Serotonin antagonists for the treatment of opioid-induced nausea and vomiting in non-surgical patients

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CRD summary
The authors concluded that the evidence for the use of serotonin antagonists in treating opioid-induced nausea and vomiting in non-surgical patients was limited. Some benefits were reported, but only two trials in very disparate populations could be included. The review had methodological limitations and relevant studies may have been overlooked, but the conclusions are appropriate for the data presented.

Authors' objectives
To assess the effectiveness of serotonin (5-hydroxytryptamine) antagonists for the treatment of opioid-induced nausea and vomiting in non-surgical patients.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews were searched for relevant studies. Search terms were reported, but the dates of the search were not given and the search was restricted to English-language articles. Reference lists of selected studies were also searched.

Study selection
Studies were eligible if they were randomised controlled trials (RCTs), non-randomised trials, or observational studies of a serotonin antagonist used in the control of nausea or vomiting in non-surgical adult patients receiving opioids for pain. Outcomes were the control of nausea or vomiting or the need for rescue anti-emetics. Studies were excluded if they were in a palliative setting or if they were of post-surgical patients.

Two RCTs were included and both studied the effects of ondansetron. One trial included patients with acute or chronic pain (back or neck pain, fractures, other musculoskeletal pain, renal colic, etc.) and compared 8mg or 16mg of intravenous ondansetron with placebo. The other trial included patients with cancer pain and compared 24mg of oral ondansetron given once daily with 10mg oral metoclopramide given three times a day or placebo.

Titles retrieved in the electronic search were screened and checked against the inclusion criteria. Any uncertainties about the eligibility of a study for inclusion were discussed with a research pharmacist. The authors did not state how many reviewers performed the selection.

Assessment of study quality
The quality of the studies was assessed according to the criteria of the Centre for Reviews and Dissemination. Any uncertainties about the quality of a study were discussed with a research pharmacist.

Data extraction
The authors did not state how the data were extracted for the review, nor how many reviewers performed the data extraction. The efficacy data from the two RCTs were recorded and expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Methods of synthesis
The ORs for complete control of vomiting, complete control of nausea, and need for less rescue anti-emetics were summarised in a meta-analysis, but the details of methodology were not stated. Heterogeneity was assessed.

Results of the review
Two RCTs were included, with a total of 612 patients. The trials were judged to be good quality, but one of them did not state the method of randomisation. The trial authors had difficulties recruiting patients and thus the trials had power deficits.
In the trial using intravenous ondansetron in patients with acute or chronic pain (n=520 patients), both 8mg and 16mg of ondansetron were more effective for complete control of vomiting than placebo, while only the 16mg dose was more effective for complete control of nausea. There was no significant difference between the two doses in terms of control of vomiting. There was no significant difference in pain between the groups and patient satisfaction was better with ondansetron than with placebo.

In the trial of oral ondansetron in patients with cancer pain (n=92) there was no significant difference between ondansetron, metoclopramide, or placebo in control of vomiting or nausea, or in requirement of rescue anti-emetics. Similarly, there was no significant difference in pain scores or satisfaction between groups.

Overall, the pooled data showed significantly more complete control of vomiting at 24 hours with ondansetron (OR 2.21, 95% CI 1.59 to 3.08), more complete control of nausea (OR 2.19, 95% CI 1.26 to 3.81), and less need for rescue anti-emetics (OR 0.48, 95% CI 0.34 to 0.69). The incidence of adverse events was low and comparable to placebo. The most common adverse events were headache and dizziness. There was no statistically significant heterogeneity.

**Authors’ conclusions**

There was limited evidence to support the use of serotonin antagonists, but they might be useful for treating opioid-induced nausea and vomiting in non-surgical patients and their side-effect profile was favourable.

**CRD commentary**

This systematic review addressed a clear research question and was supported by appropriate inclusion criteria. However, the methods used to select studies, extract data and assess quality may have resulted in reviewer error and bias and limited descriptions were provided. The literature search included relevant databases, but the dates of the search were not stated and only studies published in English were included, which could have resulted in publication and language bias. Descriptions of the included studies and of study participants were sparse. Only two trials with very different populations and different serotonin antagonist regimens were included and a statistical summary of these may not have been appropriate. Trials were reported to be good quality, but it was also stated that they had a power problem due to difficulties in recruiting patients.

The authors’ cautious conclusions reflect the limited data, but it is unclear to what extent all the relevant data were identified.

**Implications of the review for practice and research**

**Practice:** The authors made no specific recommendations for practice.

**Research:** The authors stated that more studies were needed to establish the role of serotonin antagonists for opioid-induced nausea and vomiting in non-surgical patients.

**Funding**

Not stated.

**Bibliographic details**


**Original Paper URL**


**Indexing Status**

Subject indexing assigned by CRD
MeSH
Analgesics, Opioid; Humans; Nausea; Receptors, Serotonin, 5-HT3; Serotonin Antagonists; Vomiting

AccessionNumber
12009107557

Date bibliographic record published
11/11/2009

Date abstract record published
17/03/2010

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.