10·7 ± 7·4 mmHg) and IR 2·5 mg (− 11·1 ± 7·9 mmHg), with an equivalent efficacy as defined in the study protocol.

Long-term efficacy

Table 3 presents the baseline and changes in values of blood pressure observed at the different visits during the long-term study. The results showed that the antihypertensive efficacy observed after 3 months of treatment is maintained at 1 year.

Efficacy assessed by ambulatory blood pressure monitoring

After quality control of the ambulatory blood pressure monitoring recordings, 216 (46%) patients were selected for the efficacy analysis in the two double-blind studies: 109 patients in the dose-finding study, and 107 in the equivalence study. Of the 161 patients completing 1 year's treatment with SR 1·5 mg, 41 patients were selected for analysis of long-term efficacy. Results of the ambulatory blood pressure monitoring data analysis have been published in detail elsewhere[18,19].

Short-term efficacy

Table 4 shows the mean values of systolic and diastolic blood pressures, measured before and after treatment during the 24 h, daytime, and night-time periods in the different treatment groups. In the dose-finding study, analysis of covariance showed that the reduction in diastolic blood pressure with SR 1·5 mg differed significantly from that for placebo and did not differ significantly from that with IR 2·5 mg, except for nocturnal diastolic blood pressure.

In the equivalence study, a significant blood pressure reduction was noted in the two indapamide formulation treatment groups during the three analysed periods: 24 h, daytime, and night-time. 95% CI of mean inter-treatment differences values fell within the pre-defined equivalence intervals.

Long-term efficacy

Table 5 shows the mean values of systolic blood pressure and diastolic blood pressures measured at inclusion (M0), at 3 months (M3), and 12 months (M12) after treatment, during the 24-h, daytime, and night-time periods. The results show significant decreases in systolic blood pressure and diastolic blood pressure after 3 months of treatment with SR 1·5 mg and antihypertensive efficacy maintained at 12 months.

Efficacy over 24 h and calculation of the trough/peak ratio

Efficacy over 24 h. The antihypertensive efficacy described in the short-term and long-term studies showed significant blood pressure reduction with SR 1·5 mg, as assessed by the clinic blood pressure measurement performed 24 h after the last tablet intake (at trough), or by the ambulatory blood pressure monitoring performed over 24 h. Figure 2 shows hourly systolic and diastolic blood pressure chronograms observed in the equivalence study before and after 3 months treatment with SR 1·5 mg. Physiological circadian variations of blood pressure remained unaffected.

Calculation of trough/peak ratios. Trough/peak ratios were calculated in the dose-finding study from both

Table 4 Ambulatory blood pressure monitoring: short-term antihypertensive efficacy

Group (Number of patients) visit		Dose-finding study										Equivalence study				
		Placebo 19		IR 2·5 28		SR 1·5 21		SR 2 22		SR 2·5 19		IR 2·5 50		SR 1·5 57		
		M0	M2	M0	M2	M0	M2	MO	M2	M0	M2	M0	M3	M0	M3	SR-IR
DBP	24 h	93·4 ± 6·7	91·3‡ ± 8·5	91·3 ± 11·9	83·1*[b]‡ ± 7·8	89·1 ± 8·6	83·8*[b]† ± 9·7	93·2 ± 9·9	84·5† ± 9·0	91·7 ± 9·8	85·8† ± 9·5	88·6 ± 7·9	84·2† ± 8·0	89·8 ± 9·7	85·8† ± 9·9	0·8t
(mmHg	Day	97·7 ± 8·0	94·7‡ ± 9·2	94·7 ± 12·0	87·1*[b]† ± 8·6	93·5 ± 8·6	86·5*[b]† ± 10·0	96·8 ± 10·1	87·7† ± 9·7	94·6 ± 10·5	89·2† ± 9·5	92·3 ± 8·4	87·6† ± 8·4	92·9 ± 9·9	88·9† ± 10·3	0·7t
± SD)	Night	79·4 ± 8·4	79·1‡ ± 11·4	80·4 ± 12·8	70·0°[a]† ± 8·5	76·1 ± 9·4	73·8°[a]† ± 10·4	81·0 ± 9·3	74·3† ± 7·7	82·2 ± 10·1	74·8† ± 9·5	76·7 ± 8·4	73·3† ± 8·8	79·1 ± 10·9	75·6† ± 10·1	0·7t
SBP	24 h	144·9 ± 13·8	140·0† ± 13·9	143·3 ± 16·3	129·2*[b]† ± 11·8	142·3 ± 10·8	131·9°[b]† ± 11·3	145·1 ± 15·6	132·0† ± 14·5	144·2 ± 12·5	134·3† ± 13·3	140·8 ± 11·7	131·3† ± 12·0	141·1 ± 12·8	133·7† ± 12·2	2·3t
(mmHg	Day	150·2 ± 14·3	143·8† ± 13·7	147·2 ± 16·8	133·5*[b]† ± 12·3	147·5 ± 11·0	135·2*[b]† ± 12·0	148·7 ± 15·8	135·5† ± 15·3	147·7 ± 12·5	138·0† ± 13·3	144·7 ± 11·9	135·0† ± 12·5	144·6 ± 13·1	136·9† ± 12·4	1·9t
± SD)	Night	128·1 ± 16·7	126·7 ± 8·7	130·5 ± 17·3	115·7°[a]† ± 13·6	126·6 ± 12·8	121·4°[a]† ± 12·2	133·7 ± 16·2	121·8† ± 12·8	133·5 ± 15·0	122·2† ± 12·9	128·4 ± 12·1	120·0† ± 12·0	129·3 ± 14·0	123·4† ± 13·3	2·9t

n=number of patients, IR=indapamide immediate release, SR=indapamide sustained release, Dose-finding study: *P* value (Holm, α=5%): vs placebo (**P*<0·05, °*P*>0·05); vs IR 2·5 or SR 1·5 ([a]*P*<0·05. [b]*P*>0·05). Equivalence study (Schuir Mann procedure): t equivalence *P*<0·05. *P* value vs M0 (Student's t test, α=5%): (†*P*<0·05, ‡*P*>0·05). M0=inclusion; M2, M3=after 2 or 3 months of treatment.

Table 5 Ambulatory blood pressure monitoring: long-term antihypertensive efficacy

Long-term study SR 1·5 (n=41) Visit		M0	M3	M12
DBP	24h	87·0 ± 8·8	83·0† ± 9·6	82·9† ± 9·3
(mmHg	Day	90·5 ± 9·1	86·5† ± 9·8	86·5† ± 9·8
± SD	Night	74·9 ± 9·5	71·4† ± 9·7	70·6† ± 9·7
SBP	24 h	140·7 ± 12·7	132·0† ± 14·0	131·9† ± 12·4
(mmHg	Day	144·7 ± 13·1	135·8† ± 14·3	136·0† ± 12·9
± SD)	Night	127·2 ± 13·2	119·9† ± 13·7	118·3† ± 12·3

SR 1·5=1·5 mg indapamide sustained release; n=number of patients. M0=inclusion; M3, M12=after 3 or 12 months of treatment. †: $P \leq 0{\cdot}001$ vs M0 in Student's t test, $\alpha = 5\%$.

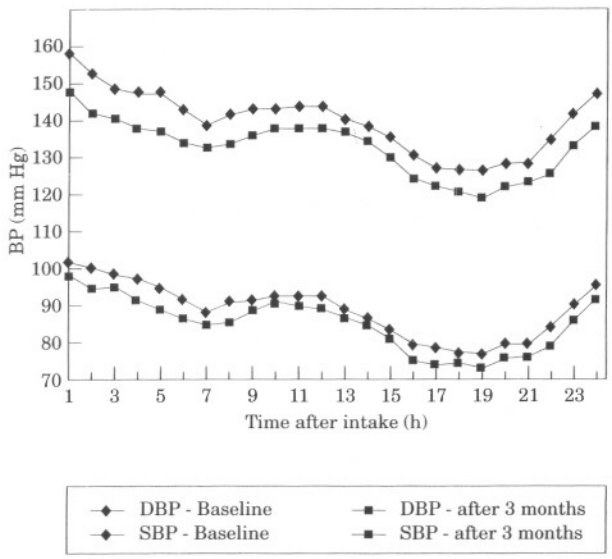

Figure 2 **Twenty-four hour ambulatory blood pressure SR 1·5 mg group (n=57).**

group and individual data. The maximal diurnal decrease in diastolic blood pressure (peak effect) after 2 months treatment with SR 1·5 mg was −9·5 mmHg (placebo subtracted) and −8·1 mmHg, 23–24 h post-dosing (trough effect). The group trough/peak ratio was 85% for diastolic blood pressure and 89% for systolic blood pressure, which meets official standard requirements[8,9]. Similar results were obtained when the trough/peak ratio was calculated according to different methods and in subgroup populations[21,27].

Safety

Clinical and biological safety data were evaluated in the intention-to-treat population, comprising 285 patients from the dose-finding study and 405 patients from the equivalence study.

In the dose-finding study, seven patients (placebo), ten patients (IR 2·5 mg), eight patients (SR 1·5 mg), six patients (SR 2·0 mg) and 14 patients (SR 2·5 mg) showed at least one adverse effect; no significant difference was noted between the different groups. Headaches and dizziness were the most frequently reported events. Nine patients stopped the treatment due to adverse events: headache (n=1, placebo), plasma potassium=2·8 mmol . l^{-1} (n=2, IR 2·5 mg and SR 1·5 mg), cutaneous allergy (n=2, SR 1·5 mg, and SR 2·0 mg), vertigo (n=2, SR 2·5 mg), asthenia (n=1, SR 2·5 mg) acute attack of gout (n=1, SR 2·5 mg). No orthostatic hypotension was reported (Table 6).

In the equivalence study, 46 patients in the SR 1·5 mg group and 50 patients in the IR 2·5 mg group reported at least one adverse event. No significant difference was noted between the two groups. Twelve patients dropped out due to the occurrence of adverse effects: five patients in the SR 1·5 mg group (one for dizziness and headache, one for tachycardia, one for dry mouth, and two for low serum potassium) and seven patients in the IR 2·5 mg group (one for dizziness, one for dyspnoea and palpitation, one for cough, three for low serum potassium, and one for uncontrolled blood pressure). No orthostatic hypotension was reported (Table 6).

Laboratory data

The dose-finding study allowed differentiation of SR 1·5 mg from the other indapamide groups, with a reduction of over 50% in the number of patients with plasma potassium less than 3·4 mmol . l^{-1}. This reduction was confirmed in the equivalence study, in which kalaemia was the main safety criteria (Table 7). In the long-term follow-up of the SR 1·5 mg group, the percentage of patients with plasma potassium less than 3·4 mmol . l^{-1} at M12 was 2·3% (3 out of 128 patients present at the visit) (Table 7). Table 8 shows the progression of the kalaemia mean values and the changes at the different visits during long-term treatment.

The other laboratory parameters, which were mainly related to lipid and carbohydrate metabolisms, were not significantly changed with SR 1·5 mg, with the exception of plasma uric acid which showed a slight increase, although to a lesser degree when compared with indapamide 2·5 mg of (Table 9).

Discussion

The results of these two studies could be pooled because of their methodological similarities: study design, inclusion and exclusion criteria, evaluation of the same principal criteria and analysis of the intention-to-treat population. Limitations of such an approach lay in the duration of treatment exposure, which was slightly different in the two short-term studies, and the absence of correction and adjusted analysis. Hence, this review should be considered descriptive.

The dose-finding study allowed the low dose of indapamide SR (1·5 mg) to be selected. Its antihypertensive efficacy evaluated in clinic at trough was better than placebo; no further benefit was obtained with the other

Table 6 Clinical adverse events

Group	Dose-finding study			Equivalence study	
Number of patients	Placebo 58 n (%)	IR 2·5 59 n (%)	SR 1·5 57 n (%)	IR 2·5 205 n (%)	SR 1·5 200 n (%)
General disorders					
Headache	5 (9)	1 (2)	3 (5)	5 (2)	8 (4)
Fatigue	3 (5)	2 (3)	2 (4)	2 (1)	4 (2)
Malaise	1 (2)	1 (2)	0 (0)	3 (2)	2 (1)
Nervous system					
Dizziness	4 (7)	5 (9)	4 (7)	5 (2)	7 (4)
Sleepiness	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)
Anxiety	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Diminution of libido	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Sleep disorders	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Nervousness	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Cardiovascular disorders					
Palpitations	1 (2)	1 (2)	0 (0)	4 (2)	6 (3)
Chest pain	2 (3)	0 (0)	0 (0)	0 (0)	1 (1)
Lower limb oedema	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Cutaneous signs					
Pruritis	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Rash	1 (2)	0 (0)	0 (0)	2 (1)	0 (0)
Desquamation	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Allergy	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Muscular signs					
Myalgias	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Cramps	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)
Uro-genital disorders					
Pollakiuria	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)
Cystitis	0 (0)	0 (0)	0 (0)	1 (1)	2 (1)
Respiratory disorders					
Dyspnoea	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)
Cough	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Gastrointestinal disorders					
Abdominal pain	2 (3)	0 (0)	0 (0)	3 (2)	1 (1)
Constipation	0 (0)	2 (3)	1 (2)	2 (1)	0 (0)
Diarrhoea	2 (3)	0 (0)	0 (0)	1 (1)	0 (0)
Nausea, vomiting	0 (0)	1 (2)	0 (0)	3 (2)	0 (0)
Dyspepsia	0 (0)	0 (0)	0 (0)	3 (2)	2 (1)
Dry mouth	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
ENT and ophthalmic disorders					
Tinnitus	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)
Ocular pain	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Metabolic disorders					
Thirst	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Loss of weight, hyperglycaemia, polyuria	1 (2)	0 (0)	1 (2)	4 (2)	0 (0)

ENT=ear, nose and throat.

Table 7 Plasma potassium course on short- and long-term treatment with indapamide

Group	Equivalence study			Long-term study
(Number of patients)	SR 1·5 (200)	IR 2·5 (205)	*P*	SR 1·5 (200)
K^+ <3·0 [mmol . l^{-1} n (%)]	3 (1·5)	7 (3)	0·34	1 (0·8)
K^+ <3·4 [mmol . l^{-1} n (%)]	18 (9)	50 (24)	<0·001	3 (2·3)

SR 1·5=indapamide 1·5 mg sustained release; IR 2·5=indapamide 2·5 mg immediate release. K^+ <3·0 or 3·4=percentage of patients with plasma potassium <3·0 or 3·4 mmol . l^{-1} evaluated after 6 weeks, treatment (equivalence study) before potassium supplementation and at visit M12 (long-term study). *P*=Fischer test for difference.

Table 8 Plasma potassium course at the different visits during the long-term treatment with indapamide SR 1·5 mg

Visit Number of patients	M3 (321)	M6 (287)	M9 (276)	M12 (261)
Kalaemia (mmol . l^{-1} ± SD)	3·92 ± 0·5	4·05 ± 0·60	4·04 ± 0·56	3·88 ± 0·46
Changes (± SD)	—	+0·14 ± 0·57	+0·14 ± 0·57	− 0·04 ± 0·46

M3=initial visit; M6, M9 and M12=visits at 6, 9 and 12 months, respectively.

Table 9 Laboratory data: mean values and changes observed with indapamide

Group (Number of patients)	Dose-finding study		Equivalence study		Long-term
	SR 1·5 (57)	IR 2·5 (59)	SR 1·5 (200)	IR 2·5 (205)	SR 1·5 (324)
Glycemia (mmol . l^{-1} ± SD)					
Baseline	5·2 ± 0·7	5·2 ± 0·7	5·4 ± 1·3	5·6 ± 2·2	5·7 ± 2·0
Changes	− 0·0 ± 0·8	+0·2 ± 0·8	+0·1 ± 1·0	+0·1 ± 1·4	− 0·0 ± 1·0
Total cholesterol (mmol . l^{-1} ± SD)					
Baseline	5·9 ± 1·1	6·2 ± 1·0	6·2 ± 1·1	5·9 ± 1·1	6·1 ± 1·1
Changes	− 0·0 ± 0·8	+0·2 ± 0·7	− 0·0 ± 0·8	+0·2 ± 0·9	− 0·0 ± 0·7
Triglycerides (mmol . l^{-1} ± SD)					
Baseline	1·5 ± 0·7	1·4 ± 0·9	1·5 ± 0·9	1·6 ± 1·1	1·7 ± 1·2
Changes	+0·1 ± 0·7	+0·4 ± 2·0	+0·0 ± 0·7	+0·2 ± 1·0	+0·1 ± 0·8
Uric acid (μmol . l^{-1} ± SD)					
Baseline	287·5 ± 82·7	284·1 ± 80·5	311·2 ± 83·1	316·3 ± 93·8	363·1 ± 100·9
Changes	+40·1 ± 48·1	+70·0 ± 85·7	+33·7 ± 66·5	+51·2 ± 67·0	− 16·0 ± 65·9
Urea (mmol . l^{-1} ± SD)					
Baseline	5·6 ± 1·5	5·9 ± 1·5	5·6 ± 1·8	5·8 ± 1·7	6·1 ± 1·8
Changes	0·5 ± 1·5	0·2 ± 1·2	0·3 ± 1·4	0·5 ± 1·5	− 0·1 ± 1·4
Creatinine (μmol . l^{-1} ± SD)					
Baseline	85·8 ± 18·4	85·3 ± 18·1	87·2 ± 17·1	88·2 ± 17·3	85·9 ± 18·0
Changes	− 0·4 ± 12·6	+2·1 ± 13·1	− 1·8 ± 12·7	− 1·4 (13·2)	+1·1 ± 10·4
Sodium (mmol . l^{-1} ± SD)					
Baseline	141·3 ± 2·6	141·7 ± 3·0	140·8 ± 2·6	141·1 ± 2·8	140·4 ± 3·0
Changes	− 0·4 ± 2·3	− 0·4 ± 4·2	− 0·3 ± 2·7	− 0·7 ± 3·2	− 0·0 ± 3·1
Chloride (mmol . l^{-1} ± SD)					
Baseline	103·3 ± 4·3	102·7 ± 4·3	103·02 ± 3·6	103·3 ± 3·3	101·1 ± 4·0
Changes	− 2·4 ± 4·5	− 3·3 ± 4·8	− 1·16 ± 4·1	− 2·9 ± 4·7	+0·3 ± 4·0

SR 1·5=indapamide 1·5 mg sustained release; IR 2·5=indapamide 2·5 mg immediate release; SD=standard deviation.

dosages and formulations of indapamide. Reducing the dosage from 2·5 mg to 1·5 mg once daily allowed a reduction of over 50% in the incidence of plasma potassium <3·4 mmol . l^{-1}, thus improving the efficacy/safety ratio of the indapamide treatment.

The results of the two studies are in agreement; the antihypertensive efficacy of SR 1·5 mg was almost the same in the two studies and did not differ from that of IR 2·5 mg. In the long-term follow-up, this antihypertensive effect was maintained at 12 months, without loss of therapeutic effect. This point is of importance since it is well known that, in the Systolic Hypertension in the Elderly Program study, only about 30% of patients were controlled with a low dose of chlorthalidone (12·5 mg)[2].

After quality control, the ambulatory blood pressure monitoring data obtained in 216 patients corroborated the results obtained using clinic blood pressure measurements and confirmed that indapamide SR 1·5 mg once daily achieves an adequate 24-h blood pressure control. This is of importance since optimal 24-h blood pressure control in hypertension is likely to be associated with a decrease in cardiovascular events and may achieve added benefit in limiting target organ damage[28]. The ability of SR 1·5 mg to decrease blood pressure over 24 h was also assessed using the trough/peak ratio and met the FDA standard requirements (>0·5), thereby confirming a 24 h activity.

The safety pooled data from 690 patients included in the two studies showed that 1% (three out of 257) patients receiving SR 1·5 mg, and 3% (eight out of 264) receiving IR 2·5 mg, had plasma potassium <3 mmol . l^{-1}, without clinical or electrocardiographic manifestations. No serum potassium <2·5 mmol . l^{-1} was reported; only two patients out of 257 in the SR 1·5 mg group and four patients out of 264 in the IR

2·5 mg group dropped out due to low serum potassium. The mean decrease in plasma potassium observed with SR 1·5 mg was 0·3 mmol . l^{-1} No adverse effect was noted with indapamide SR 1·5 mg with respect to lipid and carbohydrate metabolism.

Conclusion

Pooled ambulatory data from two international multicentre studies confirmed the antihypertensive efficacy results obtained with the conventional sphygmomanometer that indapamide SR 1·5 mg achieves adequate 24-h blood pressure control. The antihypertensive efficacy was maintained in the long-term. This new formulation with sustained release and low dosage improved the efficacy/safety ratio found for the previous indapamide formulation thereby meeting the international guideline recommendations for the treatment of essential hypertension.

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