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

Sheila A Doggrell[+1] PhD DSc and Jules C Hancox[2] PhD, FSB FBPharmcolS

[+] Author for correspondence

1. Senior Lecturer in Pharmacology, School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD4002, Australia

Tel +61 7 3138 2015 Fax +61 7 3138 1534

E-mail sheila.doggrell@qut.edu.au

2. Professor of Cardiac Electrophysiology, School of Physiology and Pharmacology, University of Bristol, Bristol, UK

Running title: Cardiac safety concerns for domperidone

1. **Introduction**
2. **Non-cardiac pharmacology**
3. **Pre-clinical cardiac electrophysiology**
4. **Human electrophysiology**
5. **Ventricular arrhythmia and sudden cardiac death**
6. **Expert opinion**

Abstract

Introduction: Domperidone is a dopamine D_2-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 gastroesphageal 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 D_2 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-1*H*-benzimidazol-1-yl)propyl]4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-on [13]. Domperidone is a dopamine D_2-receptor antagonist that acts on the D_2-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 D_2 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-oesphageal 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].

Gastroesphageal reflux is very common in childhood. A 2005 systematic review of the randomised controlled trials of domperidone in childhood gastroesphageal 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 gastroesphageal reflux remains uncertain.

2.3 Galactogogue

By antagonising dopamine D_2 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: $MAPD_{90}$) 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 $MAPD_{90}$-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 $MAPD_{90}$-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 $MAPD_{90}$ 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), $MAPD_{90}$ 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_{Ks} 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 after-depolarizations 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 QT_c 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 QT_c interval in 45 infants (0-1 yr) treated for gastro-oesophageal reflux, comparing baseline QT_c 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 QT_c 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) QT_c interval prolongation, with QT_c 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 points, 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_{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_{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_{50} thus ranges between ~3.3-3.9 with a hERG IC_{50} of 162 nM (or 1.20-1.4 if a hERG IC_{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_{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 Gastroesphageal reflux in children

Prokinetics such as cisapride and metoclopramide have been shown to be effective in gastroesphageal 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 gastroesphageal reflux there, despite the usefulness of this mechanism [59]. Domperidone has been trialled for use in gastroesphageal 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 gastroesphageal 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 gastroesphageal reflux in children. Given the low safety margin for domperidone indicated by preclinical studies, the administration of high dose domperidone should be avoided.

References

1. Barone JA. Domperidone: a peripherally acting dopamine2-receptor antagonist. Ann Pharmacother 1999, 33:429-40.

2. FDA Talk Paper: FDA warns against women using unapproved drug, domperidone, to increase mild production. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm (Accessed 13/6/2013).

***FDA issues warning against the use of domperidone in breastfeeding women**

3. FDA Safety Alert: for Human Medical Products: Domperidone http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154914.htm (Accessed 13/6/2013).

4. European Medicines Agency: Review of domperidone started. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/Procedure_started/WC500139769.pdf (Accessed 13/6/2013).

5. Joss RA, Goldhirsch A, Brunner KW, Galeazzi RL. Sudden death in cancer patient on high-dose domperidone. Lancet 1982;1:1019.

6. Roussak JR, Carey P, Parry H. Cardiac arrest after treatment with intravenous domperidone. BMJ 1984;289:1579.

7. Giaccone G, Bertetto O, Calciati A. Two sudden deaths during prophylactic antiemetic treatment with high doses of domperidone and methylprednisolone. Lancet 1984;2:1336-7

8. Osborne RJ, Slevin ML, Hunter RW, et al. Cardiotoxicity of intravenous domperidone. Lancet 1985;2:385 Letter

9. Osborne RJ, Slevin ML, Hunter RW, Hamer J. Cardiac arrhythmias during cytotoxic chemotherapy: role of domperidone. Hum Toxicol 1985;4:617-26.

10. Quinn N, Parkes D, Jackson G, et al. Cardiotoxicity of domperidone. Lancet 1985;2:724 Letter.

11. Cameron HA, Reyntjiens AJ, Lake-Bakaar G et al. Cardiac arrest after treatment with intravenous domperidone. BMJ 1985;290:160 Letter

12. Bruera E, Villamayor R. Roca E et al. QT interval prolongation and ventricular fibrillation with i.v. domperidone. Cancer Treat Rep 1986;70:545-6.

13. Meuldermans W, Hurkmands R, Swysen E et al. On the pharmacokinetics of domperidone in animals and man III. Comparative study on the excretion and metabolism of domperidone in rats, dogs and man. Eur J Drug Metab Pharmackinetic 1981;6:49-60.

14. Reddymasu SC, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gastroenterology. Am J Gastroenterol 2007;102:2036-45.

***Review of the clinical trials of domperidone showing that domperidone is effective in the treatment of dyspepsia and postoperative nausea and vomiting, and the nausea and vomiting associated with use of dopamine receptor agonists in Parkinson's disease**

15. Huang YC, Colaizzi JL, Bierman RH, Wostenborghs R, Heykants JK. Pharmacokinetics and dose proportionality of domperidone in healthy volunteers. J Clin Pharmacol 1988;26:628-32.

16. Boyce MJ, Baisley KJ, Warrington SJ. Pharmacokinetic interaction between domperidone and ketoconazole leads to QT prolongation in healthy volunteers: a randomized, placebo-controlled, double-blind, crossover study. Br J Clin Pharmacol 2012;73:411-21.

***Study showing that ketoconazole, an inhibitor of CYP3A4, increases the plasma levels of domperidone**

17. Heykants J, Hendriks R, Meuldermans M et al. On the pharmacokinetics of domperidone in animals and man IV. The pharmacokinetics of intravenous domperidone and its bioavailablity in man following intramuscular, oral and rectal administration. Eur J Drug Metab Pharmackinetic 1981;6:61-70.

18. Wan EW, Davey K, Page-Sharp M et al. Dose-effect study of domperidone as a galactogogue in preterm mothers with insufficient milk supply, and its transfer into milk. Br J Clin Pharmacol 2008;66:283-9.

19. Ward BA, Morocho A, Kandil A et al. Characterization of human cytochrome P450 enzymes catalysing domperidone N-dealkylation and hydroxylation in vitro. Br J Clin Pharmacol 2004;58:277-87.

20. Michaud V, Turgeon J. Assessment of competitive and mechanism-based inhibitor by clarithromycin: use of domperidone as a CYP3A probe-drug substrate and various enzymatic sources including a new cell-based assay with freshly isolated human hepatocytes. Drug Metab Lett 2010;4:69-76.

21. Michaud V, Simard C, Turgeon J. Characterization of CYP3A isozymes involved in the metabolism of domperidone: role of cytochrome b(5) and inhibition by ketoconazole. Drug Metab Lett 2010;4:95-103.

***Study showing that the levels of domperidone are increased by inhibiting CYP3A4**

22. Davis RH, Clench MH, Mathias JR. Effects of domperidone in patients with chronic unexplained upper gastrointestinal symptoms: a double-blind, placebo-controlled study. Dig Dis Sc1 1988;33:1505-11.

23. Roy P, Patel NH, Miller AJ. A comparison of controlled release metoclopramide and domperidone in the treatment of nausea and vomiting. Br J Clin Pract 1991;45:247-51.

24. Silvers D, Kipnes M, Broadstone V et al. Domperidone in the management of symptoms of diabetic gastroparesis: efficacy, tolerability, and quality-of-life outcomes in a multicentre controlled trial. DOM-USA-5 Study Group. Clin Ther 1998;20:438-53

25. Patterson D, Abell T, Rothstein R, Koch F, Barnett J. A double-blind multicentre comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol 1999;94:1230-4.

26. Ahmad N, Keith-Ferris J, Gooden E, Abell T. Making a case for domperidone in the treatment of gastrointestinal motility disorders. Curr Opin Pharmacol 2006;6:571-6.

27. Suqumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. Clin Gastroenterol Hepatol 2008;6:726-33.

28. Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesphageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. Br J Clin Pharmacol 2005;59:725-9.

29. Hegar B, Alatas S, Advanti N, Firmansyah A, Vandenplas Y. Domperidone versus cisapride in the treatment of infant regurgitation and increased acid gastro-oesphageal reflux: a pilot study. Acta Paediatr 2009;98:750-5.

30. Petraglia F, de Leo V, Sardelli S et al. Domperidone in defective and insufficient lactation. Eur J Obstet Gynecol Reprod Biol 1985;19:281-7.

31. Da Silva OP, Knoppert DC, Angelini MM, Forret PA. Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial. CMAJ 2001;164:17-21.

32. Jantarasaengaram S, Sreewapa S. Effect of domperidone on augmentation of lactation following cesarean delivery at full term. Int J Gynaecol Obstet 2012;116:240-3.

33. Zuppa AA, Sindico P, Orchi C et al. Safety and efficacy of galactogogues: substances that maintain and increase breast milk production. J Pharm Pharm Sci 2010;13:162-74.

34. Osadchy A, Moretti ME, Koren G. Effect of domperidone on insufficient lactation in puerperal women: a systematic review and meta-analysis of randomized controlled trials. Obstet Gynecol Int 2012;doi:10.1155/2012/642893.

35. Ingram J, Taylor H, Churchill C, Pike A, Greenwood R. Metoclopramide or domperidone for increasing maternal breast milk output: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2012;97:F241-5.

36. Drolet B, Rousseau G, Daleau P, Cardinal R, Turgeon J. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. Circulation 2000;102(16):1883-5.

*__Initial study showing that domperidone prolonged the action potential duration in guinea-pig hearts and inhibited hERG current in Chinese Hamster Ovary cells__

37. Hreiche R, Morissette P, Zakrzewski-Jakubiak H, Turgeon J. Gender-related differences in drug-induced prolongation of cardiac repolarization in prepubertal guinea pigs. J Cardiovasc Pharmacol Ther 2009 March;14(1):28-37.

38. Hondeghem LM. Domperidone: limited benefits with significant risk for sudden cardiac death. J Cardiovasc Pharmacol 2013 March;61(3):218-25.

*Contains a __recent discussion of the low cardiac safety index/safety margin for domperidone.__

39. Claassen S, Zunkler BJ. Comparison of the effects of metoclopramide and domperidone on HERG channels. Pharmacology 2005 April;74(1):31-6.

*__A comparison of potency of domperidone with metoclopramide as a hERG blocker.__

40. Stork D, Timin EN, Berjukow S et al. State dependent dissociation of HERG channel inhibitors. Br J Pharmacol 2007;151:1368-76.

41. Hreiche R, Plante I, Drolet B, Morissette P, Turgeon J. Lengthening of cardiac repolarization in isolated guinea pigs hearts by sequential or concomitant administration of two IKr blockers. J Pharm Sci 2011 June;100(6):2469-81.

42. Hancox JC, McPate MJ, El Harchi A, Zhang YH. The hERG potassium channel and hERG screening for drug-induced torsades de pointes. Pharmacology and Therapeutics 2008;119:118-32.

43. Gintant GA. Preclinical Torsades-de-Pointes screens: advantages and limitations of surrogate and direct approaches in evaluating proarrhythmic risk. Pharmacol Ther 2008 August;119(2):199-209.

44. Vargas HM. A new preclinical biomarker for risk of Torsades de Pointes: drug-induced reduction of the cardiac electromechanical window. Br J Pharmacol 2010 December;161(7):1441-3.

45. Guns PJ, Johnson DM, Weltens E, Lissens J. Negative electro-mechanical windows are required for drug-induced Torsades de Pointes in the anesthetized guinea pig. J Pharmacol Toxicol Methods 2012 September;66(2):125-34.

***Domperidone induces a negative electromechanical window and torsade des points in guinea-pigs**

46. Hondeghem LM. Low safety index of domperidone: mechanism for increased odds ratio for sudden cardiac death. Acta Cardiol 2011 August;66(4):421-5.

47. Redfern WS, Carlsson L, Davis AS et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovas Res 2003;58:32-45.

48. Rocha CMG, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in an infant. Pediatr Cardiol 2005;26:720-3.

49. Djeddi D, Kongolo G, Lafaix C, Mounard J, Léké A. Effect of domperidone on QT interval in neonates. J Pediatr 2008;153:663-6.

50. Günlemez A, Babaoğlu A, Arisoy AE, Türker A, Gökalp AS. Effect of domperidone on the QTc interval in premature infants. J Perinatol 2010;30:50-3.

51. Viera MC, Miyague NI, Van Steen K, Salvatore S, Vandenplas Y. Effects of domperidone on QTc intervals. Acta Paediatr 2012;101:494-6.

52. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf Accessed 29th July, 2013.

53. Djelouah I, Scott C. Domperidone: heart rate and rhythm disorders. Canadian Adverse Reaction Newsletter 2007;17(1)2 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v17n1-eng.pdf (Accessed 17th June, 2013)

54. Digby G, MacHaalany J, Malik P et al. Multifactorial QT interval prolongation. Cardiol J 2010;17:184-8

55. Straus SM, Sturkenboom MC, Bleumink GS et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. Eur Heart J 2005;26:2007-12.

***Case-control study showing domperidone increased risk on sudden cardiac death in older subjects; many of whom had cardiovascular disease**

56. van Noord C, Dieleman JP, van Herpen G, Verhamme K, Stukenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-base case-control study in the Netherlands. Drug Saf 2010;33:1003-14.

57. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacepidemiol Drug Saf 2010;19:881-8.

58. De Bruin ML, Langendijk PN, Koopmans RP. In-hospital cardiac arrest is associated with non-antiarrhythmic QTc-prolonging drugs. Br J Clin Pharmacol 2007;63:216-23.

59. Lightdale JR, Gremse DA. Gastroesphageal reflux: management guidance for the pediatrician. Pediatrics 2013;131:e1684-95.

60. Bozzo P, Koren G, Ito S. Health Canada advisory on domperidone – Should I avoid prescribing domperidone to women to increase milk production? Can Fam Physician 2012;58:952-3.

61. Michaud V, Turgeon J. Domperidone and sudden cardiac death: how much longer should we wait? J Cardiovasc Pharmacol 2013;3:215-7.

62. Domperidone: ventricular arrhythmia and sudden death (continued). Prescrire Int 2012;21:183.