

Drug Class Review

Newer Antiemetics

Final Report Update 1
Executive Summary

January 2009



The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Antiemetic drugs are primarily used to prevent nausea and vomiting experienced following surgery and with chemotherapy, radiation, and pregnancy. Nausea and vomiting associated with surgical procedures, chemotherapeutic agents, radiation therapy, and pregnancy are thought to be induced by stimulation of the dopamine, acetylcholine, histamine, serotonin, and substance P/neurokinin 1 (NK1) neuroreceptors involved in activating areas of the brain that coordinate the act of vomiting. Earlier pharmacologic agents commonly used as antiemetics included histamine-1 blockers such as diphenhydramine, anticholinergics, and dopamine antagonists including phenothiazines (chlorpromazine, perphenazine, prochlorperazine), metoclopramide, and droperidol. The discovery that type 3 serotonin (5-HT₃) receptor-blocking properties were contributing to the effect of one of the dopamine antagonists, metoclopramide, eventually led to the development of newer antiserotonergic drugs. There are currently four 5-HT₃ receptor antagonists approved for use in the United States and Canada. The newest antiemetic drugs, aprepitant and fosaprepitant, are antagonists of the substance P/neurokinin 1 (NK1) receptors. The objective of this review was to evaluate the comparative effectiveness and harms of newer antiemetic drugs including the 5-HT₃ and NK-1 antagonists.

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?
2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?
3. Are there subgroups of patients based on demographics (age, race, gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?

METHODS

Populations

Adults or children at risk for or with nausea and/or vomiting (including retching) following surgery or with chemotherapy, radiation therapy or pregnancy.

Drugs

Included drugs were oral and intravenous forms of aprepitant/fosaprepitant, dolasetron, granisetron, ondansetron and palonosetron.

Outcomes

Effectiveness and efficacy outcomes included prevention/reduction of emetic events (nausea, vomiting, retching), patient satisfaction, quality of life, and resource utilization. Harms included overall adverse events, withdrawals due to adverse events, and specific adverse events (including headache, constipation, dizziness, and sedation).

Study Designs

Controlled clinical trials and good-quality systematic reviews were included for effectiveness and efficacy outcomes. Controlled clinical trials and observational studies were included for harms.

Searching and Study Selection

To identify relevant citations for the original report, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2004), Cochrane Database of Systematic Reviews, MEDLINE (1966 to week 1 of February 2005), EMBASE (2nd Quarter 2005), and CancerLit (1974 to March 2005) using terms for included drugs, indications, and study designs. For update 1, we searched Medline (1996 to week 2 of 2008), Cochrane Central Register of Controlled Trials (2nd Quarter 2008), Cochrane Database of Systematic Reviews (1st Quarter 2008), and Database of Abstracts of Reviews of Effects (DARE) (2nd Quarter 2008). These searches were repeated in October 2008 in Medline and 3rd Quarter 2008 in Cochrane and DARE Databases to identify any additional publications published before the draft report was finalized. Using the criteria listed above, all citations were assessed for inclusion at the title and abstract level. Full-text articles of potentially relevant abstracts were retrieved, and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design; setting; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome.

Validity Assessment

We assessed the internal validity (quality) of trials with the predefined criteria based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom). We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist.

RESULTS

Overview

For the Original Report, searches identified a total of 3278 citations: 296 came from Medline, 41 from premedline, 2505 from Cochrane, 304 from Embase, 112 from CancerLit, 2 from peer review, 2 from public comment, and 16 from hand searching of reference lists. Dossiers were received from the manufacturers of aprepitant, dolasetron and ondansetron HCl, Zofran. 380 new citations were identified for Update 1: 40 from the Cochrane Central Register of Controlled Trials, 17 from the Cochrane Database of Systematic Reviews, 308 from Medline, 5 from DARE, 9 from dossiers submitted by manufacturers of dolasetron and palonosetron, and 1 from hand searching. Dossiers were received for Update 1 from the manufacturers of aprepitant, dolasetron, and palonosetron.

Overall, we included 185 studies, 81 of which involved direct comparisons between antiemetic drugs. An additional 55 placebo-controlled trials provided evidence on patient satisfaction, quality of life, and resource utilization outcomes. We found no studies that evaluated the effectiveness of antiemetic drugs during pregnancy or in children undergoing radiation.

Direct Comparisons

Ondansetron, dolasetron, and granisetron: Intravenous and oral formulations

Efficacy

Prevention of chemotherapy-induced nausea and vomiting

The numbers of patients with complete response (no emesis and no use of rescue medication) in the acute and delayed phase following moderately to severely emetic chemotherapy were similar with ondansetron, dolasetron, and granisetron, with no consistent statistically significant

differences. The rates of complete response in the first 24 hours ranged from 46% to 79% with ondansetron, 48% to 53% with granisetron, and 40% to 76% with dolasetron. During the delayed phase (days 2 to 7) the rates of complete response were 27% to 36% with ondansetron, 30% with granisetron, and 39% with dolasetron. The evidence does not indicate differences between oral and intravenous or between various oral formulations. Comparisons of other measures of effect did not identify statistically significant differences.

Prevention of postoperative nausea and vomiting in adults

No consistent statistically significant differences in antiemetic efficacy outcomes were seen in trials comparing dolasetron (7), granisetron (10), or the orally disintegrating tablet formulation of ondansetron (2) with conventional ondansetron or in trials comparing dolasetron with granisetron (2). Complete response rates generally ranged from 39% to 76% with dolasetron and 46% to 75% with granisetron compared with 48% to 79% with ondansetron.

Prevention of postoperative nausea and vomiting in children

No consistent statistically significant differences were seen between dolasetron and ondansetron (3 trials) in antiemetic efficacy outcomes. Complete response rates ranged from 68% to 86% with dolasetron and from 52% to 92% with ondansetron.

Treatment of established nausea and vomiting in adults

In one trial comparing dolasetron with ondansetron, dolasetron was superior in reducing the need for rescue therapy (40% compared with 70%, $P=0.004$) but showed no significant difference in the number of postoperative nausea and vomiting-related hospital admissions (2% compared with 2%). Additionally, in one trial comparing granisetron with ondansetron, no statistically significant differences were seen in complete response rates of 60% for granisetron 0.1 mg, 68% for granisetron 1 mg, and 47% for ondansetron.

Tolerability and safety

Chemotherapy

Ondansetron was associated with higher rates of dizziness and abnormal vision than dolasetron and granisetron in 3 trials and dolasetron was associated with significantly higher rates of constipation and diarrhea than ondansetron in 1 trial.

Prevention and treatment of postoperative nausea and vomiting

Tolerability and safety outcomes were rarely reported in trials of adults and were absent in trials of children. No consistent significant differences were seen in adults for overall adverse events, withdrawals due to adverse events, or any particular adverse event.

Gaps in direct comparative evidence

Chemotherapy-induced nausea and vomiting

Trials in adults or children undergoing chemotherapy did not report quality of life, patient satisfaction, or hospital stay outcomes. Evidence from placebo-controlled trials is inconclusive.

Prevention and treatment of postoperative nausea and vomiting

For treatment of established postoperative nausea and vomiting in children, ondansetron was superior to placebo and similar to droperidol in improving total control outcomes (1 trial each). For patient satisfaction, quality of life, and hospital stay outcomes, dolasetron was the only 5-HT₃ antagonist that consistently and significantly improved patient satisfaction outcomes compared with placebo in adults (3 out of 3 trials). Additionally, granisetron (3 trials) and ondansetron (2 trials) were superior to placebo in reducing hospital stay outcomes in children.

Radiation therapy-induced nausea and vomiting

No conclusions can be made regarding the indirect comparative efficacy and safety of dolasetron, granisetron, and ondansetron (including the oral disintegrating tablet form) based on active-control and placebo-controlled trials due to heterogeneity in patient populations, drug comparisons, radiation therapy regimens, and outcome reporting.

Pregnancy-induced nausea and vomiting

One trial of ondansetron and promethazine in hospitalized women with hyperemesis gravidarum did not provide evidence of comparative efficacy or safety among newer antiemetics.

Serious adverse events

There were no differences between ondansetron and other antiemetics or other nonteratogenic drugs in number of live births, number of malformations, birth weight, or gestational age at birth in 176 pregnant women who were exposed to treatment during gestational weeks 5 to 9. However, ondansetron and droperidol were associated with similarly significant lengthening of the QTc interval in a prospective, nonrandomized study (20 ms compared with 17 ms).

Aprepitant

Efficacy

Chemotherapy-induced nausea and vomiting

For acute, delayed, and combined periods, significantly more patients had complete response to a regimen of aprepitant 125 mg on day 1 and 80 mg on days 2 to 3 plus standard therapy of a 5-HT₃ antagonist on day 1 and dexamethasone on days 1 to 4 than regimens containing a 5-HT₃ antagonist on day 1 and dexamethasone on days 1 to 4 or a regimen extending 5HT₃ antagonist treatment, along with dexamethasone, to days 1 to 4. Meta-analysis of 3 studies of patients receiving highly emetic chemotherapy indicates that the addition of aprepitant to a standard antiemetic treatment results in a relative risk for complete response over the overall period (days 1 to 5) of 1.45 (95% CI 1.32 to 1.60), corresponding to a number needed to treat of 5. The improvement in complete response over standard antiemetic therapy persisted with aprepitant over 4 to 6 cycles of moderately and highly emetic chemotherapy, although the number of patients with complete response decreased with each course in both groups.

We found no trials of the fosprepitant formulation and dose (115 mg) available in the US. Two studies of a 100 mg dose were found and their results were mixed.

Postoperative nausea and vomiting

When aprepitant was compared with ondansetron (2 trials in adults; N=1727), aprepitant was noninferior for complete response 0-24 hours after surgery (45% to 65% for aprepitant 40 mg or 43% to 63% for aprepitant 120 mg compared with 42% to 55% for ondansetron) and superior for no vomiting 0-24 hours after surgery (84% to 92% for aprepitant 40 mg or 86% to 97% for aprepitant 120 mg compared with 71% to 75% for ondansetron).

Tolerability and safety

Chemotherapy and postoperative nausea and vomiting in adults

No difference between aprepitant and ondansetron was found in the rate of overall adverse events, withdrawals due to adverse events, or any particular adverse event.

Gaps in direct comparative evidence

Quality of life, patient satisfaction, and hospital stay outcomes were rarely reported in trials of adults undergoing chemotherapy or recovering from surgical procedures. No studies were found in children and no studies were found of effects on nausea and vomiting associated with radiation therapy or pregnancy or for *treatment* of established postoperative nausea and vomiting.

Palonosetron

Efficacy

Chemotherapy-induced nausea and vomiting

Palonosetron's rates of acute and delayed complete responses were noninferior to those of dolasetron (1 trial) and ondansetron (2 trials) in adults undergoing moderately and highly emetic chemotherapy.

Palonosetron 0.25 mg may be superior to dolasetron and ondansetron in patients receiving *moderately* emetic chemotherapy for mostly breast cancer, with pooled analysis of 2 studies indicating that the relative risk of acute complete response is 1.18 (95% CI 1.1 to 1.3; number needed to treat = 9) over the first 24 hours and the relative risk of delayed complete response is 1.36 (95% CI 1.20 to 1.54; number needed to treat = 6) over 2-3 days. Results for the 0.75 mg dose were similar, although the differences were smaller. Quality-of-life assessments did not differentiate the 3 drugs during the first 24 hours, but palonosetron resulted in higher scores than ondansetron and dolasetron during the delayed phase (days 2 to 3) in patients receiving moderately emetic chemotherapy. Differences were not seen at any time in patients receiving highly emetic chemotherapy.

Intravenous palonosetron 0.25 mg may be superior to intravenous ondansetron 8 mg/m² for improving early complete response rates (days 1 to 3) in children undergoing highly emetic chemotherapy.

Tolerability and safety

The most commonly reported adverse events were headache (4% to 15%), constipation (2% to 9%), and diarrhea (<2%). No differences were found between palonosetron and either ondansetron or dolasetron.

Gaps in direct comparative evidence

Only three trials were identified that directly compared palonosetron to any other newer antiemetic and all were conducted in adults undergoing chemotherapy. We found no studies that evaluated the effectiveness and harms of palonosetron in any other included population. Quality of life, patient satisfaction, and hospital stay outcomes were rarely reported in trials of palonosetron.

SUMMARY

Table 1 summarizes the evidence by key question.

Table 1. Summary of the evidence by key question

Key Question 1. What is the comparative effectiveness/efficacy of newer antiemetics in treating or preventing nausea and/or vomiting?			
Comparison	Population (No. trials)	Strength of the evidence	Conclusion
Dolasetron, granisetron, and ondansetron			
Granisetron vs ondansetron	Chemotherapy, adults (32)	Good	No consistent significant differences on any antiemetic efficacy outcomes, regardless of population or formulation
	Chemotherapy, children (3)	Fair	
	Postoperative prevention, adults (10)	Good	
	Postoperative treatment, adults (1)	Fair-Poor	
	Radiation therapy, adults (1)	Fair-Poor	
Dolasetron vs ondansetron	Postoperative prevention, adults (7)	Good	
	Chemotherapy, adults (3)	Good	
	Postoperative prevention, children (2)	Fair	
	Postoperative treatment, adults (1)	Fair-Poor	
Dolasetron vs granisetron	Chemotherapy, adults (1)	Good	
	Postoperative prevention, adults (2)	Fair	
Ondansetron: orally disintegrating tablet vs standard oral or intravenous	Chemotherapy, adults (1)	Fair-Poor	
	Postoperative prevention - Adults (2)	Fair	

Aprepitant/fosaprepitant			
Aprepitant vs ondansetron	Postoperative prevention, adults (2)	Good	Noninferior on 24-hour complete response rates; superior for 24-hour no vomiting outcomes
	Chemotherapy - Adults (1)	Fair	Superior on complete response over 5 days (NNT=9) and for improving quality of life
Fosaprepitant vs ondansetron	Chemotherapy - Adults (2)	Good	For complete response rates, inferior from 0 to 24 hours but superior from days 2 to 5
Palonosetron			
Palonosetron vs ondansetron	Chemotherapy - Adults (2)	Good	Noninferior to dolasetron and ondansetron on acute and delayed complete response following moderately to highly emetic chemotherapy
Palonosetron vs dolasetron	Chemotherapy - Adults (1)	Fair	Superior to dolasetron and ondansetron following moderately emetic chemotherapy in pooled analysis of 24-hour (NNT=9) and delayed (NNT=6) complete response rates and in improving delayed quality of life
Palonosetron vs ondansetron	Chemotherapy - Children (1)	Poor	Possibly superior for early complete response rates following highly emetic chemotherapy

Key Question 2. What are the comparative safety and tolerability of newer antiemetics in treating or preventing nausea and/or vomiting?

Comparison	Population	Quality	Conclusion
Aprepitant, dolasetron, granisetron, palonosetron, ondansetron	Mainly postoperative (prevention and treatment) and chemotherapy, adults	Good for dolasetron, granisetron, and ondansetron Fair for aprepitant and palonosetron	No consistent significant differences in overall adverse events, withdrawals due to adverse events, or specific adverse events

Key Question 3. Are there subgroups of patients based on demographics (age, race, gender), pregnancy, other medications, or comorbidities for which one newer antiemetic is more effective or associated with fewer adverse events

Comparison	Population	Quality	Conclusion
Dolasetron, granisetron, ondansetron	Demographics and other medications	Fair	No consistent differences in comparisons of 5-HT3 antagonists in different patient subgroups
	Prognostic risk factors: Patients with a predisposition to nausea/vomiting	Poor	Ondansetron superior to granisetron in preventing vomiting in a subgroup analysis of a single trial
Aprepitant	Gender, race	Poor	Inconclusive based on mixed findings across pooled subgroup analysis from 2 of 6 placebo-controlled trials and small subgroup analyses from trials of aprepitant compared with ondansetron submitted by manufacturer

Abbreviations: 5-HT3, type 3 serotonin; NNT, number needed to treat.