Cardiac safety concerns for domperidone, an antiemetic and prokinetic, and galactogogue medicine

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Abstract

**Introduction:** Domperidone is a dopamine D<sub>2</sub>-receptor antagonist developed as an antiemetic and prokinetic agents. Oral domperidone is not approved in the US, but is used in many countries to treat nausea and vomiting, gastroparesis, and as a galactogogue (to promote lactation). The US Food and Drug Administration (FDA) have issued a warning about the cardiac safety of domperidone.

**Areas covered:** The authors undertook a review of the cardiac safety of oral domperidone.

**Expert opinion:** The data from preclinical studies are unambiguous in identifying domperidone as able to produce marked hERG channel inhibition and action potential prolongation at clinically relevant concentrations. The compound’s propensity to augment instability of action potential duration and action potential triangulation are also indicative of proarrhythmic potential. Domperidone should not be administered to subjects with pre-existing QT prolongation/LQTS, subjects receiving drugs that inhibit CYP3A4, subjects with electrolyte abnormalities or with other risk factors for QT-prolongation. With these provisos, it is possible that domperidone may be used as a galactogogue without direct risk to healthy breast feeding women, but more safety information should be sought in this situation. Also, more safety information is required regarding risk to breast feeding infants or before domperidone is routinely used in gastroparesis or gastroesophageal reflux in children.

**Keywords** anti-emetic, cardiac safety, domperidone, galactogogue, gastroparesis, proarrhythmia, prokinetic, QT interval, torsades de pointes
1. Introduction

Domperidone (Motilum), a potent dopamine D₂ receptor antagonist, was developed by Janssen Pharmacutica in 1974 as an antiemetic and prokinetic agent [1]. Domperidone is approved for use to treat nausea and vomiting, and gastroparesis in most countries, but not in the US. Domperidone is also used as a galactogogue (i.e. to promote lactation), but this use is not approved.

In 2004, although domperidone was not approved in the US for any use, it was being imported into the US to enhance breast milk production, and this prompted the FDA to issue a warning that included; ‘The agency is concerned with the potential public health risks associated with domperidone. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from marketing in a number of countries. In several countries where the oral form of domperidone continues to be marketed, labels for the product contain specific warnings against use of domperidone by breastfeeding women and note that the drug is excreted in breast milk that could expose a breastfeeding infant to unknown risks. Because of the possibility of serious adverse effects, FDA recommends that breastfeeding women not use domperidone to increase milk production.’ [2]. This safety alert remains current [3].

Oral domperidone is widely available over the counter or by prescription in a number of European countries. It is available in Austria, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal and the UK. Prompted by concerns from the Belgian medicines agency, the European Medicines Agency announced on 7th March 2013 a review of all available data on the benefit-risk balance of domperidone-contained medicines, in order to determine whether the marketing authorisations should be maintained, varied, suspended or withdrawn across the EU [4]. In Australia, domperidone is available for the treatment of nausea and vomiting, gastroparesis and to stimulate lactation, but, as in many other countries, does come with a warning about prolonged QT interval.

Intravenous domperidone was taken off the market in the mid-1980s after reports linking it variously to QT prolongation, cardiac arrhythmias, cardiac arrest and sudden death [5,6,7,8,9,10,11,12], and is not considered in this review.

2. Non-cardiac pharmacology

2.1 Pharmacodynamics and pharmacokinetics
Domperidone is 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-on [13]. Domperidone is a dopamine D₂-receptor antagonist that acts on the D₂-receptors in the gut as a prokinetic agent [14]. Domperidone is a poor penetrant of the blood brain barrier, but does have an anti-emetic effect mediated by antagonising the D₂ receptors in the chemoreceptor trigger zone, which is outside of the blood brain barrier [14].

After oral administration of domperidone 20 mg to healthy volunteers, the peak plasma concentration of domperidone is about 20 ng/ml [15]. With doses of domperidone, 10 or 60 mg, to healthy volunteers, peak plasma levels (23 and 80 ng/ml, respectively) were observed after 30 mins [16]. In concentrations up to 100 ng/ml, domperidone is 93% bound to plasma proteins [16]. Domperidone undergoes extensive first pass metabolism [17]. Elimination half-life is 7.5 hours [17]. Domperidone given to lactating mothers does transfer into breast milk, but at very low levels [18].

Domperidone is readily metabolised by CYP3A4 and also metabolised by CYP1A2, CYP2B6, CYP2C8 and CYP2D6 [19]. The plasma levels of domperidone are increased by drugs that inhibit CYP3A4 [16,20,21].

### 2.2 Anti-emetic/prokinetic

Domperidone has been shown to be superior to placebo in the treatment of dyspepsia and postoperative nausea and vomiting, the nausea and vomiting associated with the use of dopamine receptor agonists in Parkinson’s disease, but not in chemotherapy-induced nausea and vomiting [14].

The main present use of domperidone, as an anti-emetic, is when a prokinetic effect is also required e.g. in gastroparesis and gastro-oesophageal reflux. Initially, domperidone 20 mg qid alone was effective at reducing nausea and vomiting in 16 subjects with unexplained upper gastrointestinal symptoms (idiopathic gastric stasis, “non-ulcer dyspepsia” and altered gastrointestinal motility) [22]). Subsequently, domperidone 10 and 20 mg tid and metoclopramide were shown to be similarly effective in reducing nausea and vomiting due to a variety of oesophageal or gastric disorders in 95 subjects [23]. Further refinement of the use of domperidone, showed that at 20 mg qid, it was particularly effective in preventing the nausea, abdominal distension/bloating, early satiety, vomiting, and abdominal pain associated with the gastroparesis in 287 subjects with diabetes [24]. Another study, in 93 subjects with gastroparesis, showed that domperidone 20 mg qid was equally effective to metoclopramide but caused fewer adverse effects [25]. Reviews in 2005 and 2008 support domperidone being efficacious in the treatment of gastroparesis [26,27].

Gastroesophageal reflux is very common in childhood. A 2005 systematic review of the randomised controlled trials of domperidone in childhood gastroesophageal reflux, found only 4 small studies with
major limitations, and concluded that there was ‘no robust evidence of efficacy……. with domperidone in young children’ [28]. However, a small study of 20 infants with regurgitation showed that domperidone (0.8 mg/kg/day tid) was equieffective to cisapride in reducing regurgitation, and that in this small population cisapride caused QT prolongation in one infant, but that domperidone had no effect on the QT intervals of the 10 infants [29]. Thus, at the present time, the clinical efficacy and toxicity of domperidone in childhood gastroesophageal reflux remains uncertain.

2.3 Galactogogue

By antagonising dopamine D₂ receptors, domperidone stimulates prolactin production and lactation, and thus domperidone is a galactogogue. The recommended dose of domperidone for stimulating lactation in Australia is 10 mg tid. In 1985, domperidone (10 mg tid) was shown to increase milk production in 32 mothers of term infants with poor lactation, compared to placebo [30]. More recently, domperidone has been compared to placebo, at 10 mg tid, shown to increase milk production in 20 mothers of preterm infants [31], and at 10 mg qid, to increase milk production in 45 mothers after caesarean delivery at full term [32]. Reviews in 2010 and 2012 of domperidone as a galactogogue stated that there were no reported side effects in the infants or mothers, and that given the warning about cardiac arrhythmias with domperidone, it is unlikely that any mothers with cardiac problems would take domperidone [33,34].

Metoclopramide is another dopamine receptor antagonist that has been used as a galactogogue, but unlike domperidone, metoclopramide crosses the blood brain barrier and very rarely has centrally-mediated extrapyramidal adverse effects. Domperidone (10 mg tid for 10 days) has been compared to metoclopramide for increasing lactation in 65 mothers of infants in a neonatal intensive care unit, and shown to be equally good, if not better, than metoclopramide at increasing lactation [35]. Fewer mothers taking domperidone than metoclopramide reported adverse effects (9.7% vs 20%) [35]. No cardiac or movement adverse effects were reported in this study with either domperidone or metoclopramide [35].

3. Pre-clinical cardiac electrophysiology

In 2000, Drolet and colleagues demonstrated direct effects of domperidone on ventricular repolarization [36]. When 100 nM (43 ng/ml) domperidone was applied to guinea-pig perfused hearts for 15 minutes, monophasic action potential duration (at 90% repolarization: MAPD₉₀) was prolonged by ~27% at a cycle length of 250 ms and ~9% at a cycle length of 150 ms [36], indicative of
a reverse-rate dependent APD prolonging effect. A subsequent study showed similar MAPD_{50}-prolongation of about 16 ms with the perfusion of domperidone 100 nM for 10 minutes in male and female hearts from prepubertal guinea-pigs [37]. A recent study, using female rabbit hearts, has suggested that the effect of domperidone on MAPD_{50}-prolongation does not reach equilibrium until 150 minutes [38]. Thus, domperidone 100 nM prolonged by 12 and 125 ms after 15 and 150 minutes, respectively [38]. With a lower dose of domperidone (60 nM), after 150 minutes, a 32% (83 ms) of MAPD_{50} was observed [38]. In this study, domperidone was also found to increase action potential instability and triangulation, both significant markers of proarrhythmia [38].

The hERG channel passes current similar to the native cardiac I_{Kr} (rapid delayed rectifier) K⁺ channel. Domperidone has been studied in experiments on hERG-expressing Chinese Hamster Ovary cells; in these, hERG current (I_{hERG}) was inhibited by domperidone in a concentration-dependent manner, with inhibition observed with 12 nM, and an estimated half-maximal inhibitory concentration (IC_{50}) of 162 nM [36]. In a subsequent independent study, in which hERG channels were expressed in Human Embryonic Kidney (HEK293) cells, I_{hERG} was inhibited by domperidone with a lower IC_{50} of 57 nM [39]. In this study, domperidone was compared with a distinct pro-kinetic drug metoclopramide, with the latter compound exhibiting a much less potent I_{hERG}-blocking effect (IC_{50} of 5.4 µM) [38]. A later study has demonstrated that domperidone 3 µM exhibits frequency independent inhibition of I_{hERG} [40]. In experiments probing effects of concomitant exposure to more than one hERG-blocking drug, with prior exposure of guinea-pig hearts to antimicrobials (erythromycin or ketoconazole), MAPD_{50} prolonging effects of domperidone, 5 and 50 nM, were attenuated and this was mirrored by effects of sequential application of these agents in experiments on hERG [41].

The foregoing data constitute strong evidence that domperidone delays ventricular repolarization and that the likely basis for this is reasonably potent (sub-micromolar IC_{50}) inhibition of hERG-mediated rapid delayed rectifier K⁺ current, I_{Kr}. Both effects may be considered surrogate markers of torsade des points (TdP) risk, although it is recognised that the presence of hERG/I_{Kr} block or delayed repolarization does not automatically result in arrhythmia induction [42,43]. Recently a novel pre-clinical marker of TdP risk called the electromechanical window (EMw) has been proposed [44]. The EMw reflects the time between completion of electrical repolarization (i.e. of the T wave) and completion of ventricular relaxation, with a reduction in EMw associated with TdP induction [44]. In anaesthetized guinea-pigs, a negative EMw has been associated with TdP induced by documented torsadogenic drugs when these are co-administered with an I_{Kr} blocker and adrenaline [45]. In this novel assay, domperidone was found to induce a significant negative EMw and to lead to TdP [45].
Furthermore, in perfused rabbit hearts, domperidone (30, 60 and 100 nM) has been associated, in a concentration-dependent fashion, with AP triangulation, instability and reverse-rate dependence of APD prolongation (TRIaD) [46,47]. At the higher concentrations, 60 and 100 nM, domperidone caused early afterdepolarizations and polymorphic ventricular tachycardia were observed [38].

4. Human electrophysiology

A case report of QT prolongation with domperidone (0.6 mg/kg tid) in 3-month-old infant appeared in 2005 [48]. In 2008, domperidone, at a mean daily dose of 1.3 mg/kg/day, was shown to prolong the QT interval in 31 neonates or infants by a mean of 14 msec [49]. In a separate study, the mean QTc interval was not altered at 3, 7 and 14 days of treatment with domperidone (0.25 mg/kg every 6 hours) administered orally or through a nasogastric tube, but prolongation without adverse clinical consequences was reported for 2 of 40 premature infants treated [50]. A subsequent study investigated effects of domperidone (0.5-1mg/kg/tid or qid) on QTc interval in 45 infants (0-1 yr) treated for gastro-oesophageal reflux, comparing baseline QTc interval with values taken 1 hour after dosing between 7-14 (a mean of 9) days after commencement of treatment [51]. Taking the group as a whole, no significant difference was seen in QTc interval with domperidone; however when separated by gender, there was a trend towards a difference in boys (p of 0.051) but not girls [51]. Two boys had clinically significant (>460 ms) QTc interval prolongation, with QTc intervals being normalized following discontinuation of domperidone [51].

There is, however, an absence of information from large-scale studies of children in this regard.

Ketoconazole is a commonly used anti-fungal agent, which inhibits CYP3A4 and P-glycoprotein. In healthy volunteers with normal ECGs, domperidone 10 mg qid alone gave a peak plasma concentration of 23 ng/ml, and this increased to 68 ng/ml in the presence of ketoconazole [16]. The area under the plasma curve also increased 3.6 fold in the presence of ketoconazole [16]. Domperidone and ketoconazole alone and in combination increased the QTc interval in men (domperidone alone, 4 msec; domperidone and ketoconazole, 16 msec), but not women [16]. Domperidone had no effect on heart rate or the ECG [16]. In their discussion, Boyce et al point out that because domperidone is 93% plasma bound [17], an in vitro concentration of 100 nM (43 ng/ml), which has been shown to prolong action potentials in guinea-pig hearts [36] is equivalent to a total plasma concentration of 860 ng/ml, which is much higher than observed when domperidone and ketoconazole were combined in this study of human volunteers [16]. However according to the ICH E14 guidelines [52], the prolongation of QT interval observed in this study for domperidone is
borderline, and that for domperidone and ketoconazole is positive, despite there being no reports of an interaction [16].

5. Ventricular arrhythmia and sudden cardiac death

Between 1985 and 2006, Health Canada received 9 reports of heart rate and rhythm disorders with domperidone: 2 prolongation of QT interval, 4 torsades de pointes, 3 of arrhythmia, atrial fibrillation, ventricular tachycardia, bradycardia, and palpitation [53].

In a case of multifactorial acquired QT prolongation and torsades de pointes, domperidone (10 mg tid) was one of 11 drugs (including amiodarone and venlafaxine) being a subject with multiple cardiac disease who also had electrolyte abnormalities (hypomagnesemia and hypokalemia), consequently the role of domperidone independent of these other risk factors is unclear [54].

In the Netherlands, a population-based case-controlled study in primary care, investigated the effects of non-cardiac QTc prolonging drugs including domperidone, in subjects with a mean age of 70 years, and many had cardiovascular disease [55]. There were 9 cases of sudden cardiac deaths with domperidone in 775 subjects, which was a significantly higher percentage than the 15 cases in the control group of 6297 [55]. Using the same database, the increase in sudden cardiac death with domperidone has been confirmed with 10 cases from 1304, compared to 28 cases from 13,480 control subjects (unadjusted odds ratio of 3.72; 95% CI 1.72, 8.08), and the effect is more pronounced with a dose of domperidone > 30 mg [adjusted odds ratio 11.4; CI 1.99, 65.2] [56].

A nested case-control study in Saskatchewan, Canada, identified 169 serious ventricular arrhythmias or sudden cardiac deaths in 1608 users of domperidone, compared to 481 of 6428 matched controls, which is 10.5 vs 7.5% (odds ratio 1.59, 95% CI 1.28, 1.98) [57]. The case subjects in this study had a mean age of 79 years, many had cardiovascular disease and 22% had diabetes [57]. The increased risk of arrhythmia and sudden cardiac death identified with domperidone in this study persisted following adjustment for multiple covariates [57].

A case-control study of in-hospital cardiac arrests with domperidone, also in the Netherlands, found 7 cases from 140 subjects (mean age 60 years), which was a significantly higher percentage than the 15 cases in the control group of 560 [adjusted odds ratio 4.7, CI 1.4, 16] [58].

6. Expert opinion

6.1 Plasma concentrations, QT prolongation and safety
Redfern and colleagues have proposed a provisional safety margin for drugs undergoing clinical evaluation of a 30-fold difference between maximal free plasma concentration and hERG blocking IC\textsubscript{50} [47]. This proposal was derived from investigating the relationship between these parameters for drugs that had been or were in clinical use [47]. The drugs were classified into 5 categories, and domperidone was in category 4, drugs that have isolated reports of causing TdP in humans, and these drugs had a large spread of ratios, ranging from 0.13 to 35700, with domperidone represented as having a ratio of ~13 between the lowest published IC\textsubscript{50} values and the upper end of the free plasma concentration [47].

In reporting APD prolongation and hERG block by domperidone for the first time, Drolet and colleagues quoted mean plasma concentrations of domperidone in humans of ~18-21 ng/mL (42-49 nM) at a dose of 30 mg/day [36]. Although plasma drug levels are those most easily measured and evaluated, they do not necessarily reflect directly those in particular tissues; issues such as local accumulation or metabolism could feasibly make cardiac myocyte intracellular drug levels different to those in plasma. With that proviso, it is noteworthy that the ratio between mean plasma concentration and hERG IC\textsubscript{50} thus ranges between ~3.3-3.9 with a hERG IC\textsubscript{50} of 162 nM (or 1.20-1.4 if a hERG IC\textsubscript{50} of 57 nM is used [39]). However, given that peak plasma domperidone levels of 23 and 80 ng/ml after oral doses of 10 mg or 60 mg administration [16] translate to 54 and 188 nM, the level of anticipated hERG block at peak domperidone concentrations may transiently be greater than expected from mean plasma levels (with transient correspondent reductions in safety margin). From rabbit TRiAD data and assuming a maximal therapeutic free plasma concentration of 19 nM, Hondeghem has estimated the safety margin for domperidone to be between ~2.5 and 5.25 [38,46]. Irrespective of whether hERG or TRiAD data are considered, it seems clear that the estimated safety margin for domperidone is much less than the 30-fold minimum for new drugs suggested by Redfern [47]. It should be noted that the approach suggested by Redfern et al was taken with a focus on the future assessment of drugs in development rather than for retrospective application to drugs that are presently clinically available. With that caveat, it is nevertheless notable that with the exception of verapamil (the Ca-channel blocking activities of which counter its hERG blocking potential), Redfern et al found a clear separation between hERG/I\textsubscript{Kr} activity and effective therapeutic unbound values for drugs for which there were no reports of TdP in humans [47].

In the following sections we consider the risk/benefit profile of domperidone in the conditions it is presently used.
6.2 Gastroparesis

Domperidone is efficacious in gastroparesis (discussed in section 2.2). Large case-controlled studies have shown an increased risk of ventricular arrhythmia and sudden cardiac death in older subjects mainly with cardiovascular disease taking domperidone [55,56,57]. In the Netherlands study, the percentage of subjects with sudden deaths was 0.21% in the control group and 0.76% in the domperidone group, which shows that the increase in sudden deaths with domperidone is less than 1% of a population where many subjects have cardiovascular disease [56]. In these large case-control studies, only small percentages of subjects had diabetic gastropathy or autonomic neuropathy, and thus it is unlikely that many were taking domperidone for gastroparesis [55,56]. Thus, further studies of the safety of domperidone in gastroparesis need to be undertaken.

6.3 Gastroesophageal reflux in children

Prokinetics such as cisapride and metoclopramide have been shown to be effective in gastroesophageal reflux in children but cisapride had been withdrawn because of its ability to cause TdP, and metoclopramide is not recommended for use as it causes a high incidence of adverse effects [59]. As domperidone is not available for use in the US, there are presently no drugs recommended as prokinetics in gastroesophageal reflux there, despite the usefulness of this mechanism [59]. Domperidone has been trialled for use in gastroesophageal reflux in children, but there were only small number of participants in the clinical trials, and the efficacy and risk of TdP in this group is uncertain (discussed in section 2.2). For any use in children, domperidone is not recommended in Australia, and is to be used with caution in the UK. Without a major trial assessing the risk/benefit of domperidone in children with gastroesophageal reflux, and more safety information, there is not enough evidence to support its use in this condition.

6.4 Galactogogue

Breastfeeding is recommended for almost all infants, as there are benefits including improved cognitive development, reduced incidence of infection, and less risk of sudden infant death syndrome [60]. A recent Canadian advisory on the use of domperidone to increase lactation points out that the studies linking the use of domperidone with cardiac adverse effects have been in older populations [56,57], and not in healthy women of childbearing age [60]. The advisory suggests that domperidone can still be used in healthy breast-feeding women, but should be used in caution with other drugs that prolong the QT interval or those that interfere with domperidone metabolism, or for women who have underlying cardiac diseases [60]. Domperidone does transfer into breast milk, but at very low levels [18]. However, there is no for safety information for domperidone in these infants,
and this needs to be obtained. A longer term solution would be the development of an alternative galactogogue that did not prolong the QT interval of the mother or child.

6.5 CYP3A4 inhibitors

Domperidone is metabolised by CYP3A4 [20,21]. In Australia, the use of domperidone is contraindicated for use with drugs that inhibit CYP3A4 and prolong the QT interval in their own right e.g. ketoconazole, fluconazole, erythromycin, clarithromycin. This contraindication should apply regardless of what domperidone is being used for. The maximum levels of domperidone are increased 3 fold by ketoconazole [16]. Thus, domperidone should also probably be contraindicated for use with drugs that inhibit CYP3A4, regardless of whether the inhibitor prolongs the QT interval in its own right.

6.6 Conclusions

The population-based analyses described in section 5 are suggestive of a significant association between domperidone and ventricular arrhythmia/sudden death. The risk may be greatest in patients with other risk factors or comorbidities, but has been found to persist following adjustment for covariates [57]. The data from preclinical studies are unambiguous in identifying domperidone as able to produce marked hERG channel inhibition and action potential prolongation at clinically relevant concentrations. The compound’s propensity to augment instability of action potential duration and action potential triangulation are also indicative of proarrhythmic potential. Considered collectively, the available data support a conclusion of a relatively low cardiac safety margin for the drug. Domperidone levels are higher if its metabolism by CYP3A4 is impaired [16,61]. Some authors [38,62] consider the risks with domperidone to be unacceptable for its continued clinical use. Without doubt, for a drug that is not administered to treat life-threatening illness, it is prudent to err on the side of caution. Domperidone should not be administered to subjects with pre-existing QT prolongation/LQTS, or to subjects receiving drugs that inhibit CYP3A4. Neither should it be given to subjects with electrolyte abnormalities or with other risk factors for QT prolongation. With these provisos, it may be possible to use domperidone as a galactogogue in healthy breast feeding women (and without a history of LQTS in other family members), but more safety information should be sought in this situation, and is also required before domperidone is routinely used in gastroparesis or gastroesophageal reflux in children. Given the low safety margin for domperidone indicated by preclinical studies, the administration of high dose domperidone should be avoided.
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*Study showing that the levels of domperidone are increased by inhibiting CYP3A4


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