Losartan: a review of its use, with special focus on elderly patients

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Authors' objectives
To assess the efficacy of losartan for the treatment of hypertension and heart failure, with particular reference to the elderly.

Searching
AdisBase, MEDLINE and EMBASE were searched from 1966 to 10th January 2000, for medical literature published in any language. The search terms were: for AdisBase terms, ‘losartan’ and ‘congestive heart failure’ or ‘hypertension’ or ‘elderly’; for MEDLINE, ‘losartan’ and ‘heart-failure-congestive’ or ‘hypertension’ or ‘aged’. The reference lists of papers were examined for additional material, and drug companies were contacted for unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

For hypertension, all the studies, bar one, were double-blind and multicentre. The duration of the trials was 12 to 24 weeks.

For heart failure, trials assessing morbidity and mortality were double-blind and of 48 weeks' duration, whilst those assessing exercise tolerance were blinded and non-blinded, ranging in duration from 2 weeks to 6 months.

Specific interventions included in the review
Patients with hypertension were treated with single daily doses of: 50 or 100 mg losartan, compared with extended release felodipine (5 or 10 mg), nifedipine gastrointestinal therapeutic system (GITS; 30 to 90 mg), enalapril (10 mg) or atenolol (50 mg). Losartan doses were increased, or hydrochlorothiazide was added, if there was a need to control blood-pressure (BP).

Patients with heart failure were treated with losartan (25 or 50 mg/day), compared with captopril (50 mg, three times per day), placebo or enalapril (10 to 20 mg/day). Concomitant therapy included: diuretics, digitalis, aspirin, calcium antagonists, hydralazine, potassium, angiotensin-converting enzyme inhibitors, digoxin, nitrates or long-acting nitrates, anticoagulant agents, beta-blockers and anti-arrhythmics.

Participants included in the review
For hypertension studies, the participants were at least 65 years of age with mild to moderate hypertension, and with a resting diastolic BP of 95 to 115 mmHg after the 4-week placebo washout period. One trial included patients with isolated systolic hypertension.

For heart failure studies assessing mortality and morbidity, the participants were at least 65 years of age with symptomatic heart failure, classified as New York Heart Association (NYHA) functional class II to IV, with left ventricular ejection fraction (LVEF) equal or less than 40%.

For heart failure studies assessing exercise tolerance, the participants were: patients aged from 53 to 79 years with asymptomatic heart failure, i.e. left ventricular diastolic dysfunction; patients aged from 25 to 83 years with symptomatic heart failure; patients with severe symptomatic heart failure (mean LVEF 27.3 and NYHA class III or IV) insufficiently controlled by their current regimen.

Outcomes assessed in the review
The outcomes assessed for hypertension were: the mean change in resting diastolic and systolic BP; the quality of life (QOL), assessed using a variety of scales and overall health perceptions, cognitive social functioning, sexual functioning...
and psychological well-being; and tolerability and adverse events.

The outcomes assessed for heart failure were: morbidity and mortality, by assessment of renal dysfunction, death or admission to hospital for heart failure; exercise tolerance, in terms of exercise time, distance in walk test, resting systolic and diastolic BP, peak systolic BP during exercise, dyspnoea-fatigue index, peak oxygen consumption (VO2); increased injection fraction; and QOL. In addition, tolerability and adverse effects were monitored with respect to laboratory anomalies in areas such as haematology, blood chemistry and urinalysis, and the number of withdrawals.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors state that they assessed the validity of trials, based on the methods section of the papers. No other details were given. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on: baseline characteristics, e.g. age range and mean age; study design, i.e. blinding, duration and the number of patients; treatment including concomitant and previous therapy; results for hypertension trials, e.g. mean drop in resting diastolic and systolic BP, response rate, adverse events and QOL; and results for heart failure trials, e.g. renal dysfunction, exercise duration, peak VO2, dyspnoea-fatigue index, peak systolic BP, LVEF, NYHA functional classification, adverse effects and the number of hospital admissions.

Methods of synthesis
How were the studies combined?
The results of the studies were not combined statistically but were discussed in the narrative.

How were differences between studies investigated?
The characteristics of the studies were given in the text and tables, and discussed in the text.

Results of the review
Eight trials (1,173 patients) assessed the treatment of patients with hypertension. For heart failure, 2 trials (3,874 patients) assessed mortality and morbidity, and 6 trials (414 patients) assessed exercise tolerance.

Hypertension: studies indicated that the antihypertensive efficacy of 50 or 100 mg losartan, administered once daily, caused a decrease in BP of less than or equal to 20 to 26 mmHg. This was similar to that for the other antihypertensive agents: enalapril (10 to 20 mg), captopril (50 to 100 mg), nifedipine GITS (30 to 90 mg) and felodipine extended release (5 to 10 mg). In addition, once daily losartan (50 mg) had similar efficacy to atenolol (50 mg) for isolated systolic hypertension. The addition of hydrochlorothiazide (12.5 to 25 mg) to losartan therapy produced additional decreases in BP. A fixed combination of 50 mg losartan with 12.5 mg hydrochlorothiazide was as effective as the combination of 50 mg captopril with 25 mg hydrochlorothiazide.

The adverse events most commonly reported, i.e. in 5 to 10% of the patients, were headache, asthenia, oedema and upper respiratory tract infections. Overall, the incidence of treatment-related adverse events in losartan-treated patients was 19 to 27%, compared with 23% for felodipine- and 21% for nifedipine-treated patients. Losartan was better tolerated in patients with isolated systolic hypertension than captopril and atenolol: the adverse events were 11 and 16% for losartan and captopril, respectively, and 10.4 and 23% for losartan and atenolol. There were significantly fewer withdrawals because of adverse events in losartan-treated patients, compared with atenolol: 1.5 and 7.2%, respectively. Fewer patients required switching to alternative therapy, because of adverse effects, with a systematic losartan-based
regimen than with usual care in a community-based study. Losartan had a more favourable effect on QOL than enalapril, but a similar effect to nifedipine GITS, although the total number of adverse events reported with nifedipine GITS was greater than in losartan recipients.

Heart failure: one trial showed a significant reduction in the risk of death or admission to hospital for heart failure in losartan-treated patients, compared with captopril-treated patients. However, a second trial found no significant differences in all-cause mortality between the two treatments. No differences were observed in sudden death, heart failure mortality, myocardial infarction, stroke or non-cardiovascular death between the two groups. Losartan was better tolerated than captopril in both trials. In the first study, losartan and captopril produced similar improvements in QOL after 48 weeks, although more captopril-treated patients withdrew from the study because of adverse events. In one trial, renal tolerability of losartan was similar to that of captopril after 48 weeks.

In patients with asymptomatic failure-left ventricular diastolic dysfunction, losartan increased exercise tolerance and reduced or delayed peak systolic BP during exercise. In patients with symptomatic heart failure, losartan and enalapril increased exercise tolerance to a similar extent. Short-term studies indicated that the addition of losartan to an angiotensin-converting enzyme inhibitor may provide additional benefits in patients with severe heart failure, insufficiently controlled by their current drug regimen.

Preliminary evidence indicated that losartan therapy also contributes to the regression of left ventricular hypertrophy associated with chronic hypertension.

Further information about the effects and tolerability of losartan can be found in an earlier review (see Other Publications of Related Interest).

Authors' conclusions
The authors state that comparative data has shown losartan to be as effective as other antihypertensive agents in the treatment of elderly patients with hypertension. Treatment with losartan is, therefore, an option for first-line therapy in all patients with hypertension, and in those who are not well managed with, or who are intolerant of, their current therapy. Morbidity and mortality data from one study show that losartan has potential in the treatment of heart failure.

CRD commentary
This was a long review which also contained information about the pharmacological properties of losartan. The search strategy was defined clearly and was adequate, although the Cochrane Library and grey literature sources were not searched. Thus, it is possible that relevant studies may have been missed. Other methods of the review were not recorded. The authors do not say how studies were selected, data were extracted or how quality was assessed. Some details of the study characteristics were given in the narrative of the review, whereas, for clarity, the use of tables may have been more appropriate. In discussing the results of the review in narrative form, the authors acknowledged the differences in the studies, and the limited amount of information relevant to various aspects of the review. Existing trials were small with apparent heterogeneous groups of patients, different clinical backgrounds and concomitant therapies. In view of these comments, caution should be exercised when interpreting the results of this review.

Implications of the review for practice and research
Practice: The authors state that losartan is an option for first-line therapy in all patients with hypertension, particularly those who are not well managed by, or are intolerant to, their current therapy. Losartan has potential in the treatment of heart failure.

Research: The authors did not state the implications for further research, however they did state that there are few reports of long-term trials of losartan in the elderly.

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