Saudi Gastroenterology Association Position Statement on Safety Issues Associated with the Use of Domperidone

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 wide spread 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.[1] More recently, its use has been limited to its oral formulation, due to toxicity associated with intravenous administration.[2,3] Its typical dose ranges from 10 mg twice a day to 20 mg four times a day.[4] 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(Cisapride) that was proven to cause QT interval prolongation and fatal torsade des points and as a result was withdrawn from the US market in 2000.[5]

DRUG EFFICACY

Several studies reported that Domperidone was superior to placebo when used as an antiemetic agent to treat acute conditions such as gastroenteritis, postoperative emesis, and drug-induced nausea and vomiting, mainly with antiparkinsonism dopamine agonists.[6-12] 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.[13-21] Domperidone has also been found to be as equally effective as metoclopramide, another prokinetic agent, but with less reported side effects.[22] It is noteworthy to mention, however, that Metoclopramide unlike Domperidone can cross the human blood–brain barrier causing extrapyramidal adverse effects. As a galactogogue 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.[23] In the pediatric literature, Domperidone has been extensively studied as a treatment option for infancy- and childhood-related GERD.[14] A recent meta-analysis suggested that the quality of studies in this area is weak and that the evidence behind this practice remains doubtful.[24] As a result, Domperidone is no longer used for this indication in many countries, including the United States.

SAFETY CONCERNS

The proarrhythmic properties of Domperidone have been previously demonstrated in animal studies.[25] Subsequently, many case reports emerged linking Domperidone with cardiac arrhythmias.[26-28] 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 in[29,30] 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.[31] 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.[32]

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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 woman 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.

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