ORIGINAL ARTICLE

Use of a prophylactic antiemetic with morphine in acute pain: randomised controlled trial

M Bradshaw, A Sen

Emerg Med J 2006;23:210–213. doi: 10.1136/emj.2005.029819

See end of article for authors' affiliations

Correspondence to:
Mr A Sen, Department of
Emergency Medicine,
Wrexham Maelor
Hospital, Wrexham LL13
7TD, UK; aruni.sen@
new-tr.wales.nhs.uk

Accepted for publication
4 October 2005

Objective: The aim of this study was to compare the incidence of nausea and vomiting in patients with acute pain treated with morphine along with prophylactic metoclopramide or placebo.

Method: A randomised controlled trial was carried out on patients requiring morphine for acute pain in the emergency department (ED) setting. Children under the age of 12, patients who had been vomiting or had already received prehospital analgesia, and those unable to give consent were excluded. All patients were given either metoclopramide (10 mg) or placebo (normal saline) followed by intravenous morphine. Pain scores (measured on a visual analogue scale) before and after morphine administration, all incidents of nausea or vomiting, the dose of morphine, and the patients' demographic data were recorded. Fisher's exact test was used for comparing the two groups of patients.

Results: A total of 259 patients were recruited. There were 123 patients in the metoclopramide group (age range 15–94 years; median age 53) and 136 patients in the placebo group (age range 17–93 years; median age 52.5). The overall incidence of nausea and vomiting in the whole study population was 2.7% (1.6% in the metoclopramide group and 3.7% in the placebo group). The difference between the two groups was not statistically significant (Fisher's exact test = 0.451; $p = 0.3$; z-test statistic = 1.02; 95% CI –6% to 2%).

Conclusion: When intravenous morphine is administered for acute pain, the overall incidence of nausea and vomiting is low, regardless of whether these patients are given prophylactic metoclopramide or not.

For many of the patients presenting to emergency departments in the UK, pain is one of the most important complaints. Moreover, acute pain relief is now one of the major performance and quality standards for emergency departments in the UK.¹

Intravenous morphine is a commonly used opioid for relief of severe pain in the emergency setting in the UK. It is widespread clinical practice to use an antiemetic prophylactically for all patients who receive an opioid for acute pain. However, there is no evidence to support this practice.

The aim of this study was to compare the incidence of nausea and vomiting in patients treated for acute pain with intravenous (IV) morphine and given either prophylactic metoclopramide 10 mg or placebo.

METHOD

We conducted a prospective, randomised, double blind, placebo controlled trial over 24 months (July 2001 – June 2003). The North East Wales NHS Trust ethics committee approved the study.

We recruited patients presenting to the emergency department of Wrexham Maelor Hospital, Wrexham, UK, with any painful condition that required IV morphine for acute pain relief. All participating patients gave informed consent, either written or verbal, if a signature was not practicable (for example, severe pain, injured dominant hand, lying on a spinal board). All recruited patients also received an information leaflet explaining the study. Patients were not recruited consecutively, as recruitment depended on patient consent and the availability of a doctor in our busy department, able to recruit the patient after due explanation of the study.

We excluded patients:

- under 12 years of age—as it is not our practice to use metoclopramide in this age group

- who presented with nausea or vomiting along with their painful condition and therefore needed an antiemetic
- who had received prehospital nalbuphine, another analgesic, or an anaesthetic prior to attending the department. These drugs may have different emetic potential
- who could not consent to the study—for example, altered mental state, critically injured, refused consent.

We designed a proforma and study information pack for all departmental staff and the participating patients.

For all participating patients, the doctor providing the treatment decided on the need for IV morphine. The patient was asked to score their pain on a visual analogue scale (VAS). This score, the patient's demographic data, and details of the painful condition were recorded.

Following this patients were randomised to receive the contents of a prefilled, numbered 2 ml syringe, administered intravenously before giving morphine. The syringe number was recorded on the trial form against the patient number. The syringe contained either metoclopramide (10 mg) or placebo (normal saline). A senior pharmacist prefilled and numbered the syringes by randomisation between drug A (metoclopramide) and drug B (saline). At the point of administration, a numbered syringe was selected at random by the nurse issuing morphine. Thus all doctors, nurses, and patients were blinded to the content of the syringe.

In accordance with departmental protocol, morphine was diluted to 1 mg/ml strength and given intravenously slowly over five minutes by the doctor and titrated to the patient's response. This continued until the patient reported adequate analgesia. At this point the doctor recorded the final VAS pain score as given by the patient. The dose range of morphine used was 0.1–0.2 mg/kg.

All patients were given oxygen via a mask and monitored with pulse oximetry. From after 15 minutes from the start of morphine administration to until the patient left the

department, an independent nurse observer recorded any incident of nausea or vomiting. The nurse asked the patient if there was any nausea (Are you feeling sick?) or vomiting (Have you been sick?). The patient was asked to answer "Yes" or "No", and the response recorded by the nurse. We believe that maximal analgesia with IV morphine is achieved in 15 minutes from the start of IV titration (which takes an average five minutes to complete), so any nausea or vomiting related to morphine would also manifest at this time. If any nausea or vomiting was reported, the patient was treated with IV cyclizine 50 mg. This was also recorded.

After the conclusion of the data collection, the pharmacist broke the randomisation code and identified the content of the numbered syringes.

Statistical analysis

We calculated that 700 patients with acute pain would need to be recruited to give this study 80% power to demonstrate a 50% reduction in the incidence of nausea or vomiting with the use of prophylactic metoclopramide along with morphine in the study population which might have had a 5% incidence of nausea/vomiting without any antiemetic. The incidence of nausea and vomiting in the two study groups was compared using Fisher's exact test (two sided). The *p* value, *z*-test statistic and 95% confidence intervals were derived to determine any statistical significance of the results.

RESULTS

A total of 259 patients were recruited over the study period of 24 months (fig 1), of which 123 patients received metoclopramide (drug group) and 136 received placebo (saline group). The two groups were evenly matched for the types of painful condition, age and sex, median dose of IV morphine, and mean reduction in pain score after the titrated dose of morphine (table 1).

Pain scores were recorded using VAS before administering morphine and after completion of titration to achieve adequate analgesia as reported by the patient. The mean reduction in the pain score was 4.1 in the metoclopramide group (median dose of morphine 8 mg) and 4.0 in the placebo group (median dose of morphine 10 mg).

The patients were observed for a variable period of time in the department, depending on their clinical condition and outcome (discharge or admission). According to our departmental protocol, the minimum period of departmental observation for all patients receiving morphine is one hour. During this period only 7/259 patients (2.7%) had nausea and/or vomiting: 2/123 (1.6%) in the drug group despite receiving metoclopramide prophylactically and 5/136 (3.7%) in the saline group after receiving a placebo prophylactically. This difference did not reach statistical significance (Fisher's exact test (two sided) = 0.451; *p* = 0.3; *z*-test statistic -1.02; 95% CI -6% to 2%). Of the seven patients, one patient (metoclopramide group) reported only nausea without any vomiting. All seven patients responded to a single dose of IV cyclizine (50 mg). There were no other adverse events recorded during the stay of these patients in the department. The mean age of the seven patients who vomited/had nausea was 51.8 years (table 2), whereas that of the rest was 52.3 years.

DISCUSSION

A major proportion of patients presenting to UK emergency departments have various painful conditions. In our department, morphine has been the intravenous opioid of choice since 1996. In our experience, the advantages of IV morphine are its titratability (dose range 0.1–0.2 mg/kg) and predictability. Traditionally, it has been the norm to use prophylactic antiemetics along with opioids to counter their emetic side

Figure 1 Study flow chart.

Table 1 Baseline characteristics of the patients in the two study groups

	Drug group (n = 123)	Saline group (n = 136)
Median age	53	52.5
Age (years) range	15–94	17–93
Sex distribution (M:F (%))	54:69 (43.9:56.1)	65:71 (47.8:52.2)
Median dose of morphine (mg)	8	10
Mean (95% CI) reduction of pain score	4.1 (3.7 to 4.5)	4.0 (3.6 to 4.4)
Painful condition (n (%))		
Limb injury	110 (89.4)	123 (90.4)
Trunk injury	10 (8.1)	12 (8.8)
Burns	3 (2.4)	1 (0.7)

effects. All opioids have the well recognised side effects of nausea and vomiting,² with some being worse than others.³ These symptoms are mediated both centrally, by stimulation of the chemoreceptive trigger zone and dopamine receptors in the medulla, and peripherally, by labyrinthine stimulation and reduced gastric emptying.⁴ Thus antiemetic prophylaxis is particularly common with the use of opioids for post-operative acute pain, where the incidence of nausea and vomiting varies between 8% and 92%.⁵

Our study clearly shows that the overall incidence of nausea and vomiting is low when morphine is used in acute

Table 2 Characteristics of the patients who had nausea and/or vomiting

Patient no.	Age	Sex	Painful condition	Morphine dose (mg)	Study group
1	74	F	Colles' fracture	7	Drug
2	78	F	Hip injury	7	Drug
3	56	F	Clavicular fracture	10	Saline
4	33	M	Shoulder injury	10	Saline
5	45	F	Colles' fracture	8	Saline
6	77	F	Femoral neck fracture	5.5	Saline
7	88	F	Femoral neck fracture	6	Saline

pain. This low incidence was equally evident in both study groups (metoclopramide and placebo groups), and there was no statistically significant difference between the two groups. All the patients who reported nausea and/or vomiting ($n = 7$) responded to a single IV dose of 50 mg cyclizine. This applied to the period of observation in the department, which was at least one hour or longer depending on the clinical condition or outcome.

There is no evidence in the literature to show that the nausea or vomiting, which occurs when morphine is used in acute pain in the emergency setting, is clinically significant. This is the first prospective, randomised, double blind, controlled study of this kind to be conducted in a UK emergency department. We have come across two similar studies in the literature with comparable conclusions. Lambie *et al*⁶ recruited a similar number of patients, but restricted the patients to those with musculoskeletal trauma. They concluded that the incidence of nausea and vomiting was 3.7% overall with more vomiting (5.4%) in the metoclopramide group compared with the placebo group (1.9%) (difference not statistically significant). Talbot-Stern and Paoloni,⁷ in a study conducted in Australia, recruited a smaller number of patients with a wide spectrum of painful conditions, and used both morphine and pethidine for acute pain in the emergency department and reported a 6.5% incidence of nausea and vomiting. This study had a slightly higher incidence of vomiting in the placebo group (not statistically significant) and concluded that routine use of prophylactic metoclopramide cannot be justified. Interestingly, a subsequent observational study of all patients receiving opioid analgesia in the same department confirmed the low incidence (2.4%) of nausea and vomiting, a higher incidence (9.3%) of pre-analgesia nausea and vomiting, and yet a persistent practice of giving prophylactic antiemetics (33%).⁸

In contrast with the setting of acute pain, the incidence of opioid induced vomiting has been reported at 28% with morphine in non-chemotherapy cancer patients, with a slightly lower incidence of nausea.² We suspect that the long tradition of prophylactic antiemetic use has derived from the experience of nausea and vomiting in postoperative acute pain, where opioids are commonly used in patient controlled analgesia. Even in this setting, the claims of opioid induced nausea and vomiting have been challenged and the symptoms ascribed to other factors related to the surgical procedure.⁵ Moreover, the expected relief of nausea and vomiting with prophylactic use of metoclopramide,⁹ droperidol, and ondansetron¹⁰ has not been reported. Dundee and Jones¹¹ using cyclizine therapeutically, not prophylactically, reported significant reduction in vomiting but not nausea in ambulatory patients with chronic pain. In another large multicentre study, Sussman *et al*¹² recommended against any prophylactic use of antiemetics for opioid induced nausea and vomiting in both acute and chronic pain in various settings. The same study also found ondansetron to be a superior therapeutic antiemetic.

Metoclopramide is a dopamine-2 receptor antagonist and acts on both the chemoreceptor trigger zone and gastric motility. The reported incidence of side effects is 11% including restlessness, drowsiness, dystonic reaction, and akathisia.¹³ In our hospital, metoclopramide is not used for children under 12 years of age receiving IV morphine for acute pain.

In the present study, apart from the exclusion criteria detailed above, we aimed to recruit any patient who needed morphine irrespective of the painful condition. Typically, musculoskeletal causes of pain predominated in keeping with the workload profile of the whole department, but we did not intend to limit recruitment to this group of patients. The randomisation process involved the supply of prefilled, numbered syringes containing either metoclopramide or normal saline from the hospital pharmacy. The nurse issuing morphine picked one of the numbered syringes at random and gave it to the treating doctor. In addition, we instructed the nurse observing the patient for nausea and vomiting to document the patient's yes/no response from after 15 minutes of starting morphine titration because this is the peak time of analgesia achieved by morphine (the titration process takes an average of five minutes). The nature of the question asked by the nurse ensured that any nausea or vomiting reported by the patient since receiving morphine was recorded, and no such event was missed.

Our study has some limitations. The sample size did not provide sufficient statistical power. Considering our annual attendance of 60 000 patients per year, with many in acute pain, the recruitment was much slower than expected and did not reach the target of 700 patients in the proposed time scale. The study was terminated as the pharmacy could not keep up with the demand for randomisation and supply of numbered syringes. We also could not recruit all consecutive patients who needed morphine. The convenience sampling appears to have been limited at the end to traumatic painful conditions—for example, musculoskeletal injury and burns. The recruited patient population has therefore resulted in a selection bias towards trauma, although this was unintended. Both limitations are partly related to patient consent but mostly to the inability of busy doctors to devote time to patient recruitment. Thus the results of this study may not be immediately applicable to the general patient population who present in acute pain. As we only used morphine as the opioid in our study, the low incidence of nausea and vomiting may not apply to other opioids used in acute pain as these drugs have varying emetic potential.

However, we believe that, in the light of our findings, we could no longer justify using metoclopramide prophylactically, and our department has discontinued this practice since. The low incidence of nausea and vomiting has continued and will be reflected in a forthcoming prospective audit. Both the authors of this paper had had anecdotal experience of this low incidence prior to the study and felt that routine use of prophylactic metoclopramide was unnecessary.

In conclusion, it would appear wise to reserve the use of antiemetics for patients who actually vomit, and then to select an antiemetic like cyclizine or ondansetron, which have a safer side effect profile. Our practice has already changed accordingly.

ACKNOWLEDGEMENTS

The authors thank all the staff at the emergency department of Wrexham Maelor Hospital for being so proactive in their management of acute pain and their help with collecting data for this study. Thanks also go to Mr S Monks, Senior Hospital Pharmacist, for the randomised trial syringes and Dr J Turner, Senior Research Fellow, Department of Clinical Audit and Research, for help with the statistical analysis, both at Wrexham Maelor Hospital.

AUTHORS' CONTRIBUTIONS

AS conceived and designed the study. MB collected, collated, and analysed the data. AS wrote the paper and is the guarantor for the study.

Authors' affiliations

M Bradshaw, A Sen, Department of Emergency Medicine, Wrexham Maelor Hospital, Wrexham, UK

Competing interests: none declared

Request for reprints: Mr Aruni Sen

REFERENCES

- 1 **British Association for Emergency Medicine**. Clinical Effectiveness Standard 3: Pain. June 2005. Available at: www.emergencymed.org.uk (accessed August 2005).
- 2 **Campora E**, Merlini L, Pace M, *et al*. The incidence of narcotic induced emesis. *J Pain Symptom Manage* 1991;**6**:428–30.
- 3 **Chambers JA**, Guly HR. Prehospital intravenous nalbuphine administered by paramedics. *Resuscitation* 1994;**27**:153–8.
- 4 **Goodman LS**, Gilman A, Hardman JG, *et al*. *The Pharmacological Basis of Therapeutics*, 10th edn., New York: McGraw Hill 2001.
- 5 **Woodhouse A**, Mather LE. Nausea and vomiting in the post operative patient controlled analgesia environment. *Anaesthesia* 1997;**52**:770–5.
- 6 **Lambie B**, Chalmers J, Herbison P. The role of prophylactic antiemetic therapy in emergency department patients receiving intravenous morphine for musculoskeletal trauma. *Emerg Med* 1999;**11**:240–3.
- 7 **Talbot-Stern J**, Paoloni R. Prophylactic metoclopramide is unnecessary with intravenous analgesia in the, eds. *Am J Emerg Med* 2000;**18**:653–7.
- 8 **Paoloni R**, Talbot-Stern J. Low incidence of nausea, vomiting with intravenous opiate analgesia in the, eds. *Am J Emerg Med* 2002;**20**:604–8.
- 9 **Chung F**, Lane R, Spraggs C, *et al*. Ondansetron is more effective than metoclopramide for the treatment of opioid induced emesis in post surgical adult patients. *Eur J Anaesth* 1999;**16**:669–77.
- 10 **Munro F**, Fisher S, Dickson U, *et al*. The addition of antiemetics to the morphine solution in patient controlled analgesia syringes used by children after an appendicectomy does not reduce the incidence of postoperative nausea and vomiting. *Paediatr Anaesth* 2002;**12**:600–3.
- 11 **Dundee JW**, Jones PO. The prevention of analgesic induced nausea and vomiting by cyclizine. *Br J Clin Prac* 1988;**22**:379–82.
- 12 **Sussman G**, Shurman J, Creed MR, *et al*. Intravenous ondansetron for the control of opioid induced nausea and vomiting. *Clin Ther* 1999;**21**:1216–27.
- 13 **Schroeder JA**, Wolfe WM, Thomas MH, *et al*. The effect of intravenous ranitidine and metoclopramide on behaviour, cognitive function and affect. *Anaesth Analg* 1994;**78**:359–64.

Committee on Publication Ethics – Seminar 2006

9.30am–5pm Friday 10th March 2006, BMA House, London, UK

This year's seminar takes an international perspective and addresses publication ethics and research in several European countries and beyond, with interactive workshops on common ethical and editorial dilemmas. The manipulation of impact factors, and whether unethical, will also be considered.

The seminar is for editors, authors, and all those interested in increasing the standard of publication ethics. The seminar will include:

- Professor Michael Farthing – the Panel for Research Integrity (UK)
- Publication ethics and research in other countries, including those in Northern Europe, Turkey, and China
- Publication ethics in animal research
- Making the COPE website work for you – real time demonstration on how to use the website
- New indexing services
- Interactive workshops – common ethical and editorial dilemmas for editors
- Opportunities to network with other editors and share your experiences and challenges

The seminar is free for COPE members and £30.00 + VAT for non-members. Numbers are limited and early booking is advisable. For registrations or more information please contact the COPE Secretary at cope@bmjgroup.com or call 020-7383-6602

For more information on COPE see www.publicationethics.org.uk