



Metoclopramide

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Introduction

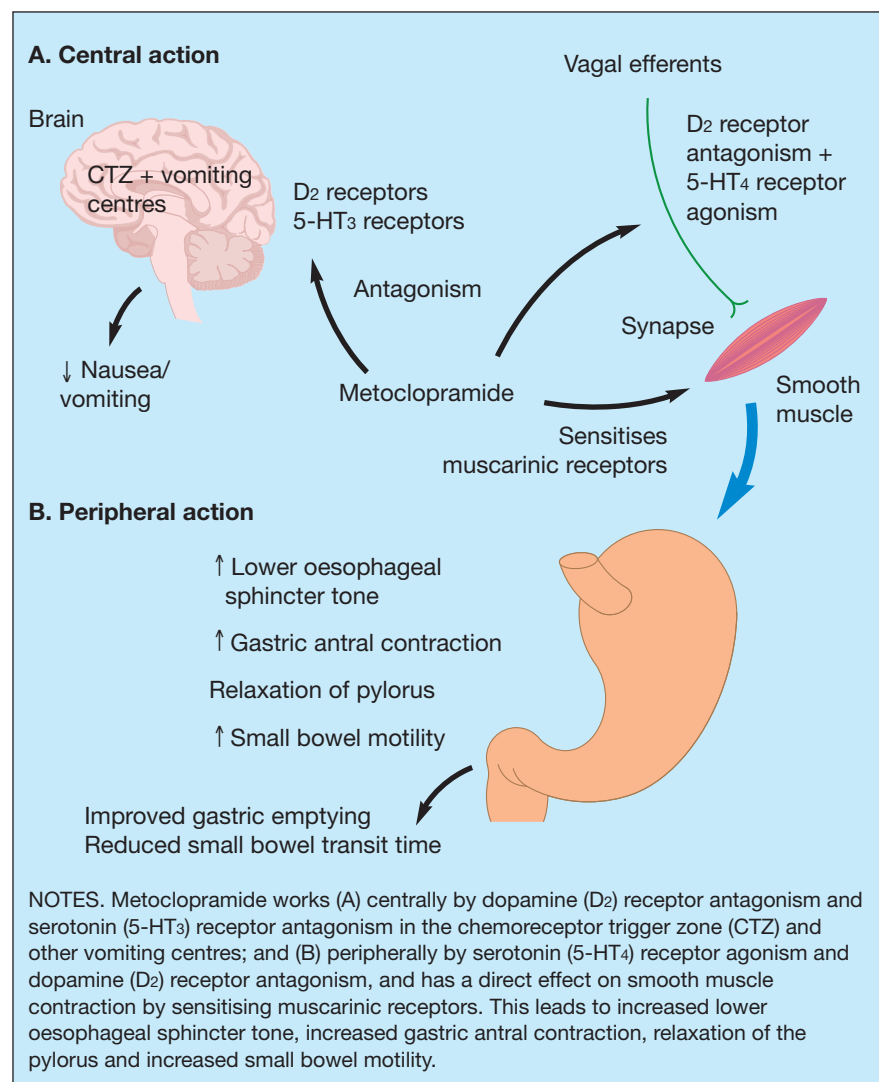
Metoclopramide was first licensed for use in Europe in the 1970s for the treatment of nausea and vomiting. Its dual action, centrally at the chemoreceptor trigger zone and peripherally at the gastric outlet, provides it with efficacy as an anti-emetic, in the treatment of gastro-oesophageal reflux disease, to aid small bowel radiological examinations and for the management of gastroparesis. The latter is a common manifestation of autonomic neuropathy in patients with long-standing diabetes and metoclopramide is part of the therapeutic armoury to manage this difficult condition.

Pharmacology

Figure 1 outlines the pharmacological action of metoclopramide. Centrally it works by dopamine (D₂) receptor antagonism and serotonin (5-HT₃) receptor antagonism in the chemoreceptor trigger zone and other emesis centres. Peripherally it stimulates smooth muscle contraction through the release of acetylcholine from enteric cholinergic neurons (serotonin 5-HT₄ receptor agonism), antagonises the inhibitory neurotransmitter dopamine and has a direct effect on smooth muscle contraction by sensitising muscarinic receptors. The results of these peripheral effects are increased lower oesophageal sphincter tone, increased gastric antral contraction, relaxation of the pylorus and increased small bowel motility resulting in improved gastric emptying and reduced transit time from duodenum to terminal ileum.

It is well absorbed orally and can be administered in tablet or liquid

Figure 1. The pharmacological action of metoclopramide



form as well as both intravenously and intramuscularly. The onset of action is 1–3 minutes when administered parenterally, and maximal plasma levels occur within 20–30 minutes of oral intake. The usual dose is 10mg three times daily but it can be given up to 20mg four times daily.

Side effects of metoclopramide develop mostly due to its readiness to cross the blood-brain barrier. Symptoms of drowsiness, fatigue and restlessness are common as is hyperprolactinaemia. Acute dystonia results in some patients, in particular young patients, and long-term use can result in extrapyramidal side effects.

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DRUG NOTES



Metoclopramide

Trials of safety and efficacy

The efficacy of metoclopramide as an anti-emetic was shown in 1969 in a double-blind trial of more than 600 patients requiring treatment of postoperative nausea and vomiting. Metoclopramide was shown to have greater efficacy than both placebo ($p < 0.001$) and prochlorperazine ($p < 0.05$) with no significant side effects.¹ Subsequent studies have shown efficacy when used in patients with chemotherapy-induced nausea and vomiting. Prior to the widespread introduction of proton pump inhibitors, metoclopramide had proven value in managing the symptoms of gastro-oesophageal reflux disease with several double-blind studies showing improved symptoms compared with both placebo and cimetidine. More recently, studies have also been published showing the benefit of metoclopramide in postoperative ileus, hyperemesis gravidarum, functional dyspepsia and gastroparesis.

Specific evidence for use in diabetes

Gastroparesis can be defined as delayed gastric emptying in the absence of any mechanical obstruction. It can occur in patients with type 1 and type 2 diabetes, but is particularly seen when there is evidence of established microvascular complications. It presents with upper gastrointestinal symptoms of nausea, early satiety, post-prandial fullness and vomiting. In severe cases it can lead to weight loss and malnutrition. The motor dysfunctions described in diabetic gastroparesis are heterogeneous and the pathophysiology is poorly understood. This makes treatment difficult and has to be tailored to each individual patient.

The efficacy of metoclopramide in the treatment of diabetic gastroparesis was shown by a small study in 1985.² Thirteen patients with subjective evidence of gastric stasis had delayed gastric emptying of an isotope-labelled semi-solid meal which was significantly accelerated ($p < 0.05$) after 10mg of metoclopramide parenterally. Patients then received 10mg of metoclopramide and placebo before meals and prior

Key points

- Metoclopramide has efficacy as a centrally acting anti-emetic and a gastrointestinal tract prokinetic
- Metoclopramide has well recognised CNS side-effects and should be used with caution in younger patients
- Metoclopramide may be of clinical benefit in the treatment of diabetic gastroparesis

to bed for three weeks in a randomised, double-blind, crossover design. There was a significant amelioration of the symptoms of nausea, vomiting, anorexia, fullness and bloating with metoclopramide therapy compared with placebo ($p < 0.05$), with an overall mean symptom reduction of 52.6%. Gastric emptying studies after completion of the trial in seven patients, subjectively improved and receiving open-labelled metoclopramide, showed significantly less gastric retention. Individual improvements in gastric emptying after parenteral or oral metoclopramide, however, could not be correlated with symptom change during the treatment trial. Since then, several other studies have been published comparing the efficacy and safety of metoclopramide against placebo, domperidone and cisapride (subsequently withdrawn from the UK market). One of the largest trials was a double-blind, multicentre comparison of the short-term use of oral metoclopramide and domperidone.³ Ninety-three insulin-dependent diabetic patients with a history of symptoms of gastroparesis for more than three months were randomised, with 45 receiving metoclopramide and 48 receiving domperidone. Nausea, vomiting, bloating/distension and early satiety were evaluated at two and four weeks. Both drugs were shown to be equally effective in alleviating symptoms of gastroparesis, but central nervous system side effects were more severe and more common in those treated with metoclopramide, including somnolence, akathisia, asthenia, anxiety, depression and reduced mental acuity. The current NICE guidelines for type 1 diabetes suggest a trial of prokinetic drugs, such as metoclopramide or domperidone, in patients with suspected or diagnosed gastroparesis.

Discussion

Metoclopramide has a role in the management of diabetic gastroparesis through both its centrally mediated anti-emetic actions and its prokinetic properties. Gastroparesis remains poorly understood and improvement in gastric emptying time does not always correlate with improved patient symptoms. Drug therapy is only a small part of the management of these patients. A full review should be made of their existing medications which may in themselves delay gastric emptying. Glucose control should be optimised as hyperglycaemia itself has been shown to slow gastric emptying. Coexisting psychiatric disorders such as depression and anxiety have been shown to be associated with an increased prevalence of gastrointestinal symptoms in diabetic patients and these should be addressed.⁴ Nutritional support may be required, and patients may also require referral to gastroenterology for consideration of Botox, naso-jejunal feeding or even gastric pacemaker insertion.

Declaration of interests

There are no conflicts of interest declared.

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