Angiotensin II antagonists for hypertension: are there differences in efficacy

Authors' objectives
To compare the antihypertensive efficacy of available drugs in the new angiotensin-II-antagonist (AIIA) class.

Searching
MEDLINE and Current Contents were searched through to October 1998.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind placebo-controlled trials of AIIAs; randomised controlled trials (RCTs) comparing AIIAs with other established classes of antihypertensive therapy (such as angiotensin-converting enzyme inhibitors, calcium-channel blockers, beta-blockers, and combinations of AIIA with thiazide diuretics, mainly HCTZ); and RCTs in which the antihypertensive efficacy of different AIIAs were compared directly with each other.

Specific interventions included in the review
The inclusion criteria specified that trials have a treatment duration of at least 4 to 6 weeks with starting dose of AIIA before dose titration, then at least another 4 to 6 weeks until final assessment. They were also required to have used one the following dosing regimens: titration as needed (or elective titration), either from starting dose to maximum dose of monotherapy, or from starting dose of monotherapy to a combination of starting dose AIIA with low-dose hydrochlorothiazide (HCTZ); parallel-group comparisons of various doses as monotherapy or AIIA-HCTZ combinations; and forced titration of dose. Trials were excluded if they examined use of AIIA after demonstration of lack of response with a drug from another class, or if they used a dose of AIIA not recommended in the product label.

Specific AIIAs included in the review were: losartan (50 mg, 50 to 100 mg); valsartan (80 mg, 80 to 160 mg); irbesartan (150 mg, 150 to 300 mg); candesartan (8 mg, 8 to 16 mg); losartan (50 mg) plus HCTZ (12.5 mg); valsartan (80 mg) plus HCTZ (12.5 mg); and candesartan (8 mg) plus HCTZ (12.5 mg).

Participants included in the review
Patients with mild-to-moderate hypertension (diastolic blood-pressure 95 to 115 mm Hg) with no concomitant diseases.

Outcomes assessed in the review
Mean blood-pressure reduction (clinical measurement of blood-pressure using sphygmomanometer and cuff). Studies using only ambulatory blood-pressure monitoring were excluded. Final assessment had to take place 4 to 6 weeks after the treatment period had ended.

How were decisions on the relevance of primary studies made?
In order to be included in the meta-analysis, the study had to satisfy the described criteria. The authors do not state how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

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: AIIA dose, first author, diastolic blood-pressure (mmHg), systolic blood-pressure (mmHg), and responders (%).
Methods of synthesis
How were the studies combined?
To calculate the mean blood-pressure reduction, the pooled data were weighted for the study size.

Data are presented as mean values with 95% confidence intervals (CIs) calculated from the mean and standard deviation (SD). Where no SD was reported in the original publication, an assumed SD was calculated from the weighted average of the same drug and dose. Comparisons of weighted average changes in blood-pressure were compared using a t-test with correction for multiple comparisons.

How were differences between studies investigated?
The pooled analysis was grouped into three separate categories: AIIA monotherapy at starting dose; AIIA monotherapy with elective or forced dose titration from the starting to the maximum dose; and starting dose AIIA-HCTZ combinations.

Results of the review
Forty-three RCTs were included (n=11,281). The number of participants in the 3 different treatment regimens were as follows: AIIA monotherapy starting dose, n=4,732; AIIA monotherapy titration, n=4,275; and starting dose AIIA- HCTZ combination, n=2,274.

The absolute, weighted average reductions in diastolic (8.2 to 8.9 mmHg) and systolic (10.4 to 11.8 mmHg) blood-pressure (not placebo-corrected) for AIIA monotherapy were comparable for all AIIAs. Responder rates for AIIA monotherapy were 48 to 55%. Dose titration resulted in slightly greater blood-pressure reduction and an increase in responder rates to 53 to 63%.

AIIA-HCTZ combinations produced substantially greater reductions in systolic (16.1 to 20.6 mmHg) and diastolic (9.9 to 13.6 mmHg) blood-pressure than AIIA monotherapy, and responder rates were 56 to 70%.

Authors’ conclusions
This comprehensive analysis shows comparable antihypertensive efficacy within the AIIA class, a near-flat AIIA-dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ.

CRD commentary
Overall, the methodology of this review was adequate and the review did address a clear question. The literature search was poorly described with omission of search terms and exact dates. Only two databases were searched, handsearching was not undertaken and no attempt was made to locate unpublished data. There is, therefore, a possibility of publication bias. There was no attempt to assess the validity of the included studies, and the process of data extraction was not described clearly. Study details were incompletely presented as some important study characteristics were missing, e.g. participant characteristics and setting, length of follow-up, and number of drop-outs. The individual studies appeared to have been synthesised with appropriate techniques, but there was no formal assessment of heterogeneity within the three categories of pooled results.

The authors’ conclusions seem inappropriately certain and should be approached with caution due to the methodological limitations outlined.

Implications of the review for practice and research
The authors did not state any implications for research and practice.

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