The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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.

Scan conducted by:
Rebecca Holmes, MD, MS
Brittany Holzhammer, MPH
Laura LaLonde, MPH
OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations’ consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #1: January 2009 (searches through October 2008).

Date of Last Preliminary Update Scan Report

July 2015

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions 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, and gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?
Inclusion Criteria

Populations
Adults or children at risk for or with nausea, vomiting (including retching), or both related to the following therapies and conditions:

- Chemotherapy of varying emetogenicity*
- Radiation therapy
- Surgical procedure
- Pregnancy

*In the last update report, we used the emetogenicity classification scale for chemotherapy regimens that Hesketh defined in 1997 and modified in 1999.\textsuperscript{1,2} Chemotherapeutic agents rated as “1” on this scale have a low emetic potential, while agents rated as “5” are considered to be severely emetic (a >90% chance of emesis).

Interventions
Included interventions are listed in Table 1.

Table 1. Included interventions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Mechanism</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant (po) or Fosaprepitant (iv)</td>
<td>Emend®</td>
<td>NK1</td>
<td>Injectable, oral</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>Anzemet®</td>
<td>5-HT3</td>
<td>Injectable, oral</td>
</tr>
<tr>
<td>Doxylamine Succinate/Pyridoxine Hydrochloride (FDCP)</td>
<td>Diclegis®</td>
<td>Other</td>
<td>Tablet, oral, delayed release</td>
</tr>
<tr>
<td>Granisetron</td>
<td>Generic, Sancuso®</td>
<td>5-HT3</td>
<td>Injectable, oral, transdermal patch</td>
</tr>
<tr>
<td>Netupitant/Palonosetron (FDCP)</td>
<td>Akynzeo®</td>
<td>NK1/5-HT3</td>
<td>Capsule, oral</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Zofran®, generics, Zuplenz®</td>
<td>5-HT3</td>
<td>Injectable, oral, orally disintegrating tablet, oral film</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>Generic, Aloxi®</td>
<td>5-HT3</td>
<td>Injectable</td>
</tr>
<tr>
<td>Rolapitant hydrochloride</td>
<td>Varubi™</td>
<td>NK1</td>
<td>Tablets, oral</td>
</tr>
</tbody>
</table>

Abbreviations: 5-HT3, serotonin receptor antagonist; FDCP, fixed-dose combination product; iv, intravenous; NK1, neurokinin 1 receptor antagonist; po, oral (per os).

Effectiveness outcomes
Treatment of established postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient
  - Early: Within or close to 6 hours after surgical procedure
  - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting, retching)
  - Early: Within or close to 6 hours after surgical procedure
  - Late: Within or close to 24 hours after surgical procedure

• Other: Patients’ satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of postoperative nausea and/or vomiting
• Success: Absence of vomiting and/or retching in the postoperative period
  o Acute: Within or close to 6 hours after surgical procedure
  o Late: Within or close to 24 hours after surgical procedure
• Success: Absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the postoperative period
  o Acute: Within or close to 6 hours after surgical procedure
  o Late: Within or close to 24 hours after surgical procedure
• Other: Patients’ satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of nausea and/or vomiting related to chemotherapy
• Success: Absence of vomiting and/or retching
  o Acute: During the first 24 hours of chemotherapy administration
    ▪ Vomiting and/or retching induced by highly emetic chemotherapy
    ▪ Vomiting and/or retching induced by moderately emetic chemotherapy
  o Late: After the first 24 hours of chemotherapy administration
    ▪ Vomiting and/or retching induced by highly emetic chemotherapy
    ▪ Vomiting and/or retching induced by moderately emetic chemotherapy
• Success: Absence of any emetic event (nausea, vomiting, retching)
  o Acute: During the first 24 hours of chemotherapy administration
    ▪ Emetic event induced by highly emetic chemotherapy
    ▪ Emetic event induced by moderately emetic chemotherapy
  o Late: After the first 24 hours of chemotherapy administration
    ▪ Emetic event induced by highly emetic chemotherapy
    ▪ Emetic event induced by moderately emetic chemotherapy
• Other: Patients’ satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention of radiation-induced nausea and/or vomiting
• Success: Absence of vomiting and/or retching
  o Acute: During the first 24 hours of onset of radiation therapy
  o Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days
• Success: Absence of any emetic event (nausea, vomiting, retching)
  o Acute: During the first 24 hours of onset of radiation therapy
  o Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days
Other: Patients’ satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, or need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Treatment of nausea and/or vomiting associated with pregnancy (including hyperemesis gravidarum)

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman
- Success: Absence of any emetic event (nausea, vomiting, retching)
- Change in Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: Patients’ satisfaction or quality of life, number of vomiting and/or retching episodes per period of time, need for rescue medications, serious emetic sequelae, number of emesis-free days, number of episodes and duration of hospitalization

Wherever possible, data on effective dose range, dose response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.

**Harms**

- Overall adverse events
- Specific adverse events (headache, constipation, dizziness, sedation, etc)
- Withdrawals due to adverse events
- Serious adverse events reported

**Study designs (from last report)**

- For effectiveness, controlled clinical trials and good-quality systematic reviews.
- For safety, controlled clinical trials and observational studies.

**METHODS FOR SCAN**

**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from June 2015 through June 2016 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan (these and older drugs are included in Table 1). We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrdrresearch.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination.
All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

**Study Selection**

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

**RESULTS**

**New Drugs or Formulations**

**Identified in this Preliminary Update Scan**

**New Drugs**

Rolapitant hydrochloride (Varubi™) was approved on 9/1/2015 and is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

**Identified in previous Preliminary Update Scans**

**New FDCPs**

Netupitant + palonosetron (Akynzeo®): fixed combination capsule approved on 10/10/2014 and indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

Doxylamine succinate/pyridoxine hydrochloride (Diclegis®) – FDA-approved April 2013 for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

**New Formulations**

Ondansetron oral film (Zuplenz®) – FDA-approved on 7/2/2010

Granisetron transdermal patch (Sancuso®) – FDA-approved on 9/12/2008

**New Populations**

**Identified in this Preliminary Update Scan**

None.

**Identified in previous Preliminary Update Scans**

None.
New Serious Harms (e.g., Boxed Warnings)

*Identified in this Preliminary Update Scan*
None.

*Identified in previous Preliminary Update Scans*

12/17/2010: Serious risk of Torsades de Pointes with injectable form of dolasetron. FDA recommends not using to prevent nausea and vomiting associated with chemotherapy in pediatric and adult patients (Appendix A).

12/4/2012: The 32 mg, single intravenous (IV) dose of ondansetron was removed from the market due to QT interval prolongation, which can lead to Torsades de Pointes (Appendix A).

9/2011: Dolasetron has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients (Appendix A).

Comparative Effectiveness Reviews

*Identified in this Preliminary Update Scan*
We identified 1 potentially relevant comparative effectiveness review that could be useful to answer specific pieces of an update report:


*Identified in previous Preliminary Update Scans*


3) A rapid response review on *Ondansetron for the management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients* was produced by CADTH in February 2013 (see Appendix B for the research questions on this topic).

Randomized Controlled Trials

*Trials identified since the most recent Full Report*
Medline searches conducted for the present scan identified 106 potentially relevant citations. Of these, 6 were new head-to-head trials of included antiemetic drugs, 10 were studies adding an NK1 inhibitor to a 5-HT3 antagonist with or without a steroid (see Appendix C for abstracts), and 7 were placebo-controlled trials of included drugs. We identified 4 studies of the newly approved drug rolapitant (1 head-to-head and 3 add-on), 2 of the combination product approved
in 2014 (netupitant + palonosetron; Akynzeo®), and 1 placebo-controlled trial of the combination product approved in 2013 (doxylamine + pyridoxine; Diclegis®).

Combined with the studies identified in previous scans, there are now a total of 31 head-to-head trials (Table 2), 17 add-on studies (Table 3), 2 secondary analyses, and 23 placebo-controlled trials that have been published since the last full report update. Characteristics of the head-to-head trials and add-on studies are shown in the tables below, while placebo-controlled trials are listed by drug of study below. Abstracts of head-to-head trials are reported in Appendix C. Abstracts of placebo-controlled trials are available upon request.

Table 2. Head-to-head trials (N=31)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs</th>
<th>N</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habib, 2011</td>
<td>Aprepitant vs ondansetron</td>
<td>104</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Kim, 2004</td>
<td>Dolasetron vs ondansetron</td>
<td>112</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Mandanas, 2005</td>
<td>Dolasetron vs ondansetron</td>
<td>197</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Soga, 2015</td>
<td>Fosaprepitant vs ondansetron</td>
<td>44</td>
<td>PONV in adult women</td>
</tr>
<tr>
<td>Tsutsumi, 2014</td>
<td>Fosaprepitant vs ondansetron</td>
<td>64</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Boccia, 2011</td>
<td>Granisetron transdermal vs Granisetron oral</td>
<td>641</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Kim, 2015</td>
<td>Granisetron transdermal vs Granisetron IV + oral</td>
<td>276</td>
<td>Chemotherapy in Korean adults</td>
</tr>
<tr>
<td>Metaxari, 2011</td>
<td>Granisetron vs ondansetron</td>
<td>203</td>
<td>PONV in adult women</td>
</tr>
<tr>
<td>Siddique, 2011</td>
<td>Granisetron vs ondansetron</td>
<td>60</td>
<td>Chemotherapy in children</td>
</tr>
<tr>
<td>Dabbous, 2010</td>
<td>Granisetron vs ondansetron</td>
<td>100</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Jain, 2009</td>
<td>Granisetron vs ondansetron</td>
<td>90</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Tan, 2010</td>
<td>Granisetron vs ondansetron</td>
<td>80</td>
<td>PONV in adult women</td>
</tr>
<tr>
<td>Kimura, 2015</td>
<td>Granisetron vs palonosetron (crossover)</td>
<td>24</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Raftopoulos, 2015</td>
<td>Granisetron vs palonosetron</td>
<td>1341</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Saito, 2009</td>
<td>Granisetron vs palonosetron</td>
<td>1143</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Tian, 2011</td>
<td>Granisetron vs palonosetron (crossover)</td>
<td>144</td>
<td>Chemotherapy in Chinese adults</td>
</tr>
<tr>
<td>Yu, 2009</td>
<td>Granisetron vs palonosetron</td>
<td>208</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Basu, 2011</td>
<td>Granisetron vs palonosetron vs ondansetron</td>
<td>75</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Gralla, 2014</td>
<td>Netupitant/palonosetron vs aprepitant + palonosetron</td>
<td>413</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Grover, 2009</td>
<td>Ondansetron ODT vs IV ondansetron</td>
<td>109</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Moon, 2014</td>
<td>Palonosetron vs apreperpitant</td>
<td>93</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Candiotti, 2014</td>
<td>Palonosetron vs ondansetron</td>
<td>98</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Moon, 2012</td>
<td>Palonosetron vs ondansetron</td>
<td>100</td>
<td>PONV in adult women (thyroidectomy)</td>
</tr>
<tr>
<td>Park, 2011</td>
<td>Palonosetron vs ondansetron</td>
<td>90</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Kim, 2013</td>
<td>Palonosetron vs ondansetron</td>
<td>109</td>
<td>PONV in adult women</td>
</tr>
<tr>
<td>Kim, 2013</td>
<td>Palonosetron vs ondansetron</td>
<td>100</td>
<td>PONV in adult women (gynecologic surgery)</td>
</tr>
<tr>
<td>Laha, 2013</td>
<td>Palonosetron vs ondansetron</td>
<td>98</td>
<td>PONV in adults</td>
</tr>
<tr>
<td>Kaushal, 2010</td>
<td>Palonosetron vs ondansetron</td>
<td>30</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Mattiuzzi, 2010</td>
<td>Palonosetron vs ondansetron</td>
<td>143</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Wenzell, 2013</td>
<td>Palonosetron vs ondansetron</td>
<td>40</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Gan, 2011</td>
<td>Rolapitant vs ondansetron</td>
<td>619</td>
<td>PONV in adult women</td>
</tr>
</tbody>
</table>

*Shading indicates trials identified in this scan; others were identified in previous scans; PONV, post-operative nausea and vomiting.
Secondary analyses of head-to-head trials

Aprepitant + ondansetron vs. fosaprepitant + ondansetron (N=1)

- Maru, 2013 (adults; chemotherapy)

**Table 3. Trials of add-on therapy (NK1 + 5-HT3 antagonist vs 5-HT3 antagonist, ± corticosteroid) (N=17 publications)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>N</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasu, 2015</td>
<td>Aprepitant + 5-HT3 vs 5-HT3 (not specified)</td>
<td>41</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Nishimura, 2015</td>
<td>Aprepitant or fosaprepitant + 5-HT3 vs 5-HT3</td>
<td>413</td>
<td>Chemotherapy in Japanese adults</td>
</tr>
<tr>
<td>Svanberg, 2015</td>
<td>Aprepitant + 5-HT3 vs 5-HT3 (not specified)</td>
<td>96</td>
<td>Chemotherapy in adults (stem cell transplant)</td>
</tr>
<tr>
<td>Hu, 2014</td>
<td>Aprepitant + granisetron vs granisetron</td>
<td>421</td>
<td>Chemotherapy in Chinese adults</td>
</tr>
<tr>
<td>Schmitt, 2014</td>
<td>Aprepitant + granisetron vs granisetron</td>
<td>362</td>
<td>Chemotherapy in adults (bone marrow transplant)</td>
</tr>
<tr>
<td>Takahashi, 2010</td>
<td>Aprepitant + granisetron vs granisetron</td>
<td>453</td>
<td>Chemotherapy in Japanese adults</td>
</tr>
<tr>
<td>Badar, 2015</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>98</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Bakhshi, 2015</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>96</td>
<td>Chemotherapy in children</td>
</tr>
<tr>
<td>Gore, 2009</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>46</td>
<td>Chemotherapy in adolescents</td>
</tr>
<tr>
<td>Kang, 2015</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>307</td>
<td>Chemotherapy in children</td>
</tr>
<tr>
<td>Rapoport, 2010</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>848</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Sinha, 2014</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>125</td>
<td>PONV in Bariatric surgery</td>
</tr>
<tr>
<td>Yeo, 2009</td>
<td>Aprepitant + ondansetron vs ondansetron</td>
<td>127</td>
<td>Chemotherapy in Chinese adults</td>
</tr>
<tr>
<td>Hesketh, 2014</td>
<td>Netupitant/palonosetron vs palonosetron</td>
<td>694</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Rapoport, 2015 HEC-1, HEC-2 (2 trials)</td>
<td>Rolapitant + granisetron vs granisetron</td>
<td>532, 555</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Schwartzberg, 2015</td>
<td>Rolapitant + granisetron vs granisetron</td>
<td>1369</td>
<td>Chemotherapy in adults</td>
</tr>
<tr>
<td>Rapoport, 2015</td>
<td>Rolapitant + ondansetron vs ondansetron</td>
<td>454</td>
<td>Chemotherapy in adults</td>
</tr>
</tbody>
</table>

*Shading indicates trials identified in this scan; others were identified in previous scans; PONV, post-operative nausea and vomiting.

Secondary analyses of add-on therapy

Aprepitant + ondansetron vs. ondansetron (N=1)

- Rapoport, 2014 (chemotherapy)
Placebo-controlled trials* (N=23)

**Aprepitant**
- Albany, 2012 (adults; PONV)
- Jung, 2013 (adults; PONV)
- Lim, 2013 (adults; PONV)
- Maehara, 2015 (adults; chemotherapy)
- Sinha, 2014 (adults; PONV)
- Tanioka, 2013 (adults; chemotherapy)
- Vallejo, 2012 (adults; PONV)

**Fosaprepitant**
- Saito, 2013 (adults; chemotherapy)

**Ondansetron**
- Barrett, 2011 (adults; PONV)
- Fattahi, 2015 (cesarean section)
- Koju, 2015 (cesarean section)
- de Orange, 2012 (children; PONV)
- Soltani, 2011 (adults; PONV)
- Terkawi, 2015 (adults; PONV)
- Zhang, 2013 (adults; PONV)
- Wager, 2007 (children; PONV)
- Chun, 2014 (adults; PONV)
- Hahm, 2015 (adults; PONV)
- Hesketh, 2012 (adults; PONV)
- Kim, 2015 (PONV in adult women)
- Koren, 2015 (pregnant women)
- Koren, 2010 (pregnant women; PONV)
- Reeve, 2005 (laparoscopic tubal ligation; PONV)

**Doxylamine succinate/pyridoxine HCL**
- Koren, 2015 (pregnant women)
- Koren, 2010 (pregnant women; PONV)
- Reeve, 2005 (laparoscopic tubal ligation; PONV)

*PONV, post-operative nausea and vomiting

**SUMMARY**

Since the last full report, we have identified 5 newly approved drugs or formulations; the last of these, rolapitant hydrochloride (Varubi™), was identified in the present scan. We have identified no new uses of newer antiemetics, but 3 new serious harms, 2 for dolasetron and 1 for ondansetron. We have identified 4 new comparative effectiveness reviews: 1 of interventions in early pregnancy, 1 of the long-term use of ondansetron, dolasetron and granisetron, and 2 of antiemetics in pediatric chemotherapy patients. Since the last update report, we have identified 31 new head-to-head trials (6 this scan) of which 2 studies were of new drugs; 17 studies adding an NK1 inhibitor to a 5-HT3 antagonist (10 this scan) of which 4 studies were of new drugs; 2 secondary analyses (none this scan); and 23 new placebo-controlled trials (7 this scan).
APPENDIX A. NEW SERIOUS HARMs (E.G., BOXED WARNINGS)

Ondansetron (Zofran) 32 mg, Single Intravenous (IV) Dose: Updated Safety
Communication – Product Removal due to Potential For Serious Cardiac Risks
[Posted: 12/4/2012]

ISSUE: FDA is notifying health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of the potential for serious cardiac risks.

BACKGROUND: The 32 mg, single IV dose of Zofran had been used to prevent chemotherapy-induced nausea and vomiting. A previous Drug Safety Communication (DSC), issued on June 29, 2012, communicated that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm. These drugs are sold pre-mixed in solutions of either dextrose or sodium chloride in plastic containers.

FDA anticipates these products will be removed from the market through early 2013. FDA does not anticipate that removal of the 32 mg intravenous dose of ondansetron currently sold as pre-mixed injections will contribute to a drug shortage of IV ondansetron, as the 32 mg dose makes up a very small percentage of the current market.

RECOMMENDATION: FDA continues to recommend the intravenous regimen of 0.15 mg/kg administered every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. Oral dosing of Ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting. At this time, there is not enough information available for FDA to recommend an alternative single IV dose regimen.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

Anzemet (dolasetron mesylate) tablet and injection-labeling revision
September 2011

Anzemet prolongs the QT interval in a dose dependent fashion. Torsade de Pointes has been reported during post-marketing experience. Avoid Anzemet in patients with congenital long QT syndrome, hypomagnesemia, or hypokalemia. Hypokalemia and hypomagnesemia must be corrected prior to Anzemet administration. Monitor these electrolytes after administration as clinically indicated. Use ECG monitoring in patients with congestive heart failure, bradycardia, renal impairment, and elderly patients.

PR and QRS Interval Prolongation

Anzemet has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients. At particular risk are patients with underlying structural heart disease and preexisting conduction system abnormalities, elderly, patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia or patients receiving drugs known to prolong the PR interval (such as verapamil) and QRS interval (e.g., flecainide or quinidine). Anzemet should be used with caution and with ECG monitoring in these patients. Anzemet should be avoided in patients with complete heart block or at risk for complete heart block, unless they have an implanted pacemaker.
Anzemet (dolasetron mesylate): Drug Safety Communication - Reports of Abnormal Heart Rhythms

[Posted 12/17/2010]

AUDIENCE: Oncology, Cardiology

ISSUE: FDA notified healthcare professionals that a contraindication is being added to the prescribing information advising that the injection form of Anzemet (dolasetron mesylate) should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric and adult patients. New data demonstrate that Anzemet injection can increase the risk of developing torsade de pointes, an abnormal heart rhythm, which in some cases can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Anzemet causes a dose-dependant prolongation in the QT, PR, and QRS intervals on an electrocardiogram.

BACKGROUND: FDA previously noted cardiovascular safety concerns which suggested Anzemet could cause QT prolongation. However, limitations of the previous data did not clearly establish the degree to which Anzemet may cause QT prolongation. FDA recommended that the drug sponsor conduct a thorough QT study in adults in order to determine the degree of the prolongation. A pediatric study was not recommended due to the wide variability in heart rate and, thus, QTc interval in the pediatric population. See the Data Summary section of the Drug Safety Communication (DSC) for information that supports this change in the prescribing information.

RECOMMENDATION: Anzemet should not be used in patients with congenital long-QT syndrome. Hypokalemia and hypomagnesemia should be corrected before administering Anzemet. These electrolytes should be monitored after administration as clinically indicated. Use electrocardiogram monitoring in patients with congestive heart failure, patients with bradycardia, patients with underlying heart disease, the elderly and in patients who are renally impaired who are taking Anzemet. Anzemet injection may still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used are less likely to affect the electrical activity of the heart and result in abnormal heart rhythms.

Anzemet tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this drug is less than that seen with the injection form. However, a stronger warning about this potential risk is being added to the Warnings and Precautions sections of the Anzemet tablet label.

See the DSC for additional recommendations for healthcare professionals and for patients.
APPENDIX B. NEW COMPARATIVE EFFECTIVENESS REVIEWS*


A B S T R A C T

Background
Nausea and vomiting remain a problem for children undergoing treatment for malignancies despite new antiemetic therapies. Optimising antiemetic regimens could improve quality of life by reducing nausea, vomiting, and associated clinical problems. This is an update of the original systematic review.

Objectives
To assess the effectiveness and adverse events of pharmacological interventions in controlling anticipatory, acute, and delayed nausea and vomiting in children and young people (aged less than 18 years) about to receive or receiving chemotherapy.

Search methods
Searches included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, PsycINFO, conference proceedings of the American Society of Clinical Oncology, International Society of Paediatric Oncology, Multinational Association of Supportive Care in Cancer, and ISI Science and Technology Proceedings Index from incept to December 16, 2014, and trial registries from their earliest records to December 2014. We examined references of systematic reviews and contacted trialists for information on further studies. We also screened the reference lists of included studies.

Selection criteria
Two review authors independently screened abstracts in order to identify randomised controlled trials (RCTs) that compared a pharmacological antiemetic, cannabinoid, or benzodiazepine with placebo or any alternative active intervention in children and young people (less than 18 years) with a diagnosis of cancer who were to receive chemotherapy.

Data collection and analysis
Two review authors independently extracted outcome and quality data from each RCT. When appropriate, we undertook meta-analysis.

Main results
We included 34 studies that examined a range of different antiemetics, used different doses and comparators, and reported a variety of outcomes. The quality and quantity of included studies limited the exploration of heterogeneity to narrative approaches only. The majority of quantitative data related to the complete control of acute vomiting (27 studies). Adverse events were reported in 29 studies and nausea outcomes in 16 studies. Two studies assessed the addition of dexamethasone to 5-HT3 antagonists for complete control of vomiting (pooled risk ratio (RR) 2.03; 95% confidence interval (CI) 1.35 to 3.04). Three studies compared granisetron 20 mcg/kg with 40 mcg/kg for complete control of vomiting (pooled RR 0.93; 95% CI 0.80 to 1.07). Three studies compared granisetron with ondansetron for complete control of acute nausea (pooled RR 1.05; 95% CI 0.94 to 1.17; 2 studies), acute vomiting (pooled RR 2.26; 95% CI 2.04 to 2.51; 3 studies), delayed nausea (pooled RR 1.13; 95% CI 0.93 to 1.38; 2 studies), and delayed vomiting (pooled RR 1.13; 95% CI 0.98 to 1.29; 2 studies). No other pooled analyses were possible.
Narrative synthesis suggests that 5-HT3 antagonists are more effective than older antiemetic agents, even when these agents are combined with a steroid. Cannabinoids are probably effective but produce frequent side effects.

Authors’ conclusions

Our overall knowledge of the most effective antiemetics to prevent chemotherapy-induced nausea and vomiting in childhood is incomplete. Future research should be undertaken in consultation with children, young people, and families that have experienced chemotherapy and should make use of validated, age-appropriate measures. This review suggests that 5-HT3 antagonists are effective in patients who are to receive emetogenic chemotherapy, with granisetron or palonosetron possibly better than ondansetron. Adding dexamethasone improves control of vomiting, although the risk-benefit profile of adjunctive steroid remains uncertain.


Interventions for nausea and vomiting in early pregnancy.
Matthews A, Haas DM, O'Mathúna DP, Dowswell T, Doyle M.

Abstract

BACKGROUND:
Nausea, retching and vomiting are very commonly experienced by women in early pregnancy. There are considerable physical, social and psychological effects on women who experience these symptoms. This is an update of a review of interventions for nausea and vomiting in early pregnancy previously published in 2010.

OBJECTIVES:
To assess the effectiveness and safety of all interventions for nausea, vomiting and retching in early pregnancy, up to 20 weeks' gestation.

SEARCH METHODS:
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register and the Cochrane Complementary Medicine Field's Trials Register (27 April 2013).

SELECTION CRITERIA:
All randomised controlled trials of any intervention for nausea, vomiting and retching in early pregnancy. We excluded trials of interventions for hyperemesis gravidarum, which are covered by another Cochrane review. We also excluded quasi-randomised trials and trials using a cross-over design.

DATA COLLECTION AND ANALYSIS:
Four review authors, in pairs, reviewed the eligibility of trials and independently evaluated the risk of bias and extracted the data for included trials.

MAIN RESULTS:
Thirty-seven trials involving 5049 women, met the inclusion criteria. These trials covered many interventions, including acupressure, acustimulation, acupuncture, ginger, chamomile, lemon oil, mint oil, vitamin B6 and several antiemetic drugs. We identified no studies of dietary or other lifestyle interventions. Evidence regarding the effectiveness of P6 acupressure, auricular (ear) acupressure and acustimulation of the P6 point was limited. Acupuncture (P6 or traditional) showed no significant benefit to women in pregnancy. The use of ginger products may be helpful to women, but the evidence of effectiveness was limited and not consistent, though two recent studies support ginger over placebo. There was only limited evidence from trials to support the use of pharmacological agents including vitamin B6, and anti-emetic drugs to relieve mild or
moderate nausea and vomiting. There was little information on maternal and fetal adverse outcomes and on psychological, social or economic outcomes. We were unable to pool findings from studies for most outcomes due to heterogeneity in study participants, interventions, comparison groups, and outcomes measured or reported. The methodological quality of the included studies was mixed.

AUTHORS' CONCLUSIONS:
Given the high prevalence of nausea and vomiting in early pregnancy, women and health professionals need clear guidance about effective and safe interventions, based on systematically reviewed evidence. There is a lack of high-quality evidence to support any particular intervention. This is not the same as saying that the interventions studied are ineffective, but that there is insufficient strong evidence for any one intervention. The difficulties in interpreting and pooling the results of the studies included in this review highlight the need for specific, consistent and clearly justified outcomes and approaches to measurement in research studies.

Update of Interventions for nausea and vomiting in early pregnancy. [Cochrane Database Syst Rev. 2010]

DATE: 23 April 2014
RESEARCH QUESTIONS
1. What is the clinical effectiveness of the long-term use (> 5 days) of ondansetron, dolasetron, and granisetron for the prevention of nausea and vomiting?
2. What is the clinical evidence on the safety and harms of the long-term use (> 5 days) of ondansetron, dolasetron, and granisetron for the prevention of nausea and vomiting?

Ondansetron for the Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients: A Review of the Clinical Effectiveness, Safety and Guidelines
http://www.cadth.ca/media/pdf/htis/apr-2013/RC0424-Ondansetron-Final.pdf
RESEARCH QUESTIONS
1. What is the clinical effectiveness of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients?
2. What is the clinical evidence on the safety and harms of ondansetron for the management of CINV in pediatric patients?
3. What are the evidence-based guidelines regarding the use of ondansetron for the management of CINV in pediatric patients?

*Shading indicates reviews identified in this scan
APPENDIX C. ABSTRACTS OF NEW POTENTIALLY RELEVANT RANDOMIZED CONTROLLED TRIALS

Shading indicates trials identified in this scan

Head-to-Head and Add-On Trials (N=50)


Background. Aprepitant is a P/neurokinin-1 receptor antagonist approved for the prevention of CINV in moderate emetic risk chemotherapy. We explored its effectiveness in patients with leukemia receiving cytarabine-based chemotherapy. Methods. Patients were randomized to ondansetron (OND) 8mg IV 30 minutes before cytarabine followed by 24mg IV continuous infusion daily until 6-12 hours after the last dose of chemotherapy alone or with aprepitant (APREP) oral 125mg 6-12hrs before chemotherapy and 80mg daily until 1 day after the last dose of chemotherapy. Results. Forty-nine patients were enrolled in each arm; 42 in OND and 41 in OND + APREP arm were evaluable for efficacy. The ORR with OND + APREP was 80% compared to 67% with OND alone (P = 0.11). On days 6 and 7, higher proportion of patients treated with OND + APREP were free from nausea (74%, 74% versus 68%, 67%; P = 0.27 and 0.18, resp.). Requirement of rescue medications on days 2 and 3 was fewer in OND + APREP arm 7% and 5% compared to 21% and 16% in the OND arm, respectively (P = 0.06 and P = 0.07). Conclusions. There was a trend for overall improvement in emesis with ondansetron plus aprepitant. The potential benefit of this approach with specific chemotherapy combinations remains to be determined.


BACKGROUND: Aprepitant, a neurokinin-1 receptor antagonist, in combination with 5HT-3 antagonist and dexamethasone is recommended in adults receiving moderately and highly emetogenic chemotherapy to reduce chemotherapy-induced vomiting (CIV). Data for use of aprepitant in children is limited and hence aprepitant is not recommended by Pediatric Oncology Group of Ontario guidelines for prevention of CIV in children <12 years.

METHODS: A randomized, double-blind, placebo-controlled trial was conducted at a single center in chemotherapy naive children (5-18 years) receiving highly emetogenic chemotherapy. All patients received intravenous ondansetron (0.15 mg/kg) and dexamethasone (0.15 mg/kg) prior to chemotherapy followed by oral ondansetron and dexamethasone. Patients randomly assigned to aprepitant arm received oral aprepitant (15-40 kg = days 1-3, 80 mg; 41-65 kg = day 1, 125 mg and days 2-3, 80 mg) 1 h before chemotherapy. Control group received placebo as add-on therapy. Primary outcome measure was the incidence of acute moderate to severe vomiting, which was defined as more than two vomiting episodes within 24 h after the administration of the first
chemotherapy dose until 24 h after the last chemotherapy dose in the block. Complete response (CR) was defined as absence of vomiting and retching during the specified phase.

RESULTS: Of the 96 randomized patients, three were excluded from analysis; 93 patients were analyzed (50 in aprepitant arm and 43 in placebo arm). Acute moderate and severe vomiting was reported in 72 % patients receiving placebo and 38 % patients receiving aprepitant (p = 0.001). Complete response rates during acute phase were significantly higher in aprepitant arm (48 vs. 12 %, p < 0.001). No major adverse effects were reported by patients/guardians.

CONCLUSIONS: This double-blind, randomized, placebo-controlled trial shows that aprepitant significantly decreases the incidence of CIV during acute phase when used as an add-on drug with ondansetron and dexamethasone in children receiving highly emetogenic chemotherapy.


The objective of the study was to compare the efficacy of palanosetron (0.25 mg), granisetron (3.0 mg) and ondansetron (8.0 mg) used as anti-emetics for the prevention of postoperative nausea/vomiting in patients undergoing middle ear surgery. The study was done among 75 adult patients (age group 30-45 years) of which 50 were males and rest (25) females, all of ASA I and ASA II. The patients were randomly allocated into 3 equal groups: Group I (n = 25) received injection palanosetron (0.25 mg) IV, group II (n = 25) received injection granisetron (3 mg) IV and group III (n = 25) received injection ondansetron (8.0 mg) IV at the end of the surgical procedure. A standard general anaesthesia technique was employed. Emetic episodes and safety assessments were performed during two periods of 0-6 hours in the postanaesthesia care unit and 6-24 hours in the ward after anaesthesia. The incidence of emesis-free patients during the 0-6 hours period was 100% for group I; 72% for group II and 56% for group III. During the 6-24 hours period incidence of emesis-free patients were 96% for group I; 56% for group II and 32% for group III. So to conclude, a single dose of palanosetron (0.25 mg) is a superior anti-emetic to granisetron (3.0 mg) or ondansetron (8.0 mg) in complete prevention of postoperative nausea and vomiting after middle ear surgery during the first 24 hours period.


PURPOSE: A novel transdermal formulation of granisetron (the granisetron transdermal delivery system (GTDS)) has been developed to deliver granisetron continuously over 7 days. This double-blind, phase III, non-inferiority study compared the efficacy and tolerability of the GTDS to daily oral granisetron for the control of chemotherapy-induced nausea and vomiting (CINV).

PATIENTS AND METHODS: Six hundred forty-one patients were randomized to oral (2 mg/day, 3-5 days) or transdermal granisetron (one GTDS patch, 7 days), before
receiving multi-day chemotherapy. The primary endpoint was complete control of CINV (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final administration. The prespecified non-inferiority margin was 15%.

RESULTS: Five hundred eighty-two patients were included in the per protocol analysis. The GTDS displayed non-inferiority to oral granisetron: complete control was achieved by 60% of patients in the GTDS group, and 65% in the oral granisetron group (treatment difference, -5%; 95% confidence interval, -13-3). Both treatments were well tolerated, the most common adverse event being constipation.

CONCLUSIONS: The GTDS provides effective, well-tolerated control of CINV associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron.


BACKGROUND: This study compared palonosetron and ondansetron as rescue medications for postoperative nausea and vomiting (PONV) in patients who received prophylactic ondansetron. Although guidelines recommend use of an agent from a different class when prophylaxis has failed, palonosetron has unique properties relative to other serotonin 5-HT3 receptor antagonists. Prior trials assessing its use for rescue have had conflicting results. Although palonosetron has compared favorably with ondansetron for PONV prevention, the drugs have not been compared in the rescue setting of failure of 5-HT3 receptor antagonist prophylaxis.

METHODS: This was a randomized, open-label, multicenter trial comparing the efficacy and safety of intravenous palonosetron 0.075 mg and intravenous ondansetron 4 mg in patients experiencing PONV following laparoscopic abdominal or gynecological surgery despite prophylactic ondansetron.

RESULTS: Of 239 patients screened, 220 were enrolled and 98 were treated for PONV: 48 and 50 in the palonosetron and ondansetron arms, respectively. Complete control during 72 hours after study drug administration was achieved in 25.0% of palonosetron recipients and 18.0% of ondansetron recipients (95% confidence interval [CI], -9.2, 23.3; p=0.40). Corresponding incidences of vomiting were 29.2% for palonosetron and 48.0% for ondansetron (95% CI, -0.06, 37.7; p=0.057), and 62.5% and 56.0% required additional rescue treatment, respectively (95% CI, -25.9, 12.9; p=0.52). Other than a similar incidence of procedural pain in the 2 groups, the most common treatment-emergent adverse events, which were generally mild, were headache (14.6% vs 12.0%), constipation (8.3% vs 10.0%), and dizziness (6.3% vs 8.0%), for the palonosetron and ondansetron groups, respectively.

CONCLUSIONS: Palonosetron and ondansetron did not show differences in the primary efficacy endpoint of CC during the 72 hours after study drug administration. There was a trend toward less emesis in the 0-72 h time period favoring palonosetron. While larger studies are needed to fully assess any clinical benefits of palonosetron to rescue patients who have failed ondansetron prophylaxis for PONV, the benefit, if any, would be limited based on this study.

TRIAL REGISTRATION: ClinicalTrials.gov, NCT00967499 (Registered August 27, 2009).

In a prospective randomized double-blind study, we compared the effectiveness of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery. Hundred ASA I and II patients scheduled for laparoscopic surgery were enrolled in the study and 84 patients completed it. Following induction of anesthesia, group I (n=42) received granisetron 1 mg and dexamethasone 8 mg, group II (n=42) received ondansetron 4 mg and dexamethasone 8 mg. Nausea and vomiting episodes, pain scores as well as side effects were recorded during the first hour and subsequently during the first 6 and 24 hours postoperatively. Satisfaction scores were obtained at discharge. There was no statistically significant difference between the 2 groups during the 1st 24 hours following surgery in regards to pain scores, satisfaction and side effects manifestations. At 0-1 hour interval, 100% of patients in group I and 97.6% in group II had no vomiting. Total response (no moderate or severe nausea and no rescue antiemetics) was 83.3% in group I and 80.95% in group II, and metoclopramide was used in 7.1% of patients in both groups. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II at 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. In conclusion, the combination of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg following induction of anesthesia in patients undergoing laparoscopic surgery showed no statistically significant difference in antiemetic efficacy with minimal side effects and excellent patient satisfaction.


BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after surgery. Neurokinin-1 (NK(1)) receptor antagonists have been shown to be safe and effective for the prevention and treatment of PONV in humans. Rolapitant is a potent, selective NK1 receptor antagonist that is rapidly absorbed, has a remarkably long half-life (up to 180 hours), and appears to have a low potential for drug-drug interactions. We evaluated the dose response for rolapitant for the prevention of PONV in subjects at high risk for this condition, and rolapitant's effects on preventing delayed PONV were explored up to 5 days after surgery.

METHODS: A randomized, multicenter, double-blind, dose-ranging study of rolapitant was conducted with placebo and active control groups. Six hundred nineteen adult women undergoing open abdominal surgery were randomly assigned in equal ratios to 1 of 6 study arms: oral rolapitant in 5-mg, 20-mg, 70-mg, or 200-mg doses; IV ondansetron 4 mg; or placebo, stratified by history of PONV or motion sickness. The primary study endpoint was absence of emetic episodes, regardless of use of rescue medication, at 24 hours after extubation.
RESULTS: Groups assigned to rolapitant 20-mg, 70-mg, and 200-mg had a higher incidence of no emesis in comparison with placebo at 24 hours after surgery. A linear relationship between rolapitant dose and primary outcome was seen. The probability of an emetic episode was significantly lower in the rolapitant 70-mg and 200-mg groups in comparison with placebo (P < 0.001 based on the log-rank test). No significant differences were noted between rolapitant and the active control (ondansetron) at 24 hours after surgery, but there was a higher incidence of no emesis (regardless of rescue medication use) in the rolapitant 200- and 70-mg groups at 72 and 120 hours, respectively.

CONCLUSION: Rolapitant is superior to placebo in reducing emetic episodes after surgery and reduces the incidence of vomiting in a dose-dependent manner. No differences in side effect profile were observed between rolapitant and placebo.


BACKGROUND: The neurokinin-1 receptor antagonist aprepitant, plus a 5HT3 antagonist and corticosteroid is well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in adults but has not been formally assessed in adolescents.

PROCEDURE: Patients age 11-19 years old receiving emetogenic chemotherapy were randomized 2:1 to aprepitant triple therapy (aprepitant [A] 125 mg p.o., dexamethasone [D] 8 mg p.o., and ondansetron [O] 0.15 mg/kg i.v. t.i.d. day 1; A 80 mg, D 4 mg, and O 0.15 mg/kg t.i.d. day 2; A 80 mg and D 4 mg day 3; and D 4 mg day 4) or a control regimen (D 16 mg and O 0.15 mg/kg t.i.d. day 1; D 8 mg and O 0.15 mg/kg t.i.d. day 2; and D 8 mg days 3 and 4). The primary endpoint was the difference in drug-related adverse events during and for 14 days following treatment. Efficacy and aprepitant pharmacokinetics were assessed.

RESULTS: Baseline characteristics were similar between aprepitant (N = 28) and control (N = 18) groups. Febrile neutropenia was more frequent in the aprepitant group (25% vs. 11.1%). Complete response (CR) rates were 35.7% for aprepitant triple therapy versus 5.6% for the control group. Mean plasma aprepitant AUC(0-24 hr) and C(max) on day 1 and mean trough concentrations on days 2 and 3 were consistently lower compared to historical data obtained from healthy adults; however, the differences were not clinically significant.

CONCLUSION: Aprepitant triple therapy was generally well tolerated; CR were greater with aprepitant, although not statistically significant. Pharmacokinetics suggest that the adult dosing regimen is appropriate for adolescents.


BACKGROUND: Safe, effective and convenient antiemetic regimens that preserve benefit over repeated cycles are needed for optimal supportive care during cancer treatment. NEPA, an oral fixed-dose combination of netupitant, a highly selective NK1 receptor antagonist (RA), and palonosetron (PALO), a distinct 5-HT3 RA, was shown to
be superior to PALO in preventing chemotherapy-induced nausea and vomiting after a single cycle of highly (HEC) or moderately (MEC) emetogenic chemotherapy in recent trials. This study was designed primarily to assess the safety but also to evaluate the efficacy of NEPA over multiple cycles of HEC and MEC.

PATIENTS AND METHODS: This multinational, double-blind, randomized phase III study (NCT01376297) in 413 chemotherapy-naive patients evaluated a single oral dose of NEPA (NETU 300 mg + PALO 0.50 mg) given on day 1 with oral dexamethasone (DEX). An oral 3-day aprepitant (APR) regimen + PALO + DEX was included as a control (3:1 NEPA:APR randomization). In HEC, DEX was administered on days 1-4 and in MEC on day 1. Safety was assessed primarily by adverse events (AEs), including cardiac AEs; efficacy by complete response (CR: no emesis, no rescue).

RESULTS: Patients completed 1961 total chemotherapy cycles (76% MEC, 24% HEC) with 75% completing >4 cycles. The incidence/type of AEs was comparable for both groups. Most frequent NEPA-related AEs included constipation (3.6%) and headache (1.0%); there was no indication of increasing AEs over multiple cycles. The majority of AEs were mild/moderate and there were no cardiac safety concerns based on AEs and electrocardiograms. The overall (0-120 h) CR rates in cycle 1 were 81% and 76% for NEPA and APR + PALO, respectively, and antiemetic efficacy was maintained over repeated cycles.

CONCLUSIONS: NEPA, a convenient single oral dose antiemetic targeting dual pathways, was safe, well tolerated and highly effective over multiple cycles of HEC/MEC. Copyright © The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology.


Peri-operative prophylactic anti-emetics are commonly used parenterally. Orally disintegrating ondansetron is efficacious during chemotherapy. Therefore, we aimed to study the efficacy of orally disintegrating ondansetron for postoperative nausea and vomiting. In a randomised, double-blind, placebo controlled trial on 109 patients scheduled for laparoscopic cholecystectomy, oral ondansetron was compared to intravenous ondansetron and placebo. The anaesthetic technique was standardised. Mean time (SD) to tolerating oral intake was delayed in the placebo group to 366.1 (77.6) min compared to oral 322.9 (63.7) min and intravenous 322.4 (65.2) min groups. This was corroborated by a higher incidence of nausea and vomiting in the control group during the first 6 h postoperatively (control 44.4%, oral 17.7%, intravenous 18.2%). There was no significant difference between oral and intravenous groups. In conclusion, orally disintegrating ondansetron was as efficacious as intravenous ondansetron in the peri-operative phase and may be a viable option for prophylaxis of emesis in day care surgery.

BACKGROUND: Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 hours. In addition to causing patient discomfort, the physical act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokinin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery, aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 hours postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia.

METHODS: Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 hours after surgery. Statistical analysis was performed using Wilcoxon’s ranked sum test and (2) test. P < 0.05 was considered statistically significant.

RESULTS: One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group (P = 0.0149). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% vs 21%, P = 0.0419) and 24 hours (14% vs 36%, P = 0.0124). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs 60%), nausea scores, need for rescue antiemetics (65% vs 60%), complete response (no PONV and no rescue, 22% vs 36%), or patient satisfaction with the management of PONV.

CONCLUSION: The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

with oral PALO 0.50 mg, all given on day 1. A standard 3-day aperpitant (APR) + IV ondansetron (OND) 32 mg regimen was included as an exploratory arm. All patients received oral dexamethasone on days 1-4. The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the overall (0-120 h) phase.

RESULTS: All NEPA doses showed superior overall CR rates compared with PALO (87.4%, 87.6%, and 89.6% for NEPA100, NEPA200, and NEPA300, respectively versus 76.5% PALO; P < 0.050) with the highest NEPA300 dose studied showing an incremental benefit over lower NEPA doses for all efficacy endpoints. NEPA300 was significantly more effective than PALO and numerically better than APR + OND for all secondary efficacy endpoints of no emesis, no significant nausea, and complete protection (CR plus no significant nausea) rates during the acute (0-24 h), delayed (25-120 h), and overall phases. Adverse events were comparable across groups with no dose response. The percent of patients developing electrocardiogram changes was also comparable.

CONCLUSIONS: Each NEPA dose provided superior prevention of chemotherapy-induced nausea and vomiting (CINV) compared with PALO following highly emetogenic chemotherapy; however, NEPA300 was the best dose studied, with an advantage over lower doses for all efficacy endpoints. The combination of NETU and PALO was well tolerated with a similar safety profile to PALO and APR + OND. Copyright © The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology.


PURPOSE: Aprepitant, an oral neurokinin-1 receptor antagonist, has demonstrated improved control of chemotherapy-induced nausea and vomiting (CINV) in previous studies. This is the first phase III study to evaluate the efficacy and tolerability of aperpitant in patients receiving highly emetogenic chemotherapy (HEC) in Asian countries.

METHODS: This multicenter, double-blind, placebo-controlled trial assessed the prevention of CINV during the acute phase (AP), delayed phase (DP), and overall phase (OP). Patients receiving HEC were randomized to either an aperpitant group (day 1, aperpitant 125 mg; days 2-3, aperpitant 80 mg) or a standard therapy group (days 1-3, placebo). Both groups received intravenous granisetron and oral dexamethasone. The primary end point was complete response (CR; no emesis and no use of rescue therapy) during the OP.

RESULTS: Of the 421 randomized patients, 411 (98%) were assessable for efficacy; 69.6% (142/204) and 57.0% (118/207) of patients reported CR during the OP in the aperpitant and standard therapy groups, respectively (P = 0.007). CR rates in the aperpitant group were higher during the DP (74.0% vs. 59.4%, P = 0.001) but were similar during the AP (79.4% vs. 79.3%, P = 0.942). Toxicity and adverse events were comparable in both groups.

CONCLUSIONS: The addition of aperpitant to standard antiemetic treatment regimens for Chinese patients undergoing HEC provided superior CINV prevention and was well tolerated.

Postoperative nausea and vomiting (PONV) are frequent and distressing complications after neurosurgical procedures. We evaluated the efficacy of ondansetron and granisetron to prevent PONV after supratentorial craniotomy. In a randomized double-blind, placebo controlled trial, 90 adult American Society of Anesthesiologists I, II patients were included in the study. A standard anesthesia technique was followed. Patients were divided into 3 groups to receive either placebo (saline), ondansetron 4 mg, or granisetron 1 mg intravenously at the time of dural closure. After extubation, episodes of nausea and vomiting were noted for 24 hours postoperatively. Statistical analysis was performed using chi2 test and 1-way analysis of variance. Demographic data, duration of surgery, intraoperative fluids and analgesic requirement, and postoperative pain (visual analog scale) scores were comparable in all 3 groups. It was observed that the incidence of vomiting in 24 hours, severe emetic episodes, and requirement of rescue antiemetics were less in ondansetron and granisetron groups as compared with placebo (P<0.001). Both the study drugs had comparable effect on vomiting. However, the incidence of nausea was comparable in all 3 groups (P=0.46). A favorable influence on the patient satisfaction scores, and number needed to prevent emesis was seen in the 2 drug groups. No significant correlation was found between neurosurgical factors (presence of midline shift, mass effect, pathologic diagnosis of tumor, site of tumor) and the occurrence of PONV. We conclude that ondansetron 4 mg and granisetron 1 mg are comparably effective at preventing emesis after supratentorial craniotomy. However, neither drugs prevented nausea effectively.


BACKGROUND: Oral aprepitant, a neurokinin-1 receptor antagonist, is recommended in combination with other anti-emetic agents for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy in adults, but its efficacy and safety in paediatric patients are unknown. We did this phase 3 trial to examine the safety and efficacy of such treatment in children.

METHODS: In this final analysis of a phase 3, randomised, multicentre, double-blind study, patients aged 6 months to 17 years with a documented malignancy who were scheduled to receive either moderately or highly emetogenic chemotherapy were randomly assigned with an interactive voice response system to an age-based and weight-based blinded regimen of aprepitant (125 mg for ages 12-17 years; 3.0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12-17 years; 2.0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3, or placebo plus ondansetron on day 1 followed by placebo on days 2 and 3; addition of dexamethasone was allowed. Randomisation was stratified according to patient age, planned use of chemotherapy associated with very high risk of emetogenicity, and planned use of dexamethasone as an anti-emetic. Ondansetron was dosed per the product label for paediatric use or local standard of care. The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, no
retching, and no use of rescue medication) during the 25-120 h (delayed phase) after initiation of emetogenic chemotherapy. Efficacy and safety analyses were done with all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01362530.

FINDINGS: Between Sept 22, 2011, and Aug 16, 2013, 307 patients were randomly assigned at 49 sites in 24 countries to either the aprepitant group (155 patients) or to the control group (152 patients). Three patients in the aprepitant group and two in the control group did not receive study medication, and thus were excluded from analyses. 77 (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase (p<0.0001). The most common grade 3-4 adverse events were febrile neutropenia (23 [15%] of 152 in the aprepitant group vs 21 [14%] of 150 in the control group), anaemia (14 [9%] vs 26 [17%]), and decreased neutrophil count (11 [7%] vs 17 [11%]). The most common serious adverse event was febrile neutropenia (23 [15%] patients in the aprepitant group vs 22 [15%] in the control group).

INTERPRETATION: Addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients being treated with moderately or highly emetogenic chemotherapy.

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INTRODUCTION: Palonosetron and ondansetron are two selective 5-hydroxytryptamine (5-HT3) receptor antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of moderately emetic anticancer chemotherapy. Their efficacy is enhanced by the concurrent administration of dexamethasone. In the present study, we aimed to compare the antiemetic efficacy of a palonosetron plus dexamethasone (PD) schedule versus an ondansetron plus dexamethasone (OD) schedule.

METHODS: A randomised, crossover trial was conducted in 30 patients with head and neck cancer who were receiving moderately emetogenic chemotherapy. The patients were divided into two groups. In the first cycle, one group was given a PD schedule and the other, an OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases.

RESULTS: Complete response in the acute phase was observed in 83.3 percent of the patients on the PD schedule and in 80 percent of those on the OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases. The overall rate of complete response was 66.7 percent in the PD group and 46.7 percent in the OD group. In the PD group, there were 73.3 percent of nausea-free patients as opposed to 66.7 percent in the OD group.

CONCLUSION: The results suggest that the PD schedule was superior to the OD schedule in controlling emesis in cancer chemotherapy, although this difference was not statistically significant.

PURPOSE: The aim of this study is to compare the antiemetic efficacy and tolerability of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed emesis.

MATERIAL AND METHODS: From April 2002 through October 2002, a total of 112 patients receiving cisplatin-based combination chemotherapy were randomized to receive a single i.v. dose of dolasetron 100 mg or ondansetron 8 mg, 30 minutes before the initiation of chemotherapy. In the ondansetron group, two additional doses of ondansetron 8 mg were given at intervals of 2 to 4 hours. To prevent delayed emesis, dolasetron 200 mg p.o. daily or ondansetron 8 mg p.o. bid was administered from the 2(nd) days to a maximum of 5 days. The primary end point was the proportion of patients that experienced no emetic episodes and required no rescue medication (complete response, CR) during the 24 hours (acute period) and during Day 2 to Day 5+/−2 days (delayed period), after chemotherapy. The secondary end points included the incidence and severity of emesis. RESULTS: 105 patients were evaluable for efficacy. CR rates during the acute period were 36.0% for a single dose of dolasetron 100 mg, and 43.6% for three doses of ondansetron 8 mg. CR rates during the delayed period were 8.0% and 10.9%, respectively. There was no significant difference in the efficacy between the two groups. Adverse effects were mostly mild to moderate and not related to study medication. CONCLUSIONS: A single i.v. dose of dolasetron 100 mg is as effective as three i.v. doses of ondansetron 8 mg in preventing acute and delayed emesis after cisplatin-based chemotherapy, with a comparable safety profile.


BACKGROUND: Postoperative nausea and vomiting (PONV) continues to be a major problem, because PONV is associated with delayed recovery and prolonged hospital stay. Although the PONV guidelines recommended the use of 5-hydroxy-tryptamine (5-HT3) receptor antagonists as the first-line prophylactic agents in patients categorized as high-risk, there are few studies comparing the efficacies of ondansetron, ramosetron, and palonosetron. The aim of present study was to compare the prophylactic antiemetic efficacies of three 5HT3 receptor antagonists in high-risk patients after laparoscopic surgery.

METHODS: In this prospective, randomized, double-blinded trial, 109 female nonsmokers scheduled for elective laparoscopic surgery were randomized to receive intravenous 4 mg ondansetron (n = 35), 0.3 mg ramosetron (n = 38), or 75 g palonosetron (n = 36) before anesthesia. Fentanyl-based intravenous patient-controlled analgesia was administered for 48 h after surgery. Primary antiemetic efficacy variables were the incidence and severity of nausea, the frequency of emetic episodes during the first 48 h after surgery, and the need to use a rescue antiemetic medication.

RESULTS: The overall incidence of nausea/retching/vomiting was lower in the palonosetron (22.2%/11.1%/5.6%) than in the ondansetron (77.1%/48.6%/28.6%) and ramosetron (60.5%/28.9%/18.4%) groups. The rescue antiemetic therapy was required less frequently in the palonosetron group than the other groups (P < 0.001). Kaplan-Meier analysis
showed that the order of prophylactic efficacy in delaying the interval to use of a rescue emetic was palonosetron, ramosetron, and ondansetron.

CONCLUSIONS: Single-dose palonosetron is the prophylactic antiemetics of choice in high-risk patients undergoing laparoscopic surgery.


BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after anesthesia and surgery. This study was designed to compare the effects of palonosetron and ondansetron in preventing PONV in high-risk patients receiving intravenous opioid-based patient-controlled analgesia (IV-PCA) after gynecological laparoscopic surgery.

METHODS: One hundred non-smoking female patients scheduled for gynecological laparoscopic surgery were randomly assigned into the palonosetron group (n = 50) or the ondansetron group (n = 50). Palonosetron 0.075 mg was injected as a bolus in the palonosetron group. Ondansetron 8 mg was injected as a bolus and 16 mg was added to the IV-PCA in the ondansetron group. The incidences of nausea, vomiting and side effects was recorded at 2 h, 24 h, 48 h and 72 h, postoperatively.

RESULTS: There were no significant differences between the groups in the incidence of PONV during 72 h after operation. However, the incidence of vomiting was lower in the palonosetron group than in the ondansetron group (18% vs 4%, P = 0.025). No differences were observed in use of antiemetics and the side effects between the groups.

CONCLUSIONS: The effects of palonosetron and ondansetron in preventing PONV were similar in high-risk patients undergoing gynecological laparoscopic surgery and receiving opioid-based IV-PCA.


BACKGROUND: The granisetron transdermal system (GTS) showed non-inferior efficacy to oral granisetron to control chemotherapy-induced nausea and vomiting (CINV) during multimodal chemotherapy. We compared the efficacy and safety of GTS with that of intravenous and oral granisetron in Korean patients receiving moderately emetogenic chemotherapy (MEC).

PATIENTS AND METHODS: A total of 276 patients were randomized into GTS (n=139, one patch on days 1-4) or control group (n=137, intravenous on day 1 and oral on days 2-4). The primary endpoint was the percentage of patients achieving complete response (CR) from chemotherapy initiation until 24 h after the final administration.

RESULTS: Out of 234 patients (112 in GTS and 122 in control group) included in the per protocol analysis, 97.9 % had gastrointestinal cancer and 76.9 % received 3-day chemotherapy. The GTS showed non-inferior efficacy achieving CR in 75.0 % of the patients; 74.6 % of the patients in the control group achieved CR (95 % confidence interval -10.73 to 11.55 %). The CR rate did not change after subgroup analyses by sex, age, and chemotherapy naivety and analysis per day and overall days of treatment. The
GTS group showed sustained CR from day 1 to day 4. Patients' satisfaction, assessed using Functional Living Index-Emesis (FLI-E), showed no difference. Both treatments were well tolerated and safe.

CONCLUSION: The GTS showed non-inferior efficacy to intravenous and oral granisetron. The safety, tolerability, and FLI-E scores of the GTS were comparable to those of control group. The GTS offers a convenient alternative option for relieving CINV in patients receiving MEC.


The first aim of this study was to evaluate combination antiemetic therapy consisting of 5-HT3 receptor antagonists, neurokinin-1 receptor antagonists (NK-1RAs), and dexamethasone for multiple high emetogenic risk (HER) anticancer agents in bone and soft tissue sarcoma. The second aim was to compare the effectiveness of single-shot palonosetron and consecutive-day granisetron in a randomized, single-blinded crossover study. A single randomization method was used to assign eligible patients to the palonosetron or granisetron arm. Patients in the palonosetron arm received a palonosetron regimen during the first and third chemotherapy courses and a granisetron regimen during the second and fourth courses. All patients received NK-1RA and dexamethasone. Patients receiving the palonosetron regimen were administered 0.75 mg palonosetron on day 1, and patients receiving the granisetron regimen were administered 3 mg granisetron twice daily on days 1 through 5. All 24 patients in this study received at least 4 chemotherapy courses. A total of 96 courses of antiemetic therapy were evaluated. Overall, the complete response CR rate (no emetic episodes and no rescue medication use) was 34%, while the total control rate (a CR plus no nausea) was 7%. No significant differences were observed between single-shot palonosetron and consecutive-day granisetron. Antiemetic therapy with a 3-drug combination was not sufficient to control chemotherapy-induced nausea and vomiting (CINV) during chemotherapy with multiple HER agents for bone and soft tissue sarcoma. This study also demonstrated that consecutive-day granisetron was not inferior to single-shot palonosetron for treating CINV. Copyright © 2014 The Authors. Cancer Medicine published by John Wiley & Sons Ltd.


OBJECTIVES: Incidence of postoperative nausea and vomiting (PONV), without active intervention, following laparoscopic cholecystectomy is unacceptably high. We evaluated the effectiveness of intravenous (IV) palonosetron in counteracting PONV during the first 24 hrs following laparoscopic cholecystectomy, using ondansetron as the comparator drug.

MATERIALS AND METHODS: In a randomized, controlled, single blind, parallel group trial, single pre-induction IV doses of palonosetron (75 mcg) or ondansetron (4 mg) were
administered to adult patients of either sex undergoing elective laparoscopic cholecystectomy. There were 49 subjects per group. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary effectiveness measure was total number of PONV episodes in the 24 hrs period following end of surgery. The frequencies of individual nausea, retching and vomiting episodes, visual analog scale (VAS) score for nausea at 2, 6 and 24 hrs, use of rescue antiemetic (metoclopramide), number of complete responders (no PONV or use of rescue in 24 hrs) and adverse events were secondary measures.

RESULTS: There was no statistically significant difference between the groups in primary outcome. Similarly, the frequencies of nausea, retching and vomiting episodes, when considered individually, did not show significant difference. Nausea score was comparable at all time points. With palonosetron, 14 subjects (28.6%) required rescue medication while 13 (26.5%) did so with ondansetron. The number of complete responders was 14 (28.6%) and 16 (32.7%), respectively. Adverse events were few and mild. QTc prolongation was not encountered.

CONCLUSION: Palonosetron is comparable to ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.


This study assessed the efficacy and safety of dolasetron compared with ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy followed by peripheral blood stem cell support. Twenty centers randomized 197 patients to receive dolasetron 100 mg intravenously (I.V.) followed 8-12 hours later by a single oral dose of dolasetron 100 mg or ondansetron 32 mg I.V., followed 8-12 hours later by a single oral dose of ondansetron 8 mg during high-dose chemotherapy (HDC) regimens for breast cancer (n = 96; 48.7%), non-Hodgkin's lymphoma (n = 83; 42.1%), or Hodgkin's disease (n = 18; 9.1%). All patients received a daily I.V. bolus of dexamethasone 10 mg with study antiemetic agents and a continuous infusion of diphenhydramine, lorazepam, and dexamethasone (ie, BAD pump) throughout the course of the study, with patient-controlled on-demand bolus doses as needed. After completing a daily diary of emetic episodes and rescue medication use, 164 of 197 patients were evaluable. Total plus complete responses (no emesis, no nausea, no rescue) over the entire study period were achieved in 45.7% and 46.9% of patients on the dolasetron and ondansetron arms, respectively. Dolasetron and ondansetron were well-tolerated. This study demonstrates that dolasetron and ondansetron are equally safe and effective in the prevention of nausea and vomiting associated with HDC (P = 0.955).


Context: Currently, there is limited data on the prevention of chemotherapy-induced nausea and vomiting (CINV) in Indian patients. Aims: This post hoc study assessed the efficacy and safety of fosaprepitant compared with aprepitant for prevention of CINV in the Indian
population. A subgroup analysis was performed from data collected in a phase 3 study of intravenous (IV) fosaprepitant or oral aprepitant, plus the 5-HT 3 antagonist ondansetron and the corticosteroid dexamethasone, in cisplatin-nave patients with solid malignancies. Materials and Methods: Patients scheduled to receive cisplatin (>70 mg/m²) were administered a single IV dose of fosaprepitant dimeglumine (150 mg) on day 1 or a 3-day dosing regimen of oral aprepitant (day 1:125 mg, days 2 and 3:80 mg) with standard doses of ondansetron and dexamethasone. Patients recorded nausea and/or vomiting episodes and their use of rescue medication and were monitored for adverse events (AEs) and tolerability. Statistical Analysis Used: Differences in response rates between fosaprepitant and aprepitant were calculated using the Miettinen and Nurminen method. Results: In the Indian subpopulation (n = 372), efficacy was similar for patients in both the fosaprepitant or aprepitant groups; complete response in the overall, acute, and delayed phases and no vomiting in all phases were approximately 4 percentage points higher in the fosaprepitant group compared with the aprepitant group. Fosaprepitant was generally well-tolerated; common AEs were similar to oral aprepitant. Conclusions: IV fosaprepitant is as safe and effective as oral aprepitant in the Indian subpopulation and offers an alternative to the oral formulation.


BACKGROUND: Nausea and vomiting in patients with acute myelogenous leukemia (AML) can be from various causes, including the use of high-dose cytarabine.

METHODS: The authors compared 2 schedules of palonosetron versus ondansetron in the treatment of chemotherapy-induced nausea and vomiting (CINV) in patients with AML receiving high-dose cytarabine. Patients were randomized to: 1) ondansetron, 8 mg intravenously (IV), followed by 24 mg continuous infusion 30 minutes before high-dose cytarabine and until 12 hours after the high-dose cytarabine infusion ended; 2) palonosetron, 0.25 mg IV 30 minutes before chemotherapy, daily from Day 1 of high-dose cytarabine up to Day 5; or 3) palonosetron, 0.25 mg IV 30 minutes before high-dose cytarabine on Days 1, 3, and 5.

RESULTS: Forty-seven patients on ondansetron and 48 patients on each of the palonosetron arms were evaluable for efficacy. Patients in the palonosetron arms achieved higher complete response rates (no emetic episodes plus no rescue medication), but the difference was not statistically significant (ondansetron, 21%; palonosetron on Days 1-5, 31%; palonosetron on Days 1, 3, and 5, 35%; P = .32). Greater than 77% of patients in each arm were free of nausea on Day 1; however, on Days 2 through 5, the proportion of patients without nausea declined similarly in all 3 groups. On Days 6 and 7, significantly more patients receiving palonosetron on Days 1 to 5 were free of nausea (P = .001 and P = .0247, respectively). CONCLUSIONS: The daily assessments of emesis did not show significant differences between the study arms. Patients receiving palonosetron on Days 1 to 5 had significantly less severe nausea and experienced significantly less impact of CINV on daily activities on Days 6 and 7.


PURPOSE: The aim of this double-blind randomized study was to compare the antiemetic efficacy of three 5-hydroxytryptamine type 3 antagonists in terms of the incidence and intensity of postoperative nausea and vomiting (PONV) in a homogenous group of female patients undergoing thyroidectomy.

METHODS: The study cohort consisted of 203 American Society of Anesthesiologists PS I-II female patients randomized into four groups to receive at induction of anesthesia an intravenous (IV) bolus of 5 ml solution of one of the following: normal saline (placebo), granisetron 3 mg, ondansetron 4 mg, or tropisetron 5 mg. Nausea and vomiting were evaluated at five time points: during the first hour in the postanesthesia care unit (PACU) and 6, 12, 18, and 24 h postoperatively. Nausea intensity was measured using a visual analogue scale score (0-10).

RESULTS: Patients in the placebo group displayed a high incidence of nausea in the PACU and at 6, 12, and 18 h postoperatively (44, 60, 50, and 34%, respectively) and of vomiting (26, 42, 30 and 10%). The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 h (26, 18, and 2%, respectively) and vomiting at 6 and 12 h (10 and 6%, respectively). Ondansetron reduced significantly the incidence of nausea and vomiting only at 6 h postoperatively (28 and 12%, respectively). The administration of tropisetron did not affect the incidence of PONV compared to placebo.

CONCLUSION: Among the female patients of this study undergoing thyroid surgery, granisetron 3 mg provided the best prophylaxis from PONV. Ondansetron 4 mg was equally effective, but its action lasted only 6 h, whereas tropisetron 5 mg was found ineffective.


BACKGROUND: Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking. This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy.

METHODS: A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue antiemetics, and adverse effects were evaluated during 0-2 and 2-24 h.

RESULTS: The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, P=0.045). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2-24 h. The only difference in the use of rescue antiemetics was at 2-24 h (10% with palonosetron compared with 28% with ondansetron, P=0.02).
CONCLUSIONS: Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2-24 h after surgery.


**BACKGROUND:** Postoperative nausea and vomiting (PONV) is one of the most common postsurgical complications. Palonosetron, a 5-hydroxytryptamine receptor antagonist, is effective for PONV prevention. Herein, we compared palonosetron and aprepitant (a neurokinin-1 receptor antagonist) for PONV prevention in patients indicated for laparoscopic gynaecologic surgery.

**METHODS:** Ninety-three patients who were scheduled to undergo laparoscopic gynaecologic surgery under general anaesthesia were assigned to receive either a single intravenous injection of 0.075-mg palonosetron or 40-mg oral aprepitant in a double-blind randomised trial. The primary efficacy end points included complete response (visual analogue scale [VAS] nausea score <4 and no use of rescue therapy) 0-48 h after surgery. Nausea severity (0-10) and use of rescue therapy were monitored for 0-48 h. The secondary efficacy end points were the effect of aprepitant quantified using a 10-point VAS for pain, consumption of intravenous patient-controlled analgesia, and use of rescue analgesics.

**RESULTS:** Aprepitant was non-inferior to palonosetron in terms of complete response 0-48 hours after surgery (74% vs. 77%). At 0 and 2 h after administration, the nausea severity with 40-mg aprepenptant was significantly lesser than that with 0.075-mg palonosetron (P<0.05). At 6 and 24 h after administration, fentanyl consumption with 40-mg aprepenptant was significantly lower than that with 0.075-mg palonosetron. Greater amounts of rescue analgesics were required in the aprepenptant group.

**CONCLUSIONS:** Palonosetron and aprepenptant were both effective for PONV prevention in the patients indicated for laparoscopic gynaecologic surgery. The drugs can be used in combination for multimodal therapy because they bind to different receptors. More research is needed to evaluate the effects of aprepenptant on pain management in humans.


Chemotherapy-induced nausea and vomiting (CINV) is a serious complication of treatments of hematological malignancies. Although aprepenptant, an NK1 receptor antagonist, has been shown to control CINV in highly emetogenic therapies for solid tumors, the antiemetic effect of this agent in hematological chemotherapies is not well established. In this randomized controlled trial, we examined the additional effect of aprepenptant in combination with conventional 5HT3 blocker-based prophylaxis for CINV in highly or moderately emetic chemotherapies for hematological malignancies (n = 41). The complete response rate, defined as no emetic episodes and no salvage treatments, was significantly higher in the aprepenptant arm than the control arm (82 versus 47 %, p = 0.026), with no increase in severe adverse effects. However, the difference of nausea, measured with visual analog scale, and of oral intake impairment was moderate, which suggests insufficiency of blocking NK receptor for these events. Furthermore, sub-group
analysis revealed that merit of aprepitant addition depends on treatment regimens. Our results indicate the overall advantage of applying aprepitant in the control of CINV in hematological malignancies and the need for further refinement of anti-CINV strategies, including stratification according to regimen.


INTRODUCTION: The oral neurokinin-1 antagonist aprepitant is recommended in several guidelines for preventing chemotherapy-induced nausea & vomiting (CINV) due to highly emetogenic cancer chemotherapy. Little is known about the feasibility and safety of aprepitant in patients treated with oxaliplatin.

METHODS: In this multicentre, open label, randomised, phase 3 trial, we recruited patients with colorectal cancer who underwent an oxaliplatin-based chemotherapy. Patients were centrally randomised in 1:1 ratio to the control group (5-HT3-receptor antagonist+dexamethasone) or aprepitant group (5-HT3-receptor antagonist+dexamethasone+aprepitant or fosaprepitant) in the first course. All patients were treated with aprepitant/fosaprepitant therapy in the second course. The primary endpoint was the proportion of patients with no emesis.

RESULTS: A total of 413 patients entered this clinical trial from 25 centres in Japan. Significantly more patients in the aprepitant group achieved no vomiting overall and delayed phase than those in the control group (95.7% versus 83.6%, and 95.7% versus 84.7%, respectively). The aprepitant group also had statistically significantly higher percentages of no significant nausea, complete response and complete protection than the control group overall. In the control group, the percentages of no vomiting were higher in the second cycle than in the first cycle. The incidence of vomiting occurred day 7 or later was significantly higher in the control group compared with the aprepitant group. Other adverse events were not significant between the groups.

CONCLUSION: The aprepitant therapy was more effective than the control therapy for prevention of CINV in colorectal cancer patients receiving an oxaliplatin-based regimen. Copyright © 2015 Elsevier Ltd. All rights reserved.


This randomized, double-blind study evaluated the relative efficacy of palonosetron (a new, selective 5-hydroxytryptamine type 3 [5-HT(3)] receptor antagonist) and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 45) or ondansetron 8 mg (n = 45), intravenously, immediately before induction of general anaesthesia. The occurrence of nausea and vomiting and the severity of nausea according to a visual analogue scale were monitored immediately after the end of surgery and during the following 24 h. The incidence of PONV was significantly lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale...
for nausea. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.


PURPOSE: Subcutaneous APF530 provides controlled sustained release of granisetron to prevent acute (0-24 h) and delayed (24-120 h) chemotherapy-induced nausea and vomiting (CINV). This randomized, double-blind phase 3 trial compared APF530 and palonosetron in preventing acute and delayed CINV after moderately (MEC) or highly emetogenic chemotherapy (HEC).

METHODS: Patients receiving single-day MEC or HEC received single-dose APF530 250 or 500 mg subcutaneously (SC) (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg. Primary objectives were to establish APF530 noninferiority to palonosetron for preventing acute CINV following MEC or HEC and delayed CINV following MEC and to determine APF530 superiority to palonosetron for preventing delayed CINV following HEC. The primary efficacy end point was complete response (CR [using CI difference for APF530-palonosetron]). A lower confidence bound greater than -15 % indicated noninferiority.

RESULTS: In the modified intent-to-treat population (MEC = 634; HEC = 707), both APF530 doses were noninferior to palonosetron in preventing acute CINV after MEC (CRs 74.8 % [-9.8, 9.3] and 76.9 % [-7.5, 11.4], respectively, vs. 75.0 % palonosetron) and after HEC (CRs 77.7 % [-11.5, 5.5] and 81.3 % [-7.7, 8.7], respectively, vs. 80.7 % palonosetron). APF530 500 mg was noninferior to palonosetron in preventing delayed CINV after MEC (CR 58.5 % [-9.5, 12.1] vs. 57.2 % palonosetron) but not superior in preventing delayed CINV after HEC. Adverse events were generally mild and unrelated to treatment, the most common (excluding injection-site reactions) being constipation.

CONCLUSIONS: A single subcutaneous APF530 injection offers a convenient alternative to palonosetron for preventing acute and delayed CINV after MEC or HEC.


PURPOSE: Aprepitant was shown previously to be effective for prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately emetogenic chemotherapy (MEC) in breast cancer patients receiving an anthracycline and cyclophosphamide (AC)-based regimen. This study assessed aprepitant in patients receiving a broad range of MEC regimens with a variety of tumor types.

METHODS: This phase III, randomized, gender-stratified, double-blind trial enrolled patients with confirmed malignancies, naive to MEC or highly emetogenic chemotherapy, who were scheduled to receive a single dose of at least one MEC agent. Patients received an aprepitant triple-therapy regimen (aprepitant, ondansetron, and dexamethasone) or a control regimen (ondansetron and dexamethasone) administered orally. Primary and key secondary efficacy endpoints were proportions of patients with no vomiting and complete...
RESULTS: Of 848 randomized patients, 77% were female, and 52% received non-AC-based antineoplastic regimens. Significantly, more patients in the aprepitant group achieved no vomiting and complete response, regardless of whether they received AC or non-AC regimens, in the 120 h after chemotherapy. Overall, the incidences of adverse events were generally similar in the aprepitant (62.8%) and control groups (67.2%).

CONCLUSIONS: The aprepitant regimen provided superior efficacy in the treatment of CINV in a broad range of patients receiving MEC (non-AC or AC) in both no vomiting and complete response endpoints. Aprepitant was generally well tolerated. These results show the benefit of including aprepitant as part of the standard antiemetic regimen for cancer patients receiving MEC.


OBJECTIVE: To determine the variability in treatment responses to antiemetic therapy (ondansetron and dexamethasone vs ondansetron and dexamethasone plus aprepiant) given with moderately emetogenic chemotherapy.

RESEARCH DESIGN AND METHODS: Post hoc subgroup analysis of data from a phase III, randomized, double-blind clinical trial evaluated whether the efficacy of aprepiant triple therapy (ondansetron and dexamethasone plus aprepiant) versus control (ondansetron and dexamethasone) varies by gender, age, or region in 848 men and women >18 years old with histologically confirmed malignancies and who were naive to moderately or highly emetogenic chemotherapeutic agents. Endpoints compared were the incidences of no vomiting, complete response, and no use of rescue therapy, all during the overall period (0-120h).

MAIN OUTCOME MEASURES: Regardless of age, gender, or region, the aprepiant regimen provided better control for the no-vomiting and complete-response (no vomiting, no rescue therapy) endpoints.

RESULTS: The aprepiant regimen provided better control for the no-vomiting and complete-response (no vomiting, no rescue therapy) endpoints. Overall response rates were higher in men and in older (>55y) patients, but treatment differences were greater among women and younger patients, known to be at increased chemotherapy-induced nausea and vomiting (CINV) risk. Aprepitant showed a benefit versus control across regions, although the between-treatment difference appeared to be smaller for patients in Central/South America versus North America or international regions.

CONCLUSIONS: Although we acknowledge that subset numbers in this post hoc analysis may be too small to allow definitive conclusions, the data suggest that aprepiant triple therapy provides a benefit over control therapy for the prevention of CINV in patients receiving anthracycline and cyclophosphamide (AC)- or non-AC-based moderately emetogenic chemotherapy across age, gender, and region. (Original trial results available at ClinicalTrials.gov: NCT00337727.).
PURPOSE: Rolapitant is a novel, long-acting neurokinin-1 (NK-1) receptor antagonist. This study evaluated the safety and efficacy of four different doses of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) due to highly emetogenic chemotherapy (HEC).

METHODS: This randomized, double-blind, active-controlled, global study was conducted in patients receiving cisplatin-based chemotherapy >70 mg/m(2). Patients received a 9, 22.5, 90, or 180 mg oral dose of rolapitant or placebo with ondansetron and dexamethasone on day 1 of chemotherapy. The primary end point was complete response (CR; no emesis and no use of rescue medication) in the overall (0 to 120 h) phase of cycle 1. Other assessments were CR in delayed (24-120 h) and acute (0-24 h) phases, no emesis, no significant nausea, and no nausea.

RESULTS: Four hundred fifty-four patients were randomized. All doses of rolapitant improved CR with the greatest benefit observed with rolapitant 180 mg vs. active control in the overall phase (62.5 and 46.7 %, p = 0.032) and in the acute (87.6 vs. 66.7 %, p = 0.001) and delayed (63.6 vs. 48.9 %, p = 0.045) phases. Rates for no emesis and no significant nausea were significantly (p < 0.05) higher with rolapitant 180 mg vs. active control in the overall, acute, and delayed phases. Treatment-related adverse events were largely considered related to the chemotherapy and included constipation, headache, fatigue, and dizziness which were mostly mild or moderate and were similar across treatment groups.

CONCLUSION: All doses of rolapitant were well tolerated and showed greater CR rates than active control. Rolapitant 180 mg demonstrated significant clinical efficacy for preventing CINV in the overall, delayed, and acute phases for patients receiving HEC.

BACKGROUND: Highly emetogenic chemotherapy induces emesis in almost all patients in the absence of prophylaxis. Guidelines recommend use of a neurokinin-1 (NK-1) receptor antagonist in conjunction with a 5-HT3 receptor antagonist and corticosteroid in patients receiving highly emetogenic chemotherapy. We aimed to assess rolapitant, an NK-1 receptor antagonist, for prevention of chemotherapy-induced nausea and vomiting in patients with cancer after administration of cisplatin-based highly emetogenic chemotherapy.

METHODS: We conducted two global, randomised, double-blind, active-controlled, phase 3 trials (HEC-1 and HEC-2) at 155 cancer centres (76 in HEC-1 and 79 in HEC-2) in 26 countries (17 in HEC-1 and 14 in HEC-2). We enrolled patients with cancer aged 18 years or older, who had not previously been treated with cisplatin, with a Karnofsky performance score of 60 or higher, and a predicted life expectancy of 4 months or longer. We used an interactive web-based randomisation system to randomly assign patients to treatment. Patients were stratified by sex and randomly allocated to either oral rolapitant (180 mg dose; rolapitant group) or a placebo that was identical in appearance (active control group) about 1-2 h before administration of highly emetogenic chemotherapy. All patients received granisetron (10 mug/kg intravenously) and dexamethasone (20 mg orally) on day 1, and dexamethasone (8 mg orally) twice daily on days 2-4. Every cycle
was a minimum of 14 days. In up to five subsequent cycles, patients were allowed to receive the same study drug they were assigned in cycle 1, unless removed at the clinician's discretion. Patients could also choose to leave the study at any point. Efficacy analysis was done in the modified intention-to-treat population (comprising all patients who received at least one dose of study drug at a cancer centre compliant with Good Clinical Practice [GCP]). The primary endpoint was the proportion of patients achieving a complete response (no emesis or use of rescue medication) in the delayed phase (>24-120 h after initiation of chemotherapy) in cycle 1. These studies are registered with ClinicalTrials.gov, numbers NCT01499849 and NCT01500213. Both studies have been completed.

FINDINGS: Between Feb 21, 2012, and March 12, 2014, 532 patients in HEC-1 and 555 patients in HEC-2 were randomly assigned to treatment. 526 patients in HEC-1 (264 rolapitant and 262 active control) and 544 in HEC-2 (271 rolapitant and 273 active control) received at least one dose of study drug at a GCP-compliant site and were included in the modified intention-to-treat population. A significantly greater proportion of patients in the rolapitant group had complete responses in the delayed phase than did patients in the active control group (HEC-1: 192 [73%] vs 153 [58%]; odds ratio 1.9, 95% CI 1.3-2.7; p=0.0006; HEC-2: 190 [70%] vs 169 [62%]; 1.4, 1.0-2.1; p=0.0426; pooled studies: 382 [71%] vs 322 [60%]; 1.6, 1.3-2.1; p=0.0001). The incidence of adverse events was similar across treatment groups. The most commonly reported treatment-related treatment-emergent adverse events in the rolapitant versus active control groups were headache (three [<1%] vs two [<1%]), hiccups (three [<1%] vs four [<1%]), constipation (two [<1%] vs three [<1%]), and dyspepsia (two [<1%] vs three [<1%]). For cycle 1, the most common grade 3-5 adverse events in patients allocated rolapitant versus active control were neutropenia (HEC-1: nine [3%] vs 14 [5%]; HEC-2: 16 [6%] vs 14 [5%]), anaemia (HEC-1: one [<1%] vs one [<1%]; HEC-2: seven [3%] vs two [<1%]), and leucopenia (HEC-1: six [2%] vs two [<1%]; HEC-2: two [<1%] vs two [<1%]). No serious treatment-emergent adverse events were treatment related, and no treatment-related treatment-emergent adverse events resulted in death.

INTERPRETATION: Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone is well-tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the at-risk period (120 h) after administration of highly emetogenic cisplatin-based chemotherapy.

FUNDING: TESARO, Inc.Copyright © 2015 Elsevier Ltd. All rights reserved.


BACKGROUND: Palonosetron is a second-generation 5-hydroxytryptamine 3 (5-HT3)-receptor antagonist that has shown better efficacy than ondansetron and dolasetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy, and similar efficacy to ondansetron in preventing CINV in patients receiving highly emetogenic chemotherapy. In this phase III, multicentre, randomised, double-blind, double-dummy, stratified, parallel-group, active-comparator trial, we assessed the efficacy and safety of palonosetron versus granisetron
for chemotherapy-induced nausea and vomiting, both of which were administered with dexamethasone in patients receiving highly emetogenic chemotherapy. METHODS: Between July 5, 2006, and May 31, 2007, 1143 patients with cancer who were receiving highly emetogenic chemotherapy (ie, cisplatin, or an anthracycline and cyclophosphamide combination [AC/EC]) were recruited from 75 institutions in Japan, and randomly assigned to either single-dose palonosetron (0.75 mg), or granisetron (40 microg/kg) 30 min before chemotherapy on day 1, both with dexamethasone (16 mg intravenously) on day 1 followed by additional doses (8 mg intravenously for patients receiving cisplatin or 4 mg orally for patients receiving AC/EC) on days 2 and 3. A non-deterministic minimisation method with a stochastic-biased coin was applied to the randomisation of patients. Covariates known to effect emetic risk, such as sex, age, and type of highly emetogenic chemotherapy, were used as stratification factors of minimisation to ensure balance between the treatment groups. Primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute phase (0-24 h postchemotherapy; non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24-120 h postchemotherapy; superiority comparison with granisetron). The non-inferiority margin was predefined in the study protocol as a 10% difference between groups in the proportion of patients with complete response. The palonosetron dose of 0.75 mg was chosen on the basis of two dose-determining trials in Japanese patients. All patients who received study treatment and highly emetogenic chemotherapy were included in the efficacy analyses (modified intention to treat). This trial is registered with ClinicalTrials.gov, number NCT00359567. FINDINGS: 1114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. 418 of 555 patients (75.3%) in the palonosetron group had complete response during the acute phase compared with 410 of 559 patients (73.3%) in the granisetron group (mean difference 2.9% [95% CI -2.70 to 7.27]). During the delayed phase, 315 of 555 patients (56.8%) had complete response in the palonosetron group compared with 249 of 559 patients (44.5%) in the granisetron group (p<0.0001). The main treatment-related adverse events were constipation (97 of 557 patients [17.4%] in the palonosetron group vs 88 of 562 [15.7%] in the granisetron group) and raised concentrations of serum aminotransferases (aspartate aminotransferase: 24 of 557 [4.3%] vs 34 of 562 [6.0%]; alanine aminotransferase: 16 of 557 [2.9%] vs 33 of 562 [5.9%]); no grade 4 main treatment-related adverse events were reported. INTERPRETATION: When administered with dexamethasone before highly emetogenic chemotherapy, palonosetron exerts efficacy against chemotherapy-induced nausea and vomiting which is non-inferior to that of granisetron in the acute phase and better than that of granisetron in the delayed phase, with a comparable safety profile for the two treatments. FUNDING: Taiho Pharmaceutical (Tokyo, Japan).


PURPOSE: The optimal regimen to prevent chemotherapy-induced nausea and vomiting (CINV) for patients undergoing high-dose chemotherapy and autologous stem-cell
transplantation (ASCT) is unclear. To evaluate the effect of aprepitant in addition to a standard regimen, we conducted this randomized, placebo-controlled phase III trial.

PATIENTS AND METHODS: Patients with multiple myeloma were randomly assigned at a one-to-one ratio to receive either aprepitant (125 mg orally on day 1 and 80 mg orally on days 2 to 4), granisetron (2 mg orally on days 1 to 4), and dexamethasone (4 mg orally on day 1 and 2 mg orally on days 2 to 3) or matching placebo, granisetron (2 mg orally on days 1 to 4), and dexamethasone (8 mg orally on day 1 and 4 mg orally on days 2 to 3). Melphalan 100 mg/m(2) was administered intravenously on days 1 to 2. ASCT was performed on day 4. The primary end point (complete response) was defined as no emesis and no rescue therapy within 120 hours of melphalan administration. Quality of life was assessed by modified Functional Living Index-Emesis (FLIE) questionnaire on days -1 and 6.

RESULTS: Overall, 362 patients were available for the efficacy analysis (181 in each treatment arm). Significantly more patients receiving aprepitant reached the primary end point (58% v 41%; odds ratio [OR], 1.92; 95% CI, 1.23 to 3.00; P = .0042). Absence of major nausea (94% v 88%; OR, 2.37; 95% CI, 1.09 to 5.15; P = .026) and emesis (78% v 65%; OR, 1.99; 95% CI, 1.25 to 3.18; P = .0036) within 120 hours was increased by aprepitant. Mean total FLIE score (+/- standard deviation) was 114 +/- 18 for aprepitant and 106 +/- 26 for placebo (P < .001).

CONCLUSION: The addition of aprepitant resulted in significantly less CINV and had a positive effect on quality of life. Copyright © 2014 by American Society of Clinical Oncology.


BACKGROUND: Chemotherapy-induced nausea and vomiting is a common side-effect of many antineoplastic regimens and can occur for several days after treatment. We aimed to assess the neurokinin-1 receptor antagonist rolapitant, in combination with a serotonin (5-HT3) receptor antagonist and dexamethasone, for the prevention of chemotherapy-induced nausea and vomiting in patients with cancer after administration of moderately emetogenic chemotherapy or regimens containing an anthracycline and cyclophosphamide.

METHODS: We conducted a global, randomised, double-blind, active-controlled, phase 3 study at 170 cancer centres in 23 countries. We included patients with cancer aged 18 years or older, who had not received moderately or highly emetogenic chemotherapy before, with a Karnofsky performance score of 60 or higher, and a predicted life expectancy of 4 months or longer. We used an interactive web-based randomisation system to randomly allocate patients to receive either oral rolapitant (one 180 mg dose; rolapitant group) or a placebo that was identical in appearance (active control group) 1-2 h before administration of moderately emetogenic chemotherapy. Patients were stratified by sex. All patients also received granisetron (2 mg orally) and dexamethasone (20 mg orally) on day 1 (except for patients receiving taxanes as part of moderately emetogenic chemotherapy, who received dexamethasone according to the package insert) and granisetron (2 mg orally) on days 2-3. Every cycle was a minimum of 14 days. In up to five subsequent cycles, patients received the same study drug they were assigned in cycle.
1, unless they chose to leave the study or were removed at the treating clinician's discretion. Efficacy analysis was done in the modified intention-to-treat population (comprising all patients who received at least one dose of study drug at a study site compliant with Good Clinical Practice [GCP]). The primary endpoint was the proportion of patients achieving a complete response (defined as no emesis or use of rescue medication) in the delayed phase (>24-120 h after initiation of chemotherapy) in cycle 1. This study is registered with ClinicalTrials.gov, number NCT01500226. The study has been completed.

FINDINGS: Between March 5, 2012, and Sept 6, 2013, 1369 patients were randomised to receive either rolapitant (n=684) or active control (n=685). 666 patients in each group received at least one dose of study drug at a GCP-compliant site and were included in the modified intention-to-treat population. A significantly greater proportion of patients receiving rolapitant had complete responses in the delayed phase than did those receiving active control (475 [71%] vs 410 [62%]; odds ratio 1.6, 95% CI 1.2-2.0; p=0.0002). The incidence of adverse events was similar in the rolapitant and control groups, with the most frequently reported treatment-related treatment-emergent adverse events being fatigue, constipation, and headache. For cycle 1, the most common grade 3-4 adverse event in the rolapitant versus active control groups was neutropenia (32 [5%] vs 23 [3%] patients). No serious adverse event was treatment-related, and no treatment-related treatment-emergent adverse event resulted in death.

INTERPRETATION: Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone is well tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the 5-day (0-120 h) at-risk period after administration of moderately emetogenic chemotherapy or regimens containing an anthracycline and cyclophosphamide.

FUNDING: TESARO, Inc.


Effect of ondansetron and granisetron were evaluated in sixty (60) children (age 4-11 years) irrespective of sex, diagnosed case of acute lymphoblastic leukemia (ALL) who received high dose methotrexate and did not receive any antiemetic 24 hours prior to HDXT. This was a prospective, randomized, double-blind, single center study. Of 60 children, 30 received oral ondansetron (4mg) and rest 30 granisetron (1mg) half an hour before therapy. Drugs were randomly allocated with appropriate code. The patients were followed up from day 1 to day 5 of therapy. Episodes of nausea and vomiting were recorded and scorings was done every 24 hours following chemotherapy. No significant difference was found between two groups according to acute emesis (Day-1) (p=0.053). In day two and day three it was significant (p<0.05). In day four it was significant (p=0.002). Early chemotherapy induced nausea and vomiting (CINV) were controlled 90% in children who received granisetron and 70% in children who received ondansetron. Delayed (Day 2-4) CINV were controlled in 80% of children who received granisetron and 43.4% who received ondansetron (p<0.05). Granisetron group required additional doses only 3.3% cases and ondansetron group 30% cases on the second day (p<0.05). Result was significant between two groups. About 36.7% patients had episodes
of nausea on day four of chemotherapy in ondansetron group and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself \( (p=0.001) \). Maximum episodes of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% \( (p=0.003) \). Though adverse effects like headache, constipation, abdominal pain and loose motion were common in both group of children but their number was much less in children who received granisetron. On second day of therapy score of nausea and vomiting was maximum in ondansetron and minimum in granisetron treated on day 4 and the result was significant. So, to prevent acute and delayed CINV in children with ALL, oral granisetron can be considered as more effective and well tolerated with minimum adverse effects compared with ondansetrons.


**BACKGROUND:** Postoperative nausea and vomiting is a major cause of patient dissatisfaction towards surgery. For bariatric surgery, increased vomiting/retching is detrimental to surgical anastomosis. The present study evaluated the efficacy of aprepitant (neurokinin-1 inhibitor) as a prophylactic antiemetic in morbidly obese patients for laparoscopic bariatric surgery.

**METHODS:** After institutional review board approval, 125 morbidly obese patients were recruited into this double-blind placebo-controlled trial. On random division, the patients received a tablet of aprepitant (80 mg) in group A, or a similar-appearing placebo in group P, an hour prior to surgery. All patients received intravenous ondansetron (4 mg) intraoperatively. Postoperatively, the patients were evaluated for nausea and vomiting by a blinded evaluator at 30 min, 1, 2, 6, 24, 48, and 72 h.

**RESULTS:** Both groups were evenly distributed for age, body mass index, type, and length of surgery. Cumulative incidence of vomiting at 72 h was significantly lower in group A (3%) compared to group P (15%, \( p=0.021 \)). Odds ratio for vomiting in group P compared to group A was 5.47 times. On Kaplan-Meier plot, time to first vomiting was also significantly delayed in group A \( (p=0.019) \). A higher number of patients showed complete absence of nausea or vomiting in group A compared to group P (42.18 vs 36.67%). On the other hand, nausea scores were unaffected by aprepitant, and no significant difference between groups was found at any of the measured time points.

**CONCLUSIONS:** In morbidly obese patients undergoing laparoscopic bariatric surgery, addition of aprepitant to ondansetron can significantly delay vomiting episodes simultaneously lowering the incidence of postoperative vomiting.


**PURPOSE:** Postoperative nausea and vomiting (PONV) is the most common postoperative complication. The postoperative use of opioids is known to increase the incidence. We compared fosaprepitant, a neurokinin-1 (NK1) receptor antagonist, and ondansetron for their preventive effects on PONV in patients who underwent gynecologic abdominal surgery with patient-controlled epidural analgesia.
METHODS: This prospective, double-blind, randomized study comprised 44 patients who underwent gynecologic abdominal surgery. They were randomly allocated to receive 150 mg intravenous fosaprepitant (n = 24; NKI group) or 4 mg ondansetron (n = 20; ONS group) before anesthesia, which was maintained with volatile anesthetics, remifentanil, fentanyl, and rocuronium. All patients received postoperative fentanyl by patient-controlled epidural anesthesia. The incidence of nausea and vomiting, complete response rate (i.e., no vomiting and no rescue antiemetic use), rescue antiemetic use, nausea score (0-3), and visual analog scale score (VAS 0-10) for pain were recorded at 2, 24, 48, and 72 h after surgery.

RESULTS: No (0 %) patient in the NKI group experienced vomiting after surgery; however, 4-6 (20-30 %) of 20 patients in the ONS group experienced vomiting. This difference was significant at 0-24, 0-48, and 0-72 h. During the study period, no significant differences existed between the NKI and ONS groups in the incidence of PONV, complete response rate, rescue antiemetic use, nausea score, and VAS score for pain.

CONCLUSION: Compared to ondansetron, fosaprepitant more effectively decreased the incidence of vomiting in patients who underwent gynecologic abdominal surgery with patient-controlled epidural analgesia.


Chemotherapy-induced nausea/vomiting (CINV) is a major problem for patients treated with high-dose chemotherapy (HDCT) conditioning before stem cell transplantation (SCT), both during chemotherapy and afterwards (delayed nausea/vomiting). The standard of care (5-HT3 antagonist and dexamethasone) appears to be ineffective against delayed nausea and vomiting. The objective of this study was to compare standard antiemetic treatment with standard treatment plus prolonged treatment with aprepitant (Emend) until 7 days after the end of chemotherapy in patients treated with HDCT before autologous SCT. Ninety-six patients were randomized to the experiment (EXP) group receiving Emend in addition to standard antiemetics or to the control (CTR) group receiving placebo. Emend or placebo treatment started 1 h before the first HDCT dose for SCT and ended 7 days after HDCT. Thirty-eight patients in the EXP group experienced complete response (no vomiting) compared to 16 patients in the CTR group. There was a significant difference between the EXP (0.63 +/- 2.71) and the CTR (3.72 +/- 4.91) group during 10 days after the end of HDCT (p = 0.001) with regard to the number of vomiting episodes. No difference with regard to days of nausea or in the use of antiemetic rescue was noted between the groups. We conclude that standard antiemetic treatment can be improved by addition of aprepitant continued for 7 days after the end of chemotherapy.


Aprepitant is a new neurokinin-1 (NK(1) ) receptor antagonist developed as a treatment for chemotherapy-induced nausea and vomiting (CINV). To evaluate the efficacy and safety of aprepitant used in combination with standard therapy (granisetron and dexamethasone), we conducted a multicenter, phase II, placebo-controlled, double-blind,
randomized study in Japanese cancer patients who received cancer chemotherapy including cisplatin (>70mg/m(2)). Aprepitant was administered for 5 days. A total of 453 patients were enrolled. In the three study groups, (i) standard therapy, (ii) aprepitant 40/25mg (40mg on day 1 and 25mg on days 2-5) and (iii) aprepitant 125/80mg (125mg on day 1 and 80mg on days 2-5), the percentage of patients with complete response (no emesis and no rescue therapy) was 50.3% (75/149 subjects), 66.4% (95/143 subjects) and 70.5% (103/146 subjects), respectively. This shows that efficacy was significantly higher in the aprepitant 40/25mg and 125/80mg groups than in the standard therapy group (chi(2) test [closed testing procedure]: P=0.0053 and P=0.0004, respectively) and highest in the aprepitant 125/80mg group. The delayed phase efficacy (days 2-5) was similar to the overall phase efficacy (days 1-5), indicating that aprepitant is effective in the delayed phase when standard therapy is not very effective. In terms of safety, aprepitant was generally well tolerated in Japanese cancer patients. (ClinicalTrials.gov number, NCT00212602.)


BACKGROUND: The incidence of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine may be 60-100%, and is a common cause of maternal dissatisfaction. Ondansetron has been shown to reduce pruritus but the effect is short-lived. The objective of this randomized double-blind trial was to evaluate the anti-pruritic efficacy of granisetron compared with ondansetron. METHODS: Eighty ASA I or II women undergoing elective caesarean section received spinal anaesthesia with 0.5% hyperbaric bupivacaine 10 mg, fentanyl 25 microg and preservative-free morphine 150 microg. After delivery of the baby and clamping of the umbilical cord, they were randomised to receive granisetron 3mg i.v. (group G) or ondansetron 8 mg i.v. (group O). RESULTS: The two groups were similar for age, gestational age, height and weight. According to visual analogue pruritus scores, patients in group G experienced less pruritus at 8h (P=0.003) and 24h (P=0.01). Fewer patients in group G (n=8) than group O (n=18) required rescue anti-pruritic medication (P=0.03). Satisfaction scores were also higher in group G than in group O (P=0.03). There was no difference in overall incidence of pruritus, nausea and vomiting, and visual analogue pain scores between the two groups. CONCLUSIONS: Administration of granisetron 3mg i.v. reduces the severity of pruritus and the use of rescue anti-pruritic medication, and improves satisfaction but does not reduce the overall incidence of pruritus in women who have received subarachnoid morphine 150 microg compared to ondansetron 8 mg i.v. Copyright 2009 Elsevier Ltd. All rights reserved.


The objective of this study was to compare the efficacy and tolerability of palonosetron and granisetron in a Chinese population receiving highly emetogenic cisplatin-based chemotherapy or moderately emetogenic chemotherapy. Patients were stratified by chemotherapy with cisplatin (yes/no) and then randomly assigned to receive either
palonosetron (0.25mg i.v.) in the first cycle followed by granisetron (3mg i.v.) in the second cycle or vice versa. The primary efficacy endpoint was the proportion of patients with complete response 0-24h post-chemotherapy administration. The proportions of patients with complete response 24-120 and 0-120h following chemotherapy were also compared. Of the 144 patients randomized, 36 (25%) received 60-80mg/m(2) cisplatin; 66 of 72 patients in the palonosetron to granisetron group and 56 of 72 patients in the granisetron to palonosetron group completed treatment with both antiemetics. The efficacy and safety analyses included 128 palonosetron treatments and 138 granisetron treatments. Palonosetron consistently produced numerically higher complete response rates than granisetron in the acute phase (0-24h, 71.09 vs 65.22%), the delayed phase (24-120h, 60.16 vs 55.80%), and overall (0-120h, 53.13 vs 50.00%) though the differences were not significant. Both palonosetron and granisetron were well tolerated. Palonosetron was well tolerated and effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in a Chinese population. When used as monotherapy, 0.25-mg palonosetron was not inferior to 3-mg granisetron for preventing vomiting following highly or moderately emetogenic chemotherapy.


The incidence of postoperative nausea and vomiting (PONV) is 30-50% after surgery. PONV occurs frequently, especially after craniotomy. In this study, we investigated the preventive effects on PONV in a randomized study by comparing patients who had been administered fosaprepitant, a neurokinin-1 (NK1) receptor antagonist, or ondansetron intravenously. Sixty-four patients undergoing craniotomy were randomly allocated to receive fosaprepitant 150 mg i.v. (NK1 group, n = 32) or ondansetron 4 mg i.v. (ONS group, n = 32) before anesthesia. The incidence of vomiting was significantly less in the NK1 group, where 2 of 32 (6%) patients experienced vomiting compared to 16 of 32 (50%) patients in the ONS group during the first 24 and 48 hours following surgery. Additionally, the incidence of complete response (no vomiting and no rescue antiemetic use) was significantly higher in the NK1 group than in the ONS group, and was 66% versus 41%, respectively, during the first 24 hours, and 63% versus 38%, respectively, during the first 48 hours. In patients undergoing craniotomy, fosaprepitant is more effective than ondansetron in increasing the rate of complete response and decreasing the incidence of vomiting at 24 and 48 hours postoperatively.


OBJECTIVES: This is a single center, randomized, double-blind placebo-controlled study to evaluate the NK(1)-receptor antagonist, aprepitant, in Chinese breast cancer patients. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy. The secondary objective was to compare the patient-reported quality of life in these two groups of patients.
PATIENTS AND METHODS: Eligible breast cancer patients were chemotherapy-naive and treated with adjuvant AC chemotherapy (i.e. doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²). Patients were randomly assigned to either an aprepitant-based regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, aprepitant 80 qd) or a control arm which consisted of standard regimen (day 1, ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary, patients quality of life were assessed by self-administered Functional Living Index-Emesis (FLIE).

RESULTS: Of 127 patients randomized, 124 were assessable. For CINV in Cycle 1 AC, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea'. The requirement of rescue medication appears to be lesser in patients treated with the aprepitant-based regimen compared to those with the standard regimen (11% vs. 20%; P = 0.06). Assessment of FLIE revealed that while there was no difference in the nausea domain and the total score between the two groups; however, patients receiving standard antiemetic regimen had significantly worse quality of life in the vomiting domain (mean score [SD] = 23.99 [30.79]) when compared with those who received the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) (P = 0.0002). Both treatments were generally well tolerated. Patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (53.2% vs. 35.5%, P = 0.0468), grade ≥3 neutropenia (21.0% vs. 45.2, P = 0.0042) and delay in subsequent cycle of chemotherapy (8.1% vs. 27.4%, P = 0.0048).

CONCLUSION: The aprepitant regimen appears to reduce the requirement of rescue medication when compared with the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide, and is associated with a better quality of life during adjuvant AC chemotherapy.


PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary
endpoint, 65% (95% CI, 40.8-84.6%) of patients in the PAD arm and 40% (95% CI, 19.1-63.9%) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.


PURPOSE: This clinical trial was conducted to evaluate the efficacy and safety of Palonosetron in preventing chemotherapy-induced vomiting (CIV) among the Chinese cancer patients. PATIENTS AND METHODS: Two hundred and forty patients were scheduled to be enrolled and randomized to receive a single intravenous dose of palonosetron 0.25 mg, or granisetron 3 mg, 30 min before receiving highly emetogenic chemotherapy. The primary efficacy endpoint was the complete response (CR) rate for acute CIV (during the 0-24-h interval after chemotherapy). Secondary endpoints included the CR rates for delayed CIV (more than 24 h after chemotherapy). RESULTS: Two hundred and eight patients were accrued and received study medication. CR rates for acute CIV were 82.69% for palonosetron and 72.12% for granisetron, which demonstrated that palonosetron was not inferior to granisetron in preventing acute CIV. Comparisons of CR rates for delayed CIV yielded no statistical difference between palonosetron and granisetron groups and did not reveal non-inferiority of palonosetron to granisetron. Adverse events were mostly mild to moderate, with quite low rates among the two groups. CONCLUSIONS: A single dose (0.25 mg) of palonosetron is not inferior to a single dose (3 mg) of granisetron in preventing CIV and possesses an acceptable safety profile in the Chinese population.