Abstract

Low-dose drug combinations have been proposed in International Guidelines for use in patients with hypertension. The fixed low-dose combination of perindopril 2mg with indapamide 0.625mg combines an angiotensin converting enzyme (ACE) inhibitor with a non-thiazide diuretic.

Coadministration of perindopril and indapamide did not have any clinically significant effects on the pharmacokinetic profile of either agent in healthy volunteers.

In experimental models of hypertension, perindopril/indapamide restored endothelial function, improved microvascular density, reduced left ventricular and aortic hypertrophy, and reversed renal end-organ damage.

Once daily oral perindopril 2mg/indapamide 0.625mg normalised blood pressure (BP) in 83.6% of elderly patients with essential hypertension (diastolic BP was reduced to ≤90mm Hg) and 81.7% of those with isolated systolic hypertension (systolic BP was reduced to <160mm Hg) after ≈1 year of treatment. BP normalisation was sustained in 79.8% of patients throughout the study.

Fixed low-dose perindopril/indapamide had a tolerability profile similar to that of placebo in clinical trials; most adverse events were of mild to moderate severity. Coadministration of the 2 agents reduced the incidence of hypokalaemia seen with indapamide alone.
The combined use of an angiotensin converting enzyme (ACE) inhibitor with a diuretic offers potential advantages over monotherapy in terms of efficacy, compliance and tolerability.[1] Moreover, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)[2] and, more recently, the 1999 World Health Organization/International Society of Hypertension (WHO/ISH) guidelines for the management of hypertension,[3] suggest that low-dose combinations of antihypertensive drugs may be appropriate for first line use in patients with hypertension.

A fixed low-dose combination of the ACE inhibitor perindopril 2mg and the non-thiazide diuretic indapamide 0.625mg has been developed which meets the requirements of these guidelines. Data for this dosage combination form the basis of this profile but, where data are not available, have been supplemented by data for other dosage combinations.

1. Pharmacodynamic Profile

The pharmacodynamic effects of perindopril and indapamide monotherapy have been reviewed previously.[4,5] This section reviews the results of studies which evaluated the pharmacodynamic effects of these 2 agents when administered together in various experimental models of hypertension.

**Blood Pressure (BP)-Lowering Effects**

- The fixed combination of perindopril/indapamide (0.25/0.08mg to 1.0/0.31 mg/kg/day) had significantly greater BP-lowering effects than oral vehicle (p < 0.05)[6,7] or either agent alone (p < 0.05)[7,8] when administered orally for 6 or 8 weeks to 10- to 16-week-old spontaneously hypertensive rats (SHR). The reduction in systolic BP (SBP) was significantly correlated with an increase in plasma renin activity (r = 0.40; p < 0.0001).[8]

- In salt-fed Dahl salt-sensitive (DSS) rats, oral administration of perindopril/indapamide 4.56/1.44 mg/kg/day for 8 weeks reduced SBP compared with salt-fed untreated controls (p < 0.05).[9] The BP-lowering effects of the fixed combination were greater than those of either agent alone.

**Endothelial Effects**

- A low-dose combination of perindopril and indapamide restores the arterial elastin/collagen ratio in SHR and improves carotid artery compliance. When given orally to SHR for 12 weeks, perindopril/indapamide 0.76/0.24 mg/kg/day significantly reduced aortic, carotid and femoral media cross-sectional areas (p < 0.05 vs untreated controls) and aortic and carotid media collagen densities (p < 0.01), and increased aortic elastin density (p < 0.05).[7] At a fixed BP value of 190mm Hg, perindopril/indapamide significantly increased carotid compliance (from 0.71 to 1.19 × 10⁻³ mm²/mm Hg; p < 0.01).[7]

- Oral perindopril/indapamide 4.5/1.44 mg/kg/day for 8 weeks restored impaired endothelial balance in salt-fed DSS rats by significantly decreasing urinary endothelin-1 excretion and improving aortic nitric oxide synthase activity (both p < 0.05 vs vehicle).[9] In addition, the combination normalised the impaired endothelium-dependent re-