Medicines Adverse Reactions Committee

Meeting date	10/09/2020	Agenda item	3.2.2
Title	**Domperidone – benefit-risk review of use in children under 12 years old**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Domperidone	Domperidone (Pharmacy Health), Tablet 10 mg	PSM Healthcare Ltd
	Motilium, Tablet 10 mg	Janssen-Cilag (New Zealand) Ltd

PHARMAC funding	Domperidone (Pharmacy Health), Tablet 10 mg
Previous MARC meetings	158th Meeting (June 2014): Domperidone benefit-risk review 120th Meeting (December 2004): Domperidone and the risk of QT prolongation
International action	In December 2019, the MHRA changed the indication for domperidone to include only adults and adolescents 12 years of age or older and weighing 35 kg or more after a study showed a lack of efficacy for nausea and vomiting in the paediatric population younger than 12 years.
Prescriber Update	Domperidone – At the Heart of the Matter (March 2015) Drug-induced QT prolongation and Torsades de Pointes – the facts (December 2010)
Classification	Prescription medicine
Usage data	National Collections data on the number of dispensings, initial dispensings and people dispensed domperidone 10 mg tablets from a community pharmacy for children aged 2-11 years, in the period 2015-2019:

Year	**2015**	**2016**	**2017**	**2018**	**2019**
Dispensings	806	874	860	830	761
Initial dispensings	471	498	490	478	479
People	262	296	271	291	296

Advice sought	**The Committee is asked to advise:** • Whether the indication for domperidone should be revised to specify use only in adults and adolescents aged 12 years or over to reflect the clinical trial population? • Whether any further restriction on use of domperidone in children should be specified? • Should the weight restriction be increased from 35 kg to 40 kg, given that the 0.25 mg/kg dose specification cannot be achieved with the 10 mg tablet dose form in individuals weighing less than 40 kg? (ie, 40 kg x 0.25 mg/kg = 10 mg)? • Whether a further review of the indications for domperidone use in adults is needed.

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1 PURPOSE

The purpose of this MARC paper is to review the balance of benefits and risks of harm of domperidone when used in children aged 2-11 years. Domperidone is contraindicated in children aged under 2 years.

2 BACKGROUND

2.1 Domperidone

Domperidone is a peripheral dopamine receptor antagonist with gastrokinetic, antiemetic and galactagogue properties. Domperidone exerts its antiemetic activity by binding to and inhibiting D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier in the area postrema on the floor of the fourth ventricle. In the gut, domperidone facilitates gastric emptying and decreases small bowel transit time by increasing oesophageal and gastric peristalsis and by lowering oesophageal sphincter pressure. [1, 2]

In New Zealand, domperidone is currently indicated for [2, 3]:

> *'Symptomatic treatment of the dyspeptic symptom complex that may be associated with delayed gastric emptying such as epigastric sense of fullness, abdominal distension or swelling, or epigastric pain or discomfort.*
>
> *Treatment of acute symptoms of nausea and vomiting.*
>
> *There is insufficient evidence to support the use of domperidone in childhood gastro-oesophageal reflux disease. Domperidone may not be suitable for chemotherapy- or radiotherapy-induced nausea and vomiting or post-operative nausea and vomiting'.*

Comments:

Age and weight restrictions are not currently stated in the indication.

The MARC is asked to consider the following revised indication:

> *Symptomatic treatment of the dyspeptic symptom complex that may be associated with delayed gastric emptying such as epigastric sense of fullness, abdominal distension or swelling, or epigastric pain or discomfort* ***in adults and children aged 12 years and over****.*
>
> *Treatment of acute symptoms of nausea and vomiting* ***in adults and children aged 12 years and over.***

The statement about insufficient evidence to support the use of domperidone in childhood GORD does not belong in the indication and should be moved to section *4.4 Special warnings and precautions for use*.

2.2 EMA review of domperidone in 2014.

In 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) completed a review of domperidone-containing medicines [4]. The review was instigated due to ongoing concerns about serious cardiac adverse effects associated with domperidone, including QT interval prolongation, torsade de pointes, serious ventricular arrhythmias and sudden cardiac death.

After reviewing the available evidence, the PRAC considered that the benefit-risk balance for domperidone for the management of symptoms of nausea and vomiting remained favourable but recommended that the dose should be reduced to 10 mg up to three times per day for adults and adolescents weighing 35 kg or more. For products licensed in children and adolescents weighing less than 35 kg, the PRAC recommended that the dose should not exceed 0.25 mg per kg bodyweight up to three times daily. The PRAC also recommended that domperidone should not be used for longer than one week.

The PRAC considered that the available evidence of efficacy did not support the use of domperidone for indications other than acute nausea and vomiting. Furthermore, there were limited data to support paediatric use for acute nausea and vomiting.

The PRAC identified a need for robust data on the efficacy of domperidone for the relief of symptoms of nausea and vomiting in children aged 2-12 years. The EMA therefore requested Janssen, the marketing authorisation holder (MAH) for Motilium, to undertake Post Authorisation Efficacy Study (PAES) to generate efficacy data for domperidone in children aged 2-12 years. The paediatric study has since been completed [5, 6] and is discussed in section 3.1.1.2 below.

In December 2019, the New Zealand sponsor for Motilium 10 mg tablets notified Medsafe that domperidone is no longer licensed in the UK for use in children younger than 12 years or in patients weighing less than 35 kg. The UK Medicines and Healthcare products Regulatory Agency (MHRA) removed the paediatric indication following the results of the PAES, which failed to demonstrate a reduction in vomiting episodes in children younger than 12 years of age with acute gastroenteritis [7].

2.3 Medsafe review of domperidone benefit-risk balance, 2014

Following the PRAC's recommendation in 2014 that use of domperidone should be restricted to the management of nausea and vomiting, the dose should not exceed 30 mg daily, and treatment should not exceed one week, Medsafe also reviewed the benefit-risk balance for domperidone. The report was presented to the MARC at the 158th meeting in June 2014.

The review examined the efficacy and safety of domperidone in adults and children for each of the approved indications. The report comprised a review of Janssen-Cilag's submission to the PRAC, a review of the literature on the cardiac safety of domperidone, dispensing data from National Collections and a summary of adverse reactions reports from CARM. The full report is provided as Annex 1.

The review found that the evidence for use of domperidone in childhood GORD was not sufficient to support this indication.

For the paediatric nausea and vomiting indication, the report noted that domperidone was comparable to metoclopramide and superior to placebo. No additional benefit was noted during chemotherapy when used in addition to dexamethasone. Efficacy studies mainly used doses up to 1 mg/kg/day. Higher doses increased the risk of extrapyramidal effects.

The report recommended restricting the dose in all indications in children aged 2 and older to maximum of 1 mg/kg/day.

For the adult indications the report concluded that domperidone has been shown to be effective in conditions other than nausea and vomiting, and these conditions may require treatment for longer than one week. The report states:

> *'Medsafe considers that the available data does not support restricting the indication of domperidone to nausea and vomiting only or a reduction in the maximum dose to 30 mg per day and a maximum duration of one week, as recommended by the PRAC'. …*
>
> *… Medsafe considers that the potential risks should be managed to allow patients requiring long-term prokinetic treatment access to treatment.*
>
> *Whilst the data sheets for domperidone contain detailed information about the risk of cardiovascular effects, consideration should be given to updating the domperidone data sheets, to strengthen information in the indications, dosage and administration, contraindications, adverse effects, and warnings and precautions sections.'*

Medsafe proposed various changes to the domperidone data sheets in line with the report's conclusions

At the 158th MARC meeting, the Committee noted that there is limited evidence for use of domperidone for gastro-oesophageal reflux disease (GORD) in children. The main adverse effects in the paediatric population

relate to nervous system disorders including extrapyramidal effects, which were already included in the data sheet. The domperidone dose specified for children in the New Zealand Formulary for Children (NZFC) was lower than the dose specified in the data sheets at the time.

The Committee recommended that the sponsors for domperidone-containing products update the paediatric dose specification with a lower recommended dose.

In contrast to the PRAC recommendation, the MARC did not recommend restricting the indication for domperidone to the management of nausea and vomiting, limiting the maximum adult daily dose to 30 mg or limiting the treatment duration to one week. However, the Committee did recommend updates to the indications, contraindications and warnings sections of the data sheets, as summarised in (medsafe.govt.nz/profs/adverse/Minutes158.htm#3.2.3)

2.4 Data sheets

2.4.1 New Zealand

Two data sheets for products containing domperidone are currently published on the Medsafe website:

- Motilium 10 mg tablets (Janssen-Cilag NZ Ltd) [2] and
- Domperidone (Pharmacy Health) 10 mg tablet (PSM Healthcare Ltd) [3].

The information in the data sheets about the use of these products in children aged 2-11 years is presented in Annex 2.

The Company Core Data Sheet (CCDS) for Motilium (domperidone) was updated on 24 January 2018. The New Zealand sponsor submitted a Changed Medicine Notification (CMN) to Medsafe on 10 April 2018 to update the data sheet with the information shown below in Box 1 (consented on 26 June 2018) [2].

Box 1. Motilium data sheet updates relevant to paediatric population, published 26 June 2018

4.2 Dose and Administration

Infants and children < 12 years of age and weighing < 35 kg

… The efficacy of MOTILIUM has not been established in infants and children < 12 years of age and weighing < 35 kg (see section 5.1 Pharmacodynamic properties - Clinical Studies - Infants and children ≤ 12 years of age).

5.1 Pharmacodynamic properties

Clinical Studies

Infants and children ≤ 12 years of age

A multicentre, double-blind, randomized, placebo-controlled, parallel-group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomized subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing the percentage of subjects with no vomiting episodes during the first 48 hours after the first treatment administration.

Domperidone (Pharmacy Health) is the only generic brand of domperidone currently available in New Zealand. It was approved on 24 May 2018, four months after the CCDS for the reference product Motilium had been

updated, but before the revised Motilium data sheet was published. The Domperidone (Pharmacy Health) data sheet has not been updated since it was first approved and does not include the changes shown in Box 1.

2.4.2 Australia

The Therapeutic Goods Administration (TGA) has approved domperidone for the following indications:

> *Short-term treatment in adults of:*
>
> - *Symptoms associated with idiopathic or diabetic gastroparesis (once control of diabetes has been established by diet and/or insulin, an attempt should be made to discontinue MOTILIUM).*
> - *Intractable nausea and vomiting from any cause.*

Section *4.2 Dose and Method of Administration* of the Australian Product Information (PI) for Motilium (domperidone) includes the following information [8]:

> **Adults (weighing ≥ 35 kg)**
>
> *10 mg three times daily. Domperidone should be initiated at the lowest effective dose for the individual situation, which may be adjusted upward with caution to achieve the desired effect. The expected benefit of an increased dose should outweigh the potential risks. Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. For other indications, the initial duration of treatment is limited to 4 weeks. Patients should undergo a benefit/risk re-analysis if treatment beyond 4 weeks is contemplated.*
>
> *The maximum daily dose is 30 mg.*
>
> *Safety and efficacy of MOTILIUM (domperidone) use beyond six months has not been established.*
>
> *MOTILIUM tablets are unsuitable for use in adults weighing less than 35 kg. MOTILIUM should not be used in children.*

2.4.3 United Kingdom and Europe

In the UK and Europe, domperidone is indicated for *'the relief of symptoms of nausea and vomiting'*.

Dose information is provided for ***'adults and adolescents (12 years of age and older and weighing 35 kg or more'***). The recommended dose for this population is '*one 10 mg tablet up to three times per day with a maximum dose of 30 mg per day'*. [9]

2.4.4 United States

Domperidone has never been approved for use in humans in the United States. (The FDA has approved domperidone as a veterinary medicine [10]).

2.5 Domperidone usage in New Zealand children aged 2-11 years

Pharmaceutical dispensing data for domperidone was obtained for the 5-year period 2015-2019 using the Pharmaceutical Dispensings Qlik application (internal Ministry of Health use only). The application uses the Pharmaceutical Collection as its data source [11]. The data includes information about pharmaceutical dispensings that are funded by PHARMAC. It does not include pharmaceutical products dispensed in hospitals or non-funded medicines.

Figure 1

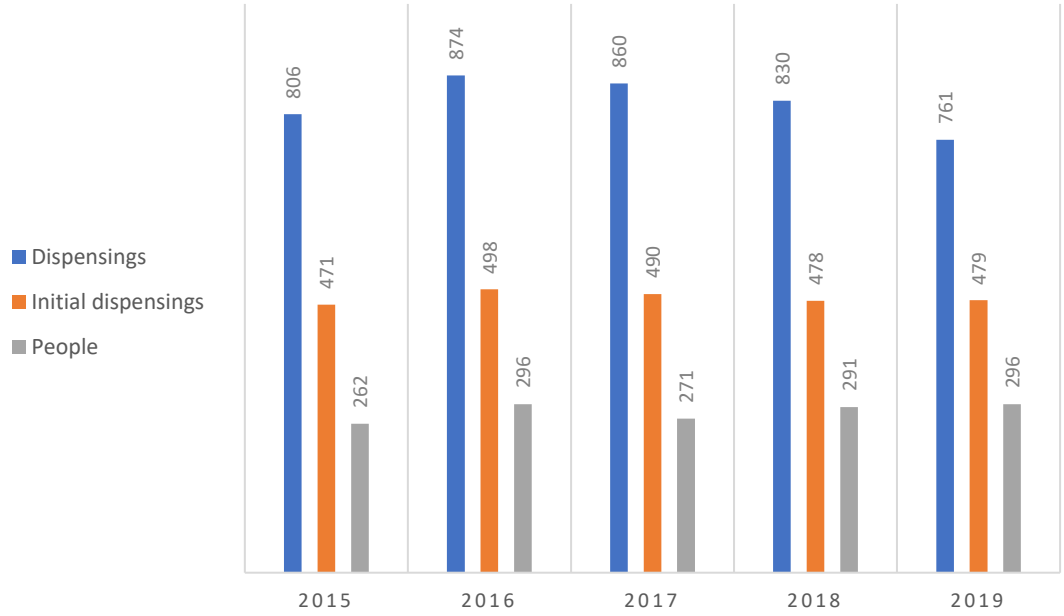


Figure 1. Domperidone dispensing from community pharmacies for children aged 2-11 years (2015-2019)

Source: Pharmaceutical Dispensings Qlik application (data derived from MOH Pharmaceutical Collection)

Comments:
Community dispensing of domperidone for children aged 2-11 years has been at a consistent level over the past five years.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Efficacy of domperidone for gastrointestinal disorders in children

3.1.1.1 Niño-Serna et al, 2020 (Pediatrics)

Antiemetics in Children with Acute Gastroenteritis: a meta-analysis [12]

Objective

To determine the effectiveness and safety of antiemetics for controlling vomiting in children with acute gastroenteritis.

Methods

Systematic review and network meta-analysis

The main data sources were: Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Latin America and the Caribbean Literature on Health Sciences, until 31 December 2018. Clinical trial registries (www.clinicaltrials.gov and World Health Organisation Clinical Trials Registry Platform) were also searched for grey literature.

Studies were eligible for inclusion in the systematic review if they were a randomized or quasi-randomised clinical trial of an antiemetic used to control vomiting in children with acute diarrhoea and gastroenteritis (ADG). Eligible studies had to include an intervention, comparison and outcome of interest.

Interventions of interest were: metoclopramide, ondansetron, domperidone, dexamethasone, dimenhydrinate, alizapride and granisetron. Comparisons of interest were: placebo, conventional treatment with oral rehydration therapy (ORT), or different doses or routes of administration of the same intervention.

The primary outcomes were **cessation of vomiting** and **hospitalisation**.

Secondary outcomes included: need for **intravenous rehydration** during Emergency Department (ED) visit and up to 3 days after discharge, **revisit to ED** within 72 hours of discharge, mean **number of vomiting** episodes during the observation period, and **side effects**.

Two reviewers independently screened abstracts and full texts, and extracted the data into a prespecified form. Risk of bias (RoB) was assessed using a modified version of the Cochrane RoB tool, which is based on the following criteria: sequence generation, allocation concealment, blinding of participants, personal and outcome assessors, completeness of follow-up, selective outcome reporting, and other biases. Bias was assessed as 'definitely low', 'probably low', 'probably high' or 'definitely high' risk.

Analysis: A pairwise random-effects meta-analysis was performed for each available direct comparison. Treatment effects were estimated using odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes and reported with 95% credible intervals (CIs). Heterogeneity was quantified using the statistic for heterogeneity in direct comparisons (I^2) expressed as a percentage of variability that is due to true differences between studies rather than sampling error. All analyses were performed using the Markov chain Monte Carlo method. A geometry plot was used to present all the available direct comparisons per outcome, in which each node represents one intervention. (Table 1)

A NMA was performed to analyse all the potential comparisons among interventions for each outcome. For each outcome and a connected network of studies, a Bayesian random-effects NMA was performed if the assumptions of between-study homogeneity, transitivity[1], and incoherence[2] across treatment comparisons were considered justifiable. In the absence of direct evidence for a given comparison, treatment effectiveness and safety were estimated indirectly. Meta-regression sensitivity and subgroup analyses were conducted to explore the potential sources of heterogeneity and incoherence.

Confidence in effect estimates was determined using the GRADE approach, and was rated as high, moderate, low or very low.

The NMA results are presented by grouping the interventions according to the magnitude of the effect in comparison to a placebo and the quality of evidence (according to GRADE). The eight categories (marked by different colours) are shown in Table 1. Dark colours represent interventions with moderate to high quality evidence. Light colours represent interventions with very low to low quality evidence.

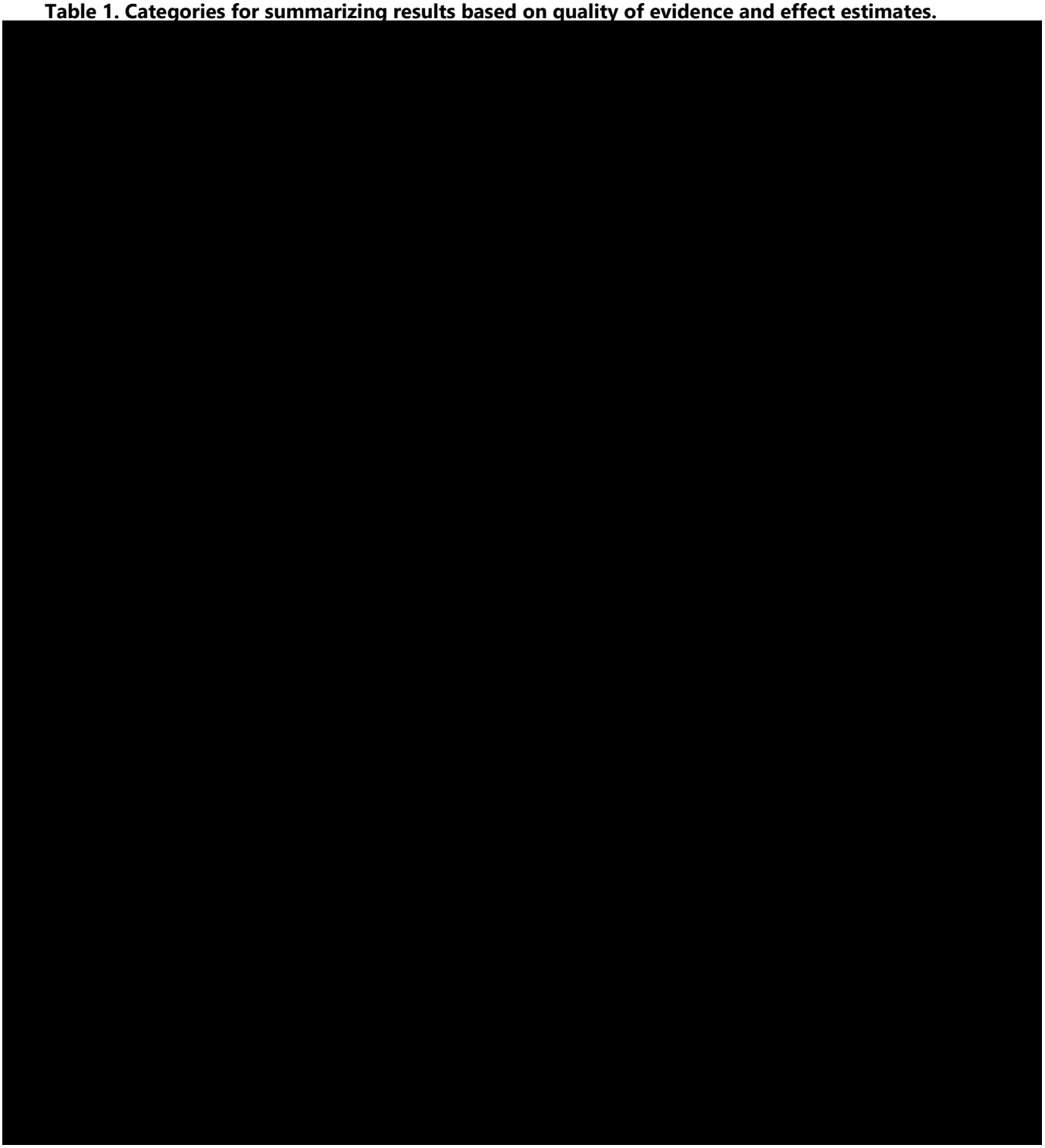
[1] Transitivity is the assumption that an indirect comparison is a valid method to compare two treatments because the studies are sufficiently similar in important clinical and methodological characteristics, ie, they are similar in their distributions of effect modifiers. 12. Niño-Serna LF, Acosta-Reyes J, Veroniki AA, et al. 2020. Antiemetics in Children With Acute Gastroenteritis: A Meta-analysis. *Pediatrics* 145(4): 10.1542/peds.2019-3260

[2] Incoherence (also called inconsistency) is defined as the statistical difference between direct and indirect treatment effects. 12. Ibid.

Comments:

As described by the authors, a NMA approach allows comparison of interventions that have not been compared directly in a RCT. For example, intervention A can be compared indirectly with intervention B if both A and B have been compared with intervention C (usually placebo). Additionally, the combination of direct and indirect comparisons allows researchers to obtain more precise estimates.

Table 1. Categories for summarizing results based on quality of evidence and effect estimates.



Results

Twenty-four studies were included in the qualitative and quantitative analysis, with a total of 3482 children (Figure 2). The interventions studied were metoclopramide, ondansetron, domperidone, dexamethasone, dimenhydrinate, and granisetron.

Figure 2. PRISMA flow diagram of study selection.

Most interventions were compared against placebo (Figure 3). Six (25%) of the included studies had high RoB due to allocation concealment and blinding of participants, and/or outcome assessors. Five studies had high RoB because of incomplete reporting and five studies because of inadequate sequence generation.

Figure 3. Network geometry plots: A. Cessation of vomiting; B. Hospitalisation; C. Revisit to ED; D. Intravenous rehydration, E. Number of vomits; F. Side effects.
Each treatment node is weighted according to the number of patients that have received the corresponding treatment, and each line is weighted according to the number of studies comparing the treatments it connects.

Cessation of vomiting: 10 studies provided data for direct comparisons of vomiting cessation (2627 patients). Ondansetron was better than metoclopramide, dexamethasone and placebo in the direct meta-analyses. There were no statistical differences for the remaining treatment comparisons. In the NMA, there were 21 paired effect estimates. Ondansetron showed the largest effect compared to placebo for cessation of vomiting (OR 0.28, 95% CI 0.16 to 0.46; quality of evidence: high). (Table 2)

Hospitalisation: 13 studies provided information on hospitalisation (2008 patients). In the pairwise meta-analyses, ondansetron was better than domperidone (OR 2.72, 95% CI 1.56-5.89) and better than placebo (OR 3.63, 95% CI 1.16 – 21.3). Heterogeneity was low in all the comparisons except for the domperidone-ondansetron comparison (I^2 = 65.9%). In the NMA, ondansetron was better than placebo (OR 2.93, 95% CI 1.69 – 6.18) and better than domperidone (OR 3.31, 95% CI 1.21 – 15.8). There were no differences for the remaining comparisons. (Table 2)[3]

[3] Note that in Table 2, the result is reported as placebo vs ondansetron, so the OR and 95% CI are reported as the inverse of the numbers reported in the text).

Table 2. League table of NMA effect estimates for the primary outcomes (cessation of vomiting and hospitalisation).

Notes: Results are presented as OR and their corresponding 95% CI. The table should be read from left to right. For vomiting cessation, an OR > 1 favours cessation of vomiting. For hospitalisation, an OR < 1 favours fewer hospitalisations. Significant results are marked with an asterisk. The colours represent the certainty of evidence: dark green – high, light green – moderate, light yellow – low, and light red – very low.

Comments:

Table 2 shows comparisons between interventions for each of the primary outcomes (vomiting cessation and hospitalisation). The table should be read from right to left. Thus, the comparisons of interest (circled in red) involving domperidone should be read as follows:

For vomiting cessation:

Placebo vs domperidone: OR 0.64 (95% CI 0.23-1.59) – not significant

Domperidone vs ondansetron: OR 0.44 (95% CI 0.17 – 1.18) – not significant

For hospitalisations:

Placebo vs domperidone: OR 1.12 (95% CI 0.38 – 4.76) – not significant

Domperidone vs ondansetron: OR 0.30 (95% CI 0.06 – 0.81) – statistically significant, in favour of ondansetron (ie, ondansetron vs domperidone OR 3.31, 95% CI 1.21 – 15.8)

Ondansetron was the only intervention that reduced the need for intravenous rehydration and the number of vomiting episodes (Table 3).

Based on the categories defined in Table 1, the NMA demonstrated that domperidone was *'similar to placebo'* for **intravenous rehydration** (OR 0.70; 95% CI 0.17 – 2.77) and for **revisiting ED** (OR 1.72; 95% CI 0.74 -5.88). Domperidone *'may be similar to placebo'* for **cessation of vomiting** (OR 1.58; 95% CI 0.62 – 4.34), **hospitalisation** (OR 1.13; 95% CI 0.38 – 5.0), and **vomiting number** (MD -0.38; 95% CI -2.03 to 1.01)[4] . (Table 3)

The NMA also demonstrated that domperidone *'may be similar to placebo'* for **side effects** (OR 1.51, 95% CI 0.05 – 4.16), and for **diarrhoea** (MD 0.41, 95% CI -1.42 – 2.27).

[4] There appears to be a typographic error in Table 3. For vomiting number, the MD for domperidone vs placebo is reported as -0.38 (95% CI **2.03** to 1.01). The negative value before 2.03 in the confidence interval appears to have been omitted.

Table 3. NMA results of comparison between active treatment and placebo for all primary and secondary outcomes, sorted by certainty of evidence. Effect estimates are presented in the last column as OR (dichotomous outcomes) or MD (continuous outcomes) and 95% CI.

[redacted]

[a] NMA estimates: OR (95% CI). [b] NMA estimates: MD (95% CI).

Comments:

Table 3 summarises the NMA results of comparisons between active treatment vs placebo for all outcomes, presented by level of certainty of evidence. Eg, for cessation of vomiting, the result is presented as ondansetron vs placebo (OR 3.57, 95% CI 2.17 – 6.25).

In the article text, the results are presented as placebo vs ondansetron 0.28 (95% CI 0.16 – 0.46). This is the inverse of the OR presented in Table 3.

Limitations

Most treatment comparisons had low- or very low–quality evidence, due to risk of biases and imprecise estimates.

Conclusions

Ondansetron is the only intervention that revealed an effect on the cessation of vomiting, on preventing hospitalisations, and in reducing the need for intravenous rehydration. Ondansetron was also considered a safe intervention.

Comments:

In this NMA, domperidone was found to be no better than placebo for the primary outcomes of vomiting cessation and hospitalisation.

The secondary outcomes (intravenous rehydration, vomiting number, revisiting ED, side effects and diarrhoea) were not statistically different to placebo.

The Supplemental Information published online lists the 24 studies that were included in the NMA. Five studies (involving a total of 632 children) were included in the analysis. The included studies are:

Marchetti et al, 2016 (PLoS One) [13] - Italy

Kita et al, 2015 (Asia Pacific Journal of Public Health) [14] - Japan

Salma-Kamal et al, 2015 (J Med Sci Clin) [15] - India

Rerksuppaphol et al, 2013 (J Clin Med Res) [16] - Thailand

Van Eygen et al, 1979 (Postgraduate Medical Journal) [17] - Belgium

These studies are not discussed further in this section.

3.1.1.2 Leitz et a, 2019 (J Pediatr Gastroenterol Nutr)

Safety and Efficacy of Low-dose Domperidone for Treating Nausea and Vomiting Due to Acute Gastroenteritis in Children [6]

Background

The PRAC review in 2014 concluded that there is an increased risk of serious cardiac adverse drug reactions associated with domperidone use and that the risks are increased in patients aged over 60 years, at doses above 30 mg/day and/or if used in combination with a QT-prolonging medicine or CYP3A4 inhibitor that can increase the plasma level of domperidone.

For adults, the benefit-risk balance for domperidone remained favourable only for the relief of nausea and vomiting at doses of up to 30 mg/day. For this indication, the PRAC recommended that domperidone should be used at the lowest effective dose and for the shortest duration possible, not exceeding one week.

For children, there were limited data available on the efficacy of domperidone. The PRAC recommended that for children and adolescents weighing less than 35 kg, domperidone should be used only in oral formulation and at a dose of 0.25 mg/kg bodyweight up to a maximum of 10 mg three times per day and requested that further data be generated to confirm efficacy in children with nausea and vomiting due to acute gastroenteritis.

Objective

This study was conducted by Janssen-Cilag in response to a request from the EMA to generate robust data on domperidone efficacy in children for the relief of symptoms of nausea and vomiting.

Methods

This randomized, double-blind, placebo-controlled, parallel group study was conducted from 7 July 2016 to 3 August 2017 at 45 sites in Austria, Belgium, Italy, the Russian Federation, South Africa, Spain and the United Kingdom. After screening, enrolled patients were stratified according to length of time vomiting had occurred before baseline (0 to <24 hours and ≥24 hours) and into two age groups (6 months to < 4 years and 4 to 12 years). Patients were randomised (1:1) to receive 0.25 mg/kg dose of domperidone (1 mg/ml suspension) or matching placebo. After the first dose of study medicine, ORT was initiated within 30-60 minutes, and second and third doses were administered at an interval of 4-6 hours on Day 1. From days 2-7, oral domperidone suspension 0.25 mg/kg (not exceeding 10 mg /day) or placebo suspension t.i.d was administered 30 minutes before a meal. Treatment was discontinued if the patient was free of vomiting for 24 hours and had also completed at least a total of 6 doses. If nausea, vomiting or diarrhoea worsened during the study, the study medicine was discontinued and rescue medication (standard-of-care used in the practice/country) or intravenous fluids were initiated. (Figure 4)

Figure 4. Study design, drug dosing, and patient allocation.
BL, baseline; ORT, oral rehydration treatment; TEAE, treatment-emergent adverse events.
On days 3, 4, and 8: investigator collected safety data via telephone contact with patients/legal guardian.
On days 3, 4, and 8: the study nurse screened for TEAEs of special interest during phone visit, using the checklist and entered the data into the patients' electronic case report form; follow-up visit on day 2: safety, hydration status and weight were recorded.

Children were eligible for enrolment if they were aged 6 months to 12 years[5] with mild-to-moderate dehydration with ≥ 3 episodes of non-bilious, non-bloody vomiting, and at least 1 episode of non-bloody diarrhoea within 24-hours before screening. Other inclusion criteria were ≥ 2 signs and symptoms of acute

[5] Children enrolled in the Russian Federation were aged > 6 years in line with the country's regulations.

gastroenteritis (fever, nausea, diarrhoea, abdominal pain, bloating or discomfort) within 3 hours before screening).

Children were excluded if they had severe dehydration or severe malnutrition, vomiting, and clinical symptoms for > 72 hours before screening or needed IV fluid replacement. Children with chronic gastrointestinal disorders or other chronic illnesses were also excluded.

The primary efficacy endpoint was the proportion of patients with no vomiting episodes within the first 48 hours of treatment administration. The key secondary efficacy endpoint was the percentage of patients aged ≥4 years with no nausea episode of nausea within 48 hours of first treatment administration.

Patients or legal guardians recorded all efficacy assessments including the total number and timing of vomiting, nausea and diarrhoea episodes, and patient weight in an electronic diary.

Safety assessments included recording of treatment-emergent adverse events (TEAEs) and serious TEAEs by severity, duration and relationship to study drug. Adverse events of special interest (AESI) included extrapyramidal signs and 'symptoms associated with QT prolongation'. A baseline ECG was not conducted as a single ECG assessment was not considered a reliable measure to exclude pre-existing QT prolongation.

An Independent Data Monitoring Committee (IDMC) twice reviewed the unblinded interim data: first when ~ 25% of patients were enrolled (to review safety) and second when ~ 50 % of the randomised patients had either completed or dropped out of the study (to review safety and efficacy).

The primary efficacy analysis was performed in the intention to treat (ITT) set, defined as all randomised patients. Safety analysis was performed on the safety analysis set, defined as all randomised patients who received one or more doses of study drug.

Results

The study was terminated early for futility based on the IDMC recommendations following the planned interim analysis. At the time of early termination, 292 patients were randomised to receive domperidone (n = 147) or placebo (n = 145), and 287 patients had completed the study. Before termination, 5 patients had discontinued the study, of which 3 patients (domperidone 1, placebo 2) had withdrawn due to adverse effects.

The median (range) age of patients was 9 (0.67 – 12) years with 53% boys and 83% Caucasian. The mean (SD) number of doses was 7.1 (2.29) in domperidone and 7.2 (2.85) in placebo group.

The proportion of patients with no vomiting episodes within 48-hours of first treatment administration was similar between domperidone (32.0%) and placebo (33.8%) groups. Similarly, there was no significant difference in proportion of patients ages ≥4 years with no nausea episodes within 48 hours of first treatment administration between domperidone (35.7%) and placebo (38.6%). (Table 4)

Table 4. Proportion of patients with no episodes of vomiting and nausea within 48 hours of first domperidone administration (ITT population)

No statistical difference was observed for the subgroup analyses based on baseline stratification by age (6 months to 4 years; 4 years to 12 years) or length of time that vomiting occurred before baseline (0 to <24 h or ≥24 hours). The results were consistent with that of the primary analysis for proportion of patients with no vomiting episode. (Table 5)

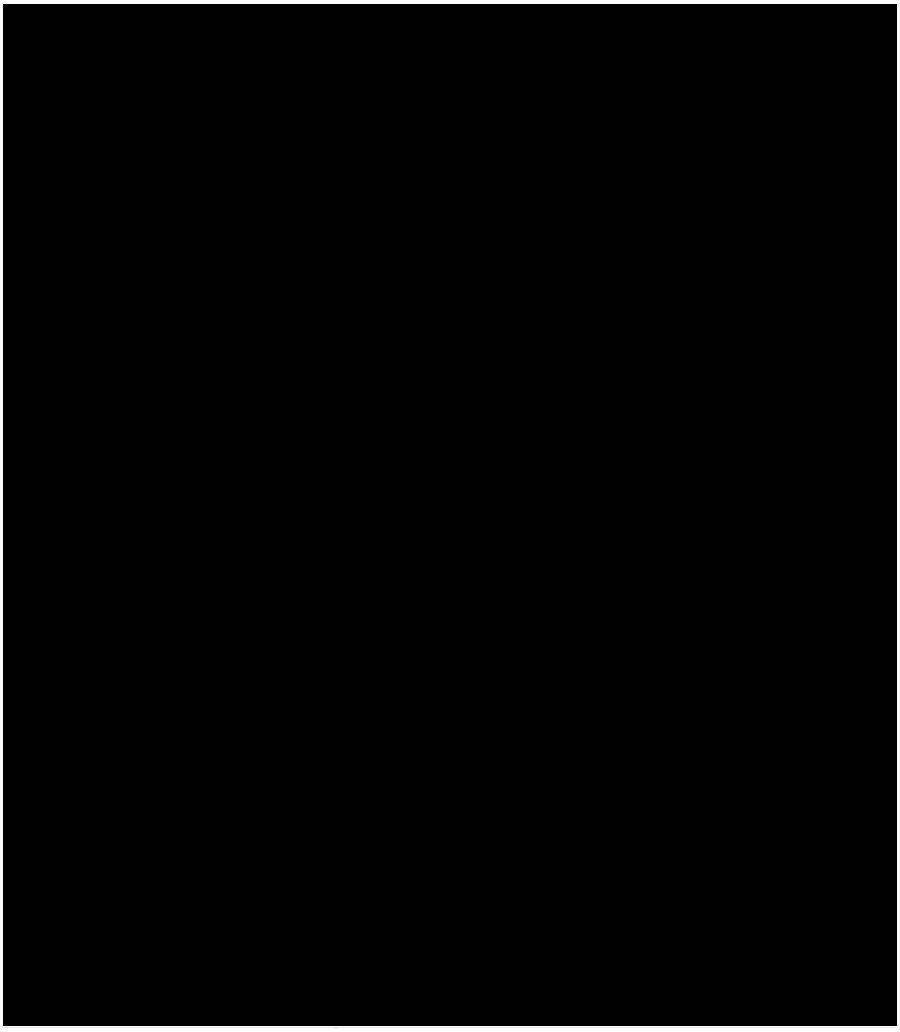
Table 5. Vomiting and nausea episodes within 0 to ≤24 hours, >24 to ≤48 hours, and >48 hours to ≤ 7 days after first treatment administration.

Generalized linear models for treatment comparison (domperidone vs placebo) was used for the number of vomiting episodes with factors for treatment, time period (0 to ≤24 hours, >24 to ≤48 hours, >48 to ≤7days),

and stratification factors of the length of time that vomiting occurred before baseline (0 to<24, or_24 hours) and age (6 months to<4 years of age vs 4– 12 years of age). SD = standard deviation.
**P value indicates 0-hour to 7-day time period.*

Thirteen patients (domperidone 5/147 [3.4%] vs placebo 8/145 [5.5%]) reported one or more treatment-emergent adverse events. No deaths or adverse events of special interest (extrapyramidal symptoms and QT prolongation) were reported. (Table 6)

Table 6. Treatment-emergent adverse events observed in safety analysis set



Conclusions

A low-dose of domperidone (0.25 mg/kg up to a maximum of 10 mg t.i.d. for up to 7 days) in combination with ORT did not significantly differ from placebo in reducing vomiting and nausea episodes in paediatric patients aged 6 months to 12 years with acute gastroenteritis. The safety profile was similar between both groups.

Comments:
This study demonstrated a lack of efficacy compared to placebo for symptoms of nausea and vomiting in children aged 6 months to 12 years.

The authors suggest that the domperidone dose used in the study is 'low dose', but it is in fact the maximum dose recommended by the PRAC for use in children and adolescents weighing less than 35 kg.

The risk of QT interval prolongation was not adequately assessed in this study. Baseline ECGs were not performed, and the emergence of QT interval prolongation was apparently assessed symptomatically. However, QT interval prolongation *per se* is asymptomatic; symptoms only develop with the advent of an arrhythmia.

There appears to be a typographic error in the methods section of the published report, which states:

> *From days 2-7, oral domperidone suspension 0.25 mg/kg (not exceeding 10 mg /day) or placebo suspension t.i.d was administered 30 minutes before a meal.*

The PRAC's dose recommendation for children was 0.25 mg/kg up to three times daily. The 10 mg limit is per dose not per day (as a child weighing 40 kg could receive a dose of 10 mg t.i.d).

This recent study was undertaken by Janssen at the request of the EMA to produce robust efficacy data on the efficacy of domperidone for symptoms of nausea and vomiting in the paediatric population. This study was not included in the network meta-analysis published in 2020 by Niño-Serna et al (section 3.1.1.1), but the demonstrated lack of efficacy would not have changed the result for domperidone in that study, ie, that is no better than placebo for the treatment of acute nausea and vomiting.

3.1.2 Safety of domperidone in children

3.1.2.1 Morris et al, 2016 (Can J Hosp Pharm)

Domperidone-Associated QT Interval Prolongation in Non-oncologic Pediatric Patients: A Review of the Literature [18]

Objective

This narrative review of the literature aimed to summarise and evaluate the evidence for domperidone-associated QT interval prolongation, ventricular arrhythmias, and sudden cardiac death to determine the safety of this drug for paediatric patients.

Methods

MEDLINE Ovid (1946 to August 2015) and EMBASE (1980 to August 2015) were searched with the following Medical Subject Headings and keywords: 'domperidone', 'arrhythmias, cardiac', 'death, sudden, cardiac', 'electrocardiography', 'heart diseases', 'long QT syndrome', 'tachycardia, ventricular', 'torsades de pointes', and 'ventricular fibrillation'. The search was limited to studies conducted in humans under 18 years of age and published in English. Studies were eligible for the review if they included original research (observational or randomised) reporting on the safety of oral domperidone. Studies were included if they reported cardiac-related safety data (eg, change in QTc interval, sudden cardiac death). Studies were excluded if they were manually identified as editorials containing no original research. Studies that were conducted in paediatric oncology patients were excluded because of potential confounding risk factors for QTc prolongation.

Data synthesis

Five studies, involving a total of 137 patients, met the inclusion criteria for the review (Figure 5):

Hegar et al, 2009 [19]	-	open label, non-placebo controlled, randomised trial
Vieira et al, 2012 [20]		
Günlemez et al, 2010 [21]		prospective cohort studies
Djeddi et al, 2008 [22]		
Rocha and Barbosa, 2005 [23]	-	case report

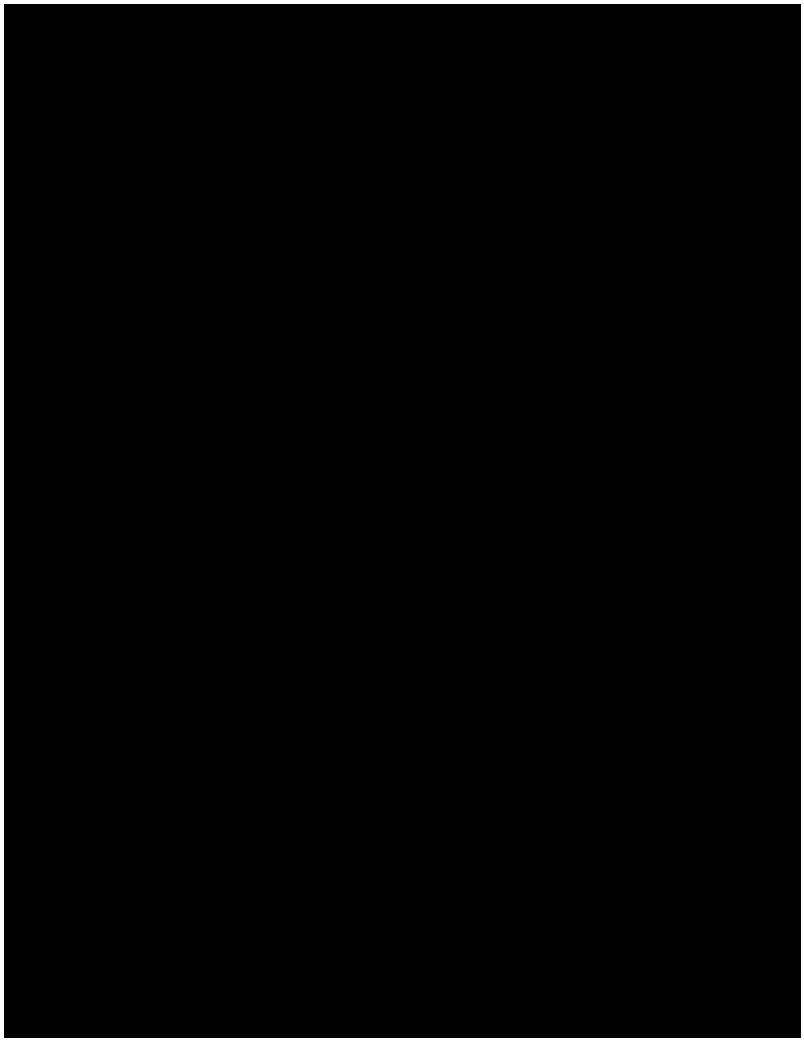


Figure 5. Study flow diagram for narrative review of domperidone-associated QTc interval prolongation in non-oncologic paediatric patients

The studies were conducted in Belgium, Brazil, France, Indonesia, and Turkey, and were published between 2005 and 2012. The studies included term and pre-term infants born as young as 24 weeks gestational age and enrolled at between 2 days and 9 months of life. None of the included studies had patients between the ages of 1 and 18 years. The most common indication for domperidone was GER. (Table 7).

Table 7. Characteristics of studies included in literature review of domperidone-associated QT interval prolongation in non-oncologic paediatric patients

Note: the RCT by Hegar et al (2009) is an open-label study comparing domperidone with cisapride.

One study reported a statistically significant change in the QTc interval (14 ms above baseline), but the clinical significance was unclear. Most of the studies reported pathological QTc intervals in one or more infants receiving domperidone. None of the studies reported ventricular arrhythmias or sudden cardiac death.

Confounding factors (e.g., abnormal electrolyte level or concurrent medications) were not consistently considered. Potential bias might have been alleviated by blinding of electrocardiogram (ECG) assessors; however, this was not consistently implemented. The designs of the included studies did not allow assessment of causality.

Conclusions

Pathological QTc intervals were noted among a small number of infants associated with the use of domperidone. Because of the potential seriousness of QT interval prolongation, individual assessment and routine ECG monitoring should be implemented for patients receiving domperidone.

Comments:

The literature search found only five studies that met the inclusion criteria. All of the studies involved infants (<12 months old) receiving domperidone for GORD. None of the studies included children aged 1-18 years or use of domperidone for acute nausea and vomiting.

The safety information from this study is difficult to extrapolate to older children. However, as QTc prolongation has been identified as an adverse effect in adults and infants, it is not unreasonable to assume that it may also affect children aged 2-12 years.

3.1.2.2 Cohen et al, 2015 (Br J Clin Pharmacol)

Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review [24]

Objective

To review reported adverse effects of pharmacological agents commonly used in the treatment of paediatric GORD.

Methods

PubMed and Cochrane Database of Systematic Reviews were searched using the following keywords: *omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, ranitidine, cimetidine, famotidine, nizatidine, domperidone, metoclopramide, bethanechol, erythromycin, baclofen, alginate*. Results were filtered for the period of interest (1 January 2003 to 31 December 2012) and population of interest ('child: birth – 18 years'). All full articles were reviewed, and only RCTs were included. The reported adverse effects and safety profile was reviewed for each drug.

Results

Fifteen articles on domperidone were retrieved but only four were found to be relevant:

Vieira et al, 2012 [20]

Günlemez et al, 2010 [21]

Djeddi et al, 2008 [22]

Rocha and Barbosa, 2005 [23]

The cumulative sample size was 120 patients, ambulatory and hospitalized, ranging in age from 0 to 12 months. Domperidone doses ranged from 0.5 mg/kg/day to 1.8 mg/kg/day. None of the four studies systematically addressed AEs, focusing only on whether domperidone prolonged the QT interval on the electrocardiogram. Two of the studies reported no change in the QT interval (n = 43 and 45, respectively), while the other two reported an increase in the QT interval (n = 31 and n = 1, respectively).

Conclusions

Prokinetic agents have many adverse effects, without major benefits to support their routine use.

Comments:

The four studies of domperidone use in this review were also included in the 2016 review by Morris et al [18]. Accordingly, as with the subsequent review, all of the patients in this review were aged less than 12 months old.

3.1.2.3 Mt-Isa et al, 2015 (J Pediatr Gastroenterol Nutr)

Prokinetics prescribing in paediatrics: evidence on cisapride, domperidone, and metoclopramide [25]

Background

Prokinetics such as cisapride, domperidone, and metoclopramide have been used to treat GORD symptoms in children, but their licensing indications in children are restricted to nausea and vomiting. Cisapride was withdrawn in July 2000 following cardiac adverse reactions in adults. Domperidone subsequently emerged as

an alternative. In May 2012, the MHRA warned of the small risk of serious ventricular arrhythmia and sudden cardiac death associated with domperidone, with elevated risk in those consuming daily doses of >30 mg. The MHRA subsequently revised the contraindications of domperidone and enforced restricted use in May 2014 for adults, while acknowledging that further research was needed in children, and later placed it under additional monitoring (Black Triangle) in July 2014. These changes triggered a revision to the off-label use of domperidone for GORD in the UK British National Formulary for Children (BNFC) in October 2014. Other treatment options are available, all with limited evidence of efficacy.

Objectives

To review chronological changes in prescribing trends of cisapride, domperidone, and metoclopramide in children using data from the Gastro-Oesophageal Reflux Medicines – Evidence for Trials (GORMET) study.

To examine external factors that may have influenced the trends observed, particularly the emergence of paediatric guidelines on the management of GORD.

To identify potential safety signals associated with the use of the medicines in children.

Methods

This study used data from the GORMET study, which was designed to explore the potential of the General Practice Research Database (GPRD)[6] to inform clinical trial design on safety of medicines used off-label in primary care for the treatment of GORD symptoms in children. The GORMET study population was extracted from approximately 3.6 million active patients from approximately 433 practices participating in the GPRD, covering 5.5% of the UK population.

This study included data for children aged less than18 years between 1990 and 2006 who were prescribed cisapride (N = 1497), domperidone (N = 9319), or metoclopramide (N = 17,985), and had at least 3 months of follow-up data recorded. Each child was matched by age and sex to 4 children who did not receive a prescription for any of the three drugs. The denominator was the number of children in GPRD<18 years old, by year, during the same time period.

Incidence rates were calculated using Poisson regression adjusted for the size of the underlying child population in the GPRD by year (number of new children per million starting prescription in a particular year). Rates were calculated for all children initially, and then for the subset of children <2 years old (<2) and for those 2 years old and older (≥2) because of the likely different indications in these two age groups.

Trends in prescriptions and the possible influence of paediatric guidelines for GORD were analysed.

Side effects for each drug that were listed in the British National Formulary for Children (BNFC) were considered known safety signals for children. Proportional reporting ratios (PRRs) were calculated for other drug/event pairs to generate hypotheses of unknown safety signals.

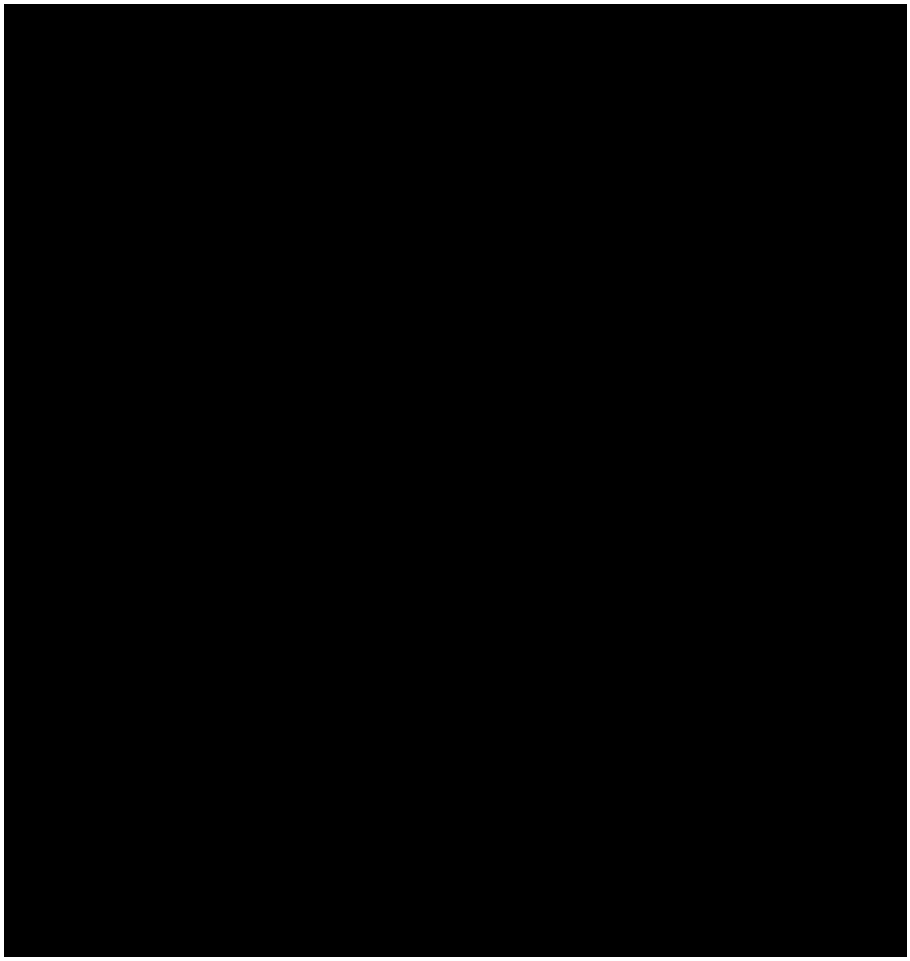
Nested case–control studies were conducted for the unknown safety signals, and the causal association was assessed using the Bradford Hill approach. [26].

Results

Prescription data for the period 1990 – 2006 is shown in Table 8. The annual incidence rates of domperidone (1990–2006) prescription in all children increased by and 7.5% (95% CI 6.8–8.1). There was a dramatic increase in incidence rates in children <2 years old being prescribed domperidone following the withdrawal of cisapride in July 2000. A much smaller increase was observed in those ≥ 2 years old.

[6] The GPRD became the Clinical Practice Research Database (CPRD) in March 2012.

Table 8. Summary data, number of children whose prescription data were analysed in that year (percentage of whom were < 2 years old) unless otherwise specified.



No new causally related safety issues were identified in children prescribed with these drugs. Only diarrhoea was associated with domperidone prescription in children<2 years old with incidence rate ratio of 1.26 (95% CI 1.08–1.47). The unknown safety signals were, in general, associated with concomitant medications and illnesses, and increased dose or duration of prokinetics use.

Conclusions

Dramatic changes in prescribing of cisapride and domperidone were observed despite the lack of good-quality supporting evidence. Prescribing trends may have been influenced by published guidelines. The lack of new safety signals during the period supports the development of suitably powered clinical trials.

Comments:

This study is poorly described and there is minimal information on the exploration of adverse effects.

This main objective of this study was to describe the prescribing patterns for prokinetic drugs in the UK over the period 1990-2006, and to see how changes in prescribing relate to the emergence of GORD guidelines.

For domperidone, there is an increase in use from 0.04% of the paediatric population in 1990 to 0.55% in 2006. Of note is the increase in prescribing to children under the age of 2 years over this period from 4% of domperidone prescriptions in 1990 to 40% in 2006 (Table 8).

In the brief paragraph on safety signals, the authors refer to the full report published by the MHRA in 2010:

> Mt-Isa S, Croft NM, Shafe A, et al. Gastro-Oesophageal Reflux Medicines – Evidence for Trials (GORMET). London, UK: Medicines and Healthcare Regulatory Agency; 2010:Report No.: SDS011.

This report could not be found online.

3.2 CARM data

As at 30 June 2020, the Centre for Adverse Reactions Monitoring (CARM) database contains one adverse reaction report in a child [redacted] in which domperidone is a suspect medicine. The case (report ID 131954) was presented to the MARC in June 2019.

[redacted]

4 DISCUSSION AND CONCLUSIONS

The paediatric indication for domperidone in New Zealand is out of step with other major regulators including the TGA, MHRA and EMA, where use of domperidone is not indicated in children aged less than 12 years or in patients of any age weighing less than 35 kg.

Following a review of the benefit-risk balance of domperidone in 2014, the EMA requested the pharmaceutical company Janssen-Cilag to conduct a post-authorisation efficacy study of domperidone in children with acute nausea and vomiting (the only remaining indication in Europe following the PRAC's review).

The study was conducted in 2016-2017 across seven countries in children aged 6 months to 12 years. The study was terminated early due to futility, as it failed to meet efficacy endpoints at the interim analysis. At the time of early termination, 292 patients had been randomised to receive domperidone (n = 147) or placebo (n = 145), and 287 patients had completed the study. The proportion of patients with no vomiting episodes within 48-hours of first treatment administration was similar between domperidone (32.0%) and placebo (33.8%) groups.

In a recent network meta-analysis, Niño-Serna et al [12] found no difference between domperidone and placebo for vomiting cessation or hospitalisation in studies of children with acute diarrhoea and gastroenteritis. Ondansetron was the only intervention that reduced the need for intravenous rehydration and the number of vomiting episodes.

Two literature reviews have examined the safety of domperidone in children: Morris et al [18] in 2016 and Cohen et al [24] in 2015. Both reviews identified three prospective cohort studies [20-22] and one published case report [23]. Additionally, the more recent review included an open-label, non-placebo-controlled, randomised trial [19]. The included studies involved only infants aged less than 12 months with symptoms of gastro-oesophageal reflux. Neither of the search strategies used in these two reviews found any studies on the safety of domperidone in children aged 1-18 years.

A UK general practice database study of three prokinetic agents (cisapride, domperidone and metoclopramide) used for symptoms of GORD in children did not identify any new causally related safety issues.

Overall, the information on the safety and efficacy of domperidone in children aged 2-11 years is lacking. The MARC is asked to consider whether the paediatric indication in the New Zealand data sheets remains tenable.

The New Zealand data sheet for Motilium contains information in section *5.1 Pharmacodynamic properties* about the lack of efficacy in children aged 6 months to 12 years. This information is not included in the data sheet for the PSM Healthcare product Domperidone (Pharmacy Health), which has not been updated since approval on 24 May 2018 (just before the most recent update to the Motilium data sheet on 1 June 2018). Accordingly, the Domperidone (Pharmacy Health) data sheet does not include the information that efficacy has not been established in infants and children < 12 years of age and weighing < 35 kg. Domperidone (Pharmacy Health) is the funded brand.

Both product data sheets include the same dose information for children aged < 12 years who weigh ≥ 35 kg. The recommended dose of 0.25 mg/kg three to four times per day with a maximum daily dose of 1.0 mg/kg is consistent with the dose recommended by the PRAC in 2014, before the efficacy study had been conducted.

In New Zealand, domperidone is only available as 10 mg tablets. At the recommended dose of 0.25 mg/kg, a patient weighing 35 kg would require a dose of 8.75 mg, which is not achievable with the current dose form. The minimum weight that would enable a patient to utilise the 10 mg tablet formulation at the recommended dose of 10 mg/kg is 40 kg. The MARC is therefore asked to consider whether the weight restriction should be increased to 40 kg.

The evidence for safety and efficacy of domperidone in the adult population was not examined in this review. However, noting that the currently approved indications for domperidone are out of step with other major regulators (section 2.4), the MARC is also asked to consider whether a further review of the indications for domperidone use in adults is needed.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the indication for domperidone should be revised to specify use only in adults and adolescents aged 12 years or over to reflect the clinical trial population?
- Whether any further restriction on use of domperidone in children should be specified?
- Should the weight restriction be increased from 35 kg to 40 kg, given that the 0.25 mg/kg dose specification cannot be achieved with the 10 mg tablet dose form in individuals weighing less than 40 kg? (ie, 40 kg x 0.25 mg/kg = 10 mg)?
- Whether a further review of the indications for domperidone use in adults is needed.

6 ANNEXES

1. Domperidone Benefit-Risk Review – June 2014 (report presented to the 158th MARC meeting)
2. Domperidone data sheet comparison table

7 REFERENCES

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