Results of a meta-analysis comparing the tolerability of lercanidipine and other dihydropyridine calcium channel blockers

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CRD summary
This review concluded that lercanidipine was associated with a lower risk of peripheral oedema and treatment withdrawal due to peripheral edema when compared with first-generation dihydropyridine calcium channel blockers, but not when compared with second-generation drugs. A degree of caution might be required in interpreting the authors' conclusions given the limited quality of included studies.

Authors' objectives
To compare the efficacy and safety of lercanidipine with other dihydropyridine calcium channel blockers in the treatment of hypertension.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and DARE were searched for English-language studies up to August 2008. An updated MEDLINE search was performed in July 2009. Search terms were reported.

Study selection
Single- or double-blind randomised controlled trials (RCTs) that compared lercanidipine with another dihydropyridine calcium channel blocker (with at least four weeks treatment duration) in patients with mild (140–159/90–99mmHg) to moderate (160–179/100–109mmHg) hypertension were eligible for inclusion. Eligible trials had to report tolerability data. The efficacy outcome reported in the review was reduction in blood pressure. Safety outcomes were incidence of adverse events associated with vasodilation (peripheral oedema, flushing and headache) and rate of withdrawals due to adverse events.

Dosage of lercanidipine in included studies ranged from 5mg/day to 20mg/day. The control arm of included studies was either a first-generation dihydropyridine calcium channel blocker (amlodipine, felodipine and nifedipine) or another second-generation lipophilic calcium channel blocker (lacidipine and manidipine). Treatment duration varied from eight to 104 weeks. Most trials excluded patients with a clinically significant renal or liver function impairment. All trials excluded patients with a major cardiovascular disease. Mean age of included patients ranged from 54 to 74 years. The proportion of females in the included studies ranged from 35% to 100%.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The quality of studies was assessed using the criteria: randomisation; allocation concealment; blinding; loss to follow-up; and intention-to-treat analysis.

Three reviewers independently performed validity assessment.

Data extraction
For continuous outcomes (reduction in blood pressure), data were extracted on means and standard deviations to enable calculation of mean differences and 95% confidence intervals (CIs). For dichotomous outcomes (vasodilators, adverse events), data were extracted on event rates to enable calculation of relative risks (RRs) and 95% CIs. The authors attempted to obtain missing data.

Three reviewers independently performed data extraction.
Methods of synthesis
Studies were combined in a meta-analysis. A random-effects model was used to calculate the pooled RRs with 95% CIs, whilst an inverse variance method was employed to calculate the weighted mean differences (WMDs) with 95% CIs. Statistical heterogeneity was assessed using $X^2$ and $I^2$ statistics. Separate analyses were conducted on the basis of different groups of comparators (first-generation and second-generation calcium channel blockers). Sensitivity analysis was performed by excluding the trial with a large sample size.

Results of the review
Eight RCTs (n=2,034) were included in the meta-analyses. All trials used intention-to-treat analyses for safety outcomes, but only five trials used intention-to-treat analyses for efficacy outcomes. Blinding was inadequately reported in all trials. Allocation concealment was adequate in one trial. Method of randomisation was not reported in most trials. Loss to follow-up was low in all trials.

When studies were pooled, there were no significant differences in reduced blood pressure between lercanidipine and first-generation or second-generation calcium channel blockers.

Compared with first-generation drugs, lercanidipine was associated with a significant reduction in peripheral edema (RR 0.44, 95% CI 0.31 to 0.62; five RCTs), but not in flushing or headache. There were no significant differences in these outcomes between lercanidipine and second-generation drugs.

Compared with first-generation drugs, lercanidipine was associated with a significant reduction in patient withdrawals due to peripheral oedema (RR 0.24, 95% CI 0.12 to 0.47; four RCTs) or due to any adverse event (RR 0.51, 95% CI 0.33 to 0.77; five RCTs). There were no significant differences in these outcomes between lercanidipine and the second-generation drugs.

Significant heterogeneity was observed only in the outcomes of headache ($I^2=63.4\%$) when lercanidipine was compared with first-generation drugs and withdrawals due to any adverse event ($I^2=66.9\%$) when lercanidipine was compared with second-generation drugs. Sensitivity analyses did not materially affect the results.

Authors' conclusions
Lercanidipine was associated with a lower risk of peripheral oedema and treatment withdrawal due to peripheral edema when compared with first-generation dihydropyridine calcium channel blockers, but not when compared with second-generation drugs.

CRD commentary
This review's inclusion criteria were clear. A number of relevant databases were searched. Efforts were made to find published studies. No efforts were made to locate unpublished studies, which introduced potential for publication bias. The decision to restrict the search to English-language studies may have increased the risk of language bias. Steps were taken to minimise biases and errors in the review process by having more than one reviewer independently undertake data extraction and validity assessment; it was unclear whether the study selection process was also performed in duplicate. Relevant criteria were used to examine study quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results. In view of the limited quality of included studies, a degree of caution might be required in interpreting the authors' conclusions.

Implications of the review for practice and research
**Practice:** The authors stated that the findings from this review may have implications for patient persistence and adherence to treatment in practice when prescribing calcium channel blockers for treatment of hypertension.

**Research:** The authors did not state any implications for research.

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