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LETTERS TO THE EDITOR

Fixed low-dose perindopril 2 mg/indapamide 0.625 mg combination in very elderly hypertensives

Diuretics are effective in lowering blood pressure in the elderly. Major trials—Swedish Trial in Old Patients (STOP), Medical Research Council (MRC) and Systolic Hypertension in the Elderly Program (SHEP)—have also shown that diuretics and/or beta-blockers lower vascular morbidity and mortality in elderly hypertensives.[1–3] However, as the elderly are less tolerant to beta-blockers, diuretics are the treatment of choice[4] in this population, despite the risks of hypokalaemia and dehydration. Low-dose combinations of angiotensin-converting enzyme (ACE) + diuretic have recently been introduced to maintain antihypertensive efficacy with fewer adverse metabolic effects.[5–7] A fixed low-dose perindopril 2 mg/indapamide 0.625 mg (Per 2/Ind 0.625) combination have recently been developed. Regarding the pharmacokinetic characteristics of each component, their similar half-life justifies the perindopril–indapamide combination with a posology of one tablet per day. This multicentre open study with a 2-week single-blind placebo run-in followed by 12 weeks active oral treatment study addressed the efficacy, safety and pharmacokinetics of Per/Ind in very elderly patients with uncomplicated essential hypertension.

Patients with essential hypertension (95 ⩽ supine diastolic blood pressure (sDBP) ⩽114 mm Hg and supine systolic blood pressure (sSBP) <210 mm Hg) aged over 70 years were eligible. Non-inclusion criteria were complicated hypertension (myocardial infarction or stroke in the previous 6 months, coronary artery disease requiring treatment, heart failure), renal failure with serum creatinine >150 μmol/l, serum potassium <3.4 mmol/l, alcohol or drug abuse, liver disease, diabetes mellitus, and glaucoma. Other antihypertensive treatments, corticosteroids, antiarrhythmic drugs and lithium were prohibited. All patients gave written informed consent and the protocol was approved by the hospital ethics committee.

The treatment was initiated with Per 2/Ind 0.625 once daily and doubled at weeks 2, 4 or 8 to Per 4/Ind 1.25 once daily if blood pressure control (sDBP) ⩾90 mm Hg. Trough blood pressure 24 h post-dosing was measured in triplicate after 10 min rest in the supine position using a standard mercury sphygmomanometer. SBP and DBP were recorded as Korotkoff phases I and V, respectively. The mean of the triplicate determinations was used for analysis.

Measures were the change (Δ) in end of study sDBP and sSBP *vs* baseline and the rates of normotension (sDBP ⩽90 mm Hg) and response (decrease in sDBP ⩾10 mm Hg or sDBP ⩽90 mm Hg).

Measures were the serum potassium, sodium, urea and creatinine monitored at weeks 0, 4, 8 and 12, with a pre- and post-study standard laboratory screen (blood cell and platelet counts, haemoglobin, haematocrit, total cholesterol, triglycerides, fasting glucose, ASAT, ALAT, alkaline phosphatase, gamma glutamyl transpeptidase and uric acid).

Plasma samples were collected at steady state at least 7 days after the week 2 visit. A trough sample (C_{min}) was obtained immediately before dosing, with two further samples randomly selected from the following post-dosing time-points: 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h. A control sample was obtained before the first dose of study treatment. The data were analysed in NONMEM software (version 4.1, 1992) with Bayesian feedback using pharmacokinetic models developed for indapamide and perindoprilat (the active metabolite of perindopril).[8] Data were analysed on an intention-to-treat basis using the baseline value (week 0) and last recorded value. ΔsSBP and ΔsDBP were analysed using a one-tailed Student's t-test for paired samples ($P < 0.05$). Heart rate and body weight were analysed using a two-tailed Student's *t*-test for paired samples.

The inclusion population ($n = 50$, males = 24%) ranged from 69 to 97 years of age (mean: 82 years). There were five dropouts due to adverse events. Two of them (85 and 75 years old) had no pre-study antihypertensive treatments. Two patients were treated by diuretics (85 and 92 years old) and one by a calcium antagonist and an ACE inhibitor (89 years old). Pre-study antihypertensive medication comprised monotherapy ($n = 28$), two-drug therapy ($n = 8$) and triple therapy ($n = 1$) and were stopped at the start of placebo run-in period.

There was a significant decrease in sDBP (-18.7 ± 9.3 mm Hg, $P < 0.001$) and sSBP (-29.5 ± 18.7 mm Hg, $P < 0.001$) at week 12 *vs* week 0 (Table 1). Antihypertensive effect was evident from week 2. At the end of the study, 80% of patients were normalised and 31 patients out of 35 without dosage adjustment. End of study response rates were 92%. There was no significant difference in standing *vs* supine blood pressure (ΔDBP: -1.6 ± 7.0 mm Hg, NS; ΔSBP: -1.6 ± 12.7 mm Hg, NS) and no symptomatic orthostatic hypotension.

Of the five dropouts due to adverse events, one was probably treatment-related (hyperkalaemia: 5.9 mmol/l). There were no statistically significant changes in body weight or heart rate, and no changes in serum electrolytes or lipids. The dosage was decreased

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Table 1 Changes from baseline to last observation in supine diastolic (DBP) and systolic blood (SBP) pressure (mm Hg, mean ± s.d.)

		Per 2/Ind 0.625	*Per 4/Ind 1.25*
Week 0	*n*	50	
Baseline	DBP	101.5 ± 5.5	
	SBP	177.9 ± 12.8	
Week 4	*n*	36	14
Change *vs* baseline	DBP	−20.9 ± 11.1	−12.6 ± 11.2
	SBP	−26.3 ± 17.4	−17.6 ± 15.8
Week 12	*n*	33	11
Change *vs* baseline	DBP	−19.6 ± 9.6	−14.8 ± 6.9
	SBP	−29.9 ± 21.5	−26.5 ± 9.5
End-point	*n*	50	
	DBP	*82.4 ± 9.2*	
Change *vs* baseline		−18.7 ± 9.3 ($P < 0.001$)	
	SBP	*148.4 ± 19.9*	
Change *vs* baseline		−29.5 ± 18.7 ($P < 0.001$)	

in one patient because of a moderate increase in creatinine. Two patients received potassium supplementation during the study but their baseline values were below 3.5 mmol/l. Total population mean serum potassium did not change between weeks 0 and 12 (4.38 *vs* 4.39 mmol/l).

Pharmacokinetic data were available in 49 patients. Age and renal function (creatinine clearance) were the major determinants of the pharmacokinetics of indapamide, with a marked increase in C_{min} and AUC_{24th} in the very elderly *vs* elderly (Table 2). AUC_{24th} values also increased in severe renal failure with both indapamide and perindoprilat (Table 2). The indapamide/perindoprilat AUC_{24th} ratio did not change significantly with age.

The main finding in this study was the satisfactory efficacy/safety ratio of first-line fixed low-dose Per/Ind therapy in an elderly population. There was a significant decrease in sDBP (−18.7 ± 9.3 mm Hg) and sSBP (−29.5 ± 18 mm Hg) at week 12, with dosage adjustment in 15/50 patients. Onset of antihypertensive effect was evident at week 2. Though an open study, the single-blind placebo run-in provided a reliable baseline for assessing active treatment effect. The present study suggests that in this fixed low-dose combination, perindopril counterbalanced the potassium reduction due to indapamide; in fact previous studies had shown a decrease in serum potassium on indapamide in the elderly: −0.7 mmol/l after treatment with 2.5 mg for 12 weeks, and −0.3 mmol/l after treatment with 1.25 mg for 8 weeks.[9] Other symptomatic side effects were infrequent, and orthostatic changes were neither statistically significant nor symptomatic. Special attention to pharmacokinetics is required in elderly and high-risk populations because of the high prevalence of hypertension and the specific features of drug disposition in these groups.[10] The population pharmacokinetic analysis devised for clinical subjects[8] which we employed in the present study showed marked increases in indapamide AUC_{24th} both in the very elderly ($75 <$ age $\leqslant 97$ years) *vs* the elderly ($69 \leqslant$ age $\leqslant 75$ years) and with increasing renal failure. Perindoprilat AUC_{24th} values also

Table 2 Effect of age and creatinine clearance on the pharmacokinetics of indapamide and perindoprilat (mean ± s.d.)

Dose (mg)	*Age (years)*	*Pts (n)*	C_{min} *(ng/ml)*	C_{max} *(ng/ml)*	AUC_{24} *(ng/ml h)*	*Ind/Per* AUC_{24} *ratio*	*Weight (kg)*
Ind 0.625	69–74	8	5.7 ± 2.9	19 ± 11	272 ± 159	2.1 ± 1.0	67 ± 5.8
	75–97	28	9.8 ± 6.5	26 ± 13	393 ± 214	2.4 ± 0.9	56 ± 8.7
Ind 1.25	69–74	5	9.9 ± 2.6	27 ± 9.5	408 ± 127	2.3 ± 0.2	70 ± 12
	75–97	8	16 ± 7	48 ± 16	691 ± 249	2.4 ± 1.2	51 ± 9.8
Dose (mg)	CL_{cr} *(ml/min)*	*Pts (n)*	C_{min} *(ng/ml)*	C_{max} *(ng/ml)*	AUC_{24} *(ng/ml h)*	*Ind/Per* AUC_{24} *ratio*	*Weight (kg)*
Ind 0.625	61–90	4	6.0 ± 4.1	20 ± 17	286 ± 235	2.5 ± 1.3	68 ± 5.2
	31–60	22	6.8 ± 2.4	21 ± 6.5	301 ± 89	2.3 ± 0.88	59 ± 8.2
	<30	10	15 ± 8.6	34 ± 18	540 ± 289	2.5 ± 1.1	54 ± 8.5
Ind 1.25	61–90	3	10 ± 2.0	27 ± 7.3	406 ± 87	2.8 ± 0.81	72 ± 16
	31–60	5	11 ± 2.7	31 ± 9.6	463 ± 130	2.7 ± 1.0	62 ± 7.6
	<30	5	19 ± 8.3	57 ± 14	807 ± 249	1.7 ± 0.74	47 ± 10
Per 2	61–90	4	1.9 ± 0.82	7.9 ± 2.5	109 ± 37	2.5 ± 1.3	68 ± 5.2
	31–60	22	3.4 ± 1.1	9.1 ± 4.3	145 ± 53	2.3 ± 0.88	59 ± 8.2
	<30	10	7.0 ± 5.7	14 ± 10	249 ± 187	2.5 ± 1.1	54 ± 8.5
Per 4	61–90	3	2.9 ± 0.81	11 ± 2.6	152 ± 34	2.8 ± 0.81	72 ± 16
	31–60	5	3.2 ± 0.50	13 ± 6.7	180 ± 63	2.7 ± 1.0	62 ± 7.6
	<30	5	11 ± 7.8	39 ± 34	619 ± 531	1.7 ± 0.74	47 ± 10

increased with renal failure. These results agree with previous monotherapy studies. There was no evidence of pharmacokinetic interaction between the two component drugs.

This study shows that the fixed low-dose perindopril 2 mg/indapamide 0.625 mg combination can provide effective systolic and diastolic blood pressure control in the very elderly hypertensives with an acceptable safety profile.

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