DISCLOSURE

This position statement from the Saudi Gastroenterology Association (SGA) is issued in response to the increasing concerns expressed by the Saudi gastroenterology community as well as the public regarding the widespread prescription of the drug Domperidone despite recent reports of an associated risk with cardiac arrhythmias, cardiac arrest, and sudden cardiac death.

In this brief report, we summarize the relevant literature surrounding this association and provide clinical advice to the Saudi community directly related to the use of this drug.

BACKGROUND

Domperidone (Motilium, Janssen Pharmaceutica, Beerse, Belgium) is a dopamine (D2) receptor antagonist that acts centrally and peripherally. Domperidone has been prescribed orally, rectally, and parenterally “off-label” to children and adults. It has been used as an antiemetic, prokinetic, and secretory galactogogue agent for several decades. More recently, its use has been limited to its oral formulation, due to toxicity associated with intravenous administration. Its typical dose ranges from 10 mg twice a day to 20 mg four times a day. The introduction of Domperidone into the market was mainly directed toward replacing a now discontinued prokinetic agent called Propulsid (Cisapride) that was proven to cause QT interval prolongation and fatal torsade des points and as a result was withdrawn from the US market in 2000.

SAFETY CONCERNS

The proarhythmic properties of Domperidone have been previously demonstrated in animal studies. Subsequently, many case reports emerged linking Domperidone with cardiac arrhythmias. Subsequently, data accumulated from several countries and health agencies suggest that Domperidone is associated with significant cardiac morbidity and early mortality. Health Canada and the FDA have independently issued warnings to this effect and as a result the drug has been completely removed from the US market but continues to be prescribed with caution in some countries such as Canada, India, Australia, and Belgium, over the counter in the United Kingdom and “in-pharmacy” only in several other countries such as Saudi Arabia, Egypt, Italy, Netherlands, and Switzerland. This prompted the European medicine Agency to initiate an ongoing review of Domperidone in 2013. More recently, in July 2014, the Saudi Food and Drug Authority (SFDA) has circulated a memo as well as posted it on their website to notify health care providers about potential serious side effects as well as restrictions to its use. Additionally, Domperidone has been used, as a prokinetic agent, to treat gastroesophageal reflux disease (GERD), dyspepsia, and gastroparesis and several studies have confirmed its efficacy in these clinical contexts. Domperidone has also been found to be as equally effective as metoclopramide, another prokinetic agent, but with less reported side effects. It is noteworthy to mention, however, that Metoclopramide unlike Domperidone can cross the human blood–brain barrier causing extrapyramidal adverse effects. As a galactagogues agent that can induce and augment lactation, Domperidone has been prescribed to postpartum females with contradictory results. A recent meta-analysis reported a relative increase in breast milk production of 74.72% (95% CI = 54.57–94.86, $P < 0.01$) with Domperidone when compared to placebo with no reported infant or maternal adverse events. In the pediatric literature, Domperidone has been extensively studied as a treatment option for infancy- and childhood-related GERD. A recent meta-analysis suggested that the quality of studies in this area is weak and that the evidence behind this practice remains doubtful. As a result, Domperidone is no longer used for this indication in many countries, including the United States.

SAFETY CONCERNS

The proarhythmic properties of Domperidone have been previously demonstrated in animal studies. Subsequently, many case reports emerged linking Domperidone with cardiac arrhythmias. Subsequently, data accumulated from several countries and health agencies suggest that Domperidone is associated with significant cardiac morbidity and early mortality. Health Canada and the FDA have independently issued warnings to this effect and as a result the drug has been completely removed from the US market but continues to be prescribed with caution in some countries such as Canada, India, Australia, and Belgium, over the counter in the United Kingdom and “in-pharmacy” only in several other countries such as Saudi Arabia, Egypt, Italy, Netherlands, and Switzerland. This prompted the European medicine Agency to initiate an ongoing review of Domperidone in 2013. More recently, in July 2014, the Saudi Food and Drug Authority (SFDA) has circulated a memo as well as posted it on their website to notify health care providers about potential serious side effects as well as restrictions to its use.
In a large population-based Dutch case–control study that examined the safety profile of Domperidone among other drugs, results showed an increased risk of sudden cardiac death with Domperidone that appeared to be dose dependent.\[^{33}\] Furthermore, results from a large Canadian nested case–control study reported an increased risk of ventricular arrhythmias or sudden cardiac death with Domperidone compared with matched controls (OR 1.59, 95% CI 1.28-1.98). The study population was predominantly composed of elderly diabetics (mean age = 79.4 years) with a large proportion of patients having previously established cardiac disease.\[^{34}\] This remains to be the main argument made by some clinicians debating that women in their childbearing age, unless proven to have baseline QT interval prolongation, might benefit from the galactogogue effect of Domperidone without much concern. Its use in children is however still coupled with much concern such that it has been recommended by the FDA not to be prescribed to children for the treatment of GERD until more evidence is gathered that favors its safety and efficacy despite the absence of any other drug in this class that can be used as a substitute. Some reports suggest that the enzymatic activity of the metabolic pathway Domperidone undergoes (CYP3A4) is directly related to its cardiac toxicity.\[^{35,36}\] This is of particular importance in countries such as Saudi Arabia where antibiotics and antifungal medications, commonly known to interfere with CYP3A4 activity, are prescribed over the counter. It is therefore recommended that drugs that inhibit this pathway not be prescribed simultaneously with Domperidone and that the presence of any potential cause of QT prolongation should preclude the use of Domperidone indefinitely.

The recommended dosages for Domperidone, if it were to be used, can be found in the referenced circulation from the SFDA.

**CONCLUSIONS**

Domperidone use as a prokinetic, antiemetic, and galactogogue agent is associated with an increased risk of ventricular arrhythmias, cardiac arrest, and sudden cardiac death, which is more pronounced in elderly patients with known cardiac risk factors and in individuals with prolonged QT interval.

**RECOMMENDATIONS**

- Physicians prescribing Domperidone are obliged to discuss the worldwide concerns of Domperidone-associated cardiac side effects with their patients during counseling
- Domperidone should be avoided in elderly patients and in patients with established cardiac disease or multiple cardiac risk factors
- The SGA does not endorse prescribing Domperidone “in-pharmacy” and recommends its use be regulated by physician prescription
- High doses of Domperidone should be avoided
- Until more evidence is available to support the safety and efficacy of Domperidone as an antiemetic agent for the treatment of infancy- and childhood-related GERD, it should be only prescribed with extreme caution
- Domperidone prescription to lactating mothers to augment breastfeeding is not recommended given the current totality of evidence
- Domperidone prescribers should pay attention to drug–drug interactions and avoid prescribing CYP3A4 inhibitors concomitantly with Domperidone
- Any cases of cardiac arrhythmias, cardiac arrest, or sudden cardiac death suspected of being related to Domperidone therapy should be reported to the ministry of health for surveillance purposes.

Mahmoud H. Mosli\(^1,2\), Bandar AlJudaibi\(^2,3\), Majid Al-Madi\(^3,4\)

\(^1\)Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, \(^2\)Department of Medicine, University of Western Ontario, London, Ontario, Canada, \(^3\)Department of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia, \(^4\)Division of Gastroenterology, The McGill University Health Center, Montreal General Hospital, McGill University, Montreal, Canada

E-mail: mahmoud.mosli@robartsinc.com

**REFERENCES**

1. Helmers JH. Preliminary report of domperidone (R 33182), a new antiemetic compound. A pilot study. Acta Anaesthesiol Belg 1977;28:245-50.
2. Osborne RJ, Slevin ML, Hunter RW, Hamer J. Cardiotoxicity of intravenous domperidone. Lancet 1985;2:385.
3. Cameron HA, Reytjens AJ, Lake-Bakaar G. Cardiac arrest after treatment with intravenous domperidone. Br Med J 1985;290:160.
4. Reddymasu SC, Soykan I, McCallum RW. Domperidone: Review of pharmacology and clinical applications in gastroenterology. Am J Gastroenterol 2007;102:2036-45.
5. Pharmaceutica J. Propulsid (Cisapride) market discontinuation. Available from: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab4d.htm, 2000. [Last accessed on 2014 Aug 03].
6. Agorastos I, Zisis NP, Kaprinis I, Goulis G. Double-blind evaluation of domperidone in acute vomiting and dyspeptic disorders. J Int Med Res 1981;9:143-7.
7. Boghaert A, Carron D, Gallant J, Stockman A. Postoperative vomiting treated with domperidone. A double-blind comparison with metoclopramide and a placebo. Acta Anaesthesiol Belg 1980;31:129-37.
8. Cooke RD, Comyn DJ, Ball RW. Prevention of postoperative nausea and vomiting by domperidone: A double-blind randomized study using domperidone, metoclopramide and a placebo. S Afr Med J 1979;56:827-9.
9. DeCamp LK, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: A systematic review and meta-analysis. Arch Pediatr Adolesc Med 2008;162:858-65.
Domperidone in the management of symptoms and postoperative vomiting:

1. Grimes JD, Magnier PO. Safety of domperidone in metoclopramide-induced parkinsonism. Arch Neurol 1984;41:363-4.

2. Zegveld C, Knappe H, Smits J, Belopavlovic M, Caron D, Gallant J, et al. Domperidone in the treatment of postoperative vomiting: A double-blind multicenter study. Anesth Analg 1978;57:700-3.

3. Bekhti A, Rutgeerts L. Domperidone in the treatment of functional dyspepsia in patients with delayed gastric emptying. Postgrad Med J 1979;55 Suppl 1:30-2.

4. De Loore I, Van Ravensteyn H, Ameryckx L. Domperidone drops for the in the symptomatic treatment of chronic paediatric vomiting and regurgitation. A comparison with metoclopramide. Postgrad Med J 1979;55 Suppl 1:40-2.

5. Heer M, Muller-Duysing W, Benes I, Weitzel M, Pirovino M, Altorfer J, et al. Diabetic gastroparesis: Treatment with domperidone—a double-blind, placebo-controlled trial. Digestion 1983;27:214-7.

6. Hiyama T, Yoshihara M, Matsuo K, Kusunoki H, Kamada T, Ito M, et al. Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia. J Gastroenterol Hepatol 2007;22:304-10.

7. Silvers D, Kipnes M, Broadstone V, Patterson D, Quigley EM, McCallum R, et al. Domperidone in the management of symptoms of diabetic gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. DOM-USA-5 Study Group. Clin Ther 1998;20:438-53.

8. Soykan I, Sarosiek I, McCallum RW. The effect of chronic oral domperidone therapy on gastrointestinal symptoms, gastric emptying, and quality of life in patients with gastroparesis. Am J Gastroenterol 1997;92:976-80.

9. Sugumar 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.

10. Van de Mierop L, Rutgeerts L, Van den Langenbergh B, Staessen A. Oral domperidone in chronic postprandial dyspepsia. A double-blind placebo-controlled evaluation. Digestion 1979;19:244-50.

11. Van Outryve M, Lauwers W, Verbeke S. Domperidone for the symptomatic treatment of chronic post-prandial nausea and vomiting. Postgrad Med J 1979;55 Suppl 1:33-5.

12. Hondeghem LM. Domperidone: Limited benefits with significant risk for sudden cardiac death. J Cardiovasc Pharmacol 2013;61:218-25.

13. 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;2012:642893.

14. Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesophageal 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.

15. Hondeghem LM. Low safety index of domperidone: Mechanism for increased odds ratio for sudden cardiac death. Acta Cardiol 2011;66:421-5.

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

17. 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.

18. Digby G, M hakkında J, Malip P, Methot M, Simpson CS, Redfearn D, et al. Multifactorial QT interval prolongation. Cardiol J 2010;17:184-8.

19. (FDA) USFDA. FDA Talk Paper: FDA Warns Against Women Using Unapproved Drug, Domperidone, to increase milk production available from: http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm173886.htm, 2004. [Last accessed on 2014 Aug 03]

20. Canada H. Domperidone maleate—association with serious abnormal heart rhythms and sudden death (cardiac arrest)—for the public. Available from: http://www.hc-sc.gc.ca/dhp-mpx/medeff/advisories-avis/ index-eng.php, 2012. [Last accessed on 2014 Aug 03]

21. Agency EM. Review of domperidone started. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/Procedure_started/WCS00139769.pdf, 2013. [Last accessed on 2014 Aug 03]

22. (SFDA) SFaDA. Restrictions on the use of domperidone. Available from: http://www.sfda.gov.sa:80/ar/drug/circulations/DocLib/35586.pdf, 2014. [Last accessed on 2014 Aug 03]

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

24. 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. Pharmacoepidemiol Drug Saf 2010;19:881-8.

25. 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.

26. Yoshizato T, Kotejawa T, Imai H, Tsutsui K, Imanaga J, Ohyama T, et al. Itraconazole and domperidone: A placebo-controlled drug interaction study. Eur J Clin Pharmacol 2012;68:1287-94.