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Clinical study of the efficacy and tolerability of combined Delapril-Indapamide in hypertension

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ABSTRACT. We compared the efficacy and tolerability of Delapril (30 mg) + Indapamide (2.5 mg) administered in a fixed combination and separately. The study population comprised 157 patients (92 m., 65 f.; mean age 51 yr, range 31-66 yr) with mild to moderate hypertension. Subjects were randomly allocated to 3 treatment groups: combined Delapril + Indapamide, Delapril alone or Indapamide alone. Treatment was in all cases administered once daily, on a double-blind basis. After 6 weeks, all groups showed a significant reduction of basal blood pressure (BP). The combined therapy also determined a significant reduction of systolic and diastolic blood pressure (SBP and DBP, respectively), by comparison with Delapril and Indapamide alone. In a group of 82 patients, divided into 3 treatment groups, 24-hour ambulatory BP monitoring was carried out before and after the 6-week treatment period. BP reduction was more marked and significant with the combination than the individual active principles. The combination also afforded complete, satisfactory 24-hour BP control. The 3 groups showed no significant differences in adverse events, the only significant laboratory finding being an increase in uricemia following the combined therapy and indapamide alone. The combination is thus an efficacious, rational treatment for mild to moderate hypertension, even in the initial stages.

Key words: Delapril, Indapamide, clinic blood pressure, ambulatory blood pressure, hypertension.

INTRODUCTION

There are many clinical trials showing that the success rate for treatment of hypertension with one drug alone is no higher than 50-70%, according to the characteristics of the series and the degree of hypertension (1, 2). Better, more lasting results can be achieved in a

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higher percentage of cases if therapy is based on a combination of agents with distinct, complementary effects (3). Rational combinations favour compliance, ensuring not only greater efficacy than the separate active principles but also fewer or no adverse events. The greater tolerability of combined regimens is related to the lower doses used and the specific compensatory effects of the compounds involved (2).

The efficacy and tolerability of combined treatment with ACE inhibitors and diuretics, in use for some time, have been established by numerous studies. Delapril, a recent ACE inhibitor, is quickly absorbed after oral administration, exerts antihypertensive activity only after transformation into two active metabolites and, despite a rapid plasma peak and short half-life, is efficacious for 24 hours (4). Indapamide, an indole derivate of chlorosulphonamide, is lipophilic and thus active mainly in vascular smooth muscle, reducing hyperactivity of the arterial wall in response to vasopressor stimuli and normalizing peripheral resistances. Indapamide neither modifies cardiac output and heart rate (HR) nor reduces blood flow and glomerular filtration (5, 6). Unlike the thiazides, it also seems to have no significant long-term effect on the glucose and lipid profile. This makes it suitable for patients with conditions which normally contraindicate Thiazide treatment (diabetes, dyslipidemia, hyperuricemia, etc.).

The aim of the present study was to evaluate efficacy (including 24-hour BP monitoring) and tolerability of Delapril 30 mg + Indapamide 2.5 mg in a fixed combination, by comparison with the two compounds individually.

MATERIALS AND METHODS

Twelve specialised hypertension centres (teaching and other hospitals) participated in this double-blind, parallel-group study. The study population comprised 157 patients (65 f., 92 m.; mean age 51 yr, range 31-66 yr). Of these, 124 and 33 were WHO grade I and II, respectively.

One hundred and forty-six patients completed the 6-week study, and 11 patients discontinued treatment before its completion. Patients were randomly allocated to once-daily treatment with the combined therapy (53 pts.), Indapamide 2.5 mg (52 pts.) or Delapril 30 mg (52 pts.). The 3 groups were homogeneous in terms of basal parameters (Table 1). The difference in HR was statistically, but not clinically significant.

A double-dummy technique was used. For allocation to the study treatments, patients were divided by a randomisation list into 3 balanced blocks. All patients received placebo for the first 15 days (run-in and wash-out, on a single-blind basis), followed by 6 weeks of active treatment (double-blind). Patients were not allowed to take other antihypertensive drugs or potassium-based agents.

Parameters recorded at the fortnightly visit were sitting and standing SBP and DBP, measured with a mercury sphygmomanometer, HR, body weight and adverse events. Patients were also subjected to basal and final laboratory and ECG evaluation. According to post-treatment BDP, patients were classed as normalized (sitting DBP <90 mmHg), improved (sitting DBP reduced by at least 10 mmHg by comparison with pre-treatment values) and non-responders (Table 2).

In 8 centres, at the end of the run-in and after 6 weeks' treatment, 82 patients (28, 26 and 28 receiving combined therapy, delapril alone and indapamide alone, respectively) under-

Table 1 - Main clinical parameters of the 3 treatment groups after wash-out.

	Delapril 30 mg	Indapamide 2.5 mg	Delapril 30 mg + Indapamide 2.5 mg
No. Pts.	52	52	53
Age (yr)	52.4	53.2	50.4
B.M.I.	26.8	26.4	26.5
HR (b/min)	74.7	74.7	72.2*
SBP (mmHg)	161.6	162.7	164.6
DBP (mmHg)	101.9	102.4	102.2

*: $p<0.05$

Table 2 - Distribution of patients in terms of the effects of treatment on DBP (office readings).

Treatment group	No.	Normalized no. pts. (%)	Improved no. pts. (%)	Non-responders no. pts. (%)
Delapril 30 mg	51	29 (56.8)	8 (15.7)	14 (27.5)
Indapamide 2.5 mg	49	30 (61.2)	8 (16.3)	11 (22.5)
Delapril 30 mg + Indapamide 2.5 mg	50	43 (86.0)	4 (8.0)	3 (6.0)

Table 3 - Reductions in AUC over time between start and end of treatments (differences from mean).

	Delapril 30 mg (No=26)	Indapamide 2.5 mg (No=28)	Delapril 30 mg + Indapamide 2.5 mg (No=28)
SBP	-22%	-25%	-58%** (*)
DBP	-19%	-38%	-69%**
MBP	-22%	-33%	-69%**

*: p<0.05, (*): vs. individual compounds; **: p<0.01

went 24-hour BP monitoring by automatic sphygmomanometer (Takeda Mod. TM2420, Takeda A. and D. Company Ltd., Japan). This comprised measurements every 15 minutes throughout the day (7.00 a.m. - 11.00 p.m.) and every 30 minutes during the night (11.00 p.m. - 7.00 a.m.). Statistical analyses were based on hourly means, which were also used to calculate the 24-hour and both 12-hour means.

Efficacy was evaluated according to DBP (office readings) reduction and the number of responders, both normalized and improved. The 24-hour BP data were subjected to evaluation of the area under the curve (AUC) over time. Mean day-time and night-time BP were also evaluated, using both the normal range proposed by the Consensus Document on Non-Invasive Ambulatory Blood Pressure Monitoring (≤135/85 mmHg) and that of White (day ≤140/90 mmHg, night ≤120/80 mmHg) (8, 9).

Statistical analysis

The homogeneity of basal values was evaluated for all parameters by one-way analysis of variance. Clinical parameters after treatment were compared by repeated-measure analysis of variance. Where the comparison of treatments showed a significant interaction of TIME x DOSE, the analysis was repeated and the combination was compared with its individual constituents.

Classes of frequency generated with these codes were subjected to the Chi-square test, to identify any differences among groups.

Since each centre used its own laboratory, with possible differences in normal ranges, analytical methods and units of measurements, it was not methodologically acceptable to set up a single pool of data. Laboratory parameters for the treatment groups were analysed by evaluating changes in the pre- and post-treatment distribution of in-range

Table 4 - Distribution of patients in terms of day-time and night-time MBP, according to the normal ranges proposed by both the Consensus Conference (8) and White et al. (9).

	No.	Day-time BP <135/85 mmHg no. pts (%)	Day-time BP <140/90 mmHg no. pts. (%)	Night-time BP <120/80 mmHg no. pts. (%)
Delapril 30 mg	26	2 (7.6)	5 (19.2)	6 (23.1)
Indapamide 2.5 mg	28	6 (21.4)	10 (35.7)	14 (50)
Delapril 30 mg + Indapamide 2.5 mg	28	8 (28.5)	16 (51.7)	15 (53.6)

and out-range values for individual measurements, in relation to the normal range for the laboratory concerned (Chi-square test). The trend in distribution for each parameter was thus classed as a fall (>5% from basal), no change (±5% from basal) or rise (>5% from basal), as a basis of comparison between doses.

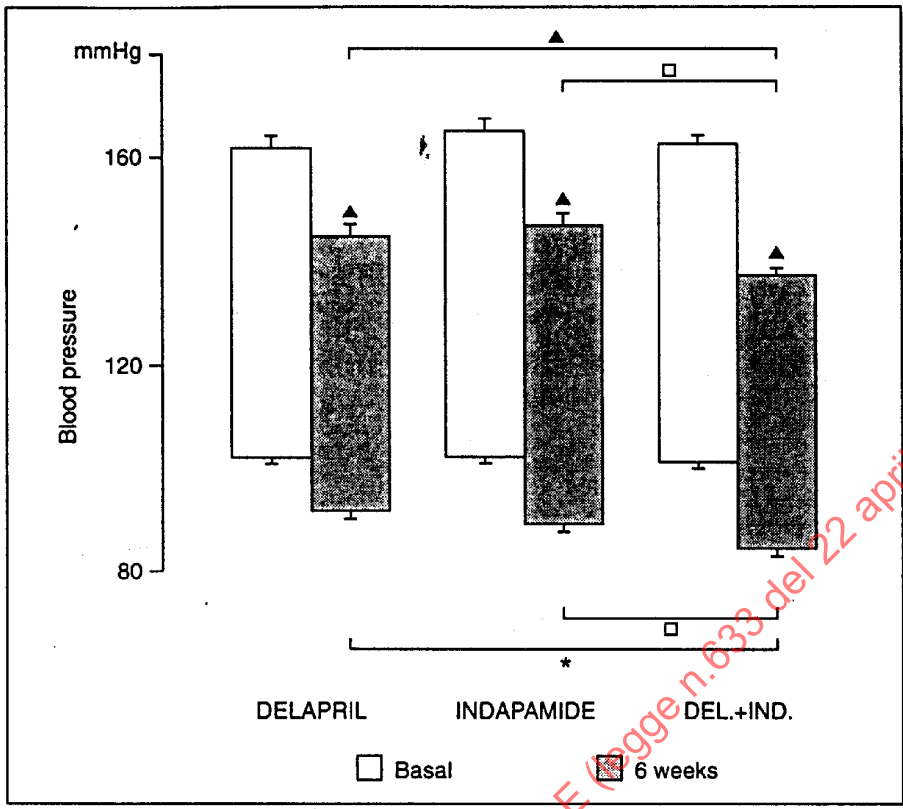

Fig. 1 - Changes in BP in the 3 treatment groups (M±ES). □: p<0.05; *: p<0.01, ▲: p<0.001.

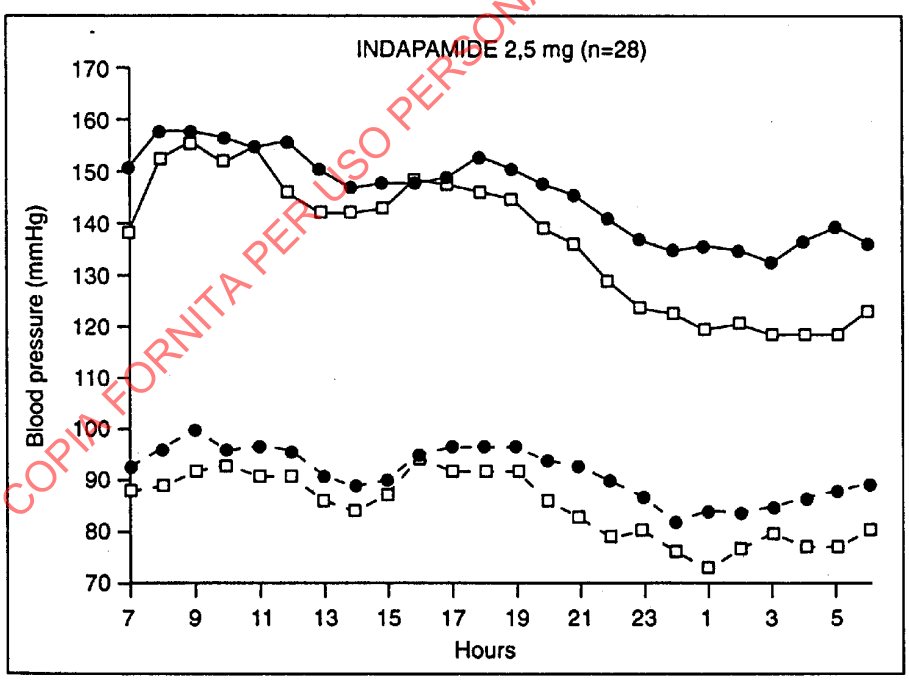

Fig. 2 - Basal (●) and post-treatment (□) BP curves obtained by ambulatory BP monitoring in the Indapamide group.

RESULTS

Each treatment significantly reduced SBP and DBP (both sitting and standing; $p<0.001$). The difference between basal and final sitting BP was 10.9-16.7 mmHg (Fig. 1).
The combined therapy determined a significantly more marked effect on sitting SBP and DBP than either of its constituent compounds alone. There was no significant change in HR.
The percentage breakdown of normalized, improved and non-responder patients differed between the combined therapy group and the others (combined 94% vs delapril 73%, $p<0.05$; vs indapamide 77%, $p<0.05$) (Table 2).

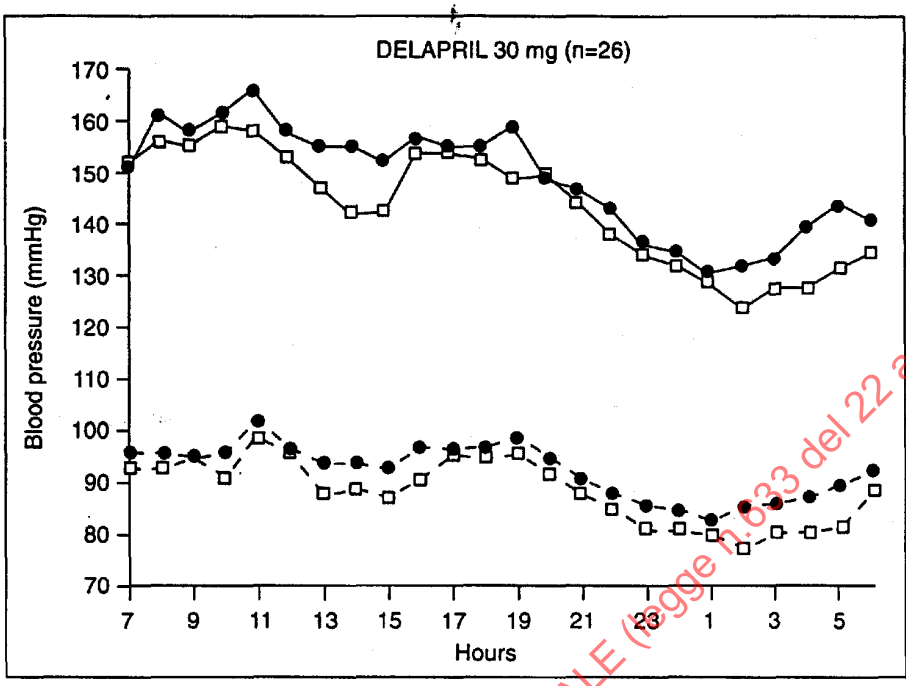

Fig. 3 - Basal (●) and post-treatment (□) BP curves obtained by ambulatory BP monitoring in the Delapril group.

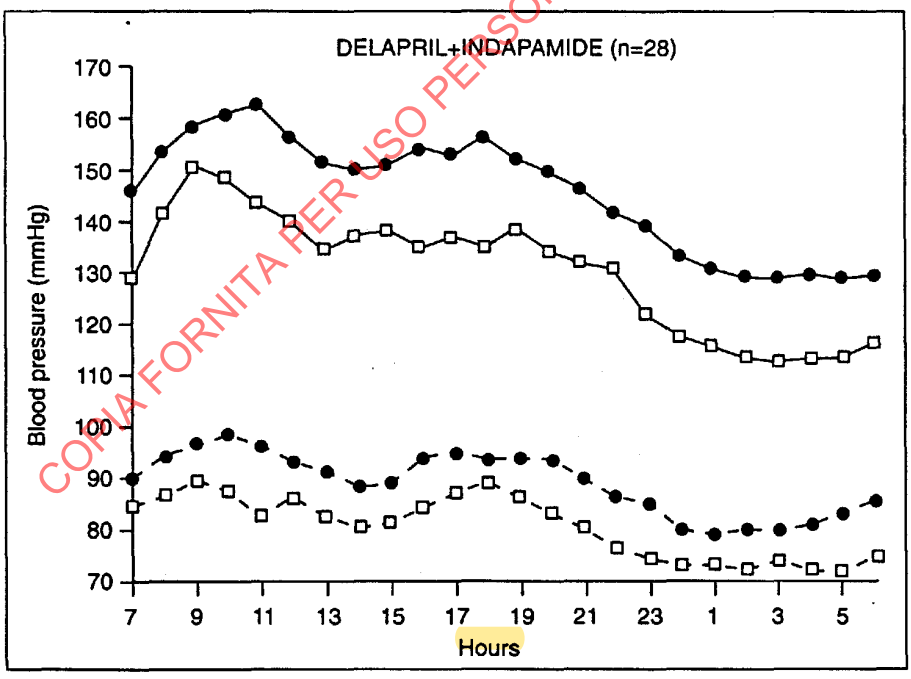

Fig. 4 - Basal (●) and post-treatment (□) BP curves obtained by ambulatory BP monitoring in the combined Delapril + Indapamide group.

Analysis of 24-hour BP data shows a significant effect of the study treatments in the comparison of the AUC over time for pre- and post-treatment SBP, DBP and mean BP (Table 3).
Reductions in BP after combined therapy are more marked and statistically more significant than after treatment with the constituent compounds alone.
The reduction in the AUC for SBP showed a significant difference between the combined therapy group and the other two ($p<0.05$). The more marked antihypertensive action of the combined therapy than the individual compounds is also readily appreciated from mean day- and night-time BP responses. The combination kept both hourly means (Figs. 2-4) and curves obtained by Fourier's transform within normal BP ranges (night-time and day-time SBP/DBP=120/80 and 140/90 mmHg, respectively) (9). Both combined and separate use of the ACE-inhibitor and diuretic afforded respect of the circadian BP profile. In terms of mean day-time and night-time BP, the combination determined a higher percentage of responders than the compounds administered separately (Table 4).
There was no significant difference among groups in the distribution of adverse events. In the group treated with Delapril, 3 patients (6%) experienced adverse events. For Indapamide, the number of patients experiencing adverse events was 5 (10%), including 2 in whom any causal relationship between the treatment and event was "doubtful". In the combined therapy group, 6 patients experienced adverse events (11%), including 3 in whom any causal relationship between the treatment and event was "doubtful". Eleven patients discontinued treatment before completing the study, for the following reasons: in the Delapril group, lack of compliance by 1 subject, inefficacy in 1 case and adverse events in 2 patients (coughing, vertigo); in the Indapamide group, 1 adverse event (gastric pyrosis), lack of compliance by 2 patients and inefficacy in 1 patient; in the combined therapy group, lack of compliance in 1 case and adverse events in 2 (vertigo and vomiting, cutaneous rash).
In terms of statistical analysis of rises, falls and no changes, the only significant finding was an increase in uric acid in the Indapamide and combined therapy groups ($p<0.01$).
In all treatment groups, the pre- and post-treatment distribution of in-range and out-range values did not differ significantly.

DISCUSSION

The results of the study are consistent with the theoretical synergy between ACE inhibitors and diuretics (10), confirming that Indapamide is a valid complement to an ACE inhibitor.
The combination Delapril + Indapamide ensured significant, rapid reduction of BP (improved or normalized in 94% of patients), with overall respect of the main metabolic indices.
Incidence of adverse events was low, their severity and frequency being comparable to those observed when the constituent compounds are used alone. The percentage of responders was higher with the combined therapy. Separate administration of the individual compounds determined effects consistent with published data (1, 2).
A number of authors recommend 24-hour ambulatory BP monitoring to evaluate the efficacy of new antihypertensives, whether alone or in combination. The rationale for this is that it affords more reproducible BP profiles than occasional measurements, and allows evaluation of the antihypertensive effect throughout the time lapse between doses (11).
Ambulatory BP monitoring has long been used to evaluate the pressure curve of hypertensives, thus eschewing any possible interference determined by the presence of the doctor or by environmental factors (12).
BP monitoring not only confirmed the results of ambulatory measurements during visits, but also showed the significantly more marked antihypertensive activity of the combination than the individual compounds. This evaluation was based on both the curve for mean values and Fourier's transform (9). The antihypertensive effect of separate therapy with indapamide and, to an even greater extent, delapril was not sufficient to ensure therapeutic cover right through to the following morning. With the combined treatment, the physiological 24-hour

BP curve was unaffected. In this respect, there is considerable emphasis in the literature on the physiological fall in BP during the night (13) and the significantly higher incidence of cerebrovascular events in subjects whose pressure does not drop at night (14). Since continuing high nocturnal BP seems to be a negative prognostic factor, treatments which are not only efficacious but also have no effect on circadian BP rhythms are arguably better (15, 16).

A still controversial problem is the definition of a normal range for BP values during 24-hour monitoring. A recent Consensus Conference suggested that, on the basis of a meta-analysis of the various studies on normotensives, day-time values in excess of 135/85 mmHg may be considered indicative of hypertension (8). White establishes 140/90 and 120/80 mmHg as the day-time and night-time threshold values, respectively (9). In the present study, combined treatment with Delapril and Indapamide determined the highest percentage of in-range values, according to White's definition.

In terms of tolerability, the combined therapy was generally good. Adverse events were neither more common than nor significantly different from those observed with the two compounds used separately.

Laboratory parameters showed no significant differences between pre- and post-treatment values for any of the three groups, with the exception of the increase in uricemia following Indapamide treatment. This is probably attributable to the compound's diuretic effect, consistent with data in the literature (17).

These results, albeit in a population with uncomplicated, mild to moderate hypertension and no selection between patients resistant to either of the constituent compounds of the combination, support combined therapy with Delapril and Indapamide. In many cases, it can be administered from the outset of antihypertensive treatment.

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