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Metoclopramide: restrictions in use

Background and Introduction

The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has recently recommended changes to the use of metoclopramide-containing medicines in the European Union, including restricting the dose and duration of use to minimise the known risks of potentially serious neurological adverse effects.

A review of metoclopramide in children in 2010 identified the risk of neurological side effects and recommended a number of risk minimisation measures. In 2011, a review carried out in children in France highlighted that despite various risk minimisation measures, side effects had continued to be reported. The French medicines agency therefore asked the CHMP to carry out an assessment of the benefit-risk balance in all populations, especially in children and the elderly.

In October 2013 the CHMP published its final recommendations:

- metoclopramide should only be authorised for short-term use (up to 5 days),
- it should not be used in children below 1 year of age and that in children over 1 year of age it should only be used as a second-choice treatment (after other treatments have been considered or tried) for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting.
- It should no longer be used in chronic conditions such as gastroparesis, dyspepsia and gastro-oesophageal reflux disease (GORD), nor as an adjunct in surgical and radiological procedures.
- In adults, metoclopramide remains indicated for prevention of post-operative nausea and vomiting, radiotherapy-induced nausea and vomiting and delayed (but not acute) chemotherapy-induced nausea and vomiting, and for symptomatic treatment of nausea and vomiting including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics).
- For adults and children the maximum dose in 24 hours is 0.5mg per kg body weight; in adults, the usual dose of conventional formulations (all routes) is 10mg up to 3 times daily.
- Oral liquid formulations have been particularly associated with overdose in children. Oral liquids containing more than 1mg/ml will be withdrawn from the market. Intravenous formulations with concentrations above 5mg/ml and suppositories containing 20mg will also be withdrawn.

Safety Issues

Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms (usually acute dystonic reactions); these are more common in children and young adults, and at daily doses above 500 micrograms/kg. Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients. The incidence of tardive dyskinesia is not fully established. The FDA quoted an estimated risk of 1-10% of patients, although other publications have quoted an incidence of approximately 1%.

The CHMP, in their review of the evidence, concluded the following:

- The evidence also indicated efficacy in nausea and vomiting associated with acute migraine, but seemed to indicate that doses above 10 mg do not result in increased efficacy. The effects of metoclopramide on gut motility may be of benefit when given orally with analgesics in this acute setting.
- There was no evidence of consistent benefit in gastroparesis, gastro-oesophageal reflux disease and dyspepsia, all of which are chronic conditions requiring prolonged treatment which puts patients at risk of chronic neurological side effects. Evidence to support a role as an adjunct in surgical and radiological procedures was also lacking.
- Extrapyramidal disorders constituted nearly half of all spontaneously reported adverse effects in a manufacturer database. The reporting rate for these disorders was calculated to be 6 times higher in children than in adults, although it was not possible to accurately account for usage patterns in different age-groups. Extrapyramidal disorders were more likely to occur after several doses, although usually early in treatment, and were less likely at slower infusion rates when metoclopramide was given intravenously. Elderly patients seemed to be more at risk of potentially irreversible tardive dyskinesia after longer term treatment. There were also a significant number of reports of overdose in children, particularly with oral liquid formulations.
- Cardiovascular reaction reports associated with metoclopramide appeared to be very rare, and mainly associated with intravenous formulations given to patients with underlying risks for cardiac disease.

The use of metoclopramide was restricted in the United States in 2009. The FDA recommended that treatment not exceed three months and manufacturers were required to add a boxed warning to their drug labels about the risk of its long-term or high-dose use.

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Clinical issues/ alternatives

There are currently two prokinetic agents on the UK market: metoclopramide and domperidone.
Domperidone does not cross the blood brain barrier and has not been associated with dystonic reactions or tardive dyskinesia. It has, however, been associated with arrhythmias due to prolongation of the QT interval. It should be used with caution for patients who have existing prolongation of cardiac conduction intervals (particularly QTc), significant electrolyte disturbances or underlying cardiac diseases, particularly for patients older than 60 years and patients who receive daily oral doses of more than 30mg. It should be avoided in patients who are taking concomitant medication known to cause QT prolongation. It is currently the subject of a European safety review due to report in December 2013.

Gastro-oesophageal reflux disease/ Dyspepsia

NICE Clinical Knowledge Service (CKS) recommends a trial of treatment with an H2 receptor antagonist or domperidone 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.
They further recommend that domperidone should be used as on-demand or intermittent therapy.
In 'on-demand' therapy, treatment is taken only when symptoms recur. Once symptoms are relieved (often after a few days), treatment is stopped again. Some people may prefer to take treatment intermittently (for example a 2–4 week course of treatment when symptoms recur).
The American College of Gastroenterology (ACG) published guidelines on the management of GORD in 2013 (http://gi.org/guideline/diagnosis-and-managemen-of-gastroesophageal-reflux-disease/). They concluded that, in the absence of gastroparesis, there is no clear role for metoclopramide in GORD. For the small number of patients who may benefit from a prokinetic, they suggested domperidone. They noted that the efficacy of domperidone has been demonstrated to be equivalent to that of metoclopramide for gastric emptying but little to no data are available in GORD.

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 optimise glycaemic control in diabetes. If symptoms still persist, prokinetic agents have been the mainstay of pharmacological therapy.
The ACG also published guidelines on the management of gastroparesis in 2013 (http://gi.org/guideline/management-of-gastroparesis/). They note that domperidone and metoclopramide have equivalent efficacy in reducing symptoms. Low-dose erythromycin is also listed as an option, although long-term effectiveness is limited by tachyphylaxis. Their recommended regimen is 250-500mg three times daily for up to four weeks. Other options, including prucalopride, tegaserod and other experimental agents have been tried although, at present, evidence for their efficacy remains to be established.
An anti-emetic may be required for the symptomatic treatment of nausea and vomiting. The ACG guidelines do not provide any hierarchy for use of antiemetics; phenothiazines (such as promethazine), antihistamines, $5HT_3$-receptor antagonists (such as ondansetron), hyoscine, aprepitant and tricyclic antidepressants are all listed as options.

Suggested action plan

- All patients receiving long-term metoclopramide should have their therapy reviewed.
- A trial of withdrawal of metoclopramide therapy should be tried in all patients, with full patient engagement.
- For GORD or dyspepsia, ensure all other therapeutic and lifestyle options are optimised.
  - If symptoms return, a trial of intermittent or 'on-demand' domperidone (up to 10mg tds) could be tried if appropriate. Domperidone should be avoided in patients with existing prolongation of cardiac conduction intervals; significant electrolyte disturbances; underlying cardiac diseases such as congestive heart failure or in patients taking concomitant drugs which are known to cause QT prolongation.
  - For patients in whom domperidone is not appropriate, options are limited. If nausea or vomiting is the predominant symptom, an antiemetic agent could be tried.
- 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 intermittent or 'on-demand' domperidone could be tried if appropriate. Domperidone should be avoided in patients with existing prolongation of cardiac conduction intervals; significant electrolyte disturbances; underlying cardiac diseases such as congestive heart failure or in patients taking concomitant drugs which are known to cause QT prolongation.
  - Short-term low-dose erythromycin (250-500mg tds for up to four weeks) may also be an option (unlicensed).
  - An antiemetic agent may be used to control any symptomatic nausea and vomiting.