Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema

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CRD summary
This review concluded that in patients with hypertension, calcium channel blockers with renin-angiotensin system blockers reduced the risk of peripheral oedema compared with monotherapy. The authors’ conclusions appear to reflect the evidence, but lack of reporting on details of individual trials mean these conclusions should be interpreted with caution as the results may not be generalisable.

Authors' objectives
To evaluate the risk of peripheral oedema in patients who received calcium channel blocker/rennin-angiotensin system combination therapy compared to calcium channel blocker monotherapy and to evaluate the difference in reducing the risk for peripheral oedema among renin-angiotensin system blockers.

Searching
Peer-reviewed published trials were identified through a search of PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from 1980 to March 2010. There were no language restrictions. Reference lists of identified studies were searched to for eligible articles. Search terms were reported. Trials published as abstracts only were excluded.

Study selection
Randomised controlled trials that compared calcium channel blockers with the combination of calcium channel blocker plus an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB) or a direct renin inhibitor in hypertensive patients were eligible for inclusion. Studies were required to have follow-up duration of at least four weeks and include a sample size of at least 100 participants. The primary outcome was risk of peripheral oedema.

In most studies peripheral oedema was either self-reported or reported in patient questionnaires; in a few trials ankle oedema was measured. Patients were followed up for an average of 9.2 weeks (±3 weeks). The average age of participants was 56 years (±5 years).

Two reviewers independently selected studies for inclusion. Disagreements were resolved through consensus.

Assessment of study quality
Methodological quality of studies was assessed using Cochrane Collaboration methodology, specifically criteria of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. Studies with high or unclear risk of bias for any of the first three criteria were deemed low quality.

The authors did not state how many assessors performed the assessment.

Data extraction
Two independent reviewers extracted data into a standard data extraction form that included mean baseline blood pressure, incidence of peripheral oedema and withdrawal rates due to peripheral oedema. The risk ratio (RR) was derived from data in each study.

Disagreements were resolved by consensus.

Methods of synthesis
Pooled risk ratios and corresponding 95% CIs were calculated using a fixed-effect meta-analysis where there was no evidence of statistical heterogeneity. All analyses were conducted by intention-to-treat. Statistical heterogeneity was assessed using $X^2$ and $I^2$ (25% was considered to be low chance of heterogeneity and greater than 75% was considered substantial heterogeneity). A random-effects model was used where $I^2$ was greater than 25% and where $X^2$ was less than 0.05.

Subgroup analysis investigated the three different combination interventions (calcium channel blockers plus ACE inhibitor, ARB and direct renin inhibitor). Sensitivity analyses were conducted to test the influence of individual trials. Publication bias was assessed using funnel plots or Egger’s test.

**Results of the review**

Twenty-five trials (17,206 participants) were included in the review: 15 trials (9,437 participants) compared calcium channel blockers with calcium channel blockers plus an ACE inhibitor; nine trials (7,224 participants) compared calcium channel blockers with calcium channel blockers plus an ARB; one trial (545 participants) compared calcium channel blockers with calcium channel blockers plus aliskiren. Overall study quality was poor. Eight studies were deemed to have a low risk of bias and 17 were considered high risk.

**Risk of peripheral oedema**
Calcium channel blockers in combination with renin-angiotensin system blockers significantly reduced the risk of peripheral oedema compared with calcium channel blocker monotherapy (RR 0.62, 95% CI 0.53 to 0.74; 25 studies). Subgroup analysis showed significant reduction in risk for calcium channel blockers in combination with ACE inhibitors (RR 0.46, 95% CI 0.37 to 0.58; 15 studies) and with ARBs (RR 0.79, 95% CI 0.64 to 0.97; nine studies). There were no significant differences between groups when compared to aliskiren (one study). Egger’s test did not report publication bias ($p=0.27$). Modest heterogeneity was noted when monotherapy was compared with calcium channel blockers in combination with ARBs; excluding one study resolved this.

**Patient withdrawal due to peripheral oedema**
Calcium channel blockers in combination with renin-angiotensin system blockers significantly reduced patient withdrawal due to peripheral oedema compared with calcium channel blocker monotherapy (RR 0.38, 95% CI 0.22 to 0.66; seven studies). Subgroup analysis showed significant reduction in withdrawals for calcium channel blockers in combination with ACE inhibitors (RR 0.42, 95% CI 0.22 to 0.80; six studies) and with ARBs (RR 0.27, 95% CI 0.09 to 0.81; one study). Egger’s test did not report publication bias ($p=0.52$). There was no evidence of heterogeneity.

**Authors’ conclusions**
In patients with hypertension, calcium channel blockers in combination with renin-angiotensin system blockers reduced the risk of calcium channel blocker-associated peripheral oedema compared with monotherapy. ACE inhibitors appeared more efficacious than ARBs, but head-to-head comparisons were needed to prove this.

**CRD commentary**
This review addressed a clear question supported by appropriate inclusion criteria. It did not address selection criteria for patients (other than hypertensive) or report on patient characteristics that may have affected generalisability. A limited number of databases were searched. There were no apparent attempts to identify unpublished data; statistical tests revealed no evidence of publication bias. Suitable methods to minimise risk of reviewer error and bias were reported for study selection and data extraction; it was unclear whether similar methods were employed during study validity.

Results were pooled appropriately using meta-analysis and heterogeneity was assessed. The authors recognised some of the methodological difficulties with the review, specifically differences in the included studies for length of follow-up, patient groups and definitions of peripheral oedema.

The authors’ conclusions appear to reflect the evidence and are likely to be accurate, but limitations around the lack of reporting on details of individual trials mean these conclusions should be interpreted with caution as they may mean that the results are not generalisable.
Implications of the review for practice and research

Practice: The authors did not report any implications for practice.

Research: The authors suggested that head-to-head comparisons of ACE inhibitors with ARBs in reducing calcium channel blocker associated peripheral oedema were required.

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