Meta-analysis: alvimopan vs. placebo in the treatment of post-operative ileus
Tan E K, Cornish J, Darzi A W, Tekkis P P

CRD summary
This review evaluated the efficacy of alvimopan after bowel resection or total abdominal hysterectomy. The authors concluded that alvimopan was beneficial for gastrointestinal recovery and reduced hospital discharge, with no increase in adverse events, compared with placebo. The conclusions appear reliable but it should be noted that they were based on a few studies with few participants.

Authors' objectives
To review the efficacy and safety of alvimopan following bowel resection or total abdominal hysterectomy.

Searching
MEDLINE, EMBASE, and the Cochrane Library were searched from 2001 to June 2006; the search terms were reported. The reference lists of retrieved articles were checked for additional studies. No language restrictions were applied.

Study selection
Specific interventions included in the review
Studies evaluating alvimopan (ADL 8-2698) with clearly reported dose versus placebo were eligible for inclusion. In the included studies alvimopan was given orally at doses of 6 or 12 mg. The first dose of alvimopan was given at least 2 hours before surgery, and subsequently twice daily starting from the day after surgery until hospital discharge or for a maximum of 7 to 10 days after the operation.

Participants included in the review
To be eligible, the studies needed to include patients undergoing bowel resection or total abdominal hysterectomy performed under general anaesthesia. The included studies were in adults undergoing elective bowel resection or total abdominal hysterectomy, who were receiving opioid analgesia post-operatively. Patients using opioid drugs in the week before the operation, as well as patients who had regularly used opioids within 2 weeks before surgery, were excluded.

Outcomes assessed in the review
The outcomes of interest were recovery of gastrointestinal tract and the treatment of emergent adverse events, either gastrointestinal tract related or not. The end points included the composite outcomes of maximum time to flatus, time to first bowel motion and time to tolerance of solid food (GI-3), or passage of stool and tolerance of solid food (GI-2). The secondary outcomes included the time to discharge, time to first bowel motion, and time to tolerance of first solid food. In addition, adverse events during hospitalisation (e.g. post-operative ileus or pruritus) were considered.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed, but the authors did not state how many reviewers performed the validity assessment. The reviewers used a modified version of the Jadad scale, evaluating patient selection, comparability of the study groups, and assessment of the outcomes.
Data extraction
Two reviewers independently performed the data extraction. Data to calculate odds ratios (ORs) for dichotomous variables or log hazard ratios (HRs) and standard errors for survival data, together with the 95% confidence interval (CI), were extracted.

Methods of synthesis
How were the studies combined?
Summary ORs and HRs were calculated using the Mantel-Haenszel random-effects model. Publication bias was visualised using a funnel plot.

How were differences between studies investigated?
The studies were grouped by outcomes, and heterogeneity was evaluated by inspecting the forest plot and by using the chi-squared test and the I-squared statistic.

Results of the review
Five RCTs (n=2,195) were included in the review.

All of the included studies received the highest score on the Jadad scale.

Compared with placebo, alvimopan 12 mg was associated with a significant improvement of GI-3 (HR 1.30, 95% CI: 1.16, 1.45, p<0.001; based on 4 studies), GI-2 (HR 1.61, 95% CI: 1.26, 2.05, p<0.001; 4 studies), time to discharge (HR 1.26, 95% CI: 1.13, 1.40, p<0.001; 4 studies), time to bowel motion (HR 1.74, 95% CI: 1.29, 2.35, p<0.001; 3 studies), and time to first solid food tolerated (HR 1.14, 95% CI: 1.01, 1.30, p=0.04; 3 studies).

Alvimopan 6 mg also significantly improved these outcomes; the effects of both doses were comparable without a clear dose-response curve. There was evidence of significant statistical heterogeneity for G-2 in studies evaluating the 12-mg alvimopan regimen (p=0.01, I-squared 73.7%), and for both G-3 (p=0.01, I-squared 73%) and G-2 (p=0.03, I-squared 65.7%) in studies evaluating the 6-mg alvimopan regimen.

The use of opioid drugs and the visual analogue scores were similar between placebo and alvimopan groups in the 5 trials that reported on these outcomes. Patients receiving alvimopan required reinsertion of the nasogastric tube after surgery less often in 2 out of 3 studies reporting this outcome. There was no difference in adverse events between the alvimopan and placebo groups.

The authors stated that the funnel plot suggested only minimal publication bias.

Authors’ conclusions
The use of alvimopan had significant benefits for gastrointestinal recovery and reduced the length of hospitalisation after major abdominal surgery. The side-effects of alvimopan administration were acceptable.

CRD commentary
The review addressed a well-defined question in terms of the participants, investigations, outcomes and study design. Several databases were searched and some attempts were made to identify unpublished articles; the potential influence of publication bias was assessed. No language restrictions were applied, thereby reducing the risk of language bias. The authors attempted to minimise bias and errors during the review process by carrying out the data extraction in duplicate. It was unclear if the study selection and quality assessment processes were also performed in duplicate, thus reviewer error and bias might have been introduced at these stages.

There was statistical heterogeneity for some of the evaluated outcomes, which makes the decision to combine the studies in a meta-analysis controversial. The authors’ conclusions seem to reflect the data presented but the small number of trials and participants, as well as the lack of reporting of the review process, have to be taken into consideration.
Implications of the review for practice and research
The authors did not state any implication for practice or further research.

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