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Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old

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Aim
To determine whether there is robust evidence of efficacy for domperidone in reducing the symptoms of gastro-oesophageal reflux (GOR) and gastro-oesophageal reflux disease (GORD) in children.

Methods
Systematic review of randomized controlled trials (RCTs). A search was made of the Cochrane Library Issue 2004 (Central Register of Controlled Trials and Database of Systematic Reviews), Medline (Pub-med) 1966 to present and Embase from 1974 to 2004, and reference citations of the RCTs that had been found electronically.

Results
Four RCTs were identified. Only the two older trials showed any benefits of domperidone on clinical symptoms of GORD in older children, which were the primary outcome measures. In the trial undertaken by Clara, a good or excellent result was obtained in 93% of the domperidone group compared with 33% of the controls ($P < 0.05$). In the trial undertaken by de Loore, after 2 weeks of treatment 75% of patients treated with domperidone were found not to be vomiting, compared with 43% in the metoclopramide group and 7% in the placebo group. The trial by Corraccio gave no detailed results regarding the primary outcomes of effect of domperidone on symptoms but simply reported 'cured', 'improved' or 'unchanged'. The secondary pH-metric outcome of the number of reflux episodes, was reduced with domperidone.

Conclusion
From the limited evidence available, there was no robust evidence of efficacy for the treatment of GOR with domperidone in young children. Given the usually benign nature of the condition, the widespread use of unlicensed medicines for GOR is not warranted.

Introduction

Gastro-oesophageal reflux (GOR) is an extremely common and usually self-liming condition, affecting 20–67% of infants [1]. GOR is the passage of gastric contents into the oesophagus. It occurs as the result of transient, inappropriate relaxation of the lower oesophageal sphincter, permitting the stomach contents to pass into the oesophagus. In most infants with GOR the outcome is benign and self-limiting. The peak incidence of GOR is around 4 months and it resolves spontaneously by 1–2 years of age in most patients [1]. There may be parental anxiety or intolerance of symptoms, which lead to medical advice being sought. This form of GOR is best managed with reassurance and on-going clinical monitoring.

In a minority of cases GOR is complicated by oesophagitis, respiratory symptoms, neuro-behavioural symptoms or failure to thrive, and is then referred to as gastro-oesophageal reflux disease (GORD). Treatment is medically indicated in such cases, which represent a small percentage of cases with GOR.

A diagnosis of GOR is usually made on clinical grounds without performing expensive and unnecessary investigations. When the diagnosis cannot be made on symptoms alone, investigations to quantify the reflux, assess the cause and detect the presence of complications include: 18–24-h oesophageal pH monitoring (E_pHM), upper gastrointestinal endoscopy, oesophageal manometry, scintigraphy or sonography. These tests correlate poorly with symptoms of reflux and are poor predictors of how children will respond to treatment [2, 3].

There are four main types of therapy for infants with GOR: dietary measures (thickened feeds, frequent small meals), position (avoidance of supine or slumped seated postures), pharmacological therapies and surgery. Surgery is reserved for children with severe complications. Pharmacological therapies include alginate combinations, prokinetic agents (e.g. cisapride, domperidone, bethanechol, metoclopramide) and acid secretion inhibitors (e.g. cimetidine, ranitidine, omeprazole, lansoprazole). Currently, omeprazole is the only treatment licensed in the UK for GORD, and it is indicated only for severe ulcerating oesophagitis in children over 2 years old.

Until 2000, cisapride was commonly used to treat GOR and GORD. Guidelines by ESPGAN (the European Society of Paediatric Gastroenterology Hepatology and Nutrition) published in 1993 [4], cited cisapride as the first-line medication for GORD. However, more recently the systematic Cochrane review [3] in 2000, a large multicentre Canadian trial published in 1999 [5] and a study by Cohn *et al.* [6], have shown that there is little evidence of efficacy of cisapride [7].

Domperidone is a peripheral dopamine D_2-receptor antagonist that increases motility and gastric emptying [2a]. It decreases postprandial reflux time and is therefore used to treat regurgitation and vomiting. Since the Marketing Authorizations for cisapride were suspended in the UK and many other countries in 2000, due to safety concerns, domperidone has been widely used by paediatricians to treat GOR. Domperidone is not licensed for this use.

In the light of the experience with cisapride, it is particularly important to review carefully the data on domperidone, especially given the largely benign nature of GOR in most cases. We therefore carried out a systematic review to answer the question of whether there is any evidence of efficacy for domperidone in reducing the symptoms of GOR and GORD.

Methods

We identified original randomized controlled trials (RCTs) by searching the following: the Cochrane Library Issue 2004 (Central Register of Controlled Trials and Database of Systematic Reviews), Medline (Pub-med) 1966 to present, and Embase from 1974 to present. The search terms included domperidone, gastro-oesophageal reflux, oesophagitis, gastro-oesophageal reflux-disease, infantile reflux, regurgitation and excessive regurgitation In addition, one further RCT was obtained by hand searching the reference citations of the RCTs that had been found electronically.

We selected studies for review if they met the following criteria:

1 randomized controlled trials and
2 compared oral domperidone therapy with either placebo or nonsurgical treatments (other drugs, dietary measures or positioning) and
3 were performed in children (<18 years) with a probable diagnosis of GOR, however defined.
4 Studies in which domperidone was administered orally for a minimum of 1 week.
5 Included studies had to report at least one of the following primary outcome measures

Types of outcome measures

Outcome measures were similar to those selected for the Cochrane review on cisapride [3] and were:

Primary outcomes

- Symptoms, or change in symptoms of GOR (regurgitation, crying, irritability, vomiting, gagging), as

assessed subjectively by the parent of the child and/or by the treating physician/other investigator.
- Presence of any adverse events.
- Occurrence of any clinical complications of GOR, e.g. respiratory symptoms.
- Weight change.

Secondary outcomes

- Episodes of reflux measured by extended oesophageal pH monitoring: percentage of time during which pH <4 ('reflux index'), number of episodes of pH <4, number of episodes of pH <4 lasting >5 min, duration of longest episode of pH <4.
- Lower oesophageal sphincter (LES) pressure measured by oesophageal manometry.
- Histological evidence of oesophagitis on biopsy.

We screened potential trials and applied selection criteria independently. The methodological quality of the included trials was also assessed by the reviewers independently.

Results

Four RCTs were identified involving the use of domperidone for GOR or GORD in children [8–11] (Table 1).

Methodological quality

Only the two older trials [8, 11] showed any benefits of domperidone on clinical symptoms of GORD in older children, which were the primary outcome measures.

The trial by Corraccio gave no detailed results regarding the primary outcomes of effect of domperidone on symptoms but simply reported 'cured', 'improved' or 'unchanged'. The secondary pH-metric outcome of the number of reflux episodes was reduced with domperidone, although there was no reduction in the total amount of reflux time.

Discussion

In this systematic review of four trials, there was very little evidence for the efficacy of domperidone for the reduction of symptoms of GOR and GORD in young children.

In all four trials there were no adverse effects noted.

Study limitations

This review included only a small number of trials, and is therefore limited. In addition, the trials assessed were heterogeneous with regard to populations, interventions and outcome measures. The RCTs were variable with regard to methodological quality. In addition, there is some evidence from the trial by Clara [8] that the optimum dosage for reduction of symptoms may not have been adequately explored in the studies.

Discussion and implications for current practice

Childhood GOR is common and usually benign and self-limiting.

In this systematic review, there was no robust evidence of efficacy for the treatment of GOR with domperidone in young children. Although the optimum dosage may not have been adequately explored in these trials, in view of the potential adverse effects of domperidone and the small numbers studied in the trial by Clara, the doubling of the dose cannot be recommended from these data alone.

The adverse effects of domperidone can be serious and may include neurological symptoms, in particular extrapyramidal ones [12]. There have been reports of oculo-gyric crisis in infants [13]. Premature infants, infants and young children are particularly at risk of developing these problems because of immaturity of the nervous systemic and blood–brain barrier. Long-term adverse effects of dopamine antagonists include hyperprolactinaemia. In addition, similar to cisapride, domperidone is metabolized by the CYP3A4 subfamily of the cytochrome P450. Concomitant use of drugs that use this pathway such as the azole antifungals (e.g. ketoconazole, fluconazole, miconazole, itraconazole) and macrolide antibiotics (e.g. erythromycin, clarithromycin), may result in increased plasma levels of domperidone and increased risk of toxicity. In addition, prolongation of the Q-T interval has been shown to occur when ketoconazole is taken orally with domperidone [14].

In view of the generally benign nature of GOR and lack of evidence of efficacy, we cannot recommend that the benefits of treatment with domperidone outweigh the associated risks. In considering domperidone, we should be aware of the experience with cisapride [3, 7]. The meta-analysis of the eight RCTs concluded that cisapride did not improve symptoms compared with placebo, although it did improve some of the proxy outcome measures. The reasons why cisapride was prescribed so frequently when there was so little evidence of efficacy have been questioned. Practice guidelines and consensus statements may influence prescribers, but the methodology used to produce these and the interests of the participants need to be explicit. ESPGAN has endorsed prokinetic therapy as a 'phase 2' therapeutic option in GORD [4], but the same organization recommended the use of cisapride and yet there was little evidence of efficacy for cisapride [3].

Table 1
Selected randomised trials for domperidone in children with GORD

Bines [10] 1992	
Methods	Randomized, double-blind, controlled trial. Randomization method not stated
Participants	Seventeen children (including 7 with other significant disease) aged 5 months to 11.3 years with GORD diagnosed clinically, radiologically and by pH-metric methods
Interventions	Four weeks of either 0.6 mg kg^{-1} domperidone or placebo, three times a day
Outcomes	No significant difference in investigator assessment of symptoms (vomiting, spitting, irritability, heartburn, coughing, choking) between domperidone and placebo after 4 weeks of therapy. The total number of reflux episodes within 2 h of eating was decreased by more than 25% in all 7 patients receiving domperidone who underwent a second pH study compared with only 1 of 8 patients receiving placebo ($P < 0.01$). The pretreatment pH monitoring lasted 17–24 h and the monitoring after 4 weeks lasted 8–12 h. Analysing only the 2 h within eating was not a prespecified outcome. The data beyond 2 h were not reported
Notes	There were striking baseline differences in the two groups. The mean age was 3.6 years in the domperidone group and 2.4 years in the placebo group. The total number of reflux episodes at baseline was 69 for the domperidone group and 16 for the placebo group. The mean age and age range is not representative of the commonest age group for which treatment for GOR and GORD is prescribed (under 18 months). The trial was very small
Summary	It is difficult to interpret this trial given the selective reporting of data, the apparent *post hoc* analysis chosen, the baseline imbalances and the older age group
Carrocio [9] 1993	
Methods	Randomized, double-blind, controlled trial. Block randomization and stratification by degree of GOR
Participants	Eighty children aged 1–18 months. Diagnosis of GOR confirmed by radiological and pH-metric criteria
Interventions	8 weeks of either: A. Domperidone 0.3 mg kg^{-1} plus magnesium hydroxide plus aluminium hydroxide B. Domperidone 0.3 mg kg^{-1} plus alginate C. Domperidone 0.3 mg kg^{-1} alone D. Placebo All were 'given before meals' but the daily frequency was not specified
Outcomes	No clinical data provided, with the exception of the number of reflux episodes. Authors reported that all patients had severe symptoms, but no details given In group C, there was a reduction in the number of reflux episodes from a median of 59 to 48.5 ($P < 0.009$). In the placebo group (D), the number of reflux episodes changed from a median of 65 to 68. There was no decrease in the total percentage reflux time in either placebo or domperidone groups
Notes	Groups A and B not included in this systematic review, as they included other therapies Authors concluded that there was no significant difference in the degree of improvement between the patients receiving domperidone alone and those receiving placebo alone. No reported adverse effects
Summary	No evidence of efficacy for symptomatic relief with domperidone
De Loore [11] 1979	
Methods	Randomized, double-blind, placebo-controlled trial. Randomization method not stated
Participants	Forty-seven children aged 3 weeks to 7 years with chronic, excessive regurgitation and vomiting. Diagnosis of GORD made clinically
Interventions	Domperidone 0.3 mg kg^{-1} t.i.d. metoclopramide 0.3 mg kg^{-1} three times a day or placebo for 2 weeks
Outcomes	Raw data not provided. Symptoms of nausea and vomiting were rated by an investigator. The cumulative percentage of patients after 2 weeks of treatment was plotted on a graph. After 2 weeks of treatment, 75% of patients treated with domperidone were found not to be vomiting, compared with 43% in the metoclopramide group and 7% in the placebo group. No adverse effects reported
Notes	Baseline ages different; domperidone group had a median age of 9 months, whereas the placebo and metoclopramide groups had a median age of 6 months. Nausea would be difficult to assess in a preverbal child of 6–9 months
Summary	Very small trial, inadequately powered. However, some efficacy for the symptomatic relief of vomiting shown
Clara [8], 1979	
Methods	Double-blind, placebo-controlled, randomized trial. Randomization method not stated
Participants	Thirty-two children aged 2.5 months to 10 years. Chronic regurgitation and vomiting diagnosed clinically—GORD not diagnosed. (Study done in 1979)
Intervention	Domperidone 0.3 mg kg^{-1} three times a day or placebo, for 2 weeks
Outcome	Investigator rated nausea, vomiting, retching and regurgitation. After 2 weeks of medication, the dose was doubled, because of poor results in 7 out of 14 patients. After 4 weeks, there was a statistical and clinical difference between the domperidone group and the placebo group, a good or excellent result was obtained in 93% of the domperidone group compared with 33% of the controls ($P < 0.05$)
Notes	The median age in the domperidone group was 4 years, compared with 6 years in the control group. No adverse effects
Summary	Very small trial. Some evidence of efficacy of domperidone for the symptomatic relief of nausea and vomiting in older children (median age of 5 years). Evidence of efficacy in 50% of patients only at higher dose (0.6 mg kg^{-1})

Suggestions for future research

In their editorial on cisapride, Bourke and Drumm [7] emphasize the need for well-designed, appropriately conducted studies of drug efficacy. In the case of domperidone, in the absence of any evidence of significant adverse effects, it would be useful to investigate further its potential to reduce further reflux episodes in proven severe cases where medical management and presurgical alternatives are limited. As GOR is a relatively common problem, it should be possible to conduct a large multicentre study to look for evidence of efficacy. In addition, further pharmacokinetic and safety studies should be undertaken.

Conclusions

Summary of key findings

In this systematic review, we found little evidence for the efficacy of domperidone in reducing the symptoms of GOR. There were no adverse effects noted. However, the trials included small numbers of children and the treatment duration was short.

From the limited evidence available, domperidone does not appear to be more effective than placebo in reducing symptoms of GOR and GORD. Given the usually benign nature of the condition, the widespread use of unlicensed medicines for GORis not warranted.

However, there is a pressing need to investigate fully the efficacy, safety and optimum dosage of domperidone in proven, severe cases, where medical management is required and other presurgical alternatives are limited. If these data provided evidence of a favourable benefit–risk profile, it would be possible to license domperidone for this indication.

Competing interests: None declared.

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