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Sodium picosulfate in opioid-induced constipation: results of an open-label, prospective, dose-ranging study

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Identification of a safe and effective dose of the laxative sodium picosulfate was investigated in a single-centre, open-label study of 23 patients (age 40–81 years) receiving ≥60 mg/day morphine sulphate and experiencing constipation. A starting dose of 5, 10 or 15 mg sodium picosulfate (1 mg/mL solution) was administered, based on the patient's clinical status at entry and recent requirements for laxatives. Dose titration was permitted (±2.5 or 5 mg increments), to a maximum daily dose of 60 mg. Bowel movements, concomitant medication and need for suppositories or enemas were recorded in daily diaries. Sixteen patients withdrew before the end of the planned 14-day treatment period because of deterioration of the underlying condition. Sodium picosulfate was well-tolerated. Serious adverse events were all related to the underlying condition. A satisfactory response (normal stool consistency, not requiring enemas, suppositories or manual evacuation, no significant adverse event) was achieved in 15/20 evaluable patients. The median daily dose to achieve this was 15 mg (range: 5–30 mg) and the median time to first bowel movement after dosing was 11.75 hours (range: 6–22.5 hours). There was no clear relationship between the opioid dose and the optimum dose of sodium picosulfate, confirming that individual dose titration is necessary. *Palliative Medicine* 2006; **20:** 419–423

Key words: constipation; dose-ranging; laxative; opioid; sodium picosulfate

Introduction

Treatment with opioids to alleviate pain related to cancer or other chronic conditions is frequently associated with adverse effects, the most common of which is constipation.[1,2] Opioids are known to reduce the propulsive motor activity of the colon and decrease fluid net secretion, resulting in prolonged transit time, less frequent stools and increased stool hardness. These effects are exacerbated by immobility. The relationship between laxative use and opioid analgesia was examined in a prospective study of 498 hospice inpatients with advanced cancer, and it was found that both the percentage of patients requiring a laxative and the dose of laxative were related to the strength and dose of opioid being administered.[3] However, for many terminally ill cancer patients, other factors may also contribute to compromised bowel function.[3,4] In addition to high doses of opioids, confinement to bed, reduced consumption of food and fluids, depression, and abdominal complications of the primary disease process may all contribute to the development of severe constipation.[5]

Different classes of laxatives differ in their mode of action (eg, bulking agents, lubricants, osmotic agents, and stimulant laxatives). Sodium picosulfate is a member of the polyphenolic group of stimulant laxatives. Following oral administration, similar to senna, it is converted in the colon to an active form through the action of bacterial enzymes.[6] As a result, its effects are directed principally in the colon, where it stimulates peristalsis and, in common with other laxatives, reduces water reabsorption leading to the softening of stools. Sodium picosulfate has been used as a laxative for many years in idiopathic constipation and for bowel preparation before colonoscopy.

The effects of sodium picosulfate in opioid-induced constipation, and the dose needed to relieve opioid effects, have not been formally evaluated. Indeed, the whole area of the treatment of constipation in opioid-dependent and terminally ill patients remains relatively poorly investigated.[7]

The aim of this study was to find an acceptable and efficacious dose of sodium picosulfate in patients who were receiving regular opioid treatment and experiencing associated opioid-induced constipation.

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Methods

This was an open, prospective, dose-ranging study, conducted at a single centre in the UK. It was approved by the Central Oxford Research Ethics Committee and all patients provided written or witnessed oral, informed consent before any study-related procedures were carried out.

Twenty-three patients (eight male, 15 female), aged between 40 and 81 years, were recruited to the study. All patients had malignant disease, were receiving a minimum of 60 mg/day morphine sulphate, and had constipation requiring treatment. After assessment to confirm eligibility and collection of baseline information, patients were switched to sodium picosulfate 1 mg/mL (Laxoberal, Boehringer Ingelheim Ltd, UK) at a dose of 5, 10 or 15 mg, to be administered at 22:00 hours ($\pm$1 hour). The initial dose was selected from an assessment of the patient's clinical status at entry and recent requirement for laxatives. Titration of the daily dose was permitted as an increase or decrease in increments of 2.5 or 5 mg, depending on the stool frequency and consistency, up to a maximum of 60 mg/day. Existing concomitant medication other than laxatives was permitted during the course of the study and this was recorded in the case record form.

Patients were treated for a total of 14 days, with diary cards used to collect details of doses of sodium picosulfate taken, frequency and consistency (each on a 4-point scale) of bowel movements, discomfort and straining. In addition, the research nurse recorded any adverse events and concomitant medications, including suppositories and enemas. Patients were assessed on a daily basis and, if a bowel movement had not occurred by 16:00 hours, a clinical decision was made as to whether the patient required suppositories, an enema or manual removal of faeces. Details of any intervention were recorded in the case record form.

The primary endpoint of this study was the frequency and consistency of bowel movements. These were evaluated in relation to the dose of sodium picosulfate required for a satisfactory bowel movement. Secondary endpoints included the requirement for suppositories, enemas or manual evacuation, the level of discomfort, need to strain, the time between administration of the study drug and the first bowel movement, the relationship between the dose of opioid and the dose of sodium picosulfate and the number of adverse events.

The dose of sodium picosulfate associated with satisfactory bowel movement was defined as that dose at which all of the following were achieved:

1) Normal stool consistency (score of 2 or 3, corresponding to loose normal or firm normal stool) throughout the day;
2) Not requiring enemas, suppositories or manual evacuation;
3) No straining or discomfort;
4) No treatment-related adverse event.

No formal statistical analysis was carried out and only descriptive statistics are reported.

Results

Twenty-three patients (mean age: 61.5; range: 40–81 years) were recruited into the study. All were inpatients or day patients at Sir Michael Sobell House (Oxford) and all had an anticipated prognosis of at least 3–4 weeks. All patients had diagnoses of malignancy (bladder (4), breast (4), cervix (2), prostate (2), squamous (2), stomach (2), lung (1), melanoma (1), oesophagus (1), testicular (1), thyroid (1), tongue (1), unknown primary (1)) ranging from <1 to 14 years' duration. A summary of the patient demographics is contained in Table 1. Patients were receiving daily doses of morphine sulphate, ranging from 60 to 2880 mg. The duration of morphine treatment varied from one week to two years. Ten of the patients had symptoms of constipation on the day of entry into the study.

Of the 23 patients recruited, 20 were deemed to be evaluable. Three patients were excluded from the analysis because of major protocol violations. Eighteen patients completed at least one week of dosing with sodium picosulfate, but only seven completed the 14-day treatment period, primarily because of worsening of their underlying disease.

Table 1 Demographics of study population

Patients recruited	23
Male	8
Female	15
Age mean (years)	61.5
Age median (range; years)	67 (40–81)
Weight range (kg)	32–112
Time since first diagnosis of malignancy (years)	<1–14
Duration of treatment for malignancy (median; weeks)	17
Duration of opioid treatment (range; weeks)	1–104
Patients with constipation on day 0	10
Daily dose of morphine sulphate (range; mg)	60–2880
Patients evaluable	20
Male	7
Female	13
Age mean (years)	68
Age median (range; years)	61.2 (40–81)

Of the 20 patients assessed, 15 patients (75%) achieved a satisfactory response to sodium picosulfate, that is, achieved normal stool consistency throughout the day, did not require enemas, suppositories or manual evacuation, and did not experience a treatment-related adverse event.

The median time to the first bowel movement after administration of the study drug was 11.75 hours (range: 6–22.5 hours) and the median dose to this point was 15 mg (range: 5–22.5 mg). In the 15 patients who achieved a satisfactory response to treatment, the median dose was 15 mg (range: 5–30 mg). No correlation was found between the dose of opioid being taken and the dose of sodium picosulfate needed to achieve a satisfactory response (Figure 1).

Eight patients (40%) required the use of suppositories at some stage during the treatment period, with two patients also needing a phosphate enema. In four of these patients, a satisfactory dose of sodium picosulfate was not achieved. No manual evacuation of faeces was required in any patient.

The incidence of adverse events considered related to the study drug was minimal, with only one patient experiencing severe diarrhoea. Overall, 11 patients (55%) withdrew from the study due to adverse events, but only in this single case of diarrhoea was the adverse event considered related to the study drug. Six patients deteriorated and died during the two-week trial period. Each of these events was related to the underlying malignant disease and considered unrelated to the study drug. The remaining four withdrawals were for one case each of severe diarrhoea (judged to be food-related), confusion, vomiting and urinary tract infection. None of these was considered related to the study medication.

Discussion

Opioid-induced constipation is a major practical problem in patients receiving chronic treatment for pain.[1,2] Frequently, the problem is compounded by other drugs that the patient is taking,[8] as well as by the underlying primary condition and associated morbidities.[5] Survey data indicate that about 80–90% of terminally ill patients taking strong opioids need a laxative; likewise, up to 75% of those taking weak opioids and about 60% of those not taking any opioid.[3,8] Several surveys have demonstrated that there is no significant correlation between the dose of opioid and the effective dose of a stimulant laxative.[3–5,8,9] Some authors advocate that laxatives should be started concurrently with opioids.[10] However, there are no clear guidelines as to the choice of laxatives or the appropriate dose to be given to such patients and few formal studies of laxatives in opioid-induced constipation have been published.

Studies in this patient population are inherently difficult because of the severity and progressive nature of the illness, co-morbidities and the large number of concomitant medications. The results of the present study are somewhat limited by the small number of patients and the severity of the underlying disease, which resulted in 70% patients not completing the full

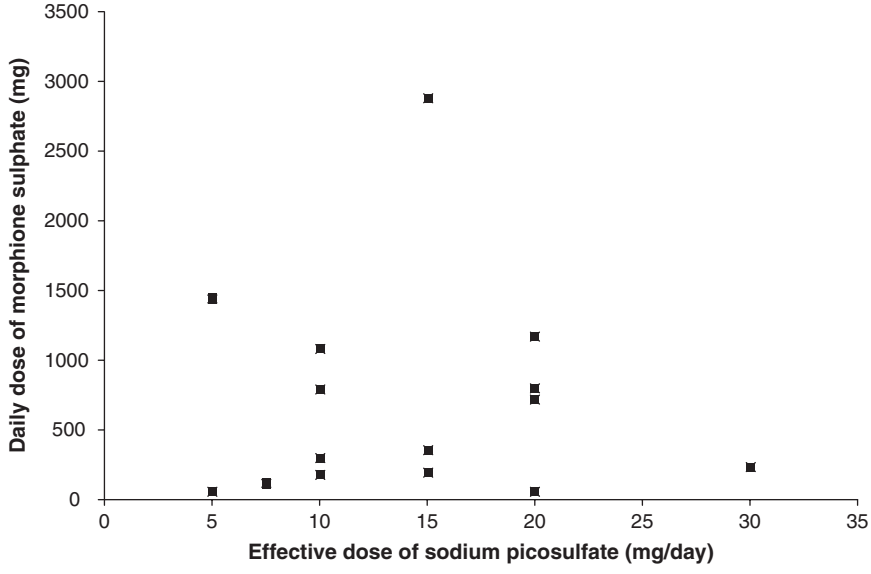

Figure 1 Relationship between dose of sodium picosulfate required (*x*-axis) and the average daily dose of morphine sulphate taken by the patient (*y*-axis) for the 15 patients who achieved a successful bowel motion without the aid of suppositories, enemas etc. There was no correlation between the two parameters (correlation coefficient −0.023).

treatment period. Nonetheless, the study has shown that for 75% of those patients who were evaluable, a satisfactory response was achieved with a median daily dose of 15 mg (range: 5–30 mg) of sodium picosulfate. This median dose is higher than the recommended upper daily dose limit of 10 mg for other patients, and indicates that some adult patients on opioids may well require a dose above the currently recommended upper limit. This agrees with other studies in terminally ill patients, which have also showed that the dose of laxative required is generally higher in patients taking opioids.[3,8]

Given that the median dose required to achieve the first bowel movement was 15 mg (range: 5–22.5 mg) in the present study, it seems reasonable to suggest that, in patients prescribed strong opioids, the starting dose should be 10 mg, followed by dose titration to achieve optimal effect. The median time to the first bowel movement after administration of sodium picosulfate in this study was <12 hours, which is substantially quicker than the 3–4 days seen with some other laxatives, such as lactulose.[11]

Treatment-related adverse events in this study were rare, with only one case of drug-related diarrhoea. This would suggest that, despite the higher than normal doses of sodium picosulfate, the adverse effect profile was similar to that seen using the manufacturer's recommended dose regimen.

Management of constipation in patients receiving opioid therapy needs to be tailored to the individual.[4,5] A change of opioid or the mode of delivery may require corresponding revision of the laxative regimen. For example, switching from slow-release morphine to transdermal fentanyl results in a reduction in the requirement for laxative treatment.[12]

An alternative approach to the treatment of constipation associated with opioid analgesia has been to administer opioid antagonists. The centrally-acting antagonist, naloxone, has been shown to reduce symptoms of constipation but, in some patients, this was at the expense of resumption of pain or precipitation of opioid withdrawal symptoms.[13] Opioid antagonists which do not cross the blood–brain barrier have been proposed as an alternative to naloxone, with the aim of antagonizing the peripheral effects of the opioid on the bowel without reducing the central pain-relieving effects. Recent studies with a peripherally acting μ-opioid receptor antagonist, alvimopan, have demonstrated beneficial effects in reducing constipation in patients receiving opioid treatment for non-malignant pain.[14,15] However, as already noted, in terminally ill patients, factors unrelated to opioid treatment contribute to constipation. As a result, simply blocking the peripheral effects of opioids may not be sufficient to normalize bowel function in this patient population and a laxative may be the preferred treatment.

In conclusion, provided the laxative dose is individually optimized, satisfactory defecation can be achieved with sodium picosulfate in terminally ill patients taking morphine regularly around-the-clock for pain relief. Higher doses of sodium picosulfate than are generally recommended are often necessary and these are well-tolerated.

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References

1 Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* 2003; **63**: 649–71.
2 Pappagallo M. Incidence, prevalence and management of opioid bowel dysfunction. *Am J Surg* 2001; **182**: 11S–18.
3 Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliat Med* 1998; **12**: 375–82.
4 Bennett M, Cresswell H. Factors influencing constipation in advanced cancer patients: a prospective study of opioid dose, dantron dose and physical functioning. *Palliat Med* 2003; **17**: 418–22.
5 Mancini IL, Hanson J, Neumann CM, Bruera ED. Opioid type and other clinical predictors of laxative dose in advanced cancer patients: a retrospective study. *J Palliat Med* 2000; **3**: 49–56.
6 Kim DH, Hyun SH, Shim SB, Kobashi K. The role of intestinal bacteria in the transformation of sodium picosulphate. *Jpn J Pharmacol* 1992; **59**: 1–5.
7 Herndon CM, Jackson KC, Hallin PA. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. *Pharmacotherapy* 2002; **22**: 240–50.
8 Twycross RG, Harcourt JMV. The use of laxatives at a palliative care centre. *Palliat Med* 1991; **5**: 27–33.
9 Fallon MT, Hanks GW. Morphine, constipation and performance status in advanced cancer patients. *Palliat Med* 1999; **13**: 159–60.
10 Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. *J Clin Pharm Ther* 2002; **27**: 107–10.
11 Crowther AG. Management of constipation in terminally ill patients. *J Int Med Res* 1978; **6**: 348–50.
12 Radbruch L, Sabatowski R, Loick G, *et al*. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. *Palliat Med* 2000; **14**: 111–19.

13 Sykes NP. An investigation into the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliat Med* 1996; **10**: 135–44.
14 Delaney CP, Weese JL, Hyman NH, *et al*. Alvimopan Postoperative Ileus Study Group. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. *Dis Colon Rectum* 2005; **48**: 1114–25.
15 Paulson DM, Kennedy DT, Donovick RA, *et al*. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction – a 21-day treatment-randomized clinical trial. *J Pain* 2005; **6**: 184–92.