Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate; a meta-analysis of randomized trials

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CRD summary
The review concluded that incidence of peripheral oedema and patient withdrawal increased with duration of calcium channel blocker therapy up to six months. Rates were lower with both non-dihydropyridines and lipophilic dihydropyridines. Given lack of clarity on quality and potential for bias in the review process, the authors’ conclusions should be considered tentative.

Authors’ objectives
To evaluate the incidence and withdrawal rate of peripheral oedema with calcium channel blockers (CCBs), effect of treatment duration on oedema incidence and compare incidence of oedema among lipophilic dihydropyridine (DHP) CCBs, older traditional DHPs and non-DHPs.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1980 to January 2011. There were no language restrictions. Search terms were reported. Reference lists of retrieved studies were searched.

Study selection
Randomised controlled trials (RCTs) of hypertensive participants that compared CCBs with other agents (including placebo) were eligible for inclusion. Trials were required to have a sample size of at least 100 participants who took CCBs. Trial duration needed to be at least four weeks. Trials had to report data on peripheral oedema. Abstracts, studies of patients with coronary heart disease or heart failure and studies of mibefradil were excluded. Participants in the included studies had a mean age of 56 years and 56% were male. CCBs included amlodipine, nifedipine, diltiazem, felodipine, isradipine, lacidipine, lercanidipine, verapamil, nitrendipine, nisoldipine, barnidipine, manidipine, nicardipine and pranidipine. CCBs were compared with control groups that included placebo and active antihypertensive therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, other CCBs, direct renin inhibitors and thiazides. A broad definition of oedema was used and was mostly assessed by self report; a few trials supplementing self report with a symptom questionnaire and/or measurement by the examiner.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality using the Cochrane Collaboration risk of bias tool; seven criteria were used but the details of these criteria were not reported. For each criterion, studies were described as being at low, unclear or high risk of bias. Composite scores for each study were also defined as low risk (seven of seven criteria at low risk of bias), intermediate risk (six of seven criteria at low risk of bias) and high risk (five or fewer criteria at low risk of bias).

The authors did not state how many reviewers assessed the included studies for quality.

Data extraction
Incidence of peripheral oedema, proportion of withdrawals from treatment, relative risks (RRs) of peripheral oedema and withdrawal due to oedema by different types of CCB and 95% confidence intervals (CIs) were calculated using the intention-to-treat principle.

Two reviewers independently extracted data in duplicate. Disagreements were resolved by consensus.

Methods of synthesis
Studies were combined and the results reported in narrative synthesis for weighted incidence of oedema and withdrawal...
from treatment. Studies were combined in meta-analyses for comparisons between CCBs with a fixed-effect model (when data were homogeneous) or a random-effects model. Subgroup analysis was performed according to duration of therapy, DHPs versus non-DHPs, newer lipophilic DHPs versus traditional DHPs and dose of CCB (high dose versus low dose). Heterogeneity was assessed with the $I^2$ value. Publication bias was assessed by visual examination of funnel plots and use of Begg’s test and Egger’s weighted regression test.

**Results of the review**

One hundred and six studies with 125 comparison arms (99,469 participants) were included in the review. Sixteen trials were at high risk of bias; the others were either low or intermediate risk of bias. Follow-up ranged from one to 66 months; for most trials follow-up was six months or less.

**Incidence of peripheral oedema:** At mean follow-up of 27 weeks and compared to control with a peripheral oedema rate of 3.2% (95% CI 3.1 to 3.3), CCBs were associated with a significantly higher peripheral oedema rate (10.7%, 95% CI 10.6 to 10.9; number of studies not reported). Incidence of peripheral oedema increased with duration of CCB therapy from 2.3% at four weeks to 23.8% at 26 weeks or greater (number of studies not reported).

Dosage of CCB significantly influenced peripheral oedema rates: incidence of oedema was 5.7% (95% CI 5.5 to 5.9) with low-dose CCBs and 16.1% (95% CI 15.9 to 16.3) with high-dose CCBs (number of studies not reported).

Compared to non-DHPs with a oedema rate of 3.1% (95% CI 2.8 to 3.4), DHPs were associated with a significantly higher incidence of peripheral oedema (12.3%, 95% CI 12.2 to 12.5; number of studies not reported). Compared to traditional DHPs, the risk of peripheral oedema with lipophilic DHPs was significantly lower (RR 0.43, 95% CI 0.34 to 0.53; six trials, no heterogeneity).

**Patient withdrawal due to peripheral oedema:** Compared to control with a patient withdrawal rate of 0.5% (95% CI 0.36 to 0.58), CCBs were associated with a significantly higher patient withdrawal rate (2.1%, 95% CI 1.9 to 2.2; 39 trials). Incidence of patient withdrawal increased with duration of CCB therapy from 1% at four weeks to 5.5% with long-term use (number of studies not reported).

Compared to non-DHPs with a withdrawal rate of 0.6% (95% CI 0.35 to 0.85), DHPs were associated with significantly higher withdrawal rates (2.4%, 95% CI 2.2 to 2.5; number of studies not reported). Compared to traditional DHPs, the risk of withdrawal with lipophilic DHPs was significantly lower (RR 0.22, 95% CI 0.12 to 0.40; six trials).

There was no evidence of publication bias.

**Authors’ conclusions**

Incidence of peripheral oedema and patient withdrawal increased with duration of therapy up to six months. Oedema and withdrawal rates were lower with both non-DHPs and lipophilic DHPs.

**CRD commentary**

The review addressed clear research questions. Inclusion criteria appeared appropriate. Several sources were used to search for relevant studies. There were no language restrictions. No attempts were made to find unpublished studies, so publication bias could not be excluded. Data were extracted using an appropriate method. Methods used for study selection and quality assessment were not reported, so reviewer error and bias could not be ruled out.

Studies were assessed for quality using an appropriate risk of bias tool. Overall scores indicated that a minority of studies were at high risk of bias. However, details of the findings were not reported and this made it difficult to determine the influence of potential lack of blinding on outcomes that were mostly self report by participants. Studies had variable follow-up and subgroup analysis was undertaken to look at the outcomes at various follow-up durations. The authors suggested that data were pooled for measuring the outcomes of incidence of oedema and withdrawal from treatment, but details of the analyses were not reported and findings were reported in narrative format. There was no evidence of heterogeneity in the meta-analyses and risk of publication bias by Egger’s test. Overall comparisons of CCBs with control did not distinguish between placebo and active treatment controls, which could have provided useful information.

Given a lack of clarity on quality and potential for bias in the review process, the authors’ conclusions should be
considered tentative.

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

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