

# Cisapride: A Novel Gastroprokinetic Drug

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## ABSTRACT

*Impaired gastrointestinal motility underlies a multitude of digestive complaints. Metoclopramide, an antidopaminergic and cholinomimetic agent, was the first prokinetic drug used to treat such conditions, but a high incidence of adverse effects has limited its use, especially in infants. Domperidone, the second prokinetic drug marketed in Canada, is a potent peripheral dopamine receptor antagonist which does not cross the blood-brain barrier well and, therefore, displays minimal CNS side effects. Cisapride is a gastroprokinetic agent which appears to act mainly by releasing acetylcholine from the myenteric plexus of the gut. It has no dopamine-blocking activity, and does not share the serious CNS side effects of other drugs in its class. These drugs stimulate gastric and small intestinal activity, but cisapride also enhances colonic motility. Cisapride is well tolerated, and seems to exhibit a more favourable benefit:risk ratio than metoclopramide or domperidone. Further studies will determine the relative place of cisapride in the treatment of GI motility disorders.*

**Key Words:** cisapride, domperidone, metoclopramide, prokinetic drugs

## RÉSUMÉ

*Une motilité gastro-intestinale pathologique est le signe d'une multitude de maladies digestives. Le métoclopramide, un agent anti-dopaminergique et cholinomimétique, fut le premier médicament procinétique utilisé pour traiter de telles conditions mais une fréquence élevée des réactions indésirables a limité son usage, surtout chez les nourrissons. Le dompéridone, le deuxième médicament procinétique commercialisé au Canada, est un antagoniste puissant des récepteurs dopaminergiques périphériques qui ne traverse pas beaucoup la barrière hémato-encéphalique et donc, provoque peu d'effets secondaires au système nerveux central (SNC). Le cisapride est un nouvel agent gastro-procinétique qui semble agir principalement par la libération de l'acétylcholine du plexus myentérique de l'intestin. Il ne bloque pas la dopamine, donc n'apporte aucun effet secondaire sérieux au SNC. Ces médicaments stimulent la motilité gastrique et celle de l'intestin grêle, mais en plus, le cisapride augmente la motilité du colon. Le cisapride est bien toléré et semble posséder un rapport avantage:risque plus favorable que le métoclopramide et le dompéridone. D'autres études détermineront la place respective du cisapride dans le traitement des troubles de la motilité GI (gastro-intestinale).*

**Mots clés:** cisapride, dompéridone, métoclopramide, procinétique médicament

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## INTRODUCTION

Impaired gastrointestinal (GI) motility underlies a multitude of digestive complaints including delayed gastric emptying and gastroesophageal reflux. Patients suffering from such conditions may benefit from enhanced GI motility. The pathophysiology of GI motility disorders normally involves neural rather than primary muscular disturbances. Therapeutically diverse pharmacologic and non-pharmacologic modalities have been used in the treatment of such disorders<sup>1</sup>.

The GI tract is innervated by the

sympathetic, parasympathetic and enteric nervous systems. Input from these systems is modulated by the central nervous system which regulates GI motility<sup>2</sup>. Cholinomimetics are a logical choice for the treatment of GI motility disorders since GI motility is largely controlled by cholinergic mechanisms. Most agents used, especially for gastroesophageal reflux (GER), either potentiate the action of acetylcholine or block dopamine receptors.

Metoclopramide, an antidopaminergic and cholinomimetic drug,

is widely used as an antiemetic and GI motility modifier<sup>1,3</sup>. Domperidone has been on the Canadian market for several years, although it is still an investigational drug in the United States<sup>4</sup>. It acts primarily as a peripheral dopamine receptor antagonist, and has a lower potential for extrapyramidal side effects. Cisapride is a novel prokinetic agent which was developed by Janssen Pharmaceutica to target effects on the GI system only. Studies indicate that cisapride modifies motility along the entire GI tract<sup>5-10</sup>.

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## Pharmacology

Cisapride has a unique mechanism of action. It is not an antidopaminergic or a cholinergic agent<sup>9,11</sup> but is believed to indirectly enhance the release of acetylcholine by stimulating receptors located on the postganglionic neurons of the myenteric (Auerbach's) plexus of the gut. This results in stimulation of cholinergic (muscarinic) receptors on smooth muscle cells of the gut. There is also some evidence that cisapride acts as an antagonist of serotonin (5-hydroxytryptamine) receptors, however, the clinical significance of this effect remains to be determined<sup>3,5,12</sup>.

Metoclopramide's mechanisms of action is complex. This procainamide derivative blocks peripheral and central dopaminergic receptors, including those at the vomiting centre. It also has peripheral cholinergic and direct smooth muscle activity<sup>13</sup>. Effects on GI motility are mediated through enhanced acetylcholine release from postganglionic neurons in the gut, and sensitization of cholinergic (muscarinic) receptors of GI smooth muscle to acetylcholine. Metoclopramide requires inherent neuronal acetylcholine storage sites to exert physiologic release of this neurotransmitter<sup>1</sup>.

Although domperidone is structurally similar to the butyrophenone compounds, it does not cross the blood-brain barrier well and, therefore, is not used as a neuroleptic. *In vitro*, domperidone has high affinity for dopamine receptors, but low affinity for muscarinic and serotonergic receptors. It is a peripheral dopamine receptor antagonist and exhibits many of the pharmacologic effects of metoclopramide in the GI tract<sup>2</sup>.

## Human Pharmacokinetics

**Absorption:** All three drugs are rapidly absorbed from the GI tract following oral administration, but absorption may be postponed or

reduced in patients with impaired gastric emptying<sup>1,2,7</sup>. Cisapride has an absolute bioavailability of 40 to 50% and undergoes an extensive first pass metabolism<sup>14</sup>. Domperidone is also subject to a large first pass effect with only about 15% of an oral dose reaching the systemic circulation. Bioavailability of metoclopramide is extremely variable with reports of 30 to 100% of an oral dose reaching the systemic circulation as unchanged drug<sup>1,2,15</sup>.

After oral administration of a single 10 mg dose, peak plasma concentrations are reached within one to two hours for all three drugs. Maximal plasma levels obtained are about 45 to 65 µg/L with cisapride, 30 to 45 µg/L with metoclopramide and 20 µg/L with domperidone. Co-administration with food increases the extent of drug absorption with the C<sub>max</sub> about 20% higher after a meal<sup>1,2,6</sup>.

**Distribution:** In adults, cisapride and metoclopramide have comparable apparent volumes of distribution: 2.4 L/kg and 2.2 to 3.4 L/kg, respectively. Domperidone's apparent volume of distribution is about 5 to 6 L/kg. Plasma protein binding is very high for cisapride and domperidone at >90% while only 25 to 30% of metoclopramide is bound<sup>1,2,6,14</sup>.

Domperidone has high affinity for dopamine receptors. It does not cross the blood-brain barrier extensively but does act at the chemoreceptor trigger zone (CTZ) to inhibit drug-induced vomiting. Metoclopramide crosses the blood-brain barrier and acts at the CTZ in the area postrema. Although cisapride also penetrates into the CNS, brain tissue concentrations are two or three times less than in plasma<sup>1,2,6,14,16</sup>.

**Metabolism and Excretion:** The metabolism and excretion profiles of these three drugs are quite different. Cisapride is extensively metabolized via two principal routes: oxidative-N-dealkylation and aro-

matic hydroxylation. The pharmacological activity of the metabolites is negligible compared to the parent compound. Cisapride and its metabolites are equally excreted in urine and feces. About 41 to 45% of a single dose is eliminated as norcisapride. Less than 1% and 4-6% of the parent drug is normally eliminated in urine and feces, respectively<sup>3,6</sup>.

Metoclopramide has a high first-pass effect. It is conjugated with sulfuric acid or glucuronic acid. Approximately 85% of an oral dose appears in the urine as parent drug and conjugates, and 5% is excreted in the feces via bile. Five to 10% of an oral dose appears in the urine as a metabolite with undetermined pharmacological activity. In total, about 20% of the drug is excreted unchanged<sup>1,17</sup>.

Domperidone undergoes hydroxylation and oxidative N-dealkylation to inactive metabolites excreted in the urine and feces. Less than 5% of a dose is excreted in the urine unchanged, although about 30% appears as glucuronide conjugates of the two principle metabolites. These metabolites are mainly excreted in the feces<sup>2</sup>.

Cisapride has a terminal half-life of about 15 hours. The half-life may be prolonged in some elderly patients and in those with impaired hepatic function. This might be expected since cisapride is mainly eliminated via hepatic oxidation. Renal insufficiency does not appear to significantly affect the elimination of cisapride, however, the manufacturer recommends an initial lower daily dose<sup>4,14,18</sup>. Metoclopramide has a much shorter terminal half-life of 2.5 to six hours<sup>1,15</sup>. In patients with severely impaired renal function, the half-life may increase markedly. It has been suggested that this is not due to decreased elimination of metoclopramide in the urine, but possibly to reduced metabolism or enterohepatic recycling<sup>16</sup>. Domperidone's interme-

diate half-life of 7 to 12 hours may be prolonged in patients with severe renal dysfunction<sup>2</sup>.

### Pharmacodynamics in Therapeutic trials

**Gastrointestinal:** Cisapride and metoclopramide appear to exert similar effects on the lower esophageal sphincter (LES) pressure and esophageal motility. They raise the amplitude but not the velocity of esophageal contractions<sup>6</sup>. Studies indicate domperidone's effect on LES pressure to be inconsistent; some find increased pressure whereas others do not. In general, cisapride has shown to be as effective as, or superior to metoclopramide and domperidone in enhancing LES tone and esophageal motor function<sup>2,19-21</sup>.

Results of a few comparative trials with healthy subjects and dyspepsia patients indicate that cisapride is similar or superior to metoclopramide in shortening or normalizing both liquid and solid gastric emptying rates. It also appears to be as effective as metoclopramide in relieving the symptoms of gastric motility disorders<sup>6,22,23</sup>. Cisapride is likely to command a definite place in the treatment of delayed gastric emptying of idiopathic, diabetic or postsurgical origin.

**Effects on the Small and Large Intestines:** All three drugs enhance small bowel transit in normal individuals and those with deficient intestinal propulsive activity. Cisapride decreases mouth to cecum transit time since it increases propulsive activity of the ileum and colon as well as the upper GI tract; metoclopramide and domperidone only decrease small intestinal transit time and augment peristalsis<sup>1,6,9</sup>. By accelerating whole gut transit, cisapride promotes stool frequency and output in most individuals<sup>24</sup>. It has the added effect of improving colonic transit and may increase the number of bowel movements in constipated subjects<sup>3</sup>. Metoclo-

pramide and domperidone have little, if any, effect on colonic motility<sup>1</sup>.

**Effects on the Dopaminergic System:** Metoclopramide blocks dopaminergic receptors in the medullary CTZ. It causes antiemetic and sedative effects while blocking the hypertensive actions of dopamine. As a result of its dopamine receptor blocking activity, prolactin release is increased<sup>1,2</sup>. Hyperprolactinemia occurs with domperidone therapy as well, and is likely due to blockade of endogenous dopamine release from the pituitary<sup>16</sup>. The advantages of cisapride is its specificity of action and lack of affinity for dopamine receptors. It is devoid of dopaminergic effects and does not appear to stimulate prolactin release<sup>6</sup>.

**Metabolic and Endocrine Effects:** Metoclopramide and domperidone do not alter gastric secretions. Metoclopramide may cause slight decreases in serum growth hormone, luteinizing hormone and follicle-stimulating hormone concentrations, while increasing serum thyrotropin levels. Both metoclopramide and domperidone stimulate a transient rise in plasma aldosterone secretion via a direct effect on adrenal tissues<sup>1,2</sup>. Single doses of cisapride result in significant but temporary increases in cholecystokinin and human pancreatic polypeptide levels, but do not alter gastrin, insulin or glucose concentrations<sup>6,25</sup>. Metabolic control of insulin-dependent diabetes mellitus remains unaltered by cisapride therapy<sup>26</sup>.

### Indications

The majority of indications for prokinetic drugs involve GI motility disorders, but the drugs with a broader pharmacologic profile, i.e., metoclopramide and domperidone, have some additional indications. The newer drug, cisapride (Prepulsid<sup>®</sup>) has a narrower pharmacologic profile and is indicated specifically for disorders of GI

motility. When metoclopramide or domperidone could be used, the latter has generally become the preferred agent because it is well tolerated and has a much lower potential for extrapyramidal side effects.

**Gastroparesis:** Gastroparesis results from poor gastric emptying. It may be idiopathic or due to a variety of conditions including diabetes mellitus, progressive systemic sclerosis (PSS), myotonic dystrophy, or postoperative GI atony. Gastroparesis typically presents as early satiety, epigastric burning or pain, bloating, nausea, vomiting and anorexia<sup>6</sup>.

Long-term metoclopramide therapy provides symptomatic relief of diabetic gastric stasis by enhancing gastric emptying, peristalsis of the duodenum and jejunum, transit time, and increasing the resting LES tone<sup>27</sup>. Metoclopramide is widely used to prevent nausea and vomiting and to improve gastric emptying in patients with postoperative gastric stasis<sup>1</sup>.

Domperidone possesses GI prokinetic activity comparable to metoclopramide<sup>14</sup>. It significantly improves gastric emptying rates and symptoms in patients with diabetic and post-vagotomy gastroparesis<sup>2</sup>.

Cisapride effectively enhances gastric emptying in scleroderma patients with gastroparesis, but symptomatic relief in these patients is underdetermined<sup>28</sup>. Trials support a prominent role for cisapride to promote gastric emptying and to alleviate GI symptoms in diabetic gastroparesis and postoperative patients<sup>6,12,29</sup>.

**Gastroesophageal Reflux:** Gastroesophageal reflux (GER) is a complex disorder involving several factors: low resting LES pressure, transient relaxation of the LES, poor esophageal clearance, elevated intraabdominal pressure, and delayed gastric emptying. The main symptoms of GER are heartburn, regurgitation, nausea, vomiting and postprandial discomfort

in adults. Chronic and excessive spitting, and vomiting are characteristic features in infants. Although the majority of infants with chronic GER are symptom-free by two years of age, this benign self-limiting disease is recognized as causing failure to thrive. It is not surprising that multiple treatment modalities have been tried in patients with this disease<sup>13,30</sup>. Although most patients with GER are treated with a combination of positional and dietary measures along with lifestyle changes, or histamine-2 blockers, some patients are refractory. It is this group of patients which may respond to GI prokinetic agents.

Metoclopramide is beneficial for symptomatic treatment of persistent GER unresponsive to conventional therapy, but its clinical use has often been limited by a high incidence of CNS side effects. In particular, marked infant irritability with metoclopramide therapy has been noted<sup>5,30</sup>. Usually, short-term treatment up to 12 weeks provides symptomatic relief in adult patients.<sup>1</sup>

Although domperidone does not improve heartburn or endoscopic healing, it is successful in relieving regurgitation, and also shows evidence of improved symptoms in infants<sup>2</sup>.

Cisapride enhances LES tone and accelerates emptying of gastric contents. The number of reflux episodes as well as incidence of side effects are decreased with cisapride therapy<sup>6,31</sup>.

**Non-ulcer Upper Gastrointestinal Discomfort:** Cisapride is at least as effective as metoclopramide and domperidone in relieving symptoms of postprandial epigastric discomfort such as bloating, belching, nausea, vomiting, heartburn and abdominal distention<sup>32,33</sup>.

**Chronic Constipation:** This common complaint may be idiopathic or associated with diabetic autonomous neuropathy, intestinal pseudo-obstruction, Hirschsprung's

disease, or laxative abuse<sup>34</sup>. Patients with chronic constipation which is unresponsive to standard dietary and therapeutic measures, or which results from laxative abuse may benefit from cisapride therapy.

To date, cisapride has shown some clinical efficacy in improving constipation. It enhances colonic propulsive activity and progressively increases the consistency and frequency of stools. This agent promotes good bowel habits while reducing laxative consumption. It is not yet known if all types of constipation may benefit from cisapride therapy, or if long-term maintenance therapy is safe and effective.<sup>6</sup> Metoclopramide and domperidone do not promote colonic motility and, therefore, are not useful for the symptomatic relief of constipation.

**Intestinal Pseudo-obstruction:** This may be induced by motility dysfunction associated with impaired propulsion of the bowel, or stasis of the stomach or intestinal contents. Cisapride acts selectively within the gut wall to facilitate or correct motility along the entire GI tract<sup>3,5,12</sup>. It restores colonic propulsive motility and may be useful in conditions where normal movement of bowel contents is impaired<sup>8,35</sup>. Metoclopramide and domperidone have no role in restoring normal colonic motility.

**Intubation of the Small Intestine:** Parenteral metoclopramide has been used to facilitate intubation when the tube does not pass through the pylorus with conventional maneuvers. However, the drug does not improve patient tolerance of the procedure<sup>1</sup>.

**Radiographic Examination of the Upper Gastrointestinal Tract:** Metoclopramide is used frequently to aid in radiological examination of the stomach and small intestine. When delayed gastric emptying interferes with the procedure, parenteral metoclopramide will stimulate gastric emptying and intes-

tinal transit of barium. It reduces the total procedure time and also prevents the nausea or regurgitation which may follow<sup>1,36</sup>. Based on its mechanism of action, it is likely that cisapride will have a similar effect.

**Prevention of Cancer Chemotherapy-induced Emesis:** Metoclopramide, like other dopaminergic antagonists, acts centrally on the CTZ to prevent emesis. Oral or parenteral metoclopramide in high doses is especially useful for patients receiving cisplatin or other antineoplastic agents. By blocking stimulation of the CTZ, domperidone also prevents nausea and vomiting associated with emetic cytotoxic drugs<sup>1,14,16</sup>.

### Adverse Effects

As expected, broader pharmacological profiles yield a wider range of indications but also a wider range of adverse drug reactions. Metoclopramide produces a multitude of side effects, primarily associated with the CNS and the GI system. These are usually mild, transient and reversible upon discontinuation of the drug. The incidence is most often related to dosage and duration of therapy<sup>1</sup>.

Being a cholinomimetic and antidopaminergic drug, metoclopramide can cause psychotropic, extrapyramidal, dystonic, and dyskinetic reactions which may limit its long-term use, especially in children. These particular side effects may be independent of dose and duration of therapy<sup>3</sup>. Parkinsonian symptoms may occur, along with the possibility of irreversible tardive dyskinesia. Restlessness, drowsiness, sedation and fatigue are obvious in about 10% of patients, while insomnia, headache, and dizziness are less frequently reported. Other adverse effects include transient flushing, constipation, diarrhea, rash, edema, and methemoglobinemia. Metoclopramide may cause galactorrhea, gynecomastia, amenorrhea, and

impotence. Most of these effects are probably due to its potent stimulation of prolactin release. Although devoid of clinically important cardiovascular activity, transient antiarrhythmic effects have been reported with therapeutic doses<sup>1</sup>.

During clinical trials, domperidone had an overall side effect incidence of less than 7%<sup>16</sup>. Most adverse reactions are due to dopamine receptor blocking activity and are reversible upon discontinuation of the drug. The incidence of adverse endocrine effects is 1.3%. Blockade of the inhibition of prolactin release and the resultant higher levels of serum prolactin may cause gynecomastia, galactorrhea and menstrual irregularities. Unlike metoclopramide, domperidone does not appear to affect growth hormone or thyroid-stimulating hormone<sup>2,16</sup>.

Side effects with cisapride therapy are few and are related to its primary pharmacological action in the GI system. Most commonly, patients experience transient abdominal cramping, borborygmi (rumbling noises), and diarrhea or loose stools. Less commonly, headache, dizziness, or lightheadedness occur. Although it crosses the blood-brain barrier, cisapride is not antidopaminergic and therefore displays no CNS effects. The adverse effects that occur do not seem to increase in incidence with long-term therapy unlike metoclopramide<sup>6</sup>. In most studies reviewed, few or no side effects were reported with cisapride<sup>3,5,9,12,24,28,32</sup>.

### **Precautions and Contraindications**

Patients on metoclopramide therapy are subject to potential impairment of mental alertness or physical activity. As well, enhanced sedation can occur with concomitant administration of alcohol, barbiturates, and other CNS depressants. Patients with impaired renal function, or those at risk of

developing fluid retention or hypokalemia should be initiated on reduced dosages and monitored closely. This is important because metoclopramide has the ability to increase plasma aldosterone and sodium retention. It may also exacerbate hypertension by elevating concentrations of circulating catecholamines<sup>1</sup>.

Pediatric patients are at increased risk of developing extrapyramidal reactions, and should be prescribed metoclopramide only when clearly indicated. Patients on MAO inhibitors and sympathomimetics are also targets for careful monitoring. Due to lack of adequate studies, metoclopramide should be used during pregnancy only when the risk:benefit ratio has been considered. Since it is distributed into breast milk, the same caution applies to nursing women. No studies to date have shown evidence of metoclopramide-induced mutagenicity, but clinicians should be aware that about one-third of human breast carcinomas are prolactin-dependent, and metoclopramide and domperidone are known prolactin secretors<sup>1</sup>.

Absolute contraindications include GI hemorrhage (except to clear the stomach of blood prior to endoscopy), mechanical obstruction or perforation, pheochromocytoma (since the tumor may be induced to release catecholamines and precipitate a hypertensive crisis), concurrent use of drugs likely to cause extrapyramidal reactions such as phenothiazines or butyrophenones, and patients in whom increased GI motility might be dangerous<sup>1,34</sup>.

Domperidone is a drug requiring few precautions. As with metoclopramide, it should be avoided in patients with GI hemorrhage, obstruction or perforation<sup>2</sup>.

Although cisapride itself does not cause sedation or drowsiness, it may increase the absorption rate of drugs such as diazepam and

alcohol, thereby enhancing their depressant effects. Caution is therefore advised when prescribing cisapride and CNS depressants concomitantly<sup>6</sup>. Careful monitoring is suggested for elderly patients and those with hepatic insufficiency.

Cisapride should not be given to infants less than 36 weeks of age unless the benefits clearly outweigh the potential risks. Women who are pregnant or breastfeeding should not take cisapride simply because there is a lack of trials to demonstrate safe and efficacious use in such patients<sup>6</sup>. Animal studies have shown an absence of mutagenic and carcinogenic effects with cisapride therapy.<sup>8</sup>

### **Drug Interactions**

Cisapride, metoclopramide and domperidone theoretically have the potential to alter the absorption and the bioavailability of some drugs. Changes in GI motility, specifically enhanced gastric emptying may modify absorption of some drugs. For example, the absorption of digoxin may be diminished while the absorption of acetaminophen, diazepam, ethanol, cimetidine and acenocoumarol may be increased<sup>1</sup>. Two studies reported significant reductions of digoxin plasma peak concentrations only with cisapride therapy. Products that rapidly dissolve and therefore are readily absorbed such as Laxoxin<sup>R</sup> avoid this problem of reduced peak levels. It is still recommended to monitor patients closely when any of the above combinations are prescribed<sup>37</sup>.

Metoclopramide has greater potential for drug interactions than cisapride. Anticholinergic drugs and narcotics may antagonize metoclopramide's GI motility effects. Metoclopramide may enhance the actions of other CNS depressants, barbiturates, or alcohol when used concomitantly. Appropriate precautions should be given to patients on these combinations<sup>14</sup>.



### Dosage and Administration

Cisapride, metoclopramide and domperidone are dosed according to the severity of the symptoms and degrees of hepatic and renal function. The duration of treatment varies with the patient and condition, but is usually short-term except in the case of cisapride therapy for chronic constipation. This symptom may be treated with cisapride for several months.

Cisapride (Prepulsid<sup>®</sup>-Janssen) is marketed in the following dosage forms: 5 mg and 10 mg oral tablets and a 1 mg/mL oral suspension<sup>4,8</sup>.

The recommended dose is 5-10 mg po three to four times daily. Resulting diarrhea necessitates a reduction in dosage in infants and children. In all instances of oral administration, cisapride should be ingested 15 minutes before meals with a beverage since food increases the rate and extent of drug absorption. There are no plans to market a parenteral form of cisapride.

No dosage adjustment is necessary in patients with renal impairment, but it is recommended to start at half the usual dose in patients with hepatic disease<sup>6,8</sup>.

Metoclopramide is marketed as Emex<sup>®</sup> by Beecham, Maxeran<sup>®</sup> by Nordic, Reglan<sup>®</sup> by A.H. Robins and as Apo-metoclop<sup>®</sup> by Apotex. It is available in Canada for oral use as 5 mg and 10 mg tablets and as a 1 mg/mL liquid. Injectable solutions are manufactured in concentrations of 5 mg/mL and 15 mg/mL<sup>38,39</sup>.

Metoclopramide is taken orally 30 minutes prior to meals. The IV preparation should be injected slowly over a one to two minute period, or infused over at least 15 minutes. A transient feeling of dizziness or faintness may occur with rapid administration. As well, IV infusions should be protected from light during administration<sup>1</sup>.

Metoclopramide is stable in 5% dextrose, 0.9% NaCl, 5% dextrose

and 0.45% NaCl, Ringer's, and lactated Ringer's solutions for 24 hours at room temperature and up to 48 hours if protected from light. Patients with renal impairment, i.e., creatinine clearance less than 40 mL/min, should be started on half the normal dosage<sup>1,14</sup>.

Domperidone (Motilium<sup>®</sup>), also a Janssen product, is marketed as a 10 mg oral tablet. It is not available in the parenteral form since cardiac arrhythmias and arrest were reported after IV administration. Such effects were not reported with the oral preparation<sup>14,16,38</sup>.

### CONCLUSION

Prokinetic drugs restore normal motility of the GI tract. Cisapride is a unique prokinetic agent with no antidopaminergic activity. It acts indirectly to enhance physiological release of acetylcholine in the gut. In contrast to metoclopramide and domperidone, cisapride enhances motor activity of the entire GI tract.

Cisapride has greater selectivity for GI motility disorders when compared to metoclopramide and domperidone. Its pharmacological specificity is demonstrated by a lack of significant CNS side effects. In particular, cisapride is effective and well-tolerated in patients with GER, non-ulcer dyspepsia, and gastroparesis. It has also had success in the treatment of patients with chronic constipation and intestinal pseudo-obstruction. Studies indicate that cisapride compares favourably with metoclopramide and domperidone in many aspects of drug disposition.

Cisapride is a useful alternative to metoclopramide and domperidone in the treatment of GI motility disorders. Further comparative clinical trials and long-term experience may allow cisapride to claim a prominent position in the therapy of patients with a variety of GI motility disorders. ☒

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