An application of meta-analysis techniques in the evaluation of adverse experiences with antihypertensive agents

Sakai H, Hayashi K, Origasa H, Kusunoki T

Authors' objectives
To assess adverse events (AEs) associated with the use of calcium channel blockers (CCBs) when compared with beta blockers or diuretics.

Searching
MEDLINE (1966-1995), EMBASE (1974-1995), JAPIC-DOC (1978-1995), and JMEDICINE (1978-1995) were searched, the latter two to select relevant Japanese trials. The following search terms were used: 'randomized controlled trials' or 'RCTs in publication type (PT)'; 'essential hypertension'; 'antihypertensive agents'; 'calcium channel blocker'. Equivalent terms for use with the Japanese databases were provided. The authors stated that the full search strategy was available on request.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) published as original articles in medical journals, with treatment and follow-up of four weeks or more.

Specific interventions included in the review
CCBs (lacidipine, diltiazem, nicardipine, nisoldipine, verapamil, tiapamil, nifedipine, isradipine, amlodipine, nisoldipine) compared with beta blockers (bisoprolol, acebutolol, atenolol, propanolol, metprolol, pindolol) and diuretics (hydrochlorothiazide, amiloride, bendrofluazide). The duration of treatment ranged from four weeks to 10 months in trials of CCBs versus diuretics, and from four weeks to five years in trials of CCBs versus beta blockers.

Participants included in the review
Patients with essential hypertension.

Outcomes assessed in the review
AEs associated with antihypertensive therapy, defined as any events reported in the articles without consideration of causality, were assessed. Serious AEs were defined as death, withdrawal from treatment, or any AE resulting in cessation of treatment. The AE terms reported in the original articles were used (i.e. re-categorisation was not carried out). Both overall symptoms and incidence of specific symptoms (headache, flushing, dizziness, vertigo, bradycardia, tachycardia, oedema, fatigue, gastrointestinal upset, nausea, dyspnoea, peripheral ischaemia, diminished libido, and nightmare) were assessed.

How were decisions on the relevance of primary studies made?
Two independent reviewers examined the title and summary of each article, and the same two reviewers further examined the complete text of each selected article. Disagreements were resolved by discussion.

Assessment of study quality
Method of randomisation; blinding; sample size; reporting method(s) for adverse events; and method(s) of monitoring AEs. Two independent reviewers examined each article. Disagreements were resolved by discussion.

Data extraction
Two independent reviewers examined each article and disagreements were resolved by discussion. The following data were extracted: method of randomisation; blinding; therapeutic class of drugs; sample size; duration of treatment;
primary end point; reporting method(s) for all adverse events; method(s) of monitoring AEs; and reported incidence of AEs.

**Methods of synthesis**

How were the studies combined?
The summary risk difference and risk ratio with associated 95% confidence intervals (CIs) of incidence of AEs between CCBs and beta-blockers or diuretics were calculated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.1).

How were differences between studies investigated?
Heterogeneity was investigated using the chi-squared test. Subgroup analysis was conducted according to treatment duration (more or less than 12 weeks). The effect of several variables (country, study size, treatment duration, drug, country*drug, study size*drug, treatment duration*drug) on the pooled risk difference was assessed using logistic regression.

**Results of the review**

Overall, 28 RCTs were included (n=3,073). There were nine trials of CCBs versus diuretics (n=751) and 19 trials of CCBs versus beta blockers (n=2,322).

There was no significant difference in the total incidence of serious AEs between CCBs and diuretics (p=0.254) or between CCBs and beta blockers (p=0.604). Patients treated with CCBs had 0.14% fewer serious AEs compared with patients treated with diuretics (95% CI: -2.42%, 2.7%). Patients treated with CCBs had 0.29% more serious AEs compared with patients treated with beta blockers (95% CI: -1.27%, 1.84%).

The pooled risk of CCBs for the subgroup with treatment durations of less than or equal to 12 weeks was 0.58% lower than that for diuretics (95% CI: -4.01, 5.17%). The pooled risk of the patients treated with CCBs was 0.31% higher than that of those treated with beta blockers (95% CI: -1.4%, 2.09%). However, for 12 weeks or longer, the pooled risk of serious AEs of CCB-treated patients was 2.27% higher than that of those treated with diuretics (95% CI: -3.46, 7.99%). The pooled risk of the patients treated with CCBs was 0.94% lower than beta blockers (95% CI: -1.73%, 3.6%).

Logistic regression: none of the covariates (country, study size, treatment duration, drug, country*drug, study size*drug, treatment duration*drug) significantly affected the pooled risk differences.

Pooled risk measures of AEs by symptoms:

Headache and oedema occurred significantly more frequently in CCB groups. The risk difference between CCBs and diuretics was 7.36% (95% CI: 1.90, 12.81%) for headache and 6.57% (95% CI: 1.29%, 11.84%) for oedema. Flushing occurred 8.75% more frequently with CCBs compared with beta blockers (95% CI: 4.00%, 13.49%). Tachycardia and oedema occurred in the CCB groups slightly more frequently than beta blockers. The rate differences between the two groups were 0.79% (95% CI: -0.31%, 1.88%) for tachycardia and 2.83% (95% CI: -0.11%, 5.77%) for oedema.

**Authors' conclusions**
The authors stated that CCBs were as safe as beta blockers and diuretics with respect to the total incidence of serious AEs; however, the specific profile of safety was different among these drugs. Since the results of the review remained robust when subgroup analyses were performed, the authors concluded that the review findings were reliable and generalisable. However, they drew attention to several limitations of the review: lack of safety data in the trials; possibility of publication bias; non-standardised reporting of AEs across the trials; non-standardised reporting of AEs among different countries; and variation in definitions of serious AEs across trials.

**CRD commentary**
Overall, this is a well-conducted systematic review. Adequate details of inclusion criteria and the search strategy are...
provided, with further information on the latter available on request from the authors of the review. Although the authors stated that study validity was assessed, the results of this are not presented, and this would have been useful. Some details of the included trials are provided in tables and plots. The methods used for data synthesis are appropriate and a test for heterogeneity was performed. Details are provided of the review process and it appears that most of the decisions about study selection, assessment and data extraction were performed independently by two reviewers. The authors’ conclusions appear to follow on from the results of the review, and the authors rightly highlight some possible limitations to the findings.

**Implications of the review for practice and research**
Practice: The authors do not state any implications for practice.

Research: The authors recommend that all RCTs with safety data be published so that their information can be accessed by other investigators.

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