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Original Contributions

Antiemetics in the ED: a randomized controlled trial comparing 3 common agents☆,☆☆

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Abstract

We sought to compare the efficacy of 3 intravenous antiemetic medications in ED patients complaining of moderate to severe nausea. This randomized, placebo-controlled, double-blind trial compares 1.25 mg droperidol, 10 mg metoclopramide, 10 mg prochlorperazine, and saline placebo. Adult ED patients complaining of nausea were eligible. Nausea was measured on a 100-mm visual analog scale at 0 and 30 minutes after treatment. A convenience sample of 100 patients was enrolled; 97 had complete data available for analysis. Of these, 22 patients received droperidol, 25 received metoclopramide, 24 received prochlorperazine, and 26 received placebo. Droperidol (−54.5 mm) was significantly better than metoclopramide (−40.2 mm) or prochlorperazine (−40.5 mm) at reducing nausea at 30 minutes ($P = .04$). There were no significant differences in rescue medication or patient satisfaction; however, droperidol had significantly higher akathisia (71.4% vs 23.5%) at 24-hour follow-up. When administered intravenously to adult patients with moderate to severe nausea, droperidol was more effective than metoclopramide or prochlorperazine but caused more extrapyramidal symptoms. Metoclopramide and prochlorperazine were not more effective than saline placebo. All patients improved over time and possibly with intravenous hydration.
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1. Introduction

There are more than 8 million ED visits in the United States each year by patients with a chief or secondary complaint of nausea or vomiting [1]. These complaints are commonly treated with intravenous antiemetic medications [1]. Although antiemetics have been studied extensively for the treatment of chemotherapy-associated and postoperative nausea and vomiting, literature from the ED has focused on a few selected diagnoses or examined a limited number of agents.

Ordog et al [2] studied the clinical effect of 2.5 to 5 mg of prochlorperazine administered to 40 patients with vomiting of various causes. This was the first study to show the effectiveness and safety of intravenous prochlorperazine for the control of vomiting in ED patients and was likely responsible for its subsequent widespread use. The study is limited, however, by the small sample

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Table 1 Reasons for subject exclusion before randomization

	n (%)
Total subjects excluded	62
Nausea rated <40 mm on VAS	35 (56.5)
Recent antiemetic use	7 (11.3)
Exceeded age eligibility (<18 or >65 y)	6 (9.7)
Allergy to study medication(s)	4 (6.5)
Treating physician preference	3 (4.8)
Pregnancy	3 (4.8)
Received >1 L intravenous fluid before enrollment	3 (4.8)
Subject left before randomization	1 (1.6)

size, patient selection, and lack of a placebo control. Wasserberger et al [3] administered small doses of prochlorperazine to 16 patients with acute myocardial infarction complaining of nausea or vomiting. Although this study provides evidence of safety and some evidence of efficacy, it has several limitations, including small sample size, no blinding or control group, focus on a single diagnosis, and no standardization in determining symptom relief. Finally, Ernst et al [4], in a randomized clinical trial, compared 10 mg of prochlorperazine with 25 mg of promethazine in 84 patients with a clinical diagnosis of gastritis or gastroenteritis. They found prochlorperazine to be significantly more effective than promethazine with less sedation. This study was limited by the absence of a placebo group and the restricted diagnoses included.

The goal of this investigation was to prospectively compare the efficacy of 3 common intravenous antiemetic agents with each other and placebo in a convenience sample of ED patients complaining of moderate to severe nausea of any etiology. We hypothesized that no treatment arm would be superior to any other.

2. Methods

This was a randomized, double-blind, placebo-controlled trial comparing intravenous droperidol, metoclopramide, and prochlorperazine in adult patients with moderate to severe symptoms of nausea and/or vomiting of any etiology. In addition, we performed a chart review to establish diagnoses, disposition, adverse medication effects, and supplemental treatment. This study was approved by the hospital institutional review board.

The study was conducted in the ED of a single urban teaching hospital with an annual census of 55 000 patients. Between December 1998 and December 1999, a convenience sample of adult patients complaining of nausea and/or vomiting of any cause was approached for study consent by one of the primary authors or trained research assistants. All patients provided written consent before actual study enrollment.

Inclusion criteria were (1) adults of 18 to 65 years of age, (2) primary or secondary complaint of nausea and/or vomiting, and (3) baseline nausea rated at least 40 mm on a 100-mm visual analog scale (VAS). Patients were excluded for the following reasons: (1) mild symptoms (nausea and/or vomiting rated <40 mm on a VAS), (2) hypotension defined as a systolic blood pressure less than 90 mm Hg, (3) greater than 1 liter of intravenous fluids administered before study enrollment, (4) use of commonly accepted antiemetic within the previous 24 hours, (5) known or suspected congestive heart failure, (6) pregnancy, (7) their primary ED physician did not wish the patient enrolled (usually because of the perceived need for urgent treatment), or (8) a reported allergy to any study medication. Patients were not excluded because of any specific diagnosis or for receiving other medications without antiemetic properties.

After the patient consented to participate, baseline information was obtained, including demographics, current

Table 2 Selected characteristics of enrolled subjects and baseline nausea, anxiety, and sedation visual analog scores for total and by treatment arm

	Total	Droperidol	Metoclopramide	Prochlorperazine	Saline placebo
Total	97	22	25	24	26
Characteristic					
Male[a]	42 (43.3)	7 (31.8)	8 (32.0)	17 (70.8)	10 (38.5)
Female	55 (56.7)	15 (68.2)	17 (68.0)	7 (29.2)	16 (61.5)
Age	37.5 ± 11.8 (19-63)	36.6 ± 12.6 (19-60)	38.9 ± 11.5 (22-63)	36.3 ± 11.0 (19-55)	38.2 ± 12.5 (19-58)
Intravenous fluid before randomization (mean ± SD [range]) (mL)	83.5 ± 218.3 (0-1000)	115.9 ± 265.2 (0-1000)	56.0 ± 172.2 (0-650)	50.0 ± 143.7 (0-600)	113.5 ± 269.7 (0-900)
Mean baseline scores ± SD (mm)					
Nausea	69.6 ± 17.6	69.8 ± 16.3	65.4 ± 17.5	72.2 ± 18.1	70.7 ± 18.8
Anxiety	56.8 ± 26.7	56.2 ± 23.9	52.6 ± 23.1	60.2 ± 31.1	58.2 ± 28.7
Sedation	40.9 ± 27.2	36.2 ± 27.7	45.1 ± 28.2	41.2 ± 24.7	40.2 ± 28.8

[a] Unequal distribution of sex by treatment group ($P = .017$).

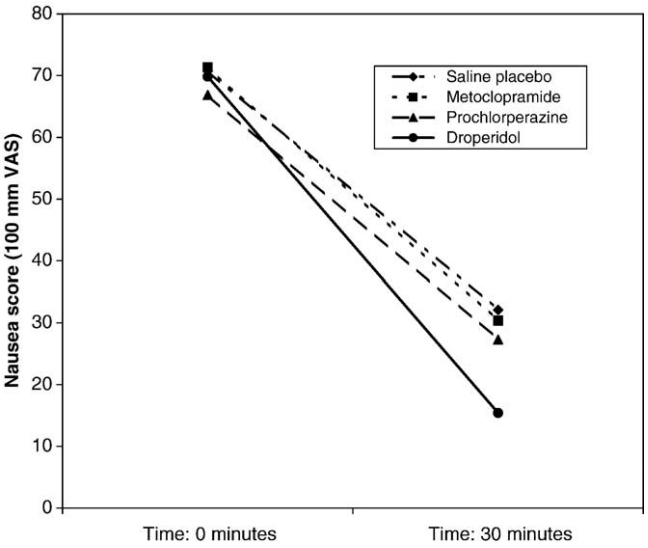

Fig. 1 Nausea score at 0 and 30 minutes, by treatment arm.

medications, duration of symptoms, and a subjective rating of nausea, sedation, and anxiety on a 100-mm VAS scale. An intravenous line of normal saline was then placed, if not already established, and set to run at a to-keep-open rate. Meanwhile, the study drug was obtained from the pharmacy. The hospital pharmacy supplied randomized prefilled syringes containing 2 mL of an identical appearing study drug: 1.25 mg of droperidol, 10 mg of metoclopramide, 10 mg of prochlorperazine, or saline. Randomization was performed with a random numbers table. Only the pharmacist knew the identity of the study drug.

At the time that the study medication was administered by one of the principal investigators or an ED nurse, the intravenous line was set to run wide open. At 30 minutes after medication administration, the subject was again queried as to their rating of nausea, sedation, and anxiety on a 100-mm VAS scale. In addition, the patient was asked if they needed further medication for their nausea and whether they were satisfied with the nausea treatment received. The 30-minute study period was selected because the investigators did not believe they could justify withholding an antiemetic agent in the placebo group for a longer period if patients were not improving.

During the 30-minute study period, intravenous fluid administration was controlled as the previous, and drugs with antiemetic properties were withheld. All other aspects of treatment continued at the discretion of the treating physician.

Nausea, sedation, and anxiety measurements were collected at 0 and 30 minutes after treatment using a VAS scale. This scale was explained to each patient and included written prompts at each end (no anxiety/severe anxiety, not sleepy/very sleepy, no nausea/severe nausea). This scale has subsequently been validated [5]. If patients incorrectly marked the scale, they were instructed again how to use it by the data collector. Patients were not shown previous marks unless they requested to see them.

Nausea, sedation, and anxiety measurements were collected from patients by either one of the authors or a trained research assistant. A structured data collection form was used to record the information.

The second author reviewed each subject's ED record for evidence of adverse reactions while still blinded to study drug. A standardized form was used to collect the data. Physician and nursing notes were reviewed for any narrative descriptions of adverse reactions such as "patient complains of feeling anxious," and subject's condition upon discharge. Physician's order sheets and nursing medication administration records were reviewed for documentation of administration of anxiolytics, diphenhydramine, or other common antiemetics after administration of the study drug.

All data were entered into a spreadsheet (Microsoft Excel, Redmond, Wash) by the second author and then imported into a statistical program (SAS version 8.2, Cary, NC) for analysis.

Table 3 Primary and secondary outcomes for total and by treatment arm

	Total	Droperidol	Metoclopramide	Prochlorperazine	Saline placebo
Total	97	22	25	24	26
Change in VAS score at 30 min less baseline score (mean ± SD)					
Nausea	−43.1 ± 22.6	−54.5 ± 18.4*	−40.2 ± 23.8	−40.5 ± 24.1	−38.7 ± 21.1
Anxiety	−25.9 ± 30.2	−23.8 ± 25.4	−25.4 ± 24.3	−21.9 ± 38.0	−31.7 ± 31.6
Sedation	3.1 ± 28.7	13.5 ± 32.2	0.4 ± 30.1	5.1 ± 26.5	−4.8 ± 25.0
Characteristic					
Intravenous fluid after randomization (mean ± SD [range]) (mL)	824.2 ± 482.3 (150-3000)	842.4 ± 488.5 (200-1990)	759.2 ± 388.0 (250-1650)	849.6 ± 396.7 (150-1750)	847.1 ± 626.1 (200-3000)
Liked the study medication (n [%])	83 (79.6)	20 (95.2)	21 (84.0)	20 (83.3)	22 (95.7)
Required rescue medication (n [%])	17 (17.5)	1 (4.5)	1 (4.0)	6 (25.0)	4 (15.4)

* $P = .04$, Dunnett test for multiple comparisons.

Table 4 Principal discharge diagnoses derived from subject medical records

	Total
Total	97
Principal diagnoses	
Acute gastroenteritis	15 (15.5)
Vomiting/abdominal pain NOS	11 (11.3)
Other medical	8 (8.2)
Acute viral syndrome	6 (6.2)
Alcohol or drug withdrawal	5 (5.2)
Gastritis/esophagitis/PUD/GI bleed	5 (5.2)
Pancreatitis	4 (4.1)
Toxicologic	4 (4.1)
Acute painful conditions	3 (3.1)
Headache	3 (3.1)
Pyelonephritis	2 (2.1)
Vertigo	2 (2.1)
Surgical emergencies	2 (2.1)
No chart available	27 (27.8)

GI indicates gastrointestinal; NOS, not otherwise specified; PUD, peptic ulcer disease.

The primary outcome measure was reduction in VAS scores for nausea. Secondary outcome measures included change in VAS scores for sedation and anxiety, need for rescue antiemetic administration, adverse medication effects, and whether or not the patient was satisfied with the medication they received.

We performed an intention-to-treat analysis using 1-way analysis of variance with Dunnett procedure for multiple comparisons with a placebo control group (saline only). We used a 2-tailed type I error rate of 0.05 to determine significance.

The study was designed to detect a clinically significant change in nausea of 20 mm with 80% power with a 2-tailed α of 5%. This corresponded to a sample size of 104 total subjects.

3. Results

One hundred eighty-one subjects were approached for study participation. Nineteen declined and 62 were excluded (Table 1), leaving 100 subjects eligible for study randomization. Three of these were excluded from the analysis because of incomplete outcome data, resulting in a final study group of 97 patients.

There were no significant differences among groups with respect to age ($P = .84$), initial degree of nausea ($P = .61$), sedation ($P = .75$), anxiety ($P = .79$), or amount of intravenous fluid received ($P = .88$). Overall, more men received prochlorperazine ($P = .02$) (Table 2).

All groups received intravenous fluids with a mean of 739 $\pm$ 445 mL. Droperidol (−54.5 mm change in nausea from baseline) was significantly better than metoclopramide (−40.2 mm) or prochlorperazine (−40.5 mm) in comparison to placebo (−38.7 mm) in reducing nausea at 30 minutes (Dunnett multiple comparisons procedure, $P = .04$). Nausea in all groups improved over 30 minutes ($P < .001$) (Fig. 1, Table 3). There were no significant differences between groups at 30 minutes with respect to subjective anxiety ($P = .70$), sedation ($P = .17$), or the need for a rescue medication ($P = .23$) (Table 3).

Final diagnoses were available for 70 (72%) of subjects (Table 4). Adverse effects data were available for 72 (74%) subjects. There was no significant difference in akathisia between groups ($P = .51$, Fisher exact test). Only 1 patient, who had received droperidol, developed a dystonic reaction.

Overall, 65 (67%) of the 97 subjects completed a follow-up interview at least 24 hours after the study (Table 5). There was no difference in follow-up by study drug ($P = .93$). There were no significant differences between groups in persistent nausea ($P = .12$). Droperidol was noted to cause significantly more self-reported anxiety or restlessness (droperidol, 71.4%, vs all others, 23.5%; difference, 47.9%; 95% confidence interval, 18.7%-67.2%). Nearly all subjects (95%, 57/62), however, were satisfied with the medication they received. Three subjects were unsure whether they were satisfied or not. There were no symptoms of dystonia reported in any group on the follow-up interviews.

4. Discussion

Our results indicate that intravenous 1.25 mg droperidol is more effective than 10 mg metoclopramide or 10 mg prochlorperazine for the relief of moderate to severe nausea in adult ED patients but is associated with a high incidence of akathisia. Akathisia is particularly problematic with droperidol and prochlorperazine. Drotts and Vinson [6]

Table 5 Results of telephone follow-up and chart review for total and by treatment arm

	Total	Droperidol	Metoclopramide	Prochlorperazine	Saline placebo
Total	97	22	25	24	26
Completed follow-up interview	65 (67.0)	14 (63.6)	16 (64.0)	17 (70.8)	18 (69.2)
Persistent nausea at 1 d after treatment	10 (15.4)	5 (35.7)	1 (6.3)	4 (23.5)	0 (0.0)
Anxiety or restlessness	22 (33.8)	10 (71.4)	4 (25.0)	6 (35.3)	2 (11.1)
Completed chart review	72 (74.2)	19 (86.4)	14 (56.0)	16 (66.7)	23 (88.5)
Restlessness or akathisia noted by staff	8 (11.1)	3 (15.8)	1 (7.1)	4 (25.0)	0 (0.0)

studied the incidence of akathisia after 1 dose of prochlorperazine 10 mg among ED patients with vomiting or severe headache. The incidence of akathisia was 44% within 1 hour and 5% within 48 hours. In those patients who developed akathisia, it was graded as moderate to severe in 30 of 44 cases. Olsen et al [7] also looked at the incidence of adverse reactions to prochlorperazine. Among 229 patients, 16% developed akathisia and 4% developed dystonia. These lower incidences may reflect the fact that their data, like ours, were not collected by direct observation.

Slow infusion has not been shown to decrease the incidence of akathisia [8,9]. It appears from our data that these symptoms develop over time and may be missed if only initial assessments are used (Table 5). Consideration may be given to prophylactic treatment of these symptoms for 24 hours if either of these medications is used, although the role of prophylaxis and the preferred agents are unclear. Despite widespread use of anticholinergic agents, β-blockers and benzodiazepines may be the most effective treatment regimens [10].

All of our patients improved over time, regardless of treatment arm. There are several possible explanations: placebo effect, hydration, relief of nausea after vomiting, general improvement over time, and regression toward the mean. We believe that hydration plays a significant role, although neither our study nor the study by Ernst et al [4] was designed to test this hypothesis.

No current discussion of droperidol is complete without mention of the black box warning added to its drug information sheet by the Food and Drug Administration in December 2001 [11]. This was based upon reports of sudden death linked to droperidol-induced QT prolongation with doses at or lower than recommended dosages. The warning states that droperidol should only be used as a second-line agent when other medications are not successful, and then only after a 12-lead EKG and continuous monitoring are initiated. Despite widespread discussion and rebuttal in the emergency medicine literature [12-15], the warning has effectively eliminated droperidol from the antiemetic armamentarium for most ED providers.

This study, however, narrows the other options that could potentially be considered "first-line" agents. Based upon our results, routine doses of metoclopramide or prochlorperazine appear to be less effective substitutes. Based upon the work of Ernst et al [4], promethazine is also dubious. Other possible treatment options include high-dose metoclopramide ($\geq$20 mg) or serotonin 5HT3 receptor antagonists such as ondansetron. Because of cost (5HT3 antagonists), side-effects (high-dose metoclopramide), and/or lack of established efficacy in the unselected adult ED patient (both agents), neither of these is currently an ideal choice. Unless the Food and Drug Administration warning is modified or eliminated, physicians will have to make individual choices weighing the risks and benefits of the available agents. Droperidol may still be the best choice in certain circumstances. However, hospital pharmacies and therapeutics committees may not make this choice available because of perceived risks.

There are several limitations to our study. We tried to select the most common dosages in clinical practice but clearly different dosages may have different effects. This is certainly true of metoclopramide where higher doses are commonly used in the chemotherapy and toxicology communities [16,17]. This is also true of droperidol where both higher and lower dosages are commonly reported [18,19]. Although promethazine is a very common antiemetic agent, it was not included in our study because it was not widely used in our department at the time of the study. The chosen 30-minute study period may have limited the maximal effect of some medications but was based upon ethical constraints with the use of a placebo arm.

We did not include a true placebo group in the sense that all groups received intravenous fluids that may have antiemetic properties. This does not interfere with our ability to ascertain a difference between the 3 agents studied. It may interfere with the overall treatment effect, but it provides a better sense of results under realistic clinical conditions.

As our population was unselected, there were potential confounding variables, including other medications administered during the study and different etiologies. It was our intention, however, to study antiemetic usage in the unselected ED patient to most closely mimic real clinical practice. We tried to eliminate any medication with antiemetic properties; however, some medications such as corticosteroids may have been inadvertently included. Medications that might stimulate nausea and vomiting were not excluded. Therefore, we believe we were biased in favor of drug underperformance.

Our assessments for akathisia consisted of self-reported symptoms during ED treatment and phone follow-up, as well as a structured chart review. We did not use any objective observational scales to detect akathisia. Previous research has shown remarkably high incidences of akathisia when specific scales are used [6]. It is possible that the incidence of akathisia was underreported.

Although the VAS scale for nausea was not validated at the time our study was conducted, it has subsequently been studied [5]. Hendey and colleagues [5] reported that a clinically meaningful change in nausea is 15 mm; we arbitrarily selected a 20-mm difference to detect a clinically significant change. Therefore, our bias was in favor of underestimated drug performance. Subsequent to this information, a post hoc analysis demonstrates our study was adequately powered (84%) to detect this difference.

Enrollment was intentionally skewed toward the moderately symptomatic patient because less symptomatic patients were systematically excluded. Clinically, however, less symptomatic patients are often not treated with an antiemetic agent. The sickest patients, those actively vomiting, may not have been enrolled because of concerns by the

nursing and physician staff, as well as the study investigators, for delaying care and obtaining informed consent in these patients.

In conclusion, when administered intravenously to adult patients with moderate to severe nausea, 1.25 mg of droperidol was more effective than 10 mg of metoclopramide or 10 mg of prochlorperazine but caused more extrapyramidal symptoms. Ten milligrams of metoclopramide and 10 mg of prochlorperazine were not more effective than saline placebo. All patients improve over time and/or with intravenous hydration.

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