

Background

In September 2014, the European Medicines Agency (EMA) endorsed Europe-wide restrictions on the use of domperidone-containing medicines.⁽¹⁾ The original recommendations by the Pharmacovigilance Risk Assessment Committee (PRAC) in March 2014 highlighted that domperidone was associated with a small increased risk of potentially life-threatening effects on the heart, especially in those:⁽²⁾

- aged over 60 years
- taking large doses (more than 30mg daily)
- taking concomitant cytochrome P450 3A4 (CYP3A4) inhibitors or medicines which prolong the QT interval

Domperidone is a dopamine receptor antagonist which stimulates gastric emptying and small intestinal transit, and enhances the strength of oesophageal sphincter contraction.⁽³⁾ Domperidone is licensed for the relief of symptoms of nausea and vomiting in adults and children.^(4,5) It has also been used as a motility stimulant in the treatment of neonatal and infant gastro-oesophageal reflux disease (GORD) in an off label manner. However, evidence for the long-term efficacy of motility stimulants in the management of GORD in children is limited and unconvincing.⁽³⁾ The EMA felt that the benefits of domperidone in dyspepsia and GORD did not outweigh the risks of the adverse effects.⁽¹⁾

MHRA / CHM advice on domperidone

The following restrictions to indication, dose and duration of treatment, and new contra-indications are now highlighted in the British National Formulary for Children (BNFc):⁽³⁾

- Domperidone should only be used for the relief of the symptoms of nausea and vomiting;
- Domperidone should be used at the lowest effective dose for the shortest possible duration (maximum treatment duration should not normally exceed 1 week);
- Domperidone is contra-indicated for use in conditions where cardiac conduction is, or could be impaired, or where there is underlying cardiac disease, when administered concomitantly with drugs that prolong the QT interval or potent CYP3A4 inhibitors, and in severe hepatic impairment;
- The recommended dose in young people over 12 years and over 35 kg is 10 mg up to 3 times daily;
- The recommended dose in children under 35 kg is 250 micrograms/kg up to 3 times daily;
- Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy.

This advice applies to the licensed uses of domperidone.

Other guidance

The National Institute for Health and Care Excellence (NICE) guidelines for GORD in children and young people were published in January 2015. These state that metoclopramide, domperidone or erythromycin

should not be offered to treat GORD without seeking specialist advice and taking into account their potential to cause adverse effects.⁽⁶⁾

The 2014 Cochrane review of the pharmacological treatment of children with gastro-oesophageal reflux could not find robust randomised controlled trial evidence to support the use of domperidone, and recommends that further studies on prokinetics are needed, including assessments of erythromycin.⁽⁷⁾

Advice for neonatal and paediatric pharmacists

There are no licensed gastric motility stimulants available for use in neonates, infants or children in the UK:

- Cisapride was withdrawn from the UK market in 2000 following reports of serious ventricular arrhythmias.⁽⁸⁾
- Metoclopramide is contraindicated in infants under 1 year. In children aged 1-18 years, metoclopramide is restricted to use as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and for treatment of established postoperative nausea and vomiting. The restrictions were put in place due to the risk of neurological effects.⁽⁹⁾
- Erythromycin is also associated with QT interval prolongation and arrhythmias. As an antibiotic, prolonged use is generally discouraged due to the potential of encouraging resistance.⁽³⁾

Consider reviewing children with established GORD who are already taking domperidone. In general, as stated by the MHRA advice, domperidone should only be used for the relief of the symptoms of nausea and vomiting.⁽³⁾

In patients who are newly diagnosed with GORD, follow the NICE guidance for the initial and pharmacological management of GORD.⁽⁶⁾

If after specialist advice a prescriber decides that the benefits of using domperidone to treat GORD outweigh the risks of the cardiac adverse events, the recommended dose in neonates and children aged 1 month-18 years is 250 micrograms/kg (maximum 10 mg) three times daily; if response inadequate, increase up to 400 micrograms/kg (maximum 20 mg) three times daily.⁽³⁾ The BNFC suggests interrupting treatment occasionally to assess recurrence of symptoms; to consider restarting if the symptoms recur; and to discontinue if the response is inadequate at the higher dose.⁽³⁾

The BNFC recommends that if there are cardiac concerns an ECG should be performed before and during treatment.⁽³⁾ There do not appear to be set guidelines on how far into treatment a repeat ECG should be done. Paediatric cardiologists at several centres within the UK were contacted, and the general recommendation was to obtain a baseline ECG and repeat this 4-7 days into treatment. A further ECG should be done following any dose changes or alterations in concomitant medicines.⁽¹⁰⁾ If the baseline ECG is abnormal, the need for domperidone should be reconsidered and, if possible, an alternative found.

Domperidone may still be used in the treatment of nausea and vomiting, at the lowest possible dose and for the shortest duration possible. It is contraindicated in children with impaired, or potentially impaired, cardiac conduction (e.g. electrolyte imbalances such as hypokalaemia, hypomagnesaemia); in those with underlying cardiac disease; in those also taking medicines which may prolong the QT interval or CYP3A4 inhibitors; and in those with severe hepatic impairment.^(4,5) The risk versus benefits analysis should be evaluated for each patient. This should include obtaining a detailed family history, e.g. long QT interval, syncope, cardiac arrest, sudden cardiac death at an early age.⁽¹⁰⁾

Use in nursing mothers to promote lactation

This is an unlicensed use of domperidone.⁽⁵⁾ For further advice on this topic, please refer to the UKMi Q&A on the drug treatment of inadequate lactation, which is available via NICE Evidence.⁽¹¹⁾

Advice for parents and carers

Reassurance should be given as the risk is small; there is a small chance that prolonged use of domperidone can increase a child's risk of developing serious problems with their heart.⁽¹²⁾ The BNFC recommends that

children and their carers should be told how to recognise signs of arrhythmia and advised to seek medical attention if symptoms such as palpitation or syncope develop.⁽³⁾ Consider directing the parents and carers to the information leaflet on domperidone for gastro-oesophageal reflux⁽¹²⁾ on the Medicines for Children website.

References

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- ◆ This document is believed to reflect the medical literature at the time of writing.

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