Effect of calcium antagonists on plasma norepinephrine levels, heart rate, and blood pressure

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Authors' objectives
To evaluate the effects of calcium antagonists on sympathetic activity in hypertensive patients.

Searching
MEDLINE was searched for trials published in the English language between 1975 and May 1996, using the terms 'calcium channel blockers' or 'calcium antagonists', 'sympathetic nervous system', and 'catecholamines'.

Study selection
Study designs of evaluations included in the review
Clinical studies (no further details were provided) were included. Studies that did not include pre- and post-treatment blood-pressure and NE levels were excluded.

Specific interventions included in the review
Calcium antagonists including the following: phenyl alkylamines, e.g. verapamil; benzothiazepines, e.g. diltiazem and dihydropyridines; nifedipine; felodipine; nitrendipine; clentiazem; nicardipine; and nisoldipine. Short-acting (SA) calcium antagonists, given twice or more daily, were compared with long-acting (LA) calcium antagonists, given once daily. The route of administration was oral, sublingual or intravenous. The duration of treatment was 1 week to 12 months for SA calcium antagonists, and 2 weeks to 12 months for LA calcium antagonists.

Participants included in the review
Men and women with essential hypertension. The mean age of the participants in the studies ranged from 33 to 67 years.

Outcomes assessed in the review
The outcomes assessed were plasma norepinephrine (NE) levels, heart rate and blood-pressure. For some studies, these outcomes were estimated from the figures. Since NE levels were measured using different methods, the change in NE levels was used as an index of change in sympathetic activity.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors 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 authors performed the data extraction. Data were extracted on the following: the number of participants (men or women); age; hypertensive drug class; the dosage and administration of each drug used; the duration of treatment; pre- and post-treatment systolic, diastolic and mean arterial pressure; heart rate; and levels of NE.

Methods of synthesis
How were the studies combined?
The means and standard errors were calculated for each study. All data of the same drug class, and of a similar duration of treatment, were combined and weighted according to the number of patients in the studies. A factorial
analysis of variance was used to compare the effects of different classes and different formulations of calcium antagonists on sympathetic stimulation. Pearson's correlation ($r$) was used to test the relation between changes in NE levels and changes in blood-pressure and heart rate. A p-value of less than 0.05 defined statistical significance.

How were differences between studies investigated?
No test for heterogeneity was performed. The sources of heterogeneity were not investigated.

Results of the review
Sixty-three studies, with a total of 1,252 participants, were included. Twenty-eight studies ($n=343$) reported the acute effects of SA calcium antagonists, 46 studies ($n=631$) reported the long-term effects of SA calcium antagonists, and 20 studies ($n=278$) reported the effects of long-term treatment with LA calcium antagonists. The duration of treatment ranged from 1 week to 12 months.

Acute effect of SA calcium antagonists (28 studies, 343 participants).

Three studies used verapamil, one study used diltiazem, and 24 studies used dihydropyridines. The mean arterial pressure decreased in all studies by $13.7\%$ (plus or minus, +/- $1.1$; range: $3.5$ to $30.7$); the decrease was similar for dihydropyridines and non-dihydropyridines. Heart rate increased in all studies by $13.7\%$ ( +/-$1.4$; range: $0$ to $29.5$); the increase was similar for dihydropyridines and non-dihydropyridines. NE levels increased in all studies except in the one that used diltiazem. The increase in NE levels was more pronounced after dihydropyridine (31.9 +/- 2.1%) than after non-dihydropyridine administration (9.2 +/- 6%), ($p<0.05$). In the studies using dihydropyridines, the change in NE levels was related to the change in heart rate ($r=0.59$, $p<0.01$), and was inversely related to the change in mean arterial pressure ($r=0.46$, $p<0.05$).

Long-term effects of SA calcium antagonists (46 studies, 631 participants).

Three studies used verapamil, 6 studies used diltiazem, and 37 studies used dihydropyridines. The mean arterial pressure decreased in all studies by $14.7\%$ ( +/-$0.6$; range: $4.4$ to $27.0$); the decrease was similar for dihydropyridines and non-dihydropyridines. Heart rate increased by $3.4\%$ ( +/-$0.9$) after dihydropyridine administration, and decreased by $5\%$ ( +/-$1.2$) after non-dihydropyridine administration ($p<0.001$). NE levels increased by a similar extent after dihydropyridine administration, but not related to either the change in heart rate or the change in mean arterial pressure.

Comparison between acute and long-term effects of SA calcium antagonists.

The mean arterial pressures decreased similarly during acute and long-term treatment. However, while acutely-administered calcium antagonists increased the heart rate, long-term treatment with calcium antagonists resulted in little change in heart rate ($p<0.001$). The increase in NE levels was less pronounced after long-term treatment with SA agents than during acute treatment ($p=0.09$).

LA calcium antagonists (20 studies, 278 participants).

Five studies used verapamil, 2 studies used diltiazem, and 13 studies used dihydropyridines. The mean arterial pressure decreased similarly after dihydropyridine (16.8 +/- 2.9%) and after non-dihydropyridine (11.2 +/- 1.2%) administration. Heart rate remained unchanged after dihydropyridine administration, but decreased by $7.1\%$ ( +/-$1.8$) after non-dihydropyridine administration ($p<0.001$ between the groups). NE levels increased by $14.5\%$ ( +/-$5$) after dihydropyridine administration, but decreased by $20.7\%$ ( +/-$9.8$) after non-dihydropyridine administration ($p<0.001$ between the groups).

Comparison between SA and LA calcium antagonists.

LA and SA agents decreased arterial blood-pressure by the same magnitude (14.8%). SA agents increased heart rate slightly (1.7%), whereas LA agents had little effect on NE levels (+2.1 +/- 6.1%). Unlike the SA drug, LA verapamil decreased NE levels ($p<0.001$). LA verapamil (GIST formulation) decreased blood-pressure more than the SA drug ($p<0.05$), without affecting the heart rate and NE levels ($p>0.05$).
Authors' conclusions
SA and LA calcium antagonists had distinctively different effects on haemodynamic status and NE levels. SA calcium antagonists consistently led to an increase in NE, regardless of their molecular structure (dihydropyridine or non-dihydropyridine) and the duration of therapy (acute effect versus long-term therapy). The only difference observed with long-term therapy was that SA non-dihydropyridine compounds decreased the heart rate significantly, compared with SA dihydropyridines.

CRD commentary
This review assessed the effects of SA and LA calcium antagonists in patients with essential hypertension. The search strategy was limited, and studies may have been missed. No details were provided as to the methods of the review, e.g. how the data were extracted, and how decisions were made as to the relevance of the studies. Although a large number of studies were included (63 studies involving 1,252 participants), no details of the study designs were provided, and the validity of the studies was not assessed. Furthermore, the effectiveness of the drugs was not assessed by direct comparisons with either a placebo or another drug. The conclusions of this review should be interpreted with extreme caution due to methodological limitations.

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

Bibliographic details

PubMedID
9399721

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Blood Pressure /drug effects; Calcium Channel Blockers /therapeutic use; Clinical Trials as Topic; Dihydropyridines /therapeutic use; Diltiazem /therapeutic use; Dose-Response Relationship, Drug; Drug Administration Routes; Follow-Up Studies; Heart Rate /drug effects; Humans; Hypertension /blood /drug therapy /physiopathology; MEDLINE; Middle Aged; Norepinephrine /blood; Retrospective Studies; Time Factors; Verapamil /therapeutic use

AccessionNumber
11998000017

Date bibliographic record published
30/11/1999

Date abstract record published
30/11/1999

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.