Persistence of anti-hypertensive effect after missed dose of perindopril

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Aims To assess the persistence of the antihypertensive effect of the ACE-inhibitor perindopril after one missed dose.

Methods After a placebo run-in period, 10 hypertensive patients were started on perindopril 4 mg once daily in the morning, increased to 8 mg once daily after 4 weeks if office diastolic BP >85 mmHg. 24 h BP monitoring was performed at the end of the placebo run-in period and during active treatment in week 9 and 10 on either active treatment or a placebo-day using a double-blind, randomized, cross-over design.

Results Office BP decreased from $155\pm3/100\pm2$ mmHg at the end of placebo to $139\pm3/89\pm2$ mmHg ($P<0.05$ *vs* placebo) after 8 weeks of active treatment. After 2 months of active treatment, 24 h ABP showed significant decreases in day BP by $-11\pm1/-7\pm1$ mmHg and in night BP by $-11\pm2/-7\pm1$ mmHg while on active treatment. During the placebo-day, daytime BP showed decreases by $-10\pm1/-5\pm1$ and night BP by $-8\pm2/-6\pm1$ mmHg (NS *vs* active treatment day).

Conclusions Perindopril 4–8 mg day^{-1} causes a persistent decrease in BP during the 24 h dosing interval, which is mostly maintained over the 24–48 h after dosing.

Keywords: ACE inhibitors, compliance, duration of action, hypertension

Introduction

Many clinical trials have demonstrated that long-term antihypertensive drug treatment decreases the adverse consequences of chronic hypertension. The actual cardiovascular events occurring on treatment appear less to be determined by the level of BP at initiation of treatment, than by the extent of BP control over subsequent years of treatment [1]. Inadequate BP control despite treatment may be the result of drugs failing to control the BP over the entire dosing-interval or relate to the patient, not taking the medication as prescribed. Intermittent BP control has both short-term and long-term negative consequences for outcome [2]. Prolonged drug action beyond the usual dosing-interval can lead to better and more persistent BP control in patients with partial compliance [3]. However, while antihypertensive drugs are carefully being evaluated for their efficacy in lowering BP, very little attention is so far being directed towards the persistence of the antihypertensive effect during periods of noncompliance.

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ACE inhibitors are generally prescribed once-daily, but do not always provide a consistent effect over the 24 h dosing interval [4]. Moreover, for most ACE inhibitors, a sustained therapeutic action beyond the end of a once-daily dosing interval has not yet been documented. Perindopril in once daily doses of 4–8 mg exerts fairly similar antihypertensive effects at 6 and 24 h [5]. One may therefore expect a continuation of this antihypertensive effect beyond the 24 h into the second day. In the present study we therefore evaluated the BP lowering effect of perindopril both on active treatment and after one 'missed dose' using a double-blind, randomized design.

Methods

Patients with uncomplicated, essential hypertension were eligible to continue in the active treatment phase of the study, if at the end of a 4 week placebo run-in period they had a sitting diastolic BP between 96 and 110 mmHg inclusive and on 24 h ambulatory BP monitoring a mean daytime diastolic B$P>90$ mmHg. Characteristics of the patients entering and completing the full active treatment phase are as follows: 10 male Caucasians, age 58 ± 3 years (range, 43–70 years), duration of hypertension 55 ± 13 months (range 10–144 months), body weight 84 ± 2 kg

and height 170 ± 3 cm. Previous antihypertensive treatment was monotherapy for all 10 patients and was an ACE inhibitor in three patients, and a calcium-antagonist in seven patients. Concomitant relevant therapy was a lipid-lowering agent in three patients. No other relevant health problems were present.

The study and associated risks were explained to the patient and written informed consent was obtained before discontinuing current antihypertensive drug treatment. The study protocol and consent form were approved by the Institutional Review Board of Institutional Review Services, Toronto, Ontario.

During the 4 week single-blind placebo run-in period, patients were asked to take one perindopril placebo tablet each morning. Compliance was evaluated by pill-count and only fully (i.e. ≤ 1 dose missed) compliant patients entered the active treatment phase. Eligible patients then started perindopril 4 mg once daily in the morning. If after 4 weeks of active treatment, the sitting diastolic BP was still above 85 mmHg, the dose was increased to 8 mg once daily. Three patients continued on 4 mg daily, *vs* seven on 8 mg. On day 4 of week 9 and week 10 on active treatment, the patients received in the office their daily treatment as double-blind tablets containing either placebo or perindopril in a randomized, cross-over manner. These tablets were all taken around 09.00 h in the presence of the investigator after the ambulatory BP monitor had been initiated.

Office BP measurements were performed in the sitting position following 10 min of rest, in triplicate at 1 min intervals using a mercury sphygmomanometer. These were all done in the morning around 09.00 h –10.00 h before the day's dose. A 24 h ambulatory BP recording was performed using a Spacelabs model 90207 device, at the end of the placebo period and during day 4 of weeks 9 and 10 on active treatment. During the daytime (06.00 h–22.00 h) four measurements per hour were obtained and during the night time two measurements per hour, and continued for 26 h. The mean BP values were calculated for each hour, and for the day [06.00–18.00 h], evening [18.00–23.00 h] and night [23.00–06.00 h] periods. The records were scanned for obvious antifactual data points, but otherwise not edited.

Values are reported as mean ± s.e. mean. The primary efficacy end-points were the absolute changes in diastolic and systolic BP as compared with the end of the placebo-period for the three periods of the day, while on active treatment *vs* the day of interrupted treatment with placebo. Changes from baseline were compared using analysis of variance for repeated measures. In addition, the within-subject differences between the decreases in BP during the days on *vs* off therapy were calculated with their 95% confidence intervals.

Results

At the end of the placebo run-in period, sitting BP in the office was 155 ± 3/100 ± 2 mmHg. After 4 weeks of active treatment, office BP at trough had decreased to 144 ± 3/93 ± 3 mmHg, and after 8 weeks to 139 ± 3/89 ± 2 mmHg ($P<0.05$ *vs* placebo).

After 4 weeks on placebo, 24 h ambulatory BP monitoring confirmed the presence of mild hypertension with averages of 150 ± 1/96 ± 1, 148 ± 4/94 ± 3 and 133 ± 2/84 ± 1 mmHg for the day, evening and night periods, respectively. Figure 1 shows the decreases in BP from placebo after 2 months on active treatment. On maintenance therapy decreases for systolic BP were in the 8–11 mmHg range and diastolic BP in the 5–7 mmHg range. During the day off therapy by placebo-insertion most of this antihypertensive effect persisted, i.e. 8–10 mmHg for systolic BP and 4–6 mmHg for diastolic BP. After 9–10 weeks on treatment, decreases in BP on active *vs* placebo-day did not differ significantly.

Mean values for within-subject differences between decreases in systolic and diastolic BP on *vs* off therapy

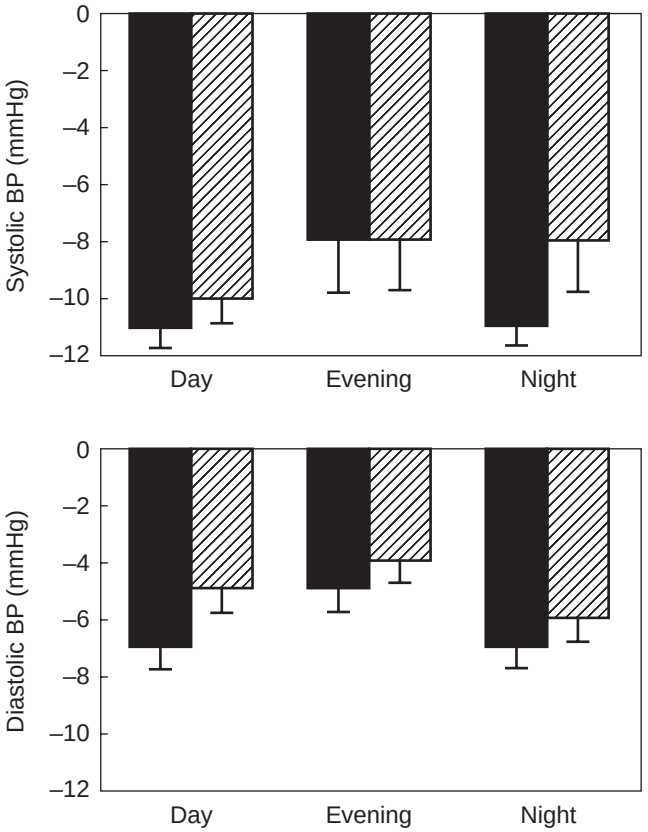

Figure 1 Persistence of the antihypertensive effect of perindopril during 1 day of placebo interrupting active treatment (▨) as compared with the effect on active treatment (■). Values represent mean (± s.e.mean) decreases from values at the end of the placebo run-in period ($n=10$). All decreases are significant, and active *vs* interrupted therapy did not differ significantly.

were 1–2 mmHg less off therapy, specifically for systolic BP 0.8 mmHg (95% confidence interval −0.9, 2.5 mmHg) for the day period and 2.3 mmHg (95% confidence interval 0.6, 4.0 mmHg, $P<0.05$) for the night period, and for the diastolic BP 0.8 mmHg (95% confidence interval 0.1, 1.5 mmHg, $P<0.05$) and 1.7 mmHg (95% confidence interval −0.2, 3.6 mmHg) for these two periods.

Discussion

The present study confirms the antihypertensive efficacy of perindopril and provides a new finding that most of its antihypertensive effect appears to persist during a day without treatment. The extent of the fall in BP achieved by perindopril 4–8 mg once daily in this group of white male hypertensives is similar to the reduction observed in previous studies with ACE inhibitors or AT_1-receptor blockers in similar patient-populations [5, 6]. The present study shows similar decreases in BP during the day, evening and night and is consistent with the study by Myers [5] showing similar BP decreases at 6 and 24 h post dosing, Perindopril therefore causes a persistent decrease in BP throughout the 24 h dosing interval. In this regard, perindopril is similar to other longer acting ACE inhibitors [4]. In contrast, most of the antihypertensive effect of shorter-acting ACE inhibitors, such as enalapril has already disappeared 16–24 h after dosing [4, 7].

During a day off therapy, most of the antihypertensive effect of perindopril appears to persist. However, considering the 95% confidence intervals a larger study is required to establish more precisely how much of the effect persists particularly by the end of the second day. The findings in this study do not exclude increases of up to 4 mmHg 24 h after discontinuation of perindopril. Intermittent BP control has the potential for negative outcome, both *per se* and relative to persistent BP control [2]. The concept of 'therapeutic coverage' [8] implies extended protection beyond a 24 h dosing interval. Drugs providing such therapeutic coverage are available for each class of antihypertensive agents, e.g. nadolol for β-adrenoceptor blockers [9], amlodipine for calcium antagonists [10] and perindopril (present study) or trandolapril [4] for ACE-inhibitors. Such drugs will likely provide better outcome as compared with shorter-acting drugs within a given class.

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