ADITUM

Journal of Pharmacy and Drug Innovations

Open Access Research Article

Clinical pharmacology of metoclopramide in infants and children
Running title: Metoclopramide in infants and children.

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Article Info

Received: January 17, 2022
Accepted: March 16, 2022
Published: March 24, 2022

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Citation: Gian Maria Pacifici (2022) "Clinical pharmacology of metoclopramide in infants and children". J Pharmacy and Drug Innovations, 3(3); DOI: http;//doi.org/03.2022/1.1044.

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Abstract
Metoclopramide is a derivative of para-aminobenzoic acid and is structurally related to procainamide. The mechanisms of action of metoclopramide are complex and involve 5-hydroxytryptamine receptor agonism, vagal and central 5-hydroxytryptamine antagonism, and possible sensitization of muscarinic receptors on smooth muscle, in addition to dopamine receptor antagonism. Metronidazole effects are confirmed largely to the upper digestive tract, where it increases lower oesophageal sphincter tone and stimulates antral and small intestinal contractions. The greatest utility of metoclopramide lies in its ability to ameliorate the nausea and vomiting that often accompany gastrointestinal dysmotility syndromes. In infants, the dose of metoclopramide is 100 µg/kg thrice-daily administered orally or intravenously. In children, the metoclopramide dose is 100 to 150 µg/kg thrice-daily given orally, intramuscularly or intravenously. The effects of metoclopramide have been studied in infants and children, and metoclopramide is metabolized by hepatic CYP2D6 into N-dealkylated metoclopramide and monodeethylmetoclopramide. In infants, the elimination half-life is 23.1 hours and 10.3 hours, at the first dose and at the steady-state, respectively, suggesting that the metoclopramide disposition undergoes modification during therapy. In children, the elimination half-life is 4.4 hours. The treatment of infants and children with metoclopramide has been studied and metoclopramide interacts with drugs. Metoclopramide freely crosses the human placenta and freely migrates into the breast-milk. The aim of this study is to review metoclopramide dosing, pharmacokinetics, and treatment in infants and children and metoclopramide metabolism, interaction with drugs, transfer across the human placenta and migration into the breast-milk.

Keywords: metoclopramide; dosing; effects; metabolism; pharmacokinetics; treatment; drug-interaction; placenta; breast-milk; infants; children

Introduction

Mechanism of action of metoclopramide

Metoclopramide is a derivative of para-aminobenzoic acid and is structurally related to procainamide. The mechanisms of action of metoclopramide are complex and involve 5-hydroxytryptamine (serotonin) receptor agonism, vagal and central 5-hydroxytryptamine antagonism, and possible sensitization of muscarinic receptors on smooth muscle, in addition to dopamine receptor antagonism. Administration of metoclopramide results in coordinated contractions that enhance transit. Its effects are confirmed largely to the upper digestive tract, where it increases lower oesophageal sphincter tone and stimulates antral and small intestinal contractions. Metoclopramide has no clinically significant effects on large-bowel mobility [1].

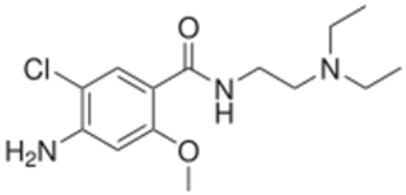
Therapeutic use of metoclopramide

Metoclopramide is indicated in patients with gastroparesis in whom the drug may cause moderate improvements of gastric emptying. Metoclopramide injection is used as an adjunctive measure in medical or diagnostic procedures such as upper endoscopy or contrast radiography of the gastrointestinal tract (single intravenous dose of 10 mg). Its greatest utility lies in its ability to ameliorate the nausea and vomiting that often accompany gastrointestinal dysmotility syndromes. Metoclopramide is available in

oral dosage forms (tablets and solution) and as a parenteral preparation for intravenous or intramuscular administration. In adults, the initial regimen is 10 mg orally, 30 min before each meal and at bedtime. The onset of action is within 30 to 60 min. In patient with severe nausea, an initial dose of 10 mg can be given intramuscularly (onset of action is 10 to 15 min) or intravenously (onset of action is 1 to 3 min). For prevention of chemotherapy-induced emesis, metoclopramide can be given as an infusion of 1 to 2 mg/kg administered over at least 15 min, beginning 30 min before the chemotherapy is begun and repeated as needed every 2 hours. Because of adverse-effects related to drug exposure, the recommended duration of use is less than 12 weeks [1]. Metoclopramide provides symptomatic relief from nausea and vomiting in pregnancy when first line treatment with antihistamine (e.g., diphenhydramine, meclizine, or dimenhydrinate) has failed. There is some evidence that metoclopramide reduces symptomatic gastroesophageal reflux in children a few months old. Clearance in the neonate and young infant is prolonged and predisposes to these adverse-effects more than at any other age [2]. Metoclopramide is used to facilitate gastric emptying and gastrointestinal motility. Metoclopramide may improve feeding intolerance and its used to treat gastroesophageal reflux in infants is controversial. Metoclopramide is well absorbed from the gastrointestinal tract and has variable first-pass metabolism by the liver and significant fraction of metoclopramide is excreted unchanged in urine in infants. In infants, the elimination half-life is longer than in children and is prolonged in patients with renal failure. Metoclopramide is incompatible with ampicillin, calcium gluconate, cefepime, chloramphenicol, erythromycin lactobionate, furosemide, penicillin G, propofol, and sodium bicarbonate [3].

Absorption, distribution, metabolism, and elimination of metoclopramide

Metoclopramide is absorbed rapidly after oral ingestion, is metabolized by CYP2D6 into hydroxy metoclopramide and monodeethylmetoclopramide in the liver, and is excreted rapidly in the urine with an elimination half-life of 4 to 6 hours in adults. The peak concentrations occur within 1 hour after a single oral dose and the duration of action is 1 to 2 hours [1].



Metoclopramide molecular structure (molecular weight = 299.8 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "metoclopramide dosing infants, children", metoclopramide effects infants, children", "metoclopramide metabolism", "metoclopramide pharmacokinetics infants, children", "metoclopramide treatment infants, children", "metoclopramide drug interaction", "metoclopramide placental transfer", and "metoclopramide breast-milk. In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] have been consulted.

Results

Administration schedules of metoclopramide to infants and children

Administration to infants [2]

Give: 100 µg/kg orally or intravenously thrice-daily.

Administration to children [4]

Oral, intramuscular, or intravenous administration for the treatment of established postoperative nausea and vomiting and for prevention of delayed chemotherapy-induced nausea and vomiting

Give: 100 to 150 µg/kg thrice-daily (maximum per dose = 10 mg), when administered by slow intravenous injection should be given over at least 3 min.

Effects of metoclopramide in infants and children

In infants, the response-rate to gastroesophageal reflux disease with lansoprazole plus metoclopramide is significantly higher than with ranitidine plus metoclopramide [5]. Metoclopramide, given intravenously to infants at a dose of 1 mg/kg, doubles the rate of gastric emptying [6]. In total, 307 children were allocated to the metoclopramide (N = 103), to domperidone (N = 100), or in the control group (N = 104). The success-rate of post-pyloric placement, after 24 hours in the metoclopramide, domperidone, and control group is 55.0%, 51.5% and 27.3%, respectively (P-value = 0.0001) [7]. Metoclopramide was given at a dose of 0.15 mg/kg or erythromycin was given at a dose of 1 mg/kg to children undergoing tonsillectomy. Erythromycin is as effective as metoclopramide as a prokinetic agent [8].

Metabolism of metoclopramide

The major metabolites of metoclopramide are formed by N-hydroxylation and N-deethylation into hydroxy metoclopramide and monodeethylmetoclopramide, respectively, and both metabolic pathways are catalysed by hepatic CYP2D6 [9]. The formation-rate of monodeethylmetoclopramide follows Michaelis-Menten kinetics with a Km of 68±16 µM and a Vmax of 183±57 pmol/min/mg [10].

Pharmacokinetics of metoclopramide in infants

Kearns et al. [11] studied the pharmacokinetics of metoclopramide in 6 infants, aged 0.9 to 5.4 months, and metoclopramide was administered orally at a dose of 0.15 mg/kg 4 times-daily. Infants were suffering from gastroesophageal reflux disease.

Peak conc. (ng/ml)	Tmax (h)	DV (L/kg)	Kel (h^{-1})	TBC (L/h/kg)	*Half-life (h)	*Half-life$_{ss}$ (h)
56.2±25.5	2.0±0.5	4.9±0.4	0.14±0.03	0.66±0.16	23.1±5.6	10.3±2.7

Table 1: Pharmacokinetic parameters of metoclopramide which are obtained in 6 infants. Figures are the mean±SD, by Kearns et al. [11].

DV = distribution volume. Kel = elimination-rate constant. TBC = total body clearance. * Half-life = elimination half-life obtained at the first dose. *Half-life$_{ss}$ = elimination half-life obtained at the steady-state.

This table shows that metoclopramide is rapidly absorbed following oral dosing as Tmax is 2 hours, the distribution volume is larger than the water volume, metoclopramide is rapidly eliminated as the elimination-rate constant is 0.14 h^{-1}, and the elimination half-life, obtained at the steady-state, is shorter than that obtained at the first dose. This last result suggests that metoclopramide disposition undergoes modification during therapy.

Bateman et al. [12] investigated the pharmacokinetics of metoclopramide in 11 children, aged 11.7±0.67 (range, 7 to 14), and metoclopramide was intravenously administered at a dose of 0.35±0.025 mg/kg (range, 0.22 to 0.46). Metoclopramide was administered for prophylaxis of cytotoxic induced vomiting.

Value	Elimination half-life (h)	Peak concentration (ng/ml)	Distribution volume (L/kg)	Total body clearance (L/h/kg)
Mean±SD	4.4±0.56	152±31	3.0±0.8	0.56±0.10
Range	1.7 – 8.3	65 - 395	1.0 – 4.8	0.12 – 1.22

Table 2: Pharmacokinetic parameters of metoclopramide which are obtained in 11 children. Figures are the mean±SD Bateman et al. [12].

This table shows that the distribution volume is larger than the water volume and metoclopramide is rapidly eliminated as the elimination half-life is 4.4 hours and there is a remarkable interindividual variability in the pharmacokinetic parameters. The elimination half-life of metoclopramide is shorter in children than in infants and for comparison with infants see table 1.

Treatment of infants and children with metoclopramide

Intravenous metoclopramide facilitates feeding intolerance in preterm infants [13]. Metoclopramide is used to treat gastroesophageal reflux disease in infants [14]. Metoclopramide is effective and safe treatment of gastroesophageal reflux disease in preterm infants [15]. Metoclopramide may have some benefits compared to placebo for the symptomatic treatment for gastroesophageal reflux disease in children [16]. In children, metoclopramide is superior to placebo and to prochlorperazine in reducing the volume of emesis (P-value = 0.001 and P-value = 0.022, respectively) and is more effective than placebo in shortening the duration of nausea (P-value = 0.042) and vomiting (P-value = 0.028) [17].

Interaction of metoclopramide with drugs

Tmax of metoclopramide is delayed when metoclopramide is co-administration with cilostazol thus cilostazol reduces the absorption-rate of metoclopramide [18]. Interaction between granisetron and metoclopramide is observed in cancer patents. Granisetron affects the pharmacokinetics of metoclopramide [19]. There is a risk of extrapyramidal activities and neurologic malign syndrome following the co-administration of olanzapine and metoclopramide [20]. A statistically significant increase in both AUC and elimination half-life of metoclopramide is observed when metoclopramide is co-administered with ranitidine [21]. A significant drug interaction is observed between metronidazole and ranitidine and between metronidazole and phenytoin [22]. Co-administration of metoclopramide with tacrolimus improves gastric motility and delivery of tacrolimus in the small intestine, thus metoclopramide increases tacrolimus bioavailability [23]. A reduction in dose of propofol, required for the induction of general anaesthesia, is required when propofol is co-administered with metoclopramide [24].

Transfer of metoclopramide across the human placenta

In literature there is only one study on the placental transfer of metoclopramide and it has been reported by Arvela et al. [25]. No statistically significant difference is observed in umbilical cord arterial or venous plasma and in the maternal plasma of metoclopramide suggesting that metoclopramide freely crosses the human placenta.

Migration of metoclopramide into the breast-milk

The migration of metoclopramide into the breast-milk was studied in 10 lactating women who were treated with metoclopramide at a single dose of 10 mg. The concentration of metoclopramide in the maternal plasma, 2 hours after dosing, is 68.5±29.6 ng/ml. The concentration of metoclopramide in breast-milk, at the same time, is 126±41.7 ng/ml indicating that metoclopramide accumulates in the breast-milk [26]. Five women were treated with metoclopramide at a dose of 10 mg thrice-daily on day 3 to 9 postpartum and metoclopramide concentration in the breast-milk ranges from 52 to 157 ng/ml. The authors did not report the concentration of metoclopramide in the maternal plasma however prevails the impression that metoclopramide migrates into the breast-milk in significant amounts [27].

Discussion

Metoclopramide is a derivative of para-aminobenzoic acid and is structurally related to procainamide. The mechanisms of action of metoclopramide are complex and involve 5-hydroxytryptamine receptor agonism, vagal and central 5-hydroxytryptamine antagonism, and possible sensitization of muscarinic receptors on smooth muscle, in addition to dopamine receptor antagonism. Administration of metoclopramide results in coordinated contractions that enhance transit. Metoclopramide effects are confirmed largely to the upper digestive tract, where it increases

lower oesophageal sphincter tone and stimulates antral and small intestinal contractions. Metoclopramide is indicated in patients with gastroparesis in whom the drug may cause moderate improvements of gastric emptying. The greatest utility of metoclopramide lies in its ability to ameliorate the nausea and vomiting that often accompany gastrointestinal dysmotility syndromes. Metoclopramide may be administered orally, intramuscularly, or intravenously and after oral dosing metoclopramide is rapidly absorbed [1]. Metoclopramide provides symptomatic relief from nausea and voting in pregnancy when first line treatment with antihistamine (e.g., diphenhydramine, meclizine, or dimenhydrinate) has failed. Metoclopramide clearance in the neonate and young infant is prolonged [2]. Metoclopramide may improve feeding intolerance and its use in gastroesophageal reflux in infants is controversial [3]. In infants, the dose of metoclopramide is 100 µg/kg thrice-daily given orally or intravenously [2] and in children, the dose of metoclopramide is 100 to 150 µg/kg thrice-daily given orally, intramuscularly, or intravenously [4]. The effects of metoclopramide have been studied in infants and children [5-8]. In infants, the response-rate to gastroesophageal reflux disease is higher with lansoprazole plus metoclopramide than with ranitidine plus metoclopramide [5], metoclopramide, given intravenously to infants at a dose of 1 mg/kg, doubles the rate of gastric emptying [6], in children, the success-rate of post-pyloric placement is higher with metoclopramide than with domperidone or with placebo [7], and metoclopramide, given at a dose of 0.15 mg/kg to children, has prokinetic activity similar to erythromycin given at a dose of 1 mg/kg [8]. Metoclopramide is metabolized into N-hydroxy metoclopramide and into monodeethylmetoclopramide by hepatic CYP2D6 [9], and the formation-rate of monodeethylmetoclopramide follows Michaelis-Menten kinetics with a Km of 68 µM and a Vmax of 183 pmol/min/mg [10]. The pharmacokinetics of metoclopramide have been studied in infants [11] and in children [12]. In infants, the elimination half-life is 23.1 hours at the first dose and 10.3 hours at the steady-state indicating that metoclopramide disposition undergoes modification during therapy [11]. In children, the elimination half-life is 4.4 hours [12] and the distribution volume is larger than the water volume in infants and children. The treatment with metoclopramide has been studied in infants and children [13-17]. Intravenous metoclopramide facilitates feeding intolerance in preterm infants [13], metoclopramide successfully treats gastroesophageal reflux disease in preterm infants [14], metoclopramide is effective and safe treatment of gastroesophageal reflux disease in preterm infants [15], metoclopramide is more active than placebo in the treatment of gastroesophageal reflux disease in children [16], and metoclopramide is superior to placebo and prochlorperazine in reducing the volume of emesis and in shortening the duration of nausea and vomiting in children [17]. Metoclopramide interacts with drugs [18-24]. Cilostazol reduces the absorption-rate of metoclopramide [18], granisetron affects the pharmacokinetics of metoclopramide in cancer patients [19], the co-administration of olanzapine and metoclopramide causes extrapyramidal activities and neurologic malign syndrome [20], the combination of ranitidine with metoclopramide increases both the AUC and elimination half-life of metoclopramide [21], a significant drug interaction is observed between metronidazole and ranitidine and between metronidazole and phenytoin [22], metoclopramide improves the gastric motility, delivery, and the bioavailability of tacrolimus [23], and the dose of propofol should be reduced for the induction of general anaesthesia when propofol is co-administered with metoclopramide [24]. Metoclopramide freely crosses the human placenta [26] and freely migrates into the breast-milk [27, 28].

In conclusion, metoclopramide is a derivative of para-aminobenzoic acid and is structurally related to procainamide. The mechanisms of action of metoclopramide are complex and involve 5-hydroxytryptamine receptor agonism, vagal and central 5-hydroxytryptamine antagonism, and possible sensitization of muscarinic receptors on smooth muscle, in addition to dopamine receptor antagonism. Metoclopramide is indicated in patients with gastroparesis in whom the drug may cause moderate improvements of gastric empting. The metoclopramide greatest utility lies in its ability to ameliorate the nausea and vomiting that often accompany gastrointestinal dysmotility syndrome. Metoclopramide may be administered orally, intramuscularly, or intravenously and following oral dosing metoclopramide is rapidly absorbed. In infants, the dose of metoclopramide is 100 µg/kg thrice-daily and in children the metoclopramide dose is 100 to 150 µg/kg thrice-daily. The effects of metoclopramide have been studied in infants and children and metoclopramide is metabolized into N-hydroxy metoclopramide and into monodeethylmetoclopramide by hepatic CYP2D6. In infants, the elimination half-life of metoclopramide is 23.1 and 10.3 hours, at the first administration and at the steady-state, respectively, indicating that metoclopramide disposition undergoes modification during therapy. In children, the elimination half-life is 4.4 hours. The treatment of infants and children with metoclopramide has been studied and metoclopramide interacts with drugs. Metoclopramide freely crosses the human placenta and freely migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of metoclopramide in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.
This article is a review and drugs have not been administered to men or animals.

Acknowledgments

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

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