PHARMACY PROFILE: Metoclopramide – PRODUCT INFORMATION CHANGES

Key Messages

- The TGA has recently updated the product information (PI) for metoclopramide to include a new contraindication and changes to dosing and duration of use, to reduce the risk of neurological adverse events.
- It is important to be alert to the risk of akathisia (motor restlessness) in patients receiving metoclopramide.
- Alternative antiemetic medicines also have adverse effects that are important to recognise in the palliative care setting.

Metoclopramide has been widely used since the 1960s for nausea and vomiting of various causes and gastrointestinal motility disorders. It works on the stomach and proximal small bowel but has little effect on colonic motility. It possesses parasympathomimetic activity as well as being a dopamine-receptor (D2) antagonist with a direct effect on the chemoreceptor trigger zone. It also has serotonin-receptor (5-HT3) antagonist properties. As a consequence it has a wide range of nonselective effects. It is available in a variety of pharmaceutical forms including oral and parenteral. [1,2]

A survey of Australian palliative medicines clinicians in Australia, published in 2014, found that for the management of nausea in palliative care, metoclopramide was the most predominant first-line agent (in 69% of responders) followed by haloperidol. Interestingly, in this study, metoclopramide doses varied dramatically in the range of 40–240 mg per day with a median maximal dose per day of 80 mg. [3] Evidence to support the use of antiemetics in palliative care patients is limited, with few controlled clinical trials outside of chemotherapy-induced nausea and vomiting. [3]

Recent changes to product information (PI)

In February this year, the Therapeutic Goods Administration (TGA) worked with the sponsor to update the product information (PI) for metoclopramide to include information about the risk of neurological adverse effects (including extrapyramidal effects and tardive dyskinesia), as well as rare cardiac conduction disorders. Some significant changes have been made with regard dose and duration of therapy. [1]

The extrapyramidal effects (including tardive dyskinesia) may continue even after the cessation of metoclopramide and may be irreversible. [1] The risk of acute neurological effects is higher in children and the risk of tardive dyskinesia appears to be more frequent in the elderly, especially with high doses or long term treatment. [2]

The changes are as follows:

- Metoclopramide is contraindicated for children aged under one year of age.
- For young adults (aged under 20 years old) and children over one year of age, metoclopramide is only indicated as second-line therapy.
- The total daily dose, especially in children and young adults, should not normally exceed 0.5 mg/kg bodyweight, with a maximum of 30 mg daily.
- **The maximum dose for adults is 10 mg three times daily.**
- **The maximum recommended treatment duration is now five days in all age groups.** [1]
Implications for the palliative care setting

- Metoclopramide is widely used in hospice/palliative care.
- This change to the maximum daily dose and duration of therapy of metoclopramide will influence treatment choices in the palliative care setting if symptom control is not achieved at these doses. It is important to acknowledge that all antiemetic options have additional limitations such there is no easy alternative (see table below).
- Careful attention to eliciting symptoms including akathisia (restlessness and motor agitation) and tremor are warranted in patients receiving metoclopramide. These side effects may be missed clinically if not specifically sought, or attributed to other causes. [4]
- The consequences of akathisia and restlessness may for example manifest as increased risk for falls. The risk of neurological adverse effects are likely to be higher when metoclopramide is prescribed with other dopamine antagonists (e.g. haloperidol, promethazine) that can also induce these adverse effects in hospice/palliative care practice. [3,4]
- Note that metoclopramide is contraindicated in suspected bowel obstruction. [5]
- Metoclopramide is metabolized by CYP2D6 and is an inhibitor of CYP2D6.6 Therefore need to be cautious if used in combination with other drugs that inhibit CYP2D6 as they may increase potential for adverse effects of metoclopramide.

Safety considerations with other antiemetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential risks and considerations</th>
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<tr>
<td>Domperidone</td>
<td>Potential for cardiac toxicity due to QT prolongation. Care needed if combining with other drugs that prolong QT interval or in patients with risk factors for QT prolongation. [6] Risk appears greater with daily doses &gt; 30 mg or in patients &gt; 60 years of age. [6] Less risk of extrapyramidal effects than metoclopramide. Predominantly metabolised by CYP3A4 – hence caution with any medications that inhibit CYP3A4 as they may increase risk of adverse effects. Only available orally.</td>
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<tr>
<td>Haloperidol</td>
<td>Has a high incidence of extrapyramidal adverse effects. Can also prolong QT interval.</td>
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<tr>
<td>Prochlorperazine</td>
<td>Commonly causes drowsiness, akathisia and other extrapyramidal adverse effects. Can prolong QT interval. Adds to overall anticholinergic burden. Cannot be given subcutaneously. [7]</td>
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<tr>
<td>5HT3 antagonists</td>
<td>Associated with QT prolongation, mainly with IV administration. Care needed if combining with other drugs that prolong QT interval or in patients with risk factors for QT prolongation. Commonly causes constipation (potential additive effect with opioids!), headache, dizziness, transient increases in LFTs. [5] Only subsidised on the PBS for nausea and vomiting within 48 hours of cytotoxic chemotherapy or from radiotherapy from malignancy.</td>
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References

2. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. Changes aim mainly to reduce the risk of neurological side effects. [Internet]. 2013 Jul 26 [cited 2015 Nov 17].

Useful resources

- Contact your local pharmacist or hospital drug information service.
- National Prescriber Service Website - ‘NPS Medicinewise’ is an excellent resource for consumers and health professionals.

This update is intended to provide practical up to date information relating to medicines management in the setting of Palliative Care and is based on critical review of available evidence. Individual patient circumstances must be considered when applying this information.

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