Drug treatment of hypertension: the reduction of pulse pressure does not necessarily parallel that of systolic and diastolic blood pressure

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Drug treatment of hypertension reduces systolic and diastolic blood pressure according to a well-established dose–response curve. Whether there is a parallel decrease in mean blood pressure and pulse pressure has not been investigated in the past. Recent analysis of the literature and personal work indicates that, during drug treatment of hypertension, a significant decrease in systolic and diastolic blood pressure may be associated with an unchanged pulse pressure, a situation that might contribute to maintaining cardiovascular risk. *J Hypertens* 2000, 18:1159–1163 © Lippincott Williams & Wilkins.

Until about 10 years ago, elevated diastolic blood pressure (DBP) was the criterion most commonly used to define hypertension and to determine the effectiveness of antihypertensive drug therapy [1]. As a result, the dose–response curve of each antihypertensive agent was mainly based on the measurement of DBP Systolic blood pressure (SBP), which is a more adequate marker of cardiovascular risk than DBP [2], has since been proposed as another major criterion by which to define hypertension and evaluate the effectiveness of drug treatment, particularly in elderly hypertensive patients [3]. However, it is not known whether the dose–response curve of each antihypertensive agent gives the same results regardless of whether SBP or DBP is taken as the principal criterion. Several clinical studies have shown that there is no strict parallelism in the decrease of SBP and DBP during long-term chronic therapy of hypertension [4–7]. More specifically, DBP may be normalized whereas SBP and hence pulse pressure, frequently remain elevated [4,7]. In the recent literature on therapeutic trials, there is a growing evidence that this does indeed occur.

The Hypertension Optimal Treatment (HOT) study [8] showed that in middle-aged subjects with systolic–diastolic hypertension, practicing physicians, who made up the vast majority of HOT investigators, can successfully reduce DBP to < 90 mmHg more than 90% of the time. Systolic blood pressure, however, was on average > 140 mmHg, even when a modern three-drug regimen was used and the goal for DBP was mandated by the protocol. Consequently, pulse pressure was frequently not normalized in this therapeutic trial [9]. In particular, in the SHEP study [9] and the STOP-2 study [10] the overnormalization of DBP contrasts with SBP which remains elevated, thus leading to an increased incidence of treated subjects with isolate systolic hypertension [11]. All these findings indicate that physicians in clinical trials can achieve goal DBPs in most subjects when forced titration is imposed. In contrast, it is difficult to reduce SBP to below 140 mmHg in a large number of subjects, which means that pulse pressure also remains elevated in a significant number of subjects. Interestingly, pulse pressure has been shown to be an independent marker of cardiovascular risk, even in treated hypertensive patients [5,12–16].

When they are taken together, these observations suggest that under chronic drug treatment SBP and DBP do not decrease in parallel and that the calculation of pulse pressure is a clear indicator of this dissociation. In order to investigate this issue, we recently developed randomized double-blind therapeutic trials enabling us to demonstrate that under drug therapy, whether with a single drug or an association of drugs, there is no strict parallelism in the decrease of SBP and DBP and that this finding is largely dependent on drug dosage.

In the first investigation, a randomized, double-blind, placebo-controlled, seven-way parallel group dose ranging study was performed to determine the optimal dose of perindopril (Per)/indapamide (Ind) in combination; results were assessed by measurement of mean arterial blood pressure and pulse pressure. Data from this study based on SBP and DBP have been previously published [17]. Four hundred and thirty-eight

patients aged between 18 and 75 years whose supine DBP was between 95 and 114 mmHg were randomly assigned to an 8-week double-blind treatment with either placebo, 2 mg Per/0.625 mg Ind, 4 mg Per/

1.25 mg Ind, 8 mg Per/2.5 mg Ind, 1.25 mg Ind, 2 mg Per/1.25 mg Ind or 8 mg Per/1.25 mg Ind. There was a linear dose–response relationship ($P < 0.001$) for doubling the dose of Per 2 mg/0.625 mg Ind up to 8 mg Per/2.5 mg Ind with a progressive fall in SBP DBP and
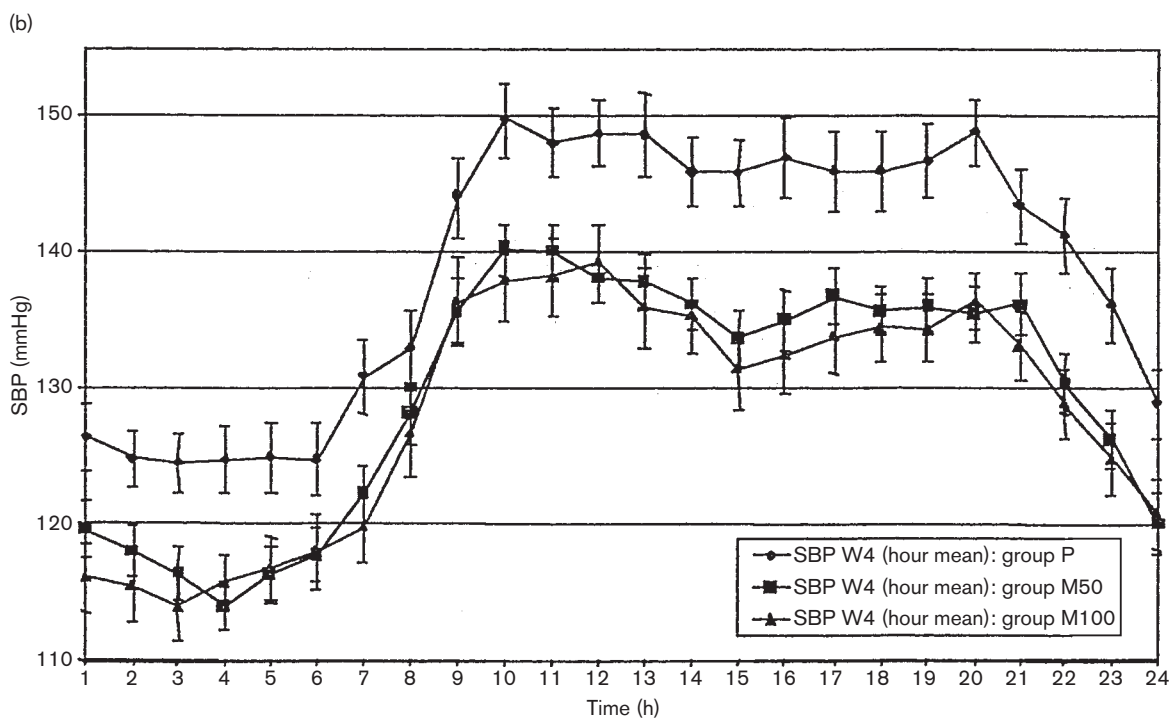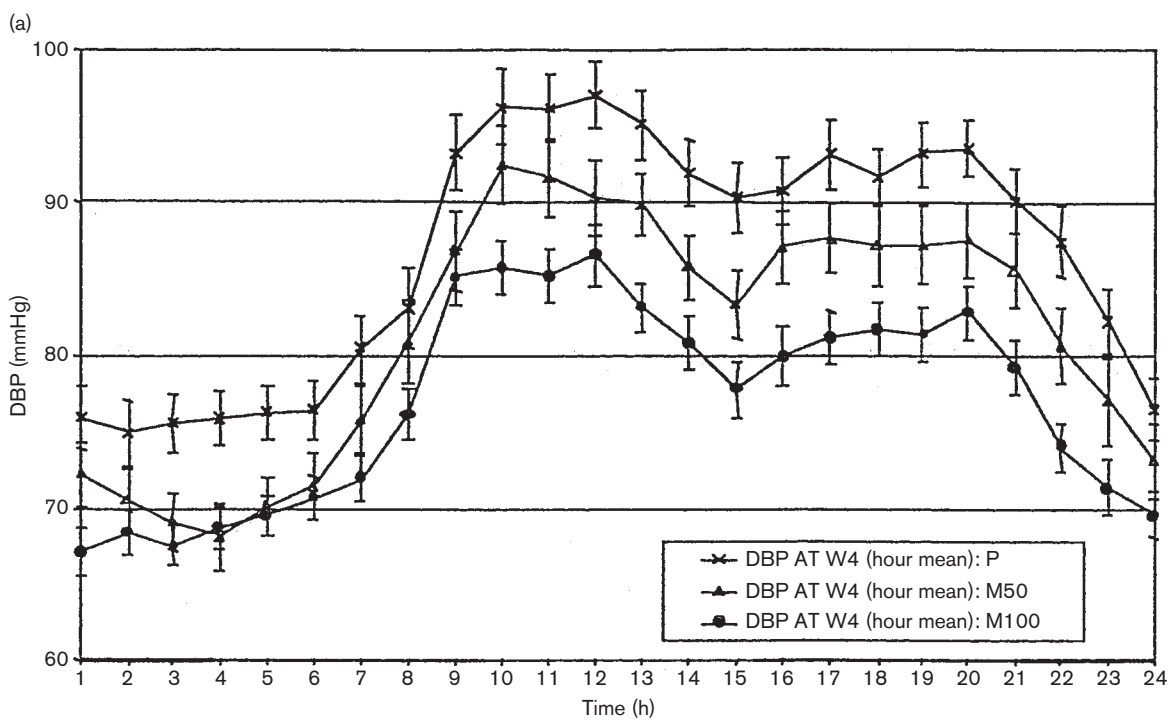
Fig. 1
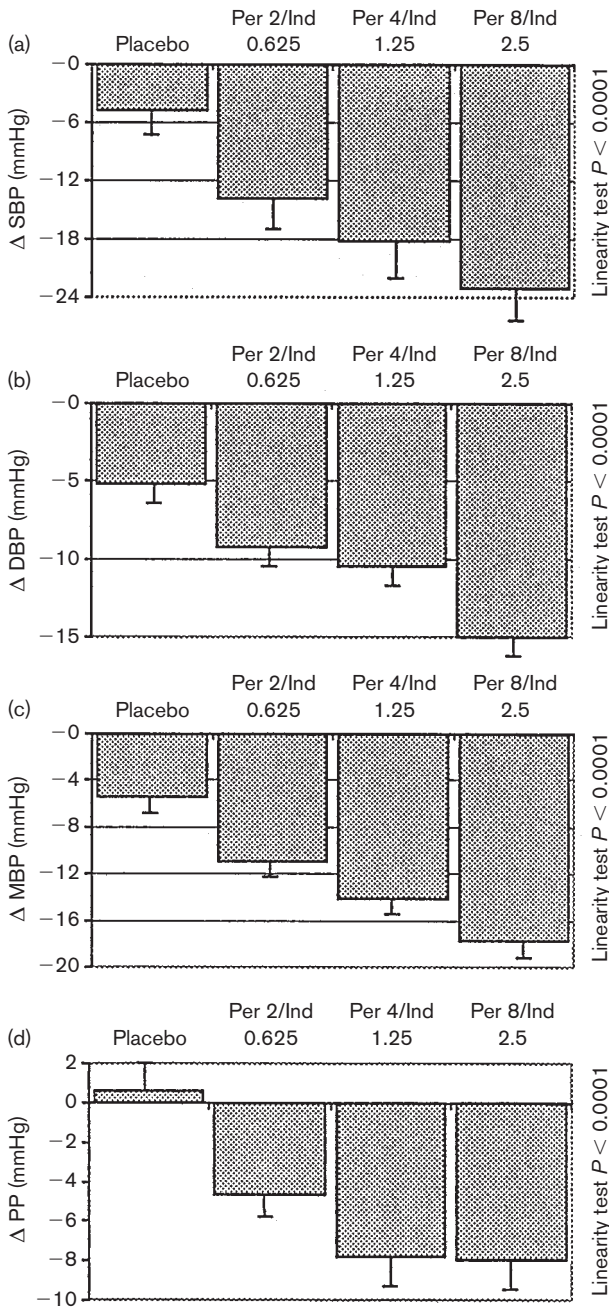
Dose–response curve relating drug dosage [doubling the dose of 2 mg perindopril (Per)/0.625 mg indapamide (Ind) up to 8 mg Per/2.5 mg Ind] (a) systolic blood pressure (SBP), (b) diastolic blood pressure (DBP), (c) mean blood pressure (MBP) and (d) pulse pressure (PP) in a population of subjects with sustained essential hypertension (see ref. 17). Values are means ± SEM. Linearity test was confirmed by two-way analysis of variance after adjustment for age, gender and baseline value.

Fig. 2
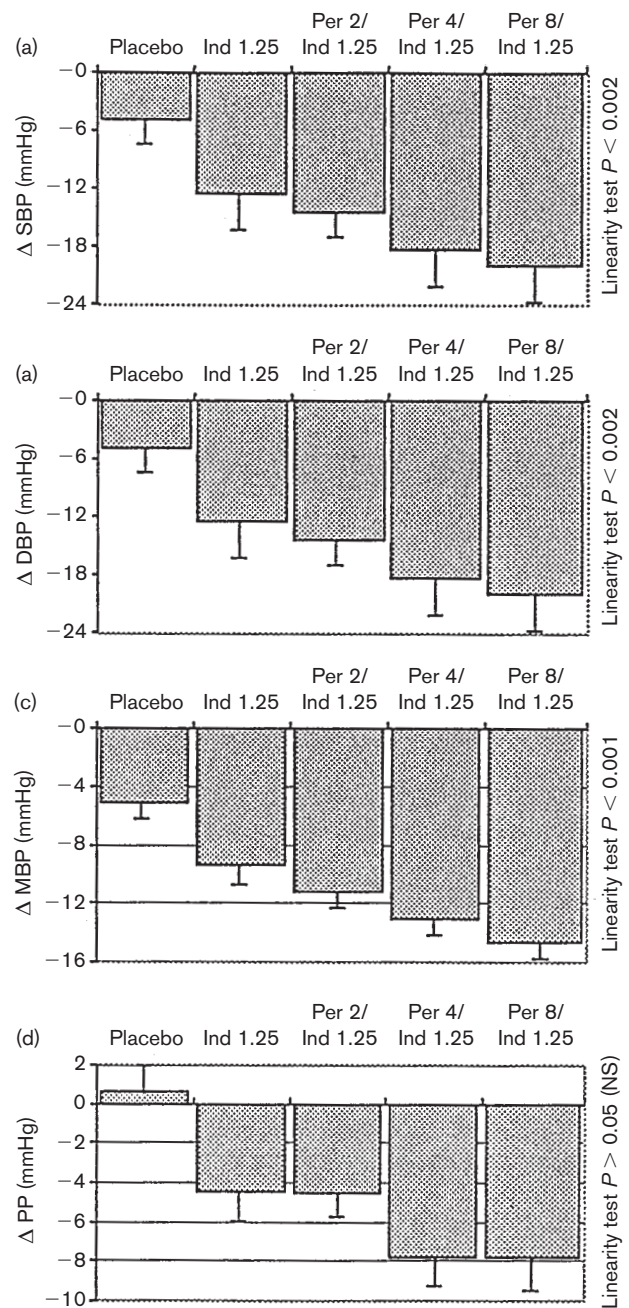
Dose–response curve relating drug dosage [increasing dose of perindopril (Per) for a given dose of indapamide (Ind)] to (a) systolic blood pressure (SBP), (b) diastolic blood pressure (DBP), (c) mean blood pressure (MBP and (d) pulse pressure (PP in a population of subjects with sustained essential hypertension (see ref. 20). Values are means ± SEM. Linearity test was confirmed by two-way analysis of variance after adjustment for age, gender and baseline value.

Fig. 3

24 h blood pressure for each mibefradil treatment group (a) diastolic blood pressure (DBP and (b) systolic blood pressure (SBP). P placebo (group A); M50, 50 mg mibefradil (group B); M100, 100 mg mibefradil (group C); W4, week 4.

mean arterial pressure (Fig. 1). Combining 1.25 mg Ind with increasing doses of Per (0, 2, 4 and 8 mg) also showed a linear dose–response relationship for the three variables ($P < 0.002$, $P < 0.007$ and $P < 0.001$ for SBP, DBP and mean arterial pressure, respectively; Fig. 2). In both dose–response relationships, the curve relating the change of pulse pressure to drug dosage was not linear; the reduction in pulse pressure reached a plateau for 4 mg Per/1.25 mg Ind. There were no significant differences between groups for higher dosages (Figs 1 and 2).

A second investigation was performed with the calcium entry-blocker mibefradil [18] in a population of 140 subjects (66 women and 74 men) with sustained essential hypertension. Mean age and body weight were 48 ± 7 years (mean $\pm$ SD) and 72 ± 13 kg, respectively. After a 4 week preselection period under placebo, patients with mild-to-moderate essential hypertension who had a DBP > 95 mmHg and an SBP < 210 mmHg (sphygmomanometer measurements) were randomly allocated to one of three groups: group A, placebo group (46 subjects); group B, with a daily oral single dose of 50 mg mibefradil (47 subjects); group C, with a daily oral single dose of 100 mg mibefradil (47 subjects), 100 mg being the top of the DBP dose–response curve [18]. After 4 weeks of treatment, casual blood pressure measurements (adjusted to baseline values) showed that DBP had decreased in a dose-dependent manner (group A: 94 ± 10, group B: 91 ± 9, group C: 88 ± 9 mmHg; ANOVA: $P = 0.005$) whereas SBP showed no further decrease in response to the higher dose of the drug (group A: 151 ± 12, group B 144 ± 11, group C: 146 ± 11 mmHg; ANOVA: $P = 0.02$). Pulse pressure was decreased in group B (53 ± 9 mmHg), but it was identical in groups A and C (58 ± 11 and 58 ± 9 mmHg, respectively; ANOVA: $P = 0.03$). The findings of 24-h blood pressure measurements, summarized in Figure 3, clearly show that, although DBP at week 4 decreased in a dose-dependent manner, SBP decreased to exactly the same extent with 50 or 100 mg/day mibefradil dose. During the day pulse pressure was 54 ± 7 mmHg in group A, 49 ± 7 mmHg in group B and 53 ± 9 mmHg in group C. The difference between the three groups was significant (ANOVA: $P < 0.005$). These differences in pulse pressure disappeared during the night. Because pulse pressure is the difference between SBP and DBP and because SBP and pulse pressure are strongly correlated [12–16], it is often difficult to dissociate unequivocally the effects of SBP and pulse pressure. The present study gives some of the first direct evidence that the lack of decrease of pulse pressure at 100 mg mibefradil dosage was due exclusively to a decrease of DBP the decrease of SBP was identical at 50 and 100 mg mibefradil.

The observed dissociations between the decrease in SBP and DBP under chronic antihypertensive therapy are difficult to explain. Because SBP is mainly influenced by ventricular ejection, arterial stiffness and the timing of wave reflection and DBP is influenced by arterial stiffness and peripheral vascular resistance [4,6], these different haemodynamic mechanisms may interfere independently with pulse pressure. For the same decrease of mean blood pressure, antihypertensive agents may have independent effects on ventricular and arterial ejection and arterial stiffness, resulting in specific changes in the SBP and pulse pressure. For instance, acute and long-term calcium blockade produces a rapid decrease in SBP and DBP without changing pulse pressure [19,20], whereas acute and long-term nitrates administration may selectively reduce SBP and pulse pressure without changing DBP as a consequence of predominant changes of arterial stiffness and wave reflections [4,6,21]. For chronic antihypertensive therapy, the MRC mild hypertension trial [15] has shown that the diuretic compound bendrofluazide but not the beta-blocker propanolol significantly decreased pulse pressure, possibly through differential effects on stroke volume. Thus, it is possible that a number of antihypertensive agents given alone or in association participate in one or more of the above-mentioned mechanisms.

In conclusion, the present report has shown that a given antihypertensive agent may act dose-dependently on DBP without a parallel and proportional decrease of SBP and pulse pressure. Further prospectives studies, especially those taking SBP as the criterion of entry, are needed to explore this important aspect of drug treatment of hypertension more fully, particularly within the framework of reduction of cardiovascular risk through changes in pulse pressure.

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