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Domperidone: Everything a Gastroenterologist Needs to Know

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Domperidone, first synthesized approximately 40 years ago, has been approved worldwide for specific clinical applications. However, in the United States it is only available through an FDA-approved Limited Access Program. Patients with functional dyspepsia, gastroparesis, gastroesophageal reflux disease and refractory nausea and vomiting may benefit from the use of domperidone. The main limitation to using domperidone has been questions raised regarding cardiac toxicity, specifically QTc elongation that could potentially lead to fatal arrhythmias. Recent studies have not shown a significantly increased incidence of cardiac side effects even when domperidone was given at very high doses, two to three-fold greater than those typically described in the majority of the available literature. In this article we review all the literature regarding its clinical efficacy and we provide a comprehensive list of recommendations and guidelines when considering initiating domperidone in patients that are suitable for this medication.

INTRODUCTION

Domperidone, first synthetized in 1974, has been approved for patient use throughout the world with specific clinical applications in gastroparesis, nausea and vomiting, gastroesophageal reflux disease, functional dyspepsia and more recently as adjunctive in small bowel capsule endoscopy. It is currently approved worldwide, however in the United States domperidone is only available through an FDA-approved Limited Access Program. It can be prescribed by physicians who apply for an Investigational New Drug (IND) protocol to provide this drug to patients with gastroparesis or other functional gastrointestinal (GI) disorders associated with nausea and vomiting where symptoms have been refractory to standard therapy or treatment limited by side effects of medications. Domperidone was not approved for use in the United States based on recommendations from the FDA review process to conduct clinical trials with larger patient numbers to further confirm its efficacy and safety.[1] These trials were not subsequently performed or submitted to the FDA.

Our purpose in this publication is to provide physicians a comprehensive analysis about how they can best utilize domperidone in their practices, as well as update on available data for domperidone's pharmacology and efficacy, with a major focus on safety

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with a full analysis of the recent questions that have been raised regarding cardiac toxicity.

PHARMACOLOGY

Pharmacokinetics

Peak plasma concentrations are attained at 10 to 30 minutes after intramuscular and oral administration of domperidone respectively. Systemic bioavailability after intramuscular administration of domperidone is about 90%, whereas oral administration is 13 to 17%. The low systemic bioavailability after oral administration is explained by first-pass effect in the liver and gut wall metabolism.[2]

Distribution data in humans are lacking, but studies in rats with radiolabeled domperidone have shown wide distribution in body tissues except the central nervous system (CNS), where only very low concentrations occur. This is explained by the fact that domperidone minimally crosses the blood-brain barrier.

Domperidone undergoes rapid and extensive biotransformation by hydroxylation and oxidative dealkylation. After oral administration of 40 mg of radiolabeled domperidone, 31% of the radioactivity is excreted in the urine and 60% in the feces over a period of 4 days. The half-life is 7.5 hours in healthy subjects and is prolonged to up to 20 hours in patients with severe renal failure. However, since renal clearance is small compared to total plasma clearance, meaningful accumulation should not occur.[2]

Pharmacodynamics

Domperidone is a dopamine (D) antagonist with particular affinity for the D2 subtype receptors in the brain and the peripheral nervous system including the GI tract. Dopamine receptors in the chemoreceptor trigger zone, which can induce nausea, are blocked by the D2 receptor domperidone (Figure 1). Its mechanism of action in the GI tract is antagonism of apomorphine and dopamine induced changes in GI function. Stimulation of dopaminergic receptors inhibits gastric motility, resulting in symptoms such as post-prandial bloating and pain, premature satiety, nausea and vomiting. Dopamine antagonists, like domperidone and metoclopramide, inhibit this dopaminergic inhibitory effect resulting in net increase in acetylcholine release leading to improved GI motility, with the main effect being in the stomach and minimal effects in proximal small bowel. Unlike metoclopramide, domperidone does not cause any CNS side-effects since it essentially does not cross the blood-brain barrier with minimal evidence of presence in the brain[3] (Figure 1.)

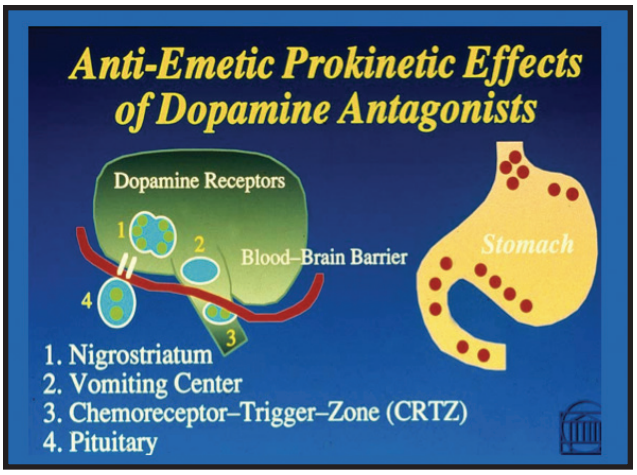

Figure 1. Illustration of the mechanisms of action of domperidone (Motilium) and metoclopramide (Reglan), Dopamine 2 receptor antagonists working centrally (antiemetic effect) and peripherally (prokinetic effect). Metoclopramide, but not domperidone, crosses the blood-brain barrier occupying receptors in the basal ganglia thus explaining its CNS side effects. In addition, both agents have a peripheral gastric prokinetic effect.

Dopamine is one of the neurotransmitters involved in mediating receptive relaxation of the stomach and dopamine antagonists partially inhibit this mechanism. Even after vagotomy, which decreases gastric motility, domperidone can still improve gastric emptying.[4]

The prokinetic effects of domperidone have broad implications in the upper GI tract, starting with small effects on the amplitude of esophageal contractions, but mainly to enhance antro-duodenal contractions, and better coordinate peristalsis across the pylorus resulting in acceleration of slow gastric emptying states.[5] It has minimal effects on motility in the duodenum and proximal small bowel.

CLINICAL USES OF DOMPERIDONE

Functional Dyspepsia

More recently, according to the Rome III criteria, functional dyspepsia (FD) is considered to consist of two main subgroups: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS).[6] PDS is characterized by early satiety, postprandial fullness, bloating, nausea and even vomiting.[7] EPS is dominated by epigastric pain with some components of nausea and fullness.

Table 1. Summary of Published Clinical Trials with Domperidone in the Treatment of Gastroparesis

Reference	Year	Type of Study	Number of Patients in Study	Diagnosis
1	2014	Retrospective	64	DG 45% IG 36% Chronic nausea and vomiting 8% Dumping Sx 5% Cyclic vomiting 5% Conditioned vomiting 1%
21	2002	RCT, PC vs. cisapride	31	DGd DG, pediatric patients
22	1999	RCT, PC vs metoclopramide	93	DG
23	1998	RCT, PC.	208	DG.
24	1997	Open label	7	DG
20	1997	Open label	17	12 IG, 3 DG, 2 PSG
25	1995	Open label	10	5 IG; 2 DG; 1 PSG; 1 scleroderma
26	1990	Retrospective	57	DG
27	1989	Open label	6	DG
28	1989	RCT, PC	13	DG
29	1988	RCT, PC	16	IG
30	1985	Open label	12	DG
31	1983	RCT, PC	6	DG
32	1981	RCT, PC	11	8 IG, 3 DG.

(Abbreviations: RCT: randomized controlled trial; PC: placebo controlled; DG: diabetic gastroparesis; IG: idiopathic gastroparesis; PSG: post-surgical gas

Dose	Duration	Results	Side Effects
80-120 mg/day	Range: 3 months-4 years Mean: 8 months	37 patients had a follow-up ECG; 10 of 37 patients developed a prolonged QTc, without cardiovascular complaints. No relationship between QTc and daily dose of domperidone.	10 patients with asymptomatic prolonged QTc.
NA	8 weeks	Symptom improvement vs baseline with domperidone (p <.001) Symptom improvement with domperidone compared to cisapride (p <.01) Domperidone significantly more effective than placebo in reducing gastric emptying time measured by ultrasound	NA
48: Domperidone 20 mg q.i.d. 45: Metoclopramide 10 mg + 1 placebo tablet q.i.d	4 weeks	41.19% improved vs baseline No significant difference vs metoclopramide	NA
105 patients with domperidone 20 mg q.i.d. 103 patients with placebo.	4 weeks	77.3% decrease in symptom score	Hyperprolactinemia in 2-3% of patients, similar to placbo
NA	12 months	56% symptom improvement from baseline (p <0.01)	NA
Initial dose: 20 mg q.i.d. Dose range: 40-120 mg/day	48 weeks	68.3% patients with symptom improvement vs baseline Gastric emptying after 2 hours reduced from 87.3 +/- 3.71% to 57.2 +/- 5.04%	Hyperprolactinemia
NA	21 months	54% in symptom improvement from baseline (p <0.01)	Hyperprolactinemia 20%
NA	377 days	70% patients improved 26.9% improvement in gastric emptying	Hyperprolactinemia in 16% of patients
NA	6 months	79.2% in symptom improvement from baseline 26.9% improvement in gastric emptying	NA
NA	8 weeks	Decrease in symptom frequency and intensity vs. placebo (<.03)	NA
Domperidone 20 mg before meals and at bedtime	6 weeks	Symptom score significantly improved in domperidone group (p < .05)	NA
NA	Single oral dose	Increase in solid and liquid emptying.	NA
10 mg IV	Single dose	Increase in solid emptying	NA
NA	4 weeks	No overall benefit over placebo	Skin rash

troparesis; NA: not available; IV: intravenous; Sx: Syndrome)

Functional dyspepsia patients display a variety of abnormal digestive functions: delayed gastric emptying (30% of patients); accelerated gastric emptying (10%), and impaired gastric accommodation after meals (40%).[8] Other data suggest that abnormal gastric sensation or visceral hypersensitivity, as well as psychosocial disturbance can be major determinants of symptom severity, particularly the epigastric pain component.[9] The treatment of (FD) can be confusing because no medication is currently approved in the US, Canada or European Union for this specific indication.[10] A reasonable treatment approach based on the current evidence, particularly in the EPS subgroup, is to initiate therapy with a daily proton pump inhibitor in Helicobacter pylori-negative patients. In the PDS subgroup where symptoms are induced or exacerbated by meals and pain is less prominent, prokinetic therapy would be preferred as an initial trial. In both settings if symptoms persist, particularly epigastric pain, a therapeutic trial with a tricyclic antidepressant may be considered for the goal of modifying brain-gut hypersensitivity, while another strategy is initiating therapy with an antinociceptive agent such as gabapentin or pregabalin.

Metoclopramide has been the only prokinetic utilized in the United States, since its approval by the FDA in the 1980's for treating GERD and diabetic gastroparesis. Domperidone has also been studied for the treatment of FD. To date, 6 meta-analyses that describe the effect of domperidone in FD have been published.[11] All of them are based on relatively small studies and numbers demonstrate superiority of domperidone over placebo in the treatment of FD. The analyzed studies using a domperidone dose of 30-60 mg/day for a total time of 2-6 weeks demonstrated a treatment effect of 30 to 63%. This data supports the theory of a treatment benefit for domperidone in FD. However an important unresolved issue is the short duration of treatment, since FD is a chronic condition. These studies in retrospect were addressing the PDS subset of patients classified by Rome criteria with primarily dysmotility-like symptoms, and this subgroup should be considered when contemplating initiating domperidone for functional dyspepsia.

Gastroparesis

Gastroparesis is a syndrome characterized by anorexia, bloating, early satiety, abdominal pain and vomiting, and is associated with objective evidence for delayed gastric emptying without evidence of any gastric obstruction. A major cause of gastroparesis is diabetes and it may be present in up to 30% to 50% of the gastroparetic patients. The idiopathic variety is also important and of equivalent frequency, and together both forms constitute more than 80% of all cases of gastroparesis.[12]

Although delayed gastric emptying is considered the cardinal finding in gastroparesis, it is clear that the pathogenesis of symptoms is complex and diffuse ranging from impaired fundic accommodation, related to impaired gastric inhibitory neurons,[13] neuropathic changes involving the myenteric plexus,[14] sensory nerve dysfunction.[15] and gastric dysrhythmias.[16]

The evidence for using prokinetics is based on trials performed two or three decades ago, which in some cases may not have been as rigorously conducted in regard to numbers and population assessment.[17] The dopamine D2-receptor antagonist, metoclopramide, is the only US FDA-approved medication for the treatment of gastroparesis and the recommended duration is no longer than a 12-week period.[18] The reported serious adverse events such as tardive dyskinesia, dystonias and parkinsonism are always a "cloud" over the head of metoclopramide in balancing its efficacy. For more than 40% of patients unable to tolerate this agent or do not respond to metoclopramide, domperidone should be the next agent utilized.

The importance of domperidone in the management of gastroparesis is undeniable. The American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis, as well as the American Gastroenterological Association medical position statement for the diagnosis and treatment of gastroparesis recognizes domperidone as one of the most important treatment options currently unavailable for gastroparesis.[19]

An early study performed in 1997 involving 17 patients with gastroparesis and symptoms of nausea, vomiting, abdominal pain and bloating utilized domperidone 20 mg q.i.d. for an average of 23 months. Results showed a decrease in hospital admissions compared with before domperidone therapy ($p < 0.05$), improvement in gastric emptying ($p < 0.05$) and enhanced quality of life of 88% of patients. More recently, a multicenter, two-phase withdrawal study involving 208 insulin-dependent diabetic patients showed that domperidone is effective in treating moderate to severe upper GI symptoms independent of their gastric emptying status.[20] This study also

investigated two health-related quality of life measures of physical and mental components. Results at the end of the single-blind phase indicated that patients with a symptomatic response to domperidone also experienced significant improvements in health-related quality of life from baseline as measured by physical and mental component scores. Patients continuing on domperidone during the double-blind withdrawal phase maintained their clinical and health-related quality of life gains. In contrast, those in the placebo group experienced more gastroparetic symptoms and a decline in quality of life. Table 1 summarizes the published clinical trials with domperidone. However, trials investigating domperidone have been generally underpowered and often uncontrolled, so results must be interpreted with this caveat.

As the IND protocol is mainly utilized by gastrointestinal specialists in centers with institutional review boards, patients who do not have access to such centers might not be able to obtain domperidone. Conversely, physicians at a university research facility might not have enough patients for a large single center report. This situation could create a mismatch between the patient in need for treatment and the availability of prescribing physicians who have access to IND.[33] Domperidone is also available through compounding pharmacies in the USA or through access to European pharmacies although this is not sanctioned as a "standard of care".

The European dose schedule utilized for more than 30 years recommends dosing of 10 mg t.i.d or up to q.i.d. On the other hand, the clinical guidelines on the management of gastroparesis published in 2013.[17] focusing on practice in the United States recommended a starting dose of 10 mg q.i.d. increasing up to 20 mg t.i.d. before meals and at betime. A recent study by Ortiz et al. showed that the use of domperidone at very high dose of 80-120 mg/day was well tolerated among the majority of the enrolled patients as well as being very efficacious, resulting in a 75% symptom improvement from baseline, for the treatment of gastroparesis and nausea and vomiting.[1]

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is defined as a pathological condition when the amount of gastric contents refluxing into the esophagus exceeds the normal limit. Typical symptoms are heartburn and regurgitation, but the spectrum of symptoms ranges from asymptomatic patients, atypical chest pain, dysphagia, hoarseness and odynophagia.[34] Complications of chronic GERD include esophageal mucosal damage, such as Barrett's esophagus or stricture.

Despite the wide spectrum of abnormalities, three primary goals are applicable to all patients with GERD: 1) alleviation of symptoms, 2) resolution and prevention of complications, 3) prevention of recurrence.[35]

Proton pump inhibitors (PPI) are the most effective agents to treat GERD when compared to antacids, prokinetics, and H2 receptor blockers. They have few adverse effects and are well tolerated for long-term use. Due to the superiority and efficacy of PPI, treatment of GERD should start with an 8-week course of PPI. In some cases, PPI monotherapy cannot completely resolve symptoms in all cases of GERD; in this setting combination therapy with a prokinetic will further improve symptoms for some patients.[36] Accompanying "dyspepsia-like" symptoms in addition to GERD are the most receptive to domperidone.

Motility modulating drugs exert their therapeutic effect in GERD by increasing the lower esophageal pressure, enhancing peristaltic contractions, improving esophageal clearance, and by accelerating gastric emptying.[37]

A randomized, double blind clinical trial by Ndraha evaluated the combination of PPI with domperidone in the treatment of GERD.[38] Sixty patients were enrolled and separated in two groups, group A 30 patients received omeprazole 20 mg b.i.d and domperidone 10 mg t.i.d for 2 weeks, while group B 30 patients were only given omeprazole 20 mg b.i.d; symptoms were assessed after 2 weeks of treatment using the Frequency Scale for the Symptoms of GERD (FSSG).[36] The FSSG score in the omeprazole + domperidone group after treatment (19.3 +- 11.3) was significantly lower than before treatment (26.7 +- 8.9, $p < 0.001$) as well as significantly better than in the omeprazole group (from 23.9 +- 7.3 to 19.3+- 7.9, $p < 0.001$). The mean improvement score in group A was 7.5 +- 5.9, while in group B was of 4.6 +- 3.3, and this difference was statistically significant ($p=0.02$). The author concluded that the combination of omeprazole with domperidone in highly symptomatic patients with GERD is superior to omeprazole monotherapy.

However, the true clinical efficacy of domperidone has not been confirmed in that data suggests ineffective healing of esophagitis despite improved symptom

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states. Ren et al. demonstrated in a recent meta-analysis [39] that combined therapy with a PPI and a prokinetic was associated with a greater symptomatic relief and a reduction in the number of reflux episodes, but there was no significant effect on 24-hour esophageal acid exposure time and healing of esophagitis demonstrated endoscopically. Their conclusion was that combining therapy can improve quality of life of patients with GERD.

Nausea and Vomiting

The antiemetic effect of dopamine is mediated by inhibition of D2 receptor activation in the area postrema and chemoreceptor trigger zone at the base of the fourth ventricle but outside the blood-brain barrier.[40] (Figure 1)

The antiemetic properties of domperidone are well documented. In patients experiencing postoperative nausea and vomiting, IV domperidone was more effective than placebo.[41] Neither domperidone nor metoclopramide was more effective than placebo when given prophylactically before induction or near the end of anesthesia for preventing nausea and vomiting.[42]

Nausea and vomiting associated with chemotherapy has been effectively controlled by domperidone when administered immediately before the cytotoxic regimen. It is more effective than placebo and compares favorably with metoclopramide in controlling vomiting as a result of moderately emetic chemotherapeutic agents.[43,44] However, this chemotherapy phase of domperidone career relied on intravenous administration which now is no longer approved or being continued.

Domperidone has also been used to treat nausea and vomiting associated with other conditions including dysmenorrhea, head injury and intracranial lesions, hemodialysis, radiotherapy and migraine headaches. Most of these studies were open trials but did show some efficacy for these indications.[3]

The management of patients who need anti-Parkinsonian medications and other centrally acting dopamine agonists is often limited by the side effects of nausea, vomiting, anorexia and postprandial fullness. Metoclopramide is contraindicated in Parkinson's disease because by crossing the blood-brain barrier it would antagonize levodopa therapy effects. On the other hand, domperidone is very useful in this setting because it inhibits peripheral dopaminergic activity without blocking central dopamine effects. Studies have shown that oral domperidone, at a dose of 60-150 mg/day, decreases the incidence of nausea and vomiting in patients treated with bromocriptine, allowing them to tolerate higher doses of bromocriptine.[45] Domperidone also improved gastric emptying and alleviated GI symptoms including nausea, vomiting, anorexia and abdominal bloating induced by levodopa. The beneficial effects of the anti-Parkinsonian drugs were not inhibited by domperidone, and no extrapyramidal side effects were reported with the use of domperidone.[46]

Small Bowel Capsule Endoscopy

Small bowel capsule endoscopy (SBCE) was introduced in 2001. It has since revolutionized the diagnostic workup for small bowel diseases.[47] One of the major limitations of SBCE is the high percentage of cases in which the capsule does not reach the cecum by the end of the recording period and/or exhaustion of capsule's battery life[48] as reported in up to 30% of the procedures. It has been demonstrated that one of the risk factors for an incomplete SBCE is a long gastric transit time (GTT).[49] Hence, there is rationale to use prokinetics to the procedure to decrease GTT and thereby potentially increase the rate of complete small bowel examinations.

Different prokinetics have been used in an attempt to increase completion rate (CR) and the diagnostic yield (DY) of SBCE. Metoclopramide remains the most commonly administered prokinetic. Domperidone has not been widely used in SBCE and the evidence base is limited.[50,51] A retrospective study by Koulaouzidis et al.,[52] analyzed the effect on CR, GTT and DY when using 10 mg of domperidone in liquid solution compared to no domperidone with the capsule ingestion. Results showed an increase in CR of 91.1% in the domperidone group vs. 84.3% in the other group ($p= 0.04$). The GTT was reduced in the domperidone group but it was not statistically significant compared to the non-domperidone group. Interestingly, the use of domperidone was associated with reduced DY for vascular, inflammatory and mass lesions. The study demonstrated that the use of domperidone increases the CR of SBCE but that there was no increase in DY, most likely secondary to interpreting the capsule images and related to domperidone use.

A prospective study by Westerhof et al.,[53] analyzed the CR in 649 patients undergoing SBCE; 410 patients received domperidone 10 mg and 239 received erythromycin 250 mg 1 hour before the procedure. Results showed that CR was 86% after erythromycin vs. 80% after domperidone ($p= 0.03$); GTT was lower

after erythromycin compared to domperidone (13 minutes vs 22 minutes, p= <0.001); however, there was no difference in DY, 50% vs 44%, respectively (p= 0.18). The authors concluded that the administration of erythromycin prior to SBCE increased the CR compared to domperidone, this is explained by the fact that domperidone's motility effects do not extend beyond the duodenum whereas erythromycin induces diffuse small bowel motility effects.

SAFETY AND TOXICITY

Cardiac Toxicity

Domperidone is regarded as having similar properties to class III antiarrhythmic agents such as prolonging the action potential through blockade of distinct voltage-dependent potassium channels, thus delaying cardiac repolarization and prolonging QT interval, which can predispose to life-threatening ventricular arrhythmias such as torsades de pointes. The criteria for QT interval prolongation on an electrocardiogram (ECG) is >450ms in males and >470ms in females. Longer QT intervals are found in women compared to men.[54] Osborn et al. reviewed the effect of intravenous use of domperidone in four women, of whom two had episodes of ventricular arrhythmias. Of note, the underlining cause for ventricular arrhythmia was attributed to hypokalemia.[55] The intravenous form of domperidone no longer exists.

Based on questions of cardiac safety in Europe, there have been some recommendations for dosing and monitoring. However, we have performed a comprehensive literature research to analyze the concerns about cardiac events.

A Dutch case-control database study involving 1366 patients assessed the association between sudden cardiac death or sudden ventricular arrhythmia and domperidone use.[56] A total of 1366 cases (62 involving sudden ventricular arrhythmia and 1304 sudden cardiac deaths) were matched to 14,114 controls by index date, sex, age, and type of practice. None of the patients who experienced sudden ventricular arrhythmia were using domperidone at the time of the event. The multivariable analysis controlled for QTc-prolonging drugs and medical conditions, smoking, alcohol use and CYP3A4 drug interactions. Among the 1304 patients with sudden cardiac death, only 10 were using domperidone at the time of the event, which translates to a statistically non-significant increased risk of sudden cardiac death (odds ratio [OR] 1.99, 95% confidence interval [CI] 0.80–4.96). When these 10 patients were further stratified by daily dose (< 30 mg, 30 mg, and > 30 mg), the multivariable analysis showed an increased risk of sudden cardiac death for patients taking more than 30 mg per day (OR 11.4, 95% CI 1.99–65.2).

A very recently published study by Ortiz et al. did not find an association between the use very high dose of domperidone (more than three times the dose schedule in Europe) and an increased risk of cardiovascular events nor significant changes in QT interval.[1] That study included 64 patients that were taking domperidone at doses of 80-120 mg/day for a mean duration of 8 months, some as long as 4 years. Results showed that 73% of the patients had symptomatic improvement in nausea and vomiting, 15.6% of patients had an increase of QTc at follow up but no cardiovascular events reported; 5% had palpitations without ECG changes and there were no sudden cardiac deaths.

Another relevant piece of information is that 2,000,000 prescriptions for domperidone were recorded in Canada in 2013 and between April 2003 and March 2010, it was recorded that 122, 333 elderly patients had domperidone on their prescription list in Ontario, Canada. Despite this large number of prescriptions and available warnings regarding cardiac side effects of domperidone, Health Canada had received only 18 (0.9 per 10,000) reports of serious adverse cardiac events but no deaths. In many of these patients, other risk factors for arrhythmias were also present.[57,58]

Moreover, to keep this in perspective, we know that other possible therapies for gastroparesis, specifically erythromycin, azithromycin, ondansetron and promethazine also have cardiac side effects.

Our conclusion from extensive literature review of the USA experience is that domperidone has the potential for cardiac side effects based on concerns for QT prolongation and increased risk of ventricular arrhythmias, but studies do not substantiate cardiac adverse events in patients receiving oral administration of domperidone, even at very high doses.

Endocrine Effects

Thyroid-stimulating hormone (TSH) and prolactin increased after domperidone administration, but there was no effect on cortisol secretion, aldosterone and 18-OHB.[59] This indicates that domperidone has a direct effect on anterior pituitary rather than through a central hypothalamic mechanism. Unlike the mechanism

of metoclopramide, domperidone has lipophobic properties therefore it effects are not based through the central dopaminergic receptors. The pituitary is outside the blood-brain barrier where domperidone can induce those hormonal effects. Domperidone's endocrine effects on TSH have no clinical significance.

Prolactin is increased in everyone on domperidone. Comparative studies have reported similar degrees of increased serum prolactin concentrations in healthy subjects receiving domperidone or oral metoclopramide.[60] However, few patients complain of symptoms including gynecomastia and nipple tenderness in 10% and galactorrhea in 5%. There is no association with prolactinomas or increased risk of breast cancer. Another observation is oligomenorrhea and rarely amenorrhea, although fertility remains unchanged. This is relevant since 80% of patients with gastroparesis are female and these side effects are regarded as more inconvenient than meaningful, and patients who benefit from domperidone are generally willing to accept them.[61]

Drug-drug Interactions

Dopamine antagonists should not be given in conjunction with monoamine oxidase inhibitors. Stimulation of D2 receptors causes inhibition of norepinephrine release from presynaptic nerve terminals. Antagonists of D2 receptors cause decreased inhibitory control, facilitating the release of norepinephrine.[62]

The main concern is a combination of domperidone with cytochrome CY3PA4 inhibitors. This enzyme is the main metabolic pathway for domperidone, therefore medications that interfere with this mechanism must be avoided. Inhibitors of CYP3A4 can block the metabolism of domperidone, resulting in increased plasma concentrations of domperidone, with the subsequent risk of increased risk of cardiovascular and endocrine side effects. These medications include azole antifungals (ketoconazole, fluconazole),[1] protease inhibitors, macrolide antibiotics, calcium channel blockers, propranolol, metoprolol, HMG-CoA reductase inhibitors and newer anticoagulants such as apixaban.

TAKE HOME MESSAGES

Domperidone has been available for the treatment of gastrointestinal motility disorders throughout the world since the 1970's. Unfortunately, domperidone is not easily available in the United States since the FDA withheld approval in 1989 due to borderline statistical significance related to sample size in the controlled clinical trials. It is mainly available through an IND process. Its efficacy relies on an anti-emetic effect by blocking D2 receptors centrally as well as the prokinetic property through blocking peripheral dopamine receptors in the gastric smooth muscle. It has an effective role in the treatment of gastric motility disorders, especially in patients that do not respond to diet modifications or develop side effects or have an inadequate response to metoclopramide. Interpreting the clinical significance and meaning of the concerns raised in the literature regarding cardiotoxicity when using domperidone require ongoing vigilance. While there are reports of QTc interval elongation and cardiovascular events related to the use of low dose domperidone, most studies and clinical experiences do not confirm this association. Moreover, data with prolonged dosing at 3-fold of the European dose shows no evidence for ventricular arrhythmias or cardiac death.

A dilemma has been created because of the statements made by authorities in some countries regarding the cardiotoxicity of domperidone. However, our extensive review does not support the conclusions made by these international agencies. At the present time, domperidone is an extremely effective treatment for gastroparesis and other disorders with nausea and vomiting and has an acceptable safety profile and risk-benefit ratio.

Our recommendations and guidelines for physicians who plan on initiating domperidone therapy in their practices are the following: 1) have a condition that would benefit from antiemetic and gastric prokinetic therapy; 2) document no response or presence of side effects secondary to metoclopramide and other anti-nausea/vomiting medications; 3) confirm no QTc elongation; 4) start at a dose of 20 mg q.i.d., 30 minutes before meals and before bedtime, to have a meaningful effect and if necessary increase gradually until achievement of therapeutic effect, sometimes requiring 120 mg/day; 5) treatment should be for a minimum of 3 months at the recommended doses in order to draw conclusions about its efficacy; 6) monitor other drug use to avoid CY3PA4 inhibitors; 7) monitor serum potassium and magnesium levels; 8) obtain ECG every 6 months; 9) discontinue domperidone if QTc interval becomes prolonged; 10) inquire about such symptoms as palpitations or chest pain.

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Domperidone, although not Dom Perignon, is indeed the "champagne" of the prokinetic/antiemetic drug world and we hope this article will allow you to appreciate its clinical indications, efficacy, and most of all, safety, so your patients can benefit by instituting this agent into your practice. So "raise your glasses for a toast", you have now acquired a new knowledge base for your practice. ■

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Answers to this month's crossword puzzle:

1 M	I	2 C	R	O	3 B	4 I	O	5 M	E		6 B	7 R	A	8 N
Y		E			9 A	B		U		10 U		E		A
11 A	L	L	E	R	G	I	E	S		R		12 S	A	C
L		I				D		C		A		O		
13 G	L	A	N	14 D	S		15 E	L	E	C	T	R	O	16 N
I		C		R		17 N		E		I		P		O
18 A	P		19 M	U	C	U	S		20 G	L	U	T	E	N
		21 H		G		T		22 P				I		U
23 P	U	F	A		24 U	R	E	A		25 F	O	O	D	S
A		H		26 J		I		N		O		N		E
27 N	28 A	S	C	E	N	T		29 C	O	D	E		30 P	
	N			T		I		R		M		31 B	I	32 G
33 L	Y	S	34 I	S		35 O	M	E	36 G	A		37 I	C	E
A			S			N		38 A	M	P	U	L		R
39 P	R	O	T	O	N			40 S	O	S		41 E	G	D