A systematic review and meta-analysis of the incidence of cancer in randomized, controlled trials of verapamil


Authors' objectives
To assess the incidence of cancer in patients receiving verapamil for the treatment of hypertension, angina pectoris or cardiac arrhythmias.

Searching
Medlars was searched from 1966 to October 20, 1996 for trials conducted in humans, using the MeSH term 'verapamil'. During the course of the project, Current Contents was also searched on a weekly basis. The searches were limited to papers published in the English language. The reference lists of all the retrieved clinical trials and review articles were also examined, and an attempt was made to obtain unpublished information from the sponsors on the incidence of cancer in major clinical trials of verapamil.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials with a minimum of 10 patients were eligible. The minimum length of treatment was 7 days.

Specific interventions included in the review
Oral verapamil (any formulation, any dosages) for at least 7 days with at least one concurrent control arm that used no treatment, placebo or non calcium-channel blocker active drug(s).

The specific interventions included in the review were verapamil, beta-blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates, anti-arrhythmics, placebo and no treatment. Verapamil was administered by either standard-release at prescribed daily doses ranging from 120 to 480 mg, or by delayed-release at a prescribed daily dosage ranging from 60 to 540 mg.

Participants included in the review
Patients with hypertension (not emergencies), stable angina pectoris (effort angina), Prinzmetal's (rest, vasospastic) angina, or cardiac arrhythmias.

Most patients (73%) were men. The mean age of the patients ranged from 41.2 to 68.6 years.

Outcomes assessed in the review
The outcomes assessed were new cancers, cancer deaths and all deaths.

How were decisions on the relevance of primary studies made?
The retrieved abstracts and papers were initially screened to exclude trials that did not report human clinical trial data. The remaining abstracts and full papers were then screened for eligibility, according to the project inclusion criteria. One research analyst and one physician screened all the abstracts and papers for eligibility. The final eligibility was determined by reconciling differences in selected trials by referring back to the full reports.

Assessment of study quality
The studies were assessed using the quality scale of Jadad et al. (see Other Publications of Related Interest). The scores ranged from 1 to 5. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.
Data extraction
Two reviewers (one physician and one research analyst, or two physicians) extracted the data from each study separately using data extraction forms developed for the project. These forms were then cross-checked against one another by the two reviewers, and any differences were resolved by referring to the original paper. Differences that could not be resolved easily were referred to an additional physician reviewer.

The patient denominators were reported to be the number randomised (intention to treat) in all but three trials. In the three exceptions, the only numbers available were those analysed for efficacy (the total number of patients was 174).

Methods of synthesis
How were the studies combined?
The meta-analysis was conducted using two approaches: the Mantel-Hanzel fixed-effect model and the random-effects model. The outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). However, only the ORs from the more conservative random-effects models were reported, since those derived using the fixed-effect models were similar. Verapamil was compared with other active controls, and with placebo, in separate analyses for cancer and cancer deaths combined, and for any death.

How were differences between studies investigated?
Statistical heterogeneity was assessed using Cochran's Q statistic. Since trials reporting cancers, cancer deaths, or any deaths were of longer duration than those not reporting these data, the sensitivity analysis was performed using trials with a duration of at least 24 weeks.

Results of the review
There were 39 randomised, parallel-group design trials (11,201 patients) included in the review. Nine trials (n=5,868) were in patients with stable angina pectoris, 6 (n=608) were in participants with cardiac arrhythmias, and 24 (n=4,725) were in patients with hypertension.

For cancer and cancer death, the OR was 1.20 (95% CI: 0.60, 2.42, p=0.61) for verapamil versus active controls, and 0.73 (95% CI: 0.39, 1.39, p=0.34) for verapamil versus placebo. For any deaths, the OR was 1.13 (95% CI: 0.70, 1.82, p=0.62) for verapamil versus active controls, and 0.85 (95% CI: 0.71, 1.00, p=0.06) for verapamil versus placebo. None of the tests for heterogeneity were significant. The results of the sensitivity analysis were similar to those of the main analyses.

Authors' conclusions
This systematic review and meta-analysis of the incidence of cancer reported in randomised, clinical trials of verapamil failed to demonstrate an increased risk in patients receiving verapamil, compared with control patients receiving either active drugs or placebo. Whereas an association is not apparent in the published literature, this analysis should not be over interpreted as the final word on the question of the hazards of calcium-channel blockers. Instead, it should be viewed as another piece of evidence to take into account when considering the safety of these agents, until such time as additional long-term, apparently powered trials are completed.

CRD commentary
This was a thorough review that was conducted in a rigorous manner using specific inclusion criteria, with a clear quality assessment of the included studies.

The authors’ conclusions appear to follow from the results presented.

Implications of the review for practice and research
Larger long-term trials to provide further information are necessary. The authors note that these are now under way.
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