Effect of prophylactic 5-HT3 receptor antagonists on pruritus induced by neuraxial opioids: a quantitative systematic review

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CRD summary
The review assessed the efficacy of prophylactic 5-HT3 receptor antagonists on neuraxial opioid-induced pruritus in patients having surgery or in labour. The authors concluded that these agents may prevent pruritus and postoperative nausea and vomiting. The review was well conducted and the conclusions appropriate, but the suggestion of publication bias made the reliability of the conclusions unclear.

Authors' objectives
To assess the efficacy of prophylactic 5-hydroxytryptamine subtype 3 (5-HT3) receptor antagonists on neuraxial opioid-induced pruritus in surgical or labour settings.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled trials were searched without language restriction for relevant studies published between January 1966 and May 2007. Search terms were reported. Reference lists of retrieved articles were searched.

Study selection
Prospective randomised placebo controlled double blind trials assessing the efficacy of single injection 5-HT3 receptor antagonists in adults in conjunction with spinal and/or epidural opioids were eligible for inclusion. Trials were required to have a quality assessment score (Oxford Validity Scale) of 3 or more. Only surgical or labour settings were considered. The primary outcome for the review was incidence of pruritus in the first 24 hours after surgery. Other eligible outcomes included assessments of the severity or request for treatment of pruritus and incidence, severity or request for treatment for postoperative nausea and vomiting (PONV). Studies were excluded if 5-HT3 receptor antagonists were used as a curative treatment or if used with other agents.

In the included studies, settings included Caesarean section, various other types of surgery and labour and opioids included water-soluble opioids (morphine alone or in combination) or lipid-soluble opioids (fentanyl and sufentanil) in various doses. In most studies 5-HT3 therapy was ondansetron, 4 mg and/or 8 mg or 0.1 mg kg⁻¹ (tropisetron, granisetron and dolasetron were also used).

Two reviewers independently assessed the studies for inclusion, unblinded to authors and results. Discrepancies were resolved by discussion with a third reviewer.

Assessment of study quality
Studies were scored by the Oxford Validity Scale (maximum of 5 points) on three items, which included randomisation (present; described and appropriate), double-blinding (reported; described and adequate) and completeness of patient follow up (numbers and reasons for withdrawal).

Two reviewers independently assessed the validity of studies. Discrepancies were resolved by discussion with a third reviewer.

Data extraction
Data were extracted on pruritus and postoperative nausea and vomiting. Authors were contacted where necessary for missing data.

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.
Methods of synthesis
Pooled odds ratios (OR) for dichotomous data and weighted mean differences (WMD) for continuous data, together with 95% confidence intervals (CIs), were calculated using a fixed-effects model. If heterogeneity was significant (p<0.1) when assessed by the Cochran Q test, random-effects analyses were performed. Where results were significant, number needed to treat (NNT) was calculated for dichotomous data. Subgroup analyses were performed according to whether patients received hydrosoluble opioids alone, hydrosoluble opioids together with lipid-soluble opioids or lipid-soluble opioids alone. Subgroup analysis was also undertaken for patients undergoing Caesarean section. A funnel plot was constructed to assess whether studies were affected by publication bias.

Results of the review
Fifteen trials were included (n=1,337, sample sizes ranged from 20 to 120 patients). The median quality score was 4 out of a maximum of 5. All studies were published in or after 1999. The funnel plot of the primary outcome was not symmetrical around the mean, so publication bias could not be ruled out.

5-HT3 antagonists significantly reduced the incidence of pruritus from 78 per cent to 66 per cent overall (OR 0.44, 95% CI: 0.3, 0.7, p=0.0002), representing a number needed to treat of six (95% CI: 4, 14). Subgroup analysis found that this benefit was in patients receiving morphine opioids and not with lipid-soluble opioids. 5-HT3 antagonists also significantly reduced the treatment request for pruritus (OR 0.58, 95% CI: 0.4, 0.8, p=0.0003) and intensity of pruritus (WMD -0.35, 95% CI: -0.6, -0.1, p=0.007). 5-HT3 antagonists significantly reduced the incidence of postoperative nausea and vomiting (Peto OR 0.43, 95% CI: 0.3, 0.6, p<0.00001), intensity of postoperative nausea and vomiting (WMD -0.12, 95% CI -0.2, 0.0, p=0.05) and need of rescue treatment (OR 0.42, 95% CI: 0.2, 0.9, p=0.02).

Authors' conclusions
5-HT3 receptor antagonists may be an effective strategy in preventing neuraxial opioid-induced pruritus and postoperative nausea and vomiting, particularly when morphine is used.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared appropriate. Several relevant sources were searched to identify potential studies and attempts were made to minimise language bias. However, there was no apparent attempt to locate unpublished material, which meant that relevant studies may have been missed. A funnel plot for the primary outcome was not symmetric about the mean, so publication bias could not be ruled out. Methods were used to minimise bias and reviewer error in the selection of studies and quality assessment. Including only those studies with an Oxford Validity Scale score of 3 or more ensured that low-quality studies were not considered. Details of the methods used to extract data were not reported, so bias during this process could not be ruled out. Significant heterogeneity was found in the overall analyses assessing pruritus and the authors used a random-effects model in the meta-analyses of these outcomes. The review was well-conducted and the authors' conclusions were appropriate. Lack of reporting of some aspects of the review process and the suggestion of a risk of publication bias made the reliability of the conclusions unclear.

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

Research: The authors stated that further large randomised controlled trials were needed to confirm the results of the review, particularly in patients undergoing Caesarean section under spinal anaesthesia with hydrosoluble and lipid-soluble opioids and with 5-HT3 receptor antagonists given before spinal anaesthesia.

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