Losartan Potassium
A Review of its Pharmacology, Clinical Efficacy and Tolerability in the Management of Hypertension

Karen L. Goa and Antona J. Wagstaff
Adis International Limited, Auckland, New Zealand

Contents

Summary ........................................ 821
1. Role of the Renin-Angiotensin System (RAS) in Hypertension ........................................ 824
2. Pharmacodynamic Properties ........................................ 826
   2.1 Inhibition of Angiotensin II (All) Activity ........................................ 826
      2.1.1 Inhibition of Receptor Binding ........................................ 826
      2.1.2 Functional Antagonism of All Activity ........................................ 826
   2.2 Effects on the RAS ........................................ 827
   2.3 Haemodynamic and Cardiovascular Effects ........................................ 827
      2.3.1 Effects on Left Ventricular Hypertrophy ........................................ 828
      2.3.2 Other Effects ........................................ 828
   2.4 Effects on Renal Haemodynamics and Function ........................................ 829
   2.5 Effects on Bradykinin ........................................ 829
   2.6 Metabolic and Neuroendocrine Effects ........................................ 829
3. Pharmacokinetic Properties ........................................ 830
   3.1 Absorption and Distribution ........................................ 830
   3.2 Metabolism and Elimination ........................................ 830
   3.3 Drug Interactions ........................................ 831
4. Clinical Efficacy of Losartan Potassium in Hypertension ........................................ 831
   4.1 Losartan Potassium Monotherapy ........................................ 833
      4.1.1 Dose-Finding Studies ........................................ 833
      4.1.2 Comparisons with Other Antihypertensive Drugs ........................................ 833
   4.2 Losartan Potassium plus Hydrochlorothiazide ........................................ 834
      4.2.1 Noncomparative Studies ........................................ 834
Losartan potassium is an orally active, nonpeptide angiotensin II (AT1) receptor antagonist. It is the first of a new class of drugs to be introduced for clinical use in hypertension. This novel agent binds competitively and selectively to the AT1 subtype 1 (AT1) receptor, thereby blocking AT1-induced physiological effects. An active metabolite, E3174, contributes substantially to its antihypertensive effect, which persists throughout 24 hours after once-daily administration.

In patients with mild to moderate hypertension, losartan potassium 50 to 100mg once daily as monotherapy lowers blood pressure to a similar degree to enalapril, atenolol and felodipine extended release (ER). Losartan potassium combined with hydrochlorothiazide reduces blood pressure further than either drug given separately. About one-third of patients with severe hypertension have responded to the combination product. Losartan potassium appears to be effective in elderly patients.

Losartan potassium is very well tolerated. In clinical trials, dizziness was the only drug-related event reported more frequently with losartan potassium monotherapy than with placebo. First-dose hypotension is uncommon. An aspect of the drug’s tolerability profile which may prove to be particularly advantageous is that it is associated with a similar incidence of cough to placebo in patients with a history of ACE inhibitor-related cough. Additionally, clinically relevant adverse metabolic effects or laboratory abnormalities have not been documented during losartan potassium therapy and renal function is preserved in patients with or without renal insufficiency. The adverse effect profile of the losartan potassium-hydrochlorothiazide combination resembles those for losartan potassium monotherapy and placebo. Long term tolerability data are limited (<2 years) but support the very good tolerability profile in shorter studies.

Elements of the drug’s profile yet to be assessed or reported fully in the literature include long term efficacy, potential to favourably influence cardiovascular and renovascular systems (and ultimately mortality) in patients with hypertension and, lastly, cost effectiveness and influence on quality of life.

In summary, losartan potassium is the first AT1 receptor antagonist to become available for the management of hypertension and, as such, it is an important new antihypertensive agent. Pending long term data as outlined above, it is likely to find initial use in patients with mild to severe hypertension who are unresponsive to, or intolerant of, their current therapy. However, with its novel mechanism of action, good efficacy and favourable tolerability profile, losartan potassium is well placed to claim a prominent position in the management of patients with essential hypertension in the future.