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Naldemedine-laxative combination: retrospective inpatient study

Miho Takemura ,[1,2] Kazuyuki Niki,[1,2] Sho Miyaguchi,[1] Mikiko Ueda[1]

[1]Department of Clinical Pharmacy Research and Education, Osaka University, Graduate School of Pharmaceutical Sciences, Suita, Osaka, Japan
[2]Department of Pharmacy, Ashiya Municipal Hospital, Ashiya, Hyogo, Japan

Correspondence to
Dr Kazuyuki Niki, Department of Clinical Pharmacy Research and Education, Osaka University, Graduate School of Pharmaceutical Sciences, Suita, Osaka, Japan;
k-niki@phs.osaka-u.ac.jp

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ABSTRACT

Objectives The initiation of peripherally acting μ-opioid receptor antagonists (PAMORAs) should be considered 2 weeks after conventional laxatives have failed to achieve an adequate response, and affected patients should be evaluated every 2 weeks thereafter. However, this guidance is difficult to implement in acute care hospitals. This study aimed to examine how naldemedine (PAMORA) should be introduced in combination with other laxatives in the acute care setting.

Methods This retrospective study evaluated 93 inpatients who received at least four doses of naldemedine. We investigated changes in the average daily defecation counts during the first 7 days after compared with before naldemedine administration and the incidence of diarrhoea.

Results Daily defecation counts during the first 7 days after compared with before naldemedine administration were greater in both the naldemedine, magnesium oxide (MgO) and another laxative group, and in the naldemedine and another laxative other than MgO group than in the naldemedine only group. The incidence rates of diarrhoea were significantly higher in the naldemedine, MgO, and another laxative group, and in the naldemedine and another laxative other than MgO group than in the naldemedine only group.

Conclusions The introduction of naldemedine alone or in combination with MgO should be considered.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The use of peripherally acting μ-opioid receptor antagonists is challenging in acute care settings, where short-term hospitalisations are common, precluding adherence to timelines outlined in applicable guidance.

WHAT THIS STUDY ADDS

⇒ This study presents novel evidence that naldemedine alone or in combination with magnesium oxide should be considered in eligible patients to ensure safety and efficacy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides novel evidence on the efficacy and safety of naldemedine and concomitant laxatives, which may directly translate to research, practice and policy development.

INTRODUCTION

Constipation is one of the most common side effects of opioids, affecting approximately 40% of patients using opioids.[1] Laxatives are classified into osmotic laxatives that soften stools by increasing the water content in the intestine, stimulant laxatives that stimulate intestinal peristalsis, peripherally acting μ-opioid receptor antagonists (PAMORAs) and laxatives with other effects.[2 3] Methylnaltrexone became the first Food and Drug Administration-approved PAMORA for opioid-induced constipation (OIC). In Japan, naldemedine, a novel PAMORA, was approved as an oral drug in 2017.

The use of PAMORA has been evaluated extensively, and clinical guidance on its use was published in 2016, based on the findings of methylnaltrexone, which was launched prior to naldemedine.[4] The clinical guidance on PAMORAs recommends that they should be considered 2 weeks after starting conventional laxatives if patients have shown inadequate responses, and that patient clinical response should be evaluated every 2 weeks thereafter. However, evidence regarding naldemedine use remains scarce and it is unclear whether this clinical guidance can be applied in practice. In fact, this guidance is difficult to implement in acute care hospitals with many short-term hospitalisations. Specifically, recommendations remain unclear on whether naldemedine should be used alone or in combination with other agents when conventional laxatives have failed, and whether it should be started concurrently

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to or after the introduction of opioids. This study aimed to clarify how naldemedine (PAMORA) should be introduced in combination with other laxatives in the acute care setting.

METHODS

Study participants

Inpatients who started naldemedine at Osaka University Hospital between July 2017 and December 2019 were included. Patients were excluded if they received naldemedine fewer than three times a week; lacked data on defecation counts for more than 4 days during the first 7 days after starting naldemedine; or had significant structural gastrointestinal abnormalities.

Assessments

We retrospectively extracted data on the following characteristics from patient medical records: age, sex, body weight, body mass index, primary cancer site, morphine-equivalent daily dose (MEDD) of prescribed opioids, use of opioid rescue drugs, laboratory test values, concomitant medications at the start of naldemedine use, daily defecation counts from baseline to 7 days after starting naldemedine and adverse events. Adverse events were defined by the common terminology criteria for adverse events V.5.0, and diarrhoea was defined in this study as a disorder characterised by an increase in frequency and/or loose or watery bowel movements. These variables had been recorded by attending physician or other medical staff, as a part of routine assessment.

Primary and secondary endpoints

The primary endpoint was the change in the average daily defecation counts during the first 7 days after compared with before naldemedine administration. The secondary endpoint was the incidence of diarrhoea within 7 days following naldemedine administration.

Statistical analysis

Dunnett's test was applied to compare average daily defecation counts between the experimental and control groups. The χ^2 test was used to compare the incidence of diarrhoea among the four groups. Single-factor analysis of variance, the χ^2 test and Kruskal-Wallis test were used to compare other values.

Based on a previous study,[5] 90 patients were required to detect any change in the average daily defecation counts between the groups with 80% power at a significance level of 0.05. All statistical analyses were performed using BellCurve for Excel (Social Survey Research Information, Tokyo, Japan). A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Two hundred and sixty-seven patients taking naldemedine were identified. Eighty-nine patients that received naldemedine fewer than three times a week, 134 patients with missing defecation count data, and 16 patients with significant structural gastrointestinal abnormalities were excluded (including duplicate cases). Finally, 93 patients were included.

Defecation counts (mean±SD) increased to 0.93±0.70 times/day during the first 7 days, compared with 0.35±0.65 times/day before the administration of naldemedine ($p<0.001$). The patients were classified into four groups according to the concomitant laxatives used: naldemedine only, naldemedine and magnesium oxide (MgO), naldemedine and another laxative other than MgO, and naldemedine, MgO and another laxative. There was no significant difference in the rate of initiation of naldemedine within 3 days after the start of opioids among the groups ($p=0.605$). No statistically significant differences were observed among the four groups in terms of baseline MEDD values ($p=0.980$).

Table 1 shows the efficacy and safety profiles of naldemedine according to the type of coadministered laxatives. Defecation counts before the initiation of naldemedine were comparable among the four groups. The average daily defecation counts on days 1 through 7 were higher than those at baseline in all groups. In terms of change in daily defecation counts during the first 7 days compared with before naldemedine administration, that of naldemedine only group (0.45±0.63 times/day) was not significantly different from those of the naldemedine and MgO group (0.49±0.69 times/day, $p=0.997$), the naldemedine and another laxative other than MgO group (0.64±1.00 times/day, $p=0.906$), or the naldemedine, MgO and another laxative group (1.10±1.75 times/day, $p=0.097$). The incidence rates of diarrhoea were significantly higher in the naldemedine and another laxative other than MgO group (54.5%) and naldemedine, MgO and another laxative group (61.5%) than in the naldemedine only group (12.1%, $p=0.008$, 0.001, respectively). The incidence rates of diarrhoea were comparable between the naldemedine only group and naldemedine and MgO group (19.4%, $p=0.310$).

DISCUSSION

This study showed that the incidence rates of diarrhoea in patients using another laxative other than MgO were significantly higher than those in the patients using only naldemedine. This result suggests that the use naldemedine alone or in combination with MgO when introducing naldemedine may be preferable. This is the first study to consider naldemedine induction methods in combination with the use of other laxatives in a manner suitable for acute care hospitals.

Changes in daily defecation counts during the first 7 days compared with before naldemedine administration were greater both in the group with another laxative other than MgO and in the group with MgO and another laxative than in the group without concomitant laxatives, although there was no significant

Table 1 Efficacy and safety of naldemedine according to the type of coadministered laxatives

	(A) Naldemedine only (n=33)	(B) Naldemedine and MgO (n=36)	(C) Naldemedine and another laxative other than MgO (n=11)	(D) Naldemedine, MgO and another laxative (n=13)	P value (A vs B)	P value (A vs C)	P value (A vs D)
Defecation counts before administration (times/day), mean±SD	0.33±0.60	0.31±0.67	0.45±0.82	0.46±0.66	0.997*	0.926*	0.899*
Defecation counts on day 1 (times/day), mean±SD	0.66±0.75 (n=32)	0.60±0.65 (n=35)	1.55±1.51 (n=11)	2.54±3.20 (n=13)	0.998*	0.202*	<0.001*
Average daily defecation counts on days 1–7 (times/day), mean±SD	0.79±0.46	0.80±0.44	1.09±0.43	1.56±1.38	0.999*	0.428*	0.002*
Change in daily defecation counts during the first 7 days compared with before naldemedine administration (times/day), mean±SD	0.45±0.63	0.49±0.69	0.64±1.00	1.10±1.75	0.997*	0.906*	0.097*
Incidence of diarrhoea, n (%)	4 (12.1)	7 (19.4)	6 (54.5)	8 (61.5)	0.310†	0.008†	0.001†

*Dunnett's test.
†$\chi 2$ for independence test.
MgO, magnesium oxide.

difference among the groups. In addition, the incidence rates of diarrhoea were significantly higher in both the group with another laxative other than MgO and in the group with MgO and another laxative than in the group without concomitant laxatives. These results suggest that patients who introduce naldemedine with laxatives other than MgO tend to have diarrhoea. The underlying mechanism may be associated with the difference in the strength of laxative action. MgO is relatively mild at promoting peristaltic movements of the large intestine; consequently, it may help prevent quality of life deterioration due to abdominal discomfort associated with other laxatives.[6] Meanwhile, naldemedine exerts its effect by restarting the motility of the gastrointestinal tract. It has been reported that the frequency of naldemedine-induced diarrhoea is the highest on day 1 due to the initial increase in gastrointestinal motility and gradually decreases after day 2.[7] In this study, defecation counts on day 1 in patients receiving laxatives other than MgO were relatively high and diarrhoea was common. These findings suggest that naldemedine may be safely introduced with MgO, which has a relatively mild laxative effect.

The change in daily defecation counts during the first 7 days compared with before naldemedine administration tended to be greater in the group with MgO than in the group without concomitant laxatives in this study. An observational study reported that preventive MgO intake attenuated OIC when patients commenced opioid therapy.[1] Therefore, concomitant use of MgO is desirable for patients with cancer who have constipation that cannot be managed by naldemedine alone.

As the number of concomitant laxatives increased, the mean change in daily defecation counts during the first 7 days compared with before naldemedine administration and the incidence of diarrhoea tended to increase. This result was consistent with those of previous studies, showing that the combined use of naldemedine and other laxatives exerted additive effects on OIC and promoted excessive defecation. When initially used laxatives yield no or an inadequate response, a combination of more than 2 types of laxatives with a complementary mechanism of action is recommended.[8 9] Based on this evidence, the risk of naldemedine-induced diarrhoea should be carefully monitored as the number of concomitant laxatives increases.

This study has some limitations. First, selection bias may exist since outpatients and patients without data on the relevant defecation counts were excluded. Second, the degree of diarrhoea was not assessed since this was a retrospective study. Future studies should validate the present findings using assessment scales, such as the Bristol Stool Form Scale.[10]

CONCLUSIONS

Naldemedine alone or in combination with MgO should be considered to ensure safety and efficacy when introducing naldemedine. This study provides novel evidence on the use of naldemedine and concomitant laxatives.

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and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved and the resolution documented in the literature.

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ORCID iD

Miho Takemura http://orcid.org/0000-0002-7170-6938

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