Original Article

A Volunteer Model for the Comparison of Laxatives in Opioid-Related Constipation

Nigel P. Sykes, MA, FRCGP
Macmillan Lecturer in Palliative Medicine, University of Leeds, Leeds, United Kingdom

Abstract
Loperamide was used to provide a source of opioid-induced constipation in healthy volunteers. Each volunteer took a sequence of three dose levels of loperamide. One of three laxatives was used to counterbalance the effect of loperamide and restore bowel function to what the individual considered normal at each stage before the dose of loperamide was increased. Lactulose, senna, and codanthrusate were selected as examples of a softening, a stimulant, and a combination laxative, respectively. Outcome measures were the doses of laxative used, stool form and frequency, ease of defecation, a rating scale of subjective bowel function, and the occurrence of adverse effects. Each laxative was taken by ten volunteers, and all proved capable of maintaining normal bowel function. A combination of stimulant and softening laxatives was most likely to maintain normal bowel function at the lowest dose and least adverse effects. The mean final dose of lactulose was excessive for use in ill patients. Senna was associated with significantly more adverse effects than the other laxatives, mainly abdominal pain ($P < 0.001$). This model of constipation may provide a standardized means of assaying the clinical effectiveness of oral laxatives.
J Pain Symptom Manage *1996;11:363–369.*

Key Words
Constipation, terminal care, opioids, cathartics, loperamide

Introduction

The comparison of laxatives in a palliative clinical setting is complicated by the severity and progression of the patients' malignant disease, which may influence the ability to take medication and report its effects, and alter the physiological responses to drugs. In addition, although opioids are probably the largest single factor in the etiology of constipation, their effect cannot be isolated in the individual patient, because it is not generally possible to stop or start opioid analgesics simply for the purposes of comparative study. Therefore, a model of opioid-induced constipation was designed for use in healthy volunteers, with the aim of comparing the effectiveness of laxatives without the confounding variables introduced by concurrent advanced cancer.

Loperamide, a butyramide derivative with structural similarities to meperidine, was chosen to mimic the effects of opioid analgesics on gut transit. It has strong affinity for opiate receptors in both brain and myenteric plexus,[1] and is displaced from the receptors by naloxone. However, it is poorly absorbed by mouth, yielding peak plasma levels that represent only 0.3% of the administered dose,[2] and does not

Address reprint requests to: Nigel P. Sykes, MA, FRCGP, St. Christopher's Hospice, Lawrie Park Road, London SE26 6DZ, United Kingdom.

Accepted for publication: August 16, 1995.

0885-3924/96/$15.00
PII S0885-3924(96)00011-5

cross the blood–brain barrier to a significant extent.[3] Therefore, oral loperamide does not have opiate-like central nervous system (CNS) effects.

Loperamide has been shown to slow gastrointestinal transit,[4] reduce stool frequency, and increase anal sphincter tension in man.[5] It is antagonized by naloxone.[6] Animal studies suggest that its actions result from inhibition of the propulsive component of myoelectrical activity, particularly in the small intestine.[7] At high doses, there is also an effect on water and electrolyte secretion in the gut, although the relevance of this in humans is unclear. Adverse effects due to loperamide are few and are less common than with other antidiarrheal drugs, such as codeine and diphenoxylate.[2] The maximum daily dose in clinical practice is 16 mg, but this has been exceeded without sequelae in clinical trials. For the purposes of this study, loperamide offered a model of opioid-induced constipation without systemic effects, which could be safely used in healthy subjects.

In this study, a laxative whose primary mode of action is to soften the stool was compared with one whose principal action is stimulation of peristalsis, and a combination preparation that produces both actions. The agents chosen were lactulose (6.7 g per 10 mL solution), senna (7.5 mg total sennosides per tablet), and codanthrusate (danthron 50 mg with docusate sodium 60 mg) respectively. These drugs were selected for the following reasons:

1. Lactulose is frequently prescribed alone, even to patients receiving opioid analgesics. In this situation, it has been considered inadequate by palliative physicians on the basis of clinical experience. Its cost as a laxative, which results both from its frequency and volume of administration, has also been criticized.[8]
2. It has been asserted, without experimental evidence, that the constipating effects of codeine can be relieved by a fixed proportion of senna given concurrently.[9] This report has been frequently cited and has been taken to indicate that senna alone may be adequate for management of opioid-related constipation. The view of most palliative physicians appears to be, however, that laxation with the minimum of adverse effects is achieved by use of a combination of stimulant and softener.
3. The benefits of combination laxative therapy are assumed and have not been tested. To do so in severely unwell cancer patients might be considered unethical, and the question might appropriately be answered in a volunteer study. At the time of planning the study, the two most frequently used softener/stimulant laxative combinations in British hospices were codanthramer and codanthrusate. The former was licensed clinically only for elderly or terminally ill patients, and, while this is now the case also for codanthrusate, it appeared at that time that codanthrusate would be the more appropriate choice for a study using volunteers.
4. The modes of action of these drugs have been summarized elsewhere.[10]

Methods

Each of the three laxatives was taken by ten healthy volunteers, who had no history of gastrointestinal disease, were not allergic to the trial medications, and were not receiving medication likely to conflict with the trial. Treatment was allocated according to the order of recruitment, without selection. Twenty-five volunteers (19 women, 6 men; ages 18–66 years, median 33 years) took part; five subjects tested two laxatives. Subjects were asked to make the following records:

1. Timing of each bowel movement. This allowed calculation of stool frequency.
2. Assessment of stool form by comparison with a standard chart of photographs, a measure which has been shown to correlate with whole gut transit time.[11]
3. An assessment of the ease of defecation for each stool on a four-point scale: 1) easy, 2) slight difficulty, 3) moderate difficulty, and 4) severe difficulty.
4. An overall assessment of each day's bowel function using a ten-point discrete response visual scale.
5. Doses of loperamide and laxative taken on each day.
6. A daily record of adverse effects attributed to the study laxative.

In addition, subjects filled in a chart of their diet during a 5-day run-in period, during which no trial drugs were taken. This enabled a dietician's assessment to be made of each volunteer's fiber intake and whether or not this differed significantly from the group norm. The run-in period also provided data on the subjects' normal bowel habit. However, as bowel function varies very considerably among healthy individuals, the assessment of normality of function was left to the personal judgment of each volunteer.

After the run-in period, subjects commenced an escalating dose of loperamide. There were three dose stages: 2 mg twice daily, 4 mg twice daily, and 6 mg twice daily. The lowest was taken first and at the same time the test laxative was begun. Volunteers were given a chart with a range of laxative doses and were instructed to start with the lowest and increase in order, according to the result they experienced.

When the subject felt that his or her bowel function was normal despite the loperamide, the dose of loperamide was increased to the next step. Laxative titration continued until normality was again restored. This process was repeated for the third level of loperamide; when the "balancing" dose of laxative had again been found, the study was concluded.

The reason for giving guidance on the doses of laxative was to ensure that subjects increased them by a significant but not excessive amount at each step and to indicate that, in marked constipation, laxatives might be needed in amounts greater than usually seen. Nevertheless, only the dose of loperamide was controlled by the investigator. Within the limits of the guidelines provided, the laxative dose was at the discretion of the subjects themselves, according to the degree of constipation or adverse effects they perceived themselves to have. Similarly, the duration of the trial was in the hands of the subjects themselves; it was considered that this might be an indicator of laxative effectiveness, in that it might take longer to find the optimum dose of a weak agent than of a more potent one.

The protocol was approved by the ethics committee of Leeds Eastern Health Authority.

Results

No significant dietary differences were found among the volunteers. Only one subject was taking additional medication, an H_2 antagonist, which was unlikely to have influenced response to the trial drugs.

Table 1
Final Doses of Laxative Taken Relative to Doses of Loperamide

	Loperamide (caps/day)		
Daily laxative dose	2	4	6
Lactulose (mL)	120	120	160
	120	160	160
	30	60	80
	80	120	120
	30	100	NA
	80	100	120
	120	120	120
	80	80	80
	40	70	80
	40	60	80
Mean	74.0	99.0	111.1
95% CI	47.2–100.8	76.0–122.0	85.5–136.7
Senna (tabs)	3	6	8
	6	8	12
	2	2	2
	2	6	6
	2	4	6
	6	6	12
	4	8	8
	2	4	12
	6	6	12
	8	8	4
Mean	4.1	5.8	8.2
95% CI	2.5–5.7	4.4–7.2	5.6–10.9
Codanthrusate (caps)	6	8	12
	3	4	8
	2	3	5
	2	3	6
	7	6	6
	3	4	8
	3	3	8
	6	6	8
	2	5	6
	3	4	5
Mean	3.7	4.6	7.2
95% CI	2.3–5.1	3.4–5.8	5.7–8.7

NA, data not available; CI, confidence interval.

The final doses of laxative at each stage of loperamide dosage are shown in Table 1. These doses are assumed to be those that achieved normal bowel function for each individual, compensating for the constipating effect of the loperamide. Most, but not all, subjects required the laxative dose to be increased as the loperamide dose went up. The degree of increase varied considerably among subjects. The final mean dose of lactulose amounted to 55 mL twice daily, two subjects took 80 mL twice daily. The lowest dose taken at this stage was 40 mL twice daily. One subject took no further lactulose after the sec-

Table 2
Measures of Laxative Effectiveness

	Lactulose	Senna	Codanthrusate
Mean stool form	4.9	5.3	5.1
Mean ease of defecation	1.6	1.6	1.8
Mean bowel function score	5.2	5.5	5.8
Mean time to complete trial (days)	18.0	19.1	18.1

ond loperamide dose level because of severe abdominal colic.

Doses of codanthrusate tended to be lower than those of senna, although this did not reach statistical significance ($P = 0.34$, Mann-Whitney). Four subjects took six senna tablets twice daily by the end of the study, but only one required as many codanthrusate capsules.

Measures of laxative effectiveness are given in Table 2. No significant difference emerged among the laxatives on either subjective (ease of defecation and rating of bowel function) or objective (stool form, stool frequency, and time to complete the trial) measures. The mean number of days taken to complete each stage of the trial was 5.6 (median, 5.0; range, 3–11) days for the lowest loperamide dose, 6.5 (median, 6.0; range, 3–17) days for the middle dose, and 6.5 (median, 6.0; range, 2–13) for the highest. In this model of opioid-induced constipation, all laxative preparations appeared capable, if used in sufficient doses, of maintaining an average of one daily bowel movement, a stool of normal consistency passed with minimal difficulty and a rating of overall bowel function very close to normal.

Reports of adverse effects, however, differed considerably between the agents (Table 3). The number of treatment days on which adverse events were recorded during senna treatment was significantly larger than either lactulose or codanthrusate treatment ($P < 0.001$), particularly because of reports of abdominal pain during use of senna. Codanthrusate also caused more days with adverse events than lactulose ($P < 0.05$), mainly because of two subjects who suffered persistent perianal soreness with the drug. No rash was reported, but it was not examined for. Diarrhea sufficient to prompt a reduction in laxative dose occurred on six occasions in five subjects while taking senna and on eight occasions in six subjects while taking either lactulose or codanthrusate.

Table 3
Adverse Effects of Laxative Therapy

	Lactulose	Senna	Codanthrusate
Mean number of days on which adverse event reported	3.8	8.7	5.5
Mean number of treatment days per adverse event	4.8	2.2	3.3
Days experienced			
Pain	14	67	18
Flatulence	11	10	6
Nausea	0	4	6
Thirst	4	0	3
Diarrhea	8	6	8
Perianal soreness	0	0	14

Occurrence of adverse effects (chi-squared tests): senna versus lactulose, $P < 0.001$; senna versus codanthrusate, $P < 0.001$; and codanthrusate versus lactulose, $P < 0.05$.

Subjects were not asked for comments on the laxatives, but three commented spontaneously. One found her maximum dose (80 mL twice daily) of lactulose "revolting"; had she been unwell she would not have been able to tolerate it. A volunteer who tested both senna and codanthrusate wrote that he felt that the latter was the better laxative as "it doesn't cause gripping pains of the stomach." A third volunteer, who presumably tended toward constipation, was pleased to have taken part, as she had never before defecated so regularly. She received codanthrusate, and the comment was made despite experiencing nausea on several days. Despite its sweetness, no subject complained of nausea with lactulose. Four of the ten subjects taking lactulose reported flatulence; clinical studies indicate a prevalence of about 20%.[10]

Discussion

Consideration had been given to arranging the doses of loperamide to provide a repeated doubling, i.e., 2 mg twice daily, 4 mg twice daily, and 8 mg twice daily. Pilot testing suggested that this might provide a degree of constipation that at least one of the test agents might have difficulty in opposing. Accordingly, the maximum dose was reduced to 6 mg twice daily. In view of the mean laxative doses that were used in the study, this change was probably appropriate. The minimum dose was

determined by the size of a loperamide tablet. Use of the elixir preparation of loperamide would have allowed total daily doses of 2 mg, 4 mg, and 8 mg, but tablets were chosen for the convenience of the volunteers, to avoid the use of more than one liquid preparation. In future use of the model, it would be possible to modulate the loperamide dose scale according to the severity of constipation it was intended to mimic or the potency of the laxatives being tested.

Perhaps surprisingly, a predominantly softening laxative proved as capable of counteracting the gut effects of an opioid as either a mainly stimulant agent or a combination preparation. However, there was a clear penalty for this effectiveness in the volume of lactulose that had to be swallowed to achieve it. The subject who wrote that, had she actually been unwell, she would not have been able to manage this medication burden was probably not alone. Essentially, the reputation of lactulose as a relatively weak laxative whose sole use is unlikely to be adequate in opioid-induced constipation was supported by these data, as few would consider it appropriate to impose 60–80 mL lactulose twice daily on a patient with advanced cancer.

The use of senna alone to prevent the gut effects of opioids is not supported by these results. Certainly, senna preserved an apparently normal bowel function in the face of escalating doses of loperamide, and there was a strong relationship between the dose of loperamide and that of senna required to antagonize it ($P = 0.002$, t test). But the prevalence of adverse effects was markedly higher than with the other two agents. That this was principally due to colic might have been expected, as this would be the result from an intestine forced to contract and propel hard fecal material. Similar findings came from a comparative study of lactulose against senna in children,[12] but, in that case, constipation was less severe than that produced by this model, as satisfactory laxation was achieved with only 10–15 mL lactulose per day. It would appear that senna should probably only be used in opioid-induced constipation in association with a softening agent. The use of senna in this way by some palliative care centers is vindicated by these findings.

Codanthrusate is a combination preparation, which is commercially available and requires no mixing by pharmacy, staff, or patient. Its availability as a capsule, as well as a liquid, would be an advantage for some users. Its dose requirement was at least as low as senna, and four or even six capsules twice daily are likely to be more widely acceptable than 80 mL twice daily of the sweet and rather viscous lactulose. The likelihood of adverse effects with codanthrusate was much lower than with senna, and would have closely approximated lactulose had it not been for the tendency of danthron to cause perianal irritation, which may necessitate cessation of treatment. As slow intestinal transit is associated with hard stool,[13] it seems logical to combine softening and stimulant actions within one laxative preparation. This is an area of therapeutic practice where combination preparations, even fixed dose ones, seem helpful and appropriate.

The penalty for such convenience may be cost. The prices of the mean quantities of laxatives used at the highest dose of loperamide were 62p for lactulose, 12p for senna, and £1.40 for codanthrusate.[14] It would be interesting to perform this type of study using a lactulose/senna mixture as the combination preparation, to assess by how much the dose of lactulose would be reduced, the adverse effects of senna relieved, and the cost of therapy curtailed.

It might have been expected that volunteers would have been unwilling to pursue the effective dose of laxative in the face of adverse effects. In fact, the very different adverse effect profiles that emerged for the three trial preparations suggested that participants had attempted to achieve the goal of the study by persisting in titrating laxative dosage until their bowel function was again normal. Their accounts give insight into what patients with opioid-induced constipation may feel but not complain of.

The site of morphine's action upon the gut is uncertain and may vary among species. In rodents, intracerebral administration of morphine more potently slows transit than intravenous administration.[15] Nevertheless, higher concentrations of morphine are found in the intestine than in the brain after peripheral administration,[16] and the consequent gut slowing can be reversed by a peripherally-acting

opioid antagonist.[17] In man, loperamide acts by a motility effect, despite its very low oral bioavailability.[3] Its gut-slowing action can be reversed by naloxone given orally,[6] a drug whose systemic availability by this route is also below 1%.[18] It appears, therefore, that a local effect of morphine on the gut is important and may be predominant in humans.

In this study, loperamide provided a source of constipation that was presumably mediated by gut opioid receptors, without giving rise to any adverse effects that could be related to the drug itself. The doses of laxative used were strongly related to those of loperamide in each case, indicating that constipation and its relief were dose related. This inference can be drawn because no relationship between loperamide and laxative dosages was stipulated by the protocol—subjects were free to take more or less laxative from the range of doses available to them, as they chose. Indeed, some did not feel the need to increase the dose of laxative as more loperamide was taken. This reflects the variability in individual susceptibility to opioid effects seen in clinical practice. Similarly, the amount by which those who increased the laxative dose did so varied considerably. Because of this variability and because of the low numbers involved in this study, it is not claimed that a scale of equivalent doses of the test laxatives has been obtained, but only an indication. If a sufficient number of subjects were studied, this method could possibly yield a form of standardization of laxatives, their potency assayed against particular doses of loperamide.

Whether the model has any relevance to the management of any other type of constipation than that associated with the use of opioid analgesics has not been shown. There is increasing evidence, however, for a role of endogenous opioids in the pathogenesis of idiopathic constipation.[19] The physiological mechanisms against whose effects a laxative has to act may therefore be similar to those by which loperamide causes constipation. Hence, the model may be a general one for at least some types of idiopathic chronic constipation. Also, the laxatives used in this study are well known, and it was apparent that the adverse effects displayed during testing were typical of those often attributed to them in clinical practice. This suggests that the model allows laxative agents to display their characteristic properties, which would be apparent in whatever context they were used, and thus may serve as a general method of testing laxatives and not one simply confined to palliative medicine.

Acknowledgment

The author is grateful for the assistance of Mrs. Susan Chell and the Pharmacy Department of St. James' Hospital, Leeds, in this study. He and Mrs. Chell were supported by Cancer Relief Macmillan Fund and the Wolfson Foundation. Co-danthrusate was generously donated by Novax, Ltd.

References

1. Wuster M, Herz A. Opiate agonist action of antidiarrhoeal agents in vitro and in vivo findings in support for selective actions. Naunyn Schmiedebergs Arch Pharmacol 1978;301:187–194.

2. Heel RC, Brogden RN, Speight TM, Avery GS. Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhoea. Drugs 1978;15:33–52.

3. Ruppin H. Review: loperamide—a potent antidiarrhoeal drug with actions along the alimentary tract. Aliment Pharmacol Ther 1987;1:179–90.

4. Snisky CA, Davis RH, Clench MH, Thomas KD, Mathias JR. Effect of lidamidine hydrochloride and loperamide on gastric emptying and transit of the small intestine. Gastroenterology 1986;90:68–73.

5. Read M, Read NW, Barber CD, Duthie HL. Effects of loperamide on anal sphincter function in patients complaining of chronic diarrhoea with faecal incontinence and urgency. Dig Dis Sci 1982;27: 807–814.

6. Basilisco G, Camboni G, Bozzani A, Paravicini M, Bianchi PA. Oral naloxone antagonizes loperamide-induced delay of orocaecal transit. Dig Dis Sci 1987;32:829–832.

7. Niemegeers CJE, Lenaerts FM, Janssen PAJ. Loperamide (R18553), a novel type of antidiarrhoeal agent. Part 2. Arzneimittelforschung (Drug Res) 1974;24:1633–1665.

8. Bateman DN, Smith JN. A policy for laxatives. BMJ 1988;297:1420–1421.

9. Maguire LC , Yon JL, Miller E. Prevention of narcotic-induced constipation. N Engl J Med 1981; 305:1651.

10. Brunton LL. Agents affecting gastrointestinal water flux and motility, digestants, and bile acids. In: Gilman AG, Rall TW, Nis AS, Tavlor P, eds. The pharmacological basis of therapeutics, 8th ed. New York: Pergamon, 1990.

11. Davies GJ, Crowder M, Reid B, Dickerson JWT. Bowel function measurements of individuals with different eating patterns. Gut 1986;27:164–169.

12. Perkin JM. Constipation in childhood: a controlled comparison between lactulose and standardised senna. Curr Med Res Opin 1977;4:540–543.

13. Sykes NP. Methods of assessment of bowel function in patients with advanced cancer. Palliat Med 1990;4:287–292.

14. Monthly Index of Medical Specialities. London: Haymarket, 1995 (August).

15. Margolin S. Decreased gastrointestinal propulsive activity after intracranial morphine. Fed Proc 1954;13:383–384.

16. Manara L, Bianchi G, Ferretti P, Tavani A. Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites. J Pharmacol Exp Ther 1986;237:945–948.

17. Manara L, Bianchi G, Ferretti P, Monferini E, Strada D, Tavani A. Local and CNS-mediated effects of morphine and narcotic antagonists on gastrointestinal propulsion in rats. In: Way EL, ed. Endogenous and exogenous opiate agonists and antagonists. New York: Pergamon, 1980.

18. Fishman J, Roffwarg H, Helman L. Disposition of naloxone-7, 8-^{3}H in normal and narcotic-dependent men. J Pharmacol Exp Ther 1973;187: 575–580.

19. Kreek MJ, Paris P, Bartol MA, Mueller D. Effects of short term oral administration of the specific opioid antagonist naloxone on faecal evacuation in geriatric patients. Gastroenterol 1984;86:1144.