Formulary Drugs used in Nausea and Vertigo - Evidence Update

Current Formulary choices

Commonly used anti-emetics
- Ondansetron
- Cyclizine
- Metoclopramide
- Domperidone

Anti-emetics for specialist indications
- Prochlorperazine
- Levomepromazine
- Dexamethasone - unlicensed
- Haloperidol
- Cinnarizine - vestibular disorders
- Granisetron - nausea and vomiting induced by cytotoxic chemotherapy
- Aprepitant - prevention of nausea and vomiting associated with moderately and highly emetogenic chemotherapy
- Fosaprepitant - prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy
- Nabilone - restricted to use for nausea and vomiting caused by cytotoxic chemotherapy unresponsive to conventional antiemetics
- Hyoscine - motion sickness
- Betahistine - vertigo, tinnitus and hearing loss associated with Meniere's disease

Current Trust guidelines regarding anti-emetics are available from the following links:

Anti-Emetic Guidelines for Adults Receiving Chemotherapy and Radiotherapy

Management of Women with Nausea and Vomiting In Early Pregnancy

Symptom Management in the last days or hours of life - Nausea and Vomiting:
http://lthweb.leedsth.nhs.uk/sites/palliative-care/pharmacy/WUN1242_Symptom_Management_in_last_days_or_hours_of_life_N-V.pdf

Evidence Update - Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclizine</td>
<td>No new safety alerts issued. However, since 2012 the price of IV cyclizine has increased by over 500%, such that it is now considerably more expensive than other anti-emetics.</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Increased risk of dose dependent QT prolongation. Some patient groups contra-indicated. Doses limited for some indications, and slower IV administration rates specified for some indications.</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Increased risk of neurological adverse effects, such that risks outweigh benefits for a number of indications. Indications restricted. Dose and duration of treatment limited.</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Increased risk of serious cardiac side effects, such that risks outweigh benefits for a number of indications. Indications restricted. Duration of treatment limited.</td>
</tr>
</tbody>
</table>
Evidence update since 2012

Cyclizine

Indication
- nausea and vomiting - post-operative, associated with vestibular disorders and in palliative care

Dosing in Adults

Oral and Intravenous
50mg up to 3 times a day

Intravenous administration
Give slowly over at least 3-5 minutes
Cyclizine can be further diluted with 5 to 10mL of glucose 5%, water for injections or sodium chloride 0.9% (unlicensed).

Dosing in Children

Oral and Intravenous
Child 1 month–5 years: 0.5–1 mg/kg up to 3 times a day (max. per dose 25 mg)
Child 6–11 years: 25 mg up to 3 times a day
Child 12–17 years: 50 mg up to 3 times a day

Intravenous administration
Give slowly over at least 3-5 minutes.
Cyclizine can be further diluted with 5 to 10mL of glucose 5%, water for injections or sodium chloride 0.9% (unlicensed).

Cost
IV cyclizine is 58 times more expensive than oral cyclizine, and 28 times more expensive than IV ondansetron

Please consider whether IV cyclizine is actually necessary - can oral cyclizine be used instead? If IV treatment is necessary, can an alternative drug be used instead?

Ondansetron

MHRA guidance from August 2012, highlights a dose-dependent risk of QT prolongation, cardiac arrhythmias, including Torsade de Pointes with ondansetron. Ondansetron should be avoided in patients with congenital long QT syndrome. Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include: electrolyte abnormalities, use of other medicines that prolong QT interval or may lead to electrolyte abnormalities, congestive heart failure, bradyarrhythmias and medicines which lower the heart rate.

Suitable Indications
- nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy
- prevention and treatment of postoperative nausea and vomiting

Dosing

Intravenous
Adults:
Maximum single dose for CINV: 16mg
Maximum single dose for PONV: 4mg
Adults >75 years:
Maximum single dose for CINV: 8mg

Repeat IV doses should be given no less than 4 hours apart, and all IV doses for CINV should be diluted in 50-100ml saline or other compatible fluid and infused over at least 15 minutes.

MHRA guidance for ondansetron for intravenous use: dose-dependent QTc prolongation – important new intravenous dose restriction is available from: 

**Metoclopramide**
MHRA guidance from August 2013 confirms that the risks of neurological effects such as short-term extrapyramidal disorders and tardive dyskinesia, outweigh the benefits in long-term or high-dose treatment with metoclopramide. Metoclopramide should only be prescribed for short-term use (up to 5 days). Children are at higher risk of neurological effects than adults.

**Suitable Indications:**
- prevention of post-operative nausea and vomiting
- radiotherapy-induced nausea and vomiting
- delayed (but not acute) chemotherapy-induced nausea and vomiting
- symptomatic treatment of nausea and vomiting, including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics).

**Dosing:**

**Oral**
Adult dose: 10mg TDS. Maximum 30mg (or 0.5mg/kg) in 24 hours.

Children 1-18 years: Only as second line option for prevention of delayed chemotherapy-induced nausea and vomiting, and for treatment of established post-operative nausea and vomiting. Dose: 0.1-0.15mg/kg up to TDS. Max dose in 24 hours 0.5mg/kg.

Children <1 year: contra-indicated

**Intravenous**
IV doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.

MHRA guidance for metoclopramide - risk of neurological adverse effects—restricted dose and duration of use is available from: 

**Domperidone**
Recent MHRA guidance from April 2014 states domperidone is associated with a small increased risk of serious cardiac side-effects. Its use is now restricted to the relief of symptoms of nausea and vomiting at the lowest effective dose for the shortest possible time (less than 1 week).

Domperidone is now contra-indicated in the following patients:
- with conditions where the cardiac conduction is, or could be, impaired
- with underlying cardiac diseases such as congestive heart failure
- receiving other medications known to prolong QT or potent CYP3A4 inhibitors
Patients at increased risk include:
- patients older than 60 years
- adults taking daily oral doses of more than 30mg
- those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly

Dosing

**Oral**

Adults >35kg: 10mg up to TDS. Max 30mg in 24 hours.

Children <12 years and <35kg: 0.25mg/kg up to TDS. Max 0.75mg/kg in 24 hours.

MHRA guidance for domperidone: risk of cardiac side effects - restricted indication, new contraindications, and reduced dose and duration of use is available from:

**Current costs**

*Based on standard doses for 3 day treatment. There is no statement of therapeutic equivalence.*

**LTH antiemetic costs (3 days of treatment) Sept 2016**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost (GBP)</th>
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<tbody>
<tr>
<td>Cyclizine 50mg/ml injection</td>
<td>£28.08</td>
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<tr>
<td>Metoclopramide 10mg/2ml injection</td>
<td>£1.26</td>
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<tr>
<td>Ondansetron 8mg tabs</td>
<td>£0.97</td>
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<tr>
<td>Cyclizine 50mg tabs</td>
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<tr>
<td>Domperidone 10mg tabs</td>
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<tr>
<td>Ondansetron 4mg tabs</td>
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<td>Metoclopramide 10mg/5ml liquid</td>
<td>£0.25</td>
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<tr>
<td>Ondansetron 4mg orodispersible films</td>
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<tr>
<td>Ondansetron 4mg orodispersible films</td>
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<tr>
<td>Domperidone 5mg/5ml suspension</td>
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<td></td>
<td>£5.14</td>
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<td>£4.27</td>
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Updated by: Louise McGivern, Specialist Clinical Pharmacist, 22/09/2016