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Domperidone: new restrictions in use

Background and Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) has recently recommended changes to the use of domperidone, including restricting the dose and duration of use in addition to its licensed indications, to minimise the known risks of potentially serious cardiac adverse effects[1].
In 2012, after a previous review the MHRA updated the product information for domperidone to advise caution in its use in high doses or in patients with cardiovascular risk factors[2]. However, cases of cardiac adverse effects with domperidone continued to be reported, and the European Pharmacovigilance Risk Assessment Committee (PRAC) was therefore asked to examine whether the benefits still outweighed the risks for domperidone in its licensed uses.
In April 2014 the European CHMP and the UK MHRA published their final recommendations:

- The benefit-risk balance of domperidone remains positive in the relief of the symptoms of nausea and vomiting. The available evidence of efficacy was not sufficient to support its use for other indications.
- Domperidone should be used at the lowest effective dose for the shortest possible duration. The maximum treatment duration should not usually exceed one week.
- The new recommended dose in adults (and adolescents ≥35kg where licensed) is 10mg orally up to three times daily (maximum dose of 30 mg daily). Adults and adolescents weighing 35kg or more may also be given 30mg twice daily rectally as suppositories.
- In children under 12 years of age and weighing less than 35kg, the recommended maximum oral dose in 24 hours is 0.75mg/kg body weight (dose interval: 0.25mg/kg body weight up to three times a day)
- Domperidone products are contraindicated in patients with severe hepatic impairment, conditions where cardiac conduction is, or could be, impaired or where there is underlying cardiac disease such as congestive heart failure, and when co-administered with QT-prolonging medicines or potent CYP3A4 inhibitors.

Thus domperidone will only be licensed for nausea and vomiting. It will no longer be licensed for the relief of symptoms of fullness, or epigastric bloating and discomfort.

Safety Issues

Cardiac risks with domperidone have been recognised for many years. The intravenous formulation was withdrawn from the market in 1985 for this reason and the drug has never been approved in the United States.
The PRAC review assessed non-clinical and clinical data, both published and unpublished, and found the following:

- A small increased risk of serious cardiac adverse reactions related to domperidone use was identified, including QTc prolongation, torsade de pointes, serious ventricular arrhythmia and sudden cardiac death. A higher risk was observed in patients older than 60 years, adults taking daily oral doses of more than 30mg, and those taking QT-prolonging medicines, CYP3A4 inhibitors or diuretics concomitantly.
- Overall there was sufficient evidence to support the use of oral domperidone 10mg up to three times a day in a general indication of treatment of nausea and vomiting in adults. There were limited data to support paediatric use in this indication, and although the mechanism of action is not expected to differ between adults and children, studies to provide further data to support efficacy in the paediatric population have been requested.
- Data in support of other indications were extremely limited. In particular, there was little evidence in support of the long-term efficacy of domperidone in dyspepsia and gastro-oesophageal reflux disorder (GORD). The benefits in these indications were therefore not considered to outweigh the risk.
- Although the results of a QT study indicate that domperidone at 10mg-20mg four times daily does not significantly prolong the QTc interval in healthy subjects, there are limitations in the study that restrict the conclusions that can be drawn.
- A review of the safety database involving 342 serious reports of cardiac events (including 57 fatalities) or vascular investigations highlighted the high frequency of associated cardiovascular risk factors, cardiovascular history, and concomitant medications associated with cardiac arrhythmias in the patients concerned. In general, about 40% of such reports have been in patients over 60 years of age.

Clinical issues/ alternatives

Domperidone and metoclopramide have been the most widely prescribed prokinetic agents in the UK.
Metoclopramide has also recently had restrictions placed on its use due to extrapyramidal adverse effects[3]. It should only be used for short-term use (up to 5 days) and should no longer be used in chronic conditions such as gastroparesis, dyspepsia and GORD, nor as an adjunct in surgical and radiological procedures.
There are now no drugs on the UK market licensed as prokinetic agents.

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Gastro-oesophageal reflux disease/ Dyspepsia

NICE Clinical Knowledge Service (CKS) currently recommends a trial of treatment with an H2 receptor antagonist or domperidone (as on-demand or intermittent therapy) for patients with GORD or dyspepsia who do not respond to a second month of full-dose proton pump inhibitor (PPI), or one month of double-dose or alternative PPI[4].

In 'on-demand' therapy, treatment is taken only when symptoms recur. Once symptoms are relieved (often after a few days), treatment is stopped again.

The American Gastroenterological Association guidelines on the management of GORD (2013) note that little or no data are available on the comparative efficacy of prokinetic agents in GORD[5]. They suggest domperidone, in the absence of gastroparesis, for the small number of patients who may benefit from a prokinetic.

Draft NICE guidelines for dyspepsia and GORD make no recommendation for the use of a prokinetic agent[6]. They note that there is currently no good quality evidence with appropriate follow-up periods in this particular area. Their draft guidelines recommend that patients of any age with gastro-oesophageal symptoms that are persistent, non-responsive to treatment or unexplained should be considered for referral to a specialist service.

Gastroparesis

Gastroparesis is characterised by delayed gastric emptying in the absence of mechanical outlet obstruction. Idiopathic, diabetes and postsurgical causes represent the most common aetiologies. The condition commonly manifests as upper gastrointestinal symptoms, including nausea, vomiting, postprandial fullness, early satiety, abdominal pain and bloating.

Initial management should include identification of any iatrogenic causes (opiate analgesics, anticholinergic agents, and some diabetic medications including exenatide can all delay gastric emptying), assessment and correction of nutritional state and optimising glycaemic control in diabetes. If symptoms still persist, prokinetic agents have been the mainstay of pharmacological therapy[7].

Recent American guidelines on the management of gastroparesis note that domperidone and metoclopramide have equivalent efficacy in reducing symptoms[7]. Low-dose erythromycin is also listed as an option, although long-term effectiveness is limited by declining benefit with repeated doses. Their recommended regimen is 250-500mg three times daily for up to four weeks. However, a NICE Evidence Summary of erythromycin in gastroparesis found that only one small trial in seven patients showed improvements in symptoms compared with metoclopramide[8]. Four other trials showed no benefit compared with placebo or baseline. Other options, including prucalopride, tegaserod have been tried although, at present, evidence for their efficacy remains to be established[3].

An anti-emetic may be required for the symptomatic treatment of nausea and vomiting. The guidelines do not provide any hierarchy for use of antiemetics; phenothiazines (such as promethazine), antihistamines (such as cyclizine), $5HT_3$-receptor antagonists (such as ondansetron), hyoscine, aprepitant and tricyclic antidepressants are all listed as options.

Suggested action plan

- All patients receiving long-term domperidone should have their therapy reviewed and risks explained to them.
- A trial of withdrawal of domperidone therapy should be tried in all patients, with full patient engagement.
- For GORD or dyspepsia, ensure all other therapeutic and lifestyle options are optimised.
  - Patients of any age with gastro-oesophageal symptoms that are persistent, non-responsive to treatment or unexplained should be considered for referral to a specialist.
- For gastroparesis, ensure any iatrogenic cause is identified. Assess and correct nutritional state and, in patients with diabetes, check glycaemic control.
  - If symptoms return, a trial of 'on-demand' domperidone (up to 10mg tds for up to one week) could be tried if appropriate. However it should be remembered that domperidone is now contra-indicated in patients with conditions where the cardiac conduction is, or could be, impaired; significant electrolyte disturbances; underlying cardiac diseases such as congestive heart failure; severe hepatic impairment or in patients taking concurrent drugs which are known to cause QT prolongation (for example erythromycin; citalopram, haloperidol or amiodarone) or potent CYP3A4 inhibitors (eg itraconazole, fluconazole). Use with less potent CYP3A4 inhibitors (eg diltiazem or verapamil) is also not recommended. Patients older than 60 years are at increased risk of arrhythmias and it is preferable to avoid domperidone in this patient group.
  - Short-term low-dose erythromycin (250-500mg tds for up to four weeks) (unlicensed) has been tried although the data are too limited and of insufficient quality to recommend it as an option.
  - An antiemetic agent (see list above) may be used to control any symptomatic nausea and vomiting.

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