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The Efficacy of Peripheral Opioid Antagonists in Opioid-Induced Constipation and Postoperative Ileus: a Systematic Review of the Literature

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Eric Schwenk, Alexander Grant, Marc Torjman, Stephen McNulty, and Jaime Baratta have no conflicts of interest to declare.

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been a paid lecturer for AcelRx, Merck, Salix, and Mallinkrodt. None of these companies were involved in any aspect of the development of this manuscript.

Running Title:
Opioid antagonists for constipation and ileus

Abstract (149 words)

Opioid-induced constipation has a negative impact on quality of life for patients with chronic pain and can affect more than a third of patients. A related but separate entity is postoperative ileus, which is an abnormal pattern of gastrointestinal motility after surgery. Non-selective μ-opioid receptor antagonists reverse constipation and opioid-induced ileus but cross the blood-brain barrier and may reverse analgesia. Peripherally acting μ-opioid receptor antagonists target the μ-opioid receptor without reversing analgesia. Three such agents are FDA-approved. We reviewed the literature for randomized, controlled trials that studied the efficacy of alvimopan, methylnaltrexone, and naloxegol in treating either opioid-induced constipation or postoperative ileus. Peripherally acting μ-opioid receptor antagonists may be effective in treating both opioid-induced bowel dysfunction and postoperative ileus but definitive conclusions are not possible due to study inconsistency and the relatively low quality of evidence. Comparisons of agents are difficult due to heterogeneous endpoints and no head-to-head studies.

Introduction

Despite recent focus on the opioid epidemic millions of patients rely on opioids to treat their chronic pain.[1] Opioid-related adverse drug effects are common, especially opioid-induced bowel dysfunction (OIBD), which is a spectrum of symptoms including dry mouth, nausea, vomiting, gastric stasis, bloating, abdominal pain, and opioid-induced constipation (OIC).[2] OIC is especially prevalent, affecting up to 41% of patients taking long-term opioids.[3] A working group of experts recently proposed that OIC be defined as a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency; development or worsening of straining to pass bowel movements; a sense of incomplete rectal evacuation; or harder stool consistency.[4]

Postoperative ileus (POI) is a related but distinct entity from OIC that also involves loss of forward propulsive motion of the gut but in the perioperative setting. A standard POI definition does not exist in the literature, but the authors of one review suggest that it is "an abnormal pattern of gastrointestinal motility, most frequently occurring after abdominal surgery" and encompasses the "interval from surgery until passage of flatus/stool and tolerance of an oral diet."[5] POI has a multifactorial etiology that is shared with OIC, including the surgical stress response,[6,7] the inflammatory response that accompanies bowel manipulation,[6,7,8] and opioids that are both endogenously released by the GI tract[7] and given by clinicians for intra- and postoperative analgesia.[9] Most importantly, POI can be a driver of poor patient satisfaction, increase hospital length of stay, and increase overall hospital costs.[10]

Throughout the hospital physicians will likely encounter patients with one or both of these conditions and need a good working knowledge of the basic mechanisms and therapeutic options that are available to treat these relatively common pathophysiologic states.

Conventional therapies, including fiber, opioid rotation, stool softeners, and laxatives, have limited data to support their use in OIC.[11] They may be used initially with relatively low risk and minimal cost but are unlikely to effectively treat the symptoms alone. Non-specific opioid antagonists can reverse OIC and POI but may reverse analgesia as well.[12] Drugs that specifically block the μ-opioid receptor outside of the central nervous system, collectively known as peripherally acting μ-opioid receptor (PAM-OR) antagonists, have been developed as a possible solution to this problem. PAM-OR antagonists specifically target the μ-opioid receptor in the peripheral nervous system and treat one of the major underlying mechanisms of both OIC and POI. In the United States three such drugs are approved for one of these two indications: alvimopan, methylnaltrexone, and naloxegol.

Currently, alvimopan has approval from the Food and Drug Administration (FDA as a "peripherally acting μ-opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis."[13] Methylnaltrexone was first approved as a subcutaneous injection "for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient"[14] and very recently was approved in the oral formulation for patients with chronic non-cancer pain and OIC.[15] The most recent addition to the PAM-OR

antagonists, naloxegol, has been in clinical use since its approval in 2014 as "an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain."[16] Several randomized trials involving PAM-OR antagonists have recently been published[17,18]; in addition, previous reviews have focused solely on a single agent[19,20] or either OIC[21] or POI[22] but not both. Therefore, an update that discusses strengths and limitations of the evidence is warranted. We conducted a systematic review for randomized, placebo-controlled trials that compared alvimopan, methylnaltrexone, and naloxegol to placebo and had efficacy as the primary endpoint. The subsequent discussion will focus on the evidence for these PAM-OR antagonists in treating OIC and POI.

Methods

We conducted the review protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] During the months of April and May 2016 and again in February 2017, we conducted searches using PubMed and Scopus databases looking for randomized, placebo-controlled trials that studied the efficacy of alvimopan, methylnaltrexone, or naloxegol in patients with OIC or postoperative ileus. The last date searched was February 3, 2017. There were no date limitations placed on the searches in either database. We used the following search protocol in PubMed: (((“alvimopan”[Supplementary Concept] OR “alvimopan”[All Fields]) OR (“methylnaltrexone”[Supplementary Concept] OR “methylnaltrexone”[All Fields]) OR (“naloxegol”[Supplementary Concept] OR “naloxegol”[All Fields])) OR “peripheral opioid antagonist”[All Fields] OR “peripherally acting opioid antagonist”[All Fields] OR (peripheral[All Fields] AND mu[All Fields] AND antagonist[All Fields]) OR (peripheral[All Fields] AND mu[All Fields] AND (“narcotic antagonists”[Pharmacological Action] OR “narcotic antagonists”[MeSH Terms] OR (“narcotic”[All Fields] AND “antagonists”[All Fields]) OR “narcotic antagonists”[All Fields] OR (“opioid”[All Fields] AND “antagonist”[All Fields]) OR “opioid antagonist”[All Fields])) OR “opioid antagonist”[All Fields]) AND (“postoperative ileus” OR “opioid-induced bowel dysfunction”[All Fields] OR “opioid-induced constipation”[All Fields]).

Our search protocol for Scopus included the following: (ALL (alvimopan) OR ALL (methylnaltrexone) OR ALL (naloxegol) OR ALL (peripheral opioid antagonist) OR ALL (peripherally acting opioid antagonist) OR ALL (opioid

antagonist) AND ALL (opioid-induced bowel dysfunction) OR ALL (opioid-induced constipation) OR ALL (postoperative ileus)) AND DOCTYPE (ar) AND (LIMIT-TO(LANGUAGE,"English")).

Inclusion Criteria

Studies that were written in English involving clinical patients who had OIC and were being given either a PAM-OR antagonist or placebo or were given a PAM-OR antagonist or placebo for the purpose of treating or preventing POI were included.

Exclusion Criteria

Studies that examined a PAM-OR antagonist in the setting of experimentally induced OIC (giving healthy volunteers codeine followed by a PAM-OR antagonist, for example) were extracted but included in a separate table and not included in the formal review. Studies that were prospective but did not include a placebo group were excluded, as were studies in which patients were not randomized. Also excluded were post-hoc or subset analyses of clinical trials that had been previously published. When applicable, only the blinded portion of a study was reviewed and analyzed.

Review Protocol and Evidence Grading

Evidence quality was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (see Tables 1 and 2).[24] Using this approach, studies are classified as high, moderate, low, or very low quality of evidence.

All articles were first reviewed independently by ES and AG and assessed for inclusion in the review. If the determination could not be made from reading the article title, the abstract was reviewed, and if ambiguity remained after that, the full article was subsequently downloaded and reviewed. Reference lists from screened articles were searched as well. Discrepancies were resolved by discussion between ES and AG. Articles that met all inclusion criteria but studied OIC treatment in healthy volunteers were not included in the formal review but are shown separately in Table 1.

Results

Study Selection

Initial search of the literature yielded 1,314 articles (Figure 1). Screening of reference lists yielded two additional studies.[25,26] One additional study that was initially excluded because it referred to alvimopan as ADL 8-2698, its investigational name, was later included in the review after confirming that it did in fact study alvimopan (Figure 1).[27] Because of the overlap between PubMed and Scopus databases, there were 158 duplicates. Reasons for exclusion are shown in Figure 1. The two most common reasons for exclusion were that PAM-OR antagonists were not studied (n=588), which primarily applied to Scopus articles, and that the studies were not randomized, controlled trials (RCTs; n=459). A total of 23 studies were included in the final review. The four RCTs that enrolled healthy volunteers were grouped separately and are shown in Table 1.[28-31]

Opioid-Induced Bowel Dysfunction Studies in Healthy Volunteers

Four Phase 1 studies enrolled healthy volunteers and administered a μ-opioid agonist to induce delay in gut transit and then administered a PAM-OR antagonist to evaluate its effects on gut transit time compared to placebo (Table 1).[28-31] In the single study on alvimopan,[30] 12 mg was given along with codeine 30 mg four times a day and alvimopan reversed the codeine-induced delay in gut transit and improved gut transit in patients not given codeine as well.

In one of the studies that enrolled healthy volunteers who were given morphine and then randomly assigned to one of two doses of subcutaneous methylnaltrexone or placebo,[29] both the 0.1 and 0.3 mg/kg doses reversed morphine-induced delay in gut

transit time. Wong et al, however, did not find any difference between subcutaneous methylnaltrexone 0.3 mg/kg and placebo in reducing the codeine-induced delay in gut transit.[31] Yuan et al gave healthy volunteers intravenous methylnaltrexone 0.45 mg/kg after giving them morphine and found that methylnaltrexone prevented 97% of morphine-induced delay in gut transit time.[28]

Opioid-Induced Constipation Studies

A total of 14 RCTs that studied PAM-OR antagonists in the setting of OIC were included in the review (Table 2). All alvimopan studies included patients with non-cancer pain who were given oral alvimopan in either a 0.5- or 1-mg dose. The primary outcome for two studies was the percentage of patients with at least three spontaneous bowel movements (SBMs) per week.[32,33] One study's primary outcome was the mean frequency of weekly SBMs[34] and in another it was the percentage of patients that had a BM within eight hours.[35] When analyzing the primary outcome of the four studies on alvimopan, three showed a positive result for the alvimopan group[32,34,35] and one showed no difference.[33] Study quality was low for all four studies.

The effects of alvimopan on μ-opioid receptors in the central nervous system were minimal. Three alvimopan studies reported no differences in pain scores or opioid consumption between study groups,[32,33,34] while one study described two patients in the 1-mg alvimopan group who had increases in pain but no difference between groups receiving the 0.5-mg dose.[35]

There were seven studies on methylnaltrexone for OIC.[17,18,36-40] Four studies included patients with non-cancer pain only,[18,36,39,40] while the other three enrolled

patients with both cancer and non-cancer pain.[17,37,38] The selected dose for studies with subcutaneous methylnaltrexone was 12 mg in two studies,[39,40] 8 or 12 mg in one study,[17] 0.15 mg/kg in one study, 0.15 or 0.3 mg/kg in one study,[38] and up to 0.365 mg/kg in the study that used intravenous methylnaltrexone.[36] The single study of oral methylnaltrexone included doses of 150, 300, and 450 mg.[18] The primary outcome was positive in all seven studies. In five studies, the primary outcome was achievement of a spontaneous bowel movement (SBM) within 4 hours of receiving the study drug[17,37-383940] Another study had no primary endpoint but reported that laxation occurred within one minute of initiating methylnaltrexone intravenous infusion in 10 of 11 patients.[36] In the single study of the oral formulation, the primary endpoint was the percentage of patients with a mean number of dosing days resulting in a SBM within four hours of dosing. Although this endpoint was greater in both 300- and 450-mg groups, it was lower than the response rate for the subcutaneous formulation.[18] The 450-mg dose had highest efficacy without increasing adverse events. Study quality was moderate for two studies,[17,18] low for three studies,[37-3839] and very low for two studies.[36,40]

In five of the studies, analgesia was preserved based on no differences in pain scores, opioid consumption, or both between treatment groups.[17,37-383940] For oral methylnaltrexone, pain scores did not change from baseline.[18] In the remaining study, pain and opioid use were not assessed but patients reported no change in subjective withdrawal symptoms.[36] In the largest study by Michna et al,[39] rescue laxatives were used by 61.7% of the placebo group versus 38.7% in the daily dosing group and 41.7% in the every-other-day dosing group.

There were two published articles for naloxegol, one of which described a study involving patients with cancer and non-cancer pain[41] while the other studied only non-cancer pain and consisted of two smaller trials.[42] Both studies had positive outcomes for the primary outcome which was a greater number of SBMs per week for both 25- and 50-mg doses in the article by Webster et al[41] and accelerated time to first rescue-free bowel movement (RFBM) for 25 mg in both trials for Chey et al and 12.5 mg in one of two trials.[42] Study quality was moderate for one study[42] and low for the other.[41]

In both naloxegol studies, analgesia was preserved with no differences in pain scores or opioid consumption existing between study groups. The use of rescue laxatives was high in placebo and treatment groups for the study by Chey et al (72.0, 63.4, and 54.7% in study 04 and 70.7, 57.3, and 57.3% in study 05).[42] When comparing naloxegol to oral methylnaltrexone, 50% of patients who received 25 mg of naloxegol had a RFBM within six hours of the first dose, compared to approximately 30% of patients who received 450 mg of oral methylnaltrexone.[18,41] However, the incidence of GI adverse events was greater for naloxegol than for oral methylnaltrexone.

Postoperative Ileus Studies

A total of 10 studies on POI were included in the review (Table 3). Primary endpoints of the studies varied but most used the achievement of either GI-2 recovery (toleration of solid food and first bowel movement) or GI-3 recovery (toleration of solid food and flatus or first bowel movement). Of the eight studies that examined alvimopan, five enrolled patients who underwent major abdominal surgery,[43-47] one included bowel resection,[48] one included patients undergoing total abdominal hysterectomy,[49] and one

included radical cystectomy.[50] Aside from the study by Taguchi et al,[43] which was a Phase I study, four of the other alvimopan studies examined both 6- and 12-mg doses,[44-47] while the remaining three only used 12 mg.[48-50] These doses were three- to six-fold greater than the doses used for OIC. Of note, six alvimopan studies excluded chronic opioid users.[43,45,46,47,48,49] Six studies reported positive results for the primary outcome of accelerated GI recovery (flatus, GI-2, or GI-3),[43,44,45,48,49,50] while two alvimopan studies found no difference between groups,[46,47] although Viscusi et al did report an accelerated time to GI-2 recovery (secondary endpoint) in the alvimopan group for both 6- and 12-mg doses. Study quality was moderate for four studies,[45-48] low for two,[49,50] and very low for one.[43]

Analgesia was preserved in seven of the studies for all groups,[43-50] with the exception of the 6-mg group in one study which demonstrated greater opioid consumption than placebo.[44]

Yu et al[51] studied methylnaltrexone intravenously (IV) for POI at both 12- and 24-mg doses in two identical, parallel-group studies for patients who underwent segmental colectomy. For the primary endpoint of time until first SBM, they found no difference between groups. They also found no difference among any secondary endpoints. Study quality was moderate. Preservation of analgesia was unclear because the authors did not report pain scores nor opioid consumption, although they stated that "there was no evidence that methylnaltrexone increased the requirement for opioids to relieve postsurgical pain." Viscusi et al,[26] in contrast, studied IV methylnaltrexone in the setting of POI and found that it accelerated time to first SBM; however, this study was

exploratory with a small sample size (n=65) that was not determined prior to patient enrollment.

Discussion

This review demonstrates that PAM-OR antagonists may be effective for OIC and POI without reversing opioid-mediated analgesia but study design inconsistency and variable endpoints makes definitive conclusions impossible. PAM-OR antagonists as a class prevent opioid-induced increases in gut transit time in healthy volunteers and provide specific, targeted treatment of OIC and POI that result from a loss of coordinated propulsive action in the gut due to opioids.

The studies reviewed ranged from very low to moderate quality according to the GRADE recommendations for rating study quality.[24] There is especially a need for comparative studies that directly compare two or more of the three agents studied here. Heterogeneity in endpoints as well as study protocols was a problem throughout the literature.

Our results agree with the meta-analysis by Ford et al,[21] who found that methylnaltrexone was more effective than placebo in treating OIC. While their analysis included six trials, ours included eight. They also concluded that alvimopan was superior to placebo for OIC and included four trials, as we did. They too noted considerable heterogeneity among studies, more so with methylnaltrexone. Subsequent pooled analyses confirmed the efficacy of methylnaltrexone[52,53] and suggested that it may be particularly effective in those patients taking large daily opioid doses. Rauck et al reported that gastrointestinal side effects with oral methylnaltrexone occurred at the same rate as in the placebo group,[18] which did not appear to be the case with the subcutaneous formulation.[17,39] This should be considered when choosing between the two formulations, although this finding needs additional confirmatory studies.

Although alvimopan was studied in the setting of OIC, it is approved only for the treatment of POI in hospitalized patients who have undergone partial small or large bowel resection surgery.[54] This is reflected by the existence of fewer studies for alvimopan in OIC and the lack of recent, late-phase studies and post-hoc analyses. As stated by Irving et al, "alvimopan was under clinical development for long-term treatment of opioid-induced constipation but this program has been discontinued."[33] Concerns by the Food and Drug Administration over the "imbalance" in the number of cardiovascular events (more myocardial infarctions) in the alvimopan group versus placebo group prompted the discontinuation of the OIC program and limited its approved indication to inpatient use only.[55] Positive results in one of the two replicate Phase 3 studies[32] but not the other[33] speak to the lack of evidence for a specific dose and inconsistent study design between these and an earlier Phase 2 study.[34]

Naloxegol, the newest PAM-OR antagonist in the group, has demonstrated positive results in both studies in this review and agrees with the findings of other reviews.[19] Leppart and Woron reported that naloxegol was effective in up to 49% of patients not responsive to standard laxatives and that naloxegol has been shown to be more effective than placebo in patients with OIC and noncancer pain. No studies have been performed in cancer patients.[19] The approved dose is 25 mg.[16] Comparison of naloxegol to oral methylnaltrexone is difficult because the primary endpoints are not the same from the published studies. However, the available data suggest that while both agents are effective, adverse effects occurred at a greater frequency with naloxegol compared to placebo[41,42] while patients who received oral methylnaltrexone had a similar

rate of adverse effects as the placebo group.[18] Although confirmatory studies are needed, this suggests oral methylnaltrexone may have a superior side-effects profile.

For POI, the only PAM-OR antagonist FDA-approved for this indication is alvimopan. Heterogeneity in endpoints was a problem throughout the literature with most studies using some composite form of return to GI function. When given preoperatively and continued postoperatively, we found that alvimopan is effective in reducing POI. An important exclusion in many of the studies was opioid use prior to surgery. This could limit the number of patients who can receive alvimopan.

Viscusi et al reported that both methylnaltrexone and alvimopan do not cross the blood brain barrier for different reasons: for methylnaltrexone, this is due to its polarity and low lipid solubility that results from the addition of a fourth methyl group to naltrexone, making it a quaternary structure; for alvimopan, this is due its high polarity as a zwitterion.[7] Our review included three additional alvimopan studies and one additional methylnaltrexone study not included in theirs. We found no evidence for reversal of opioid-mediated analgesia, although one study did not include any measurements.[51]

Methylnaltrexone studies for POI had conflicting evidence in this review. In the two studies that evaluated it in this context,[26,51] the IV formulation was given postoperatively. It should be noted that the study that reported positive results enrolled 65 patients, while the study that found no improvement with methylnaltrexone was actually the results of two identical studies with n=515 and n=533.

It should be noted that three alvimopan studies[45,47,50] and one methylnaltrexone[51] POI study specified that they did not allow epidural analgesia in the protocols, which is understandable given the existing evidence for epidurals.[56] In the other POI studies it was

not stated whether epidural analgesia was excluded. In a multimodal or enhanced recovery after surgery (ERAS) pathway involving epidural analgesia, the duration of ileus in the placebo group would likely be shorter. Similarly, intravenous lidocaine has been shown to reduce duration of ileus and this was excluded from the studies as well.[57] Therefore, clinicians should consider this when evaluating the potential improvement in POI duration that a PAM-OR antagonist may produce.

Comparative-effectiveness studies in this field are clearly needed. None of the studies included in this review compared one PAM-OR antagonist to another. This makes direct comparisons difficult especially when heterogeneity in endpoints for the individual studies is taken into account. In addition, laxatives were permitted in some studies and not others, further complicating the picture. Although we did not analyze medication cost in this review, these charges as well as insurance coverage are additional considerations that may affect choice of agent.

This review has some limitations. We were unable to determine if there were unpublished studies that did not show positive results, and it is possible that some of these stopped prematurely. This may be particularly true with alvimopan, which was studied for OIC and subsequently abandoned for that indication. Second, there may be some studies that were not located through our search protocols. We attempted to minimize this limitation by combining two search databases, using two reviewers, and using as broad of a selection of search terms as feasible. However, studies with different key words or search terms could have been omitted.

Conclusion

In conclusion, PAM-OR antagonists may be effective in both OIC and POI but the inconsistency of study design, study endpoints, and lack of comparative studies limits the strength of our recommendations. Within the class methylnaltrexone has the most consistent evidence, and its oral formulation may be slightly less effective than the subcutaneous formulation but cause fewer gastrointestinal adverse effects. Although naloxegol is more effective than placebo for OIC, it appears to cause more adverse effects than oral methylnaltrexone. Alvimopan is the only FDA-approved and most well-studied agent for POI. Comparative studies are lacking. A multimodal treatment strategy for OIC and POI is recommended for these multifactorial disease states and evaluation of these agents combined with epidural analgesia and intravenous lidocaine is needed. Additional PAM-OR antagonists are currently under development but the potential market for these agents may become smaller as efforts to fight the opioid epidemic intensify.

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