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## Domperidone ? keeping abreast of the controversies

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### Domperidone - keeping abreast of the controversies

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The drug information service at DPIC regularly receives questions about the role of domperidone in enhancing the production of breast milk in lactating women. Recently, calls to DPIC are being prompted by drug interaction alerts, when domperidone is to be given concurrently with an agent that has the potential to prolong the QT interval. The amount of information available regarding both of these issues is limited because domperidone is not available in the USA.

Following the withdrawal of cisapride from the market, domperidone has been utilized with increasing frequency for the symptomatic treatment of upper gastrointestinal tract motility disorders such as nonulcer dyspepsia and diabetic gastroparesis.<sup>1</sup> It is also used to control nausea and vomiting caused by the administration of antineoplastic agents, dopamine agonists in the treatment of Parkinson's disease<sup>1</sup>, and that associated with migraine headaches.<sup>2,3</sup> Limited data suggest a possible role of this agent to produce an acceleration of gastric emptying in the treatment of anorexia nervosa.<sup>4,5</sup> Domperidone acts as a peripheral dopamine antagonist and it is thought to increase breast milk production by stimulation of the secretion of prolactin.<sup>6,7</sup>

## Domperidone and lactation:

The adequate production of breast milk is governed by the concept of supply and demand. Lactation insufficiency occurs only rarely. Nursing mothers experiencing lactation insufficiency should be assessed for improper latching on of the baby, positioning, or suckling technique, nursing sessions which are too infrequent, or the use of pacifiers and/or bottles.<sup>7</sup> Expression of breast milk following nursing sessions to increase supply, use of breast compression to increase the intake of milk, and sessions with a lactation consultant are other strategies which should be employed prior to initiating pharmacologic therapy.<sup>8</sup> Although used therapeutically to induce lactation and increase the supply of breast milk, these are not approved indications for domperidone in Canada. Few studies, using limited numbers of subjects, have been conducted to evaluate the use of this agent for these indications.<sup>6,9</sup>

A double-blind, randomized, placebo-controlled trial, in mothers with premature infants and insufficient milk production, evaluated therapy with domperidone 10 mg three times daily for 7 days.<sup>6</sup> Compared with baseline values, the mean increase in breast milk volume production was 49.5 mL ( $\pm$  29.4 mL) in the women treated with domperidone (n=7) compared with 8.0 mL ( $\pm$  39.5 mL) in the placebo group (n=9), which represents percentage increases of 44.5% and 16.6%, respectively ( $p < 0.05$ ). At day 5, the mean concentration of domperidone was 6.6 ng/mL in serum and 1.2 ng/mL in breast milk (n=6). It was calculated that an infant would ingest less than 0.2 mcg/kg of domperidone daily, assuming a daily breast milk intake of 150 mL/kg.

A double-blind, randomized trial in mothers with lactation failure (treated n=8, placebo n=7) or inadequate lactation (treated n=9, placebo n=8) evaluated treatment with domperidone 10 mg three times daily compared to placebo.<sup>9</sup> Daily breast milk production, measured by weighing the infants before and after nursing, was significantly increased in the domperidone-treated subjects (by two to four times the baseline value). The infants of mothers with lactation failure treated with domperidone showed significantly higher weight gain compared to those treated with placebo.

No adverse effects were reported by the mothers, nor observed in the infants evaluated in these studies. It has been reported that an infant is exposed to less than 0.1% of a maternal dose of domperidone.<sup>7</sup> When used by a lactating mother, the theoretic infant dose is less than 0.2 mcg/kg/day.<sup>6,10</sup> The American Pediatric Association considers domperidone compatible with breastfeeding.<sup>11</sup> Motherisk advises that no adverse effects have been noted in infants when domperidone is used as an antiemetic in breastfeeding women.<sup>12</sup> In a standard reference on the use of medications during lactation, it is considered the "ideal galactagogue."<sup>10</sup>

The usual dose of domperidone for lactation augmentation is 10 to 20 mg three to four times daily<sup>7,10</sup> for two weeks, followed by tapering of the dose to the lowest effective dose.<sup>7</sup> Because dosage regimens have not been properly evaluated in clinical trials, suggested

regimens vary. To determine efficacy, a trial of four weeks, and up to six weeks of therapy is recommended by one source.<sup>8</sup>

On June 7, 2004, the United States Food and Drug Administration (FDA) published an advisory which warned against the use of domperidone to increase milk production because of "safety concerns."<sup>13</sup> The advisory stated that domperidone is not approved for use in any country for this indication and noted that 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". It further stated that because domperidone is excreted in breast milk, it "could expose a breastfeeding infant to unknown risks." However, it did not provide specific concerns or examples of possible serious adverse effects. Of note, domperidone has not been approved by the FDA for any indication and is not marketed in the United States. Patients were receiving domperidone from compounding pharmacies or from other countries. The FDA sent letters to compounding pharmacies and domperidone suppliers that distributing the drug violated the law. It also issued an import alert to refuse admission of the drug into the United States.

### **Domperidone and QT prolongation:**

*In vitro* studies in isolated guinea pig hearts<sup>14</sup> and human embryonic kidney cells<sup>15</sup> have revealed that domperidone, at clinically relevant levels, has cardiac electrophysiological effects similar to class III antiarrhythmic drugs and cisapride, and therefore is potentially torsadogenic. It is advised that concurrent use of two or more medications with the potential to cause QT prolongation be avoided, due to the additive risk of causing a potentially fatal ventricular arrhythmia.<sup>16</sup>

Four review articles list domperidone as a medication with the potential to cause QT prolongation and torsades de pointes.<sup>16-19</sup> Additionally, a frequently cited source for information on QT prolongation, the website of the University of Arizona Center for Education and Research on Therapeutics (AZCERT), lists domperidone on lists of drugs with (a) risk of torsades de pointes, defined as "drugs that are generally accepted by the Scientific Advisory Board of the AZCERT to *have a risk* of causing Torsades de Pointes" and (b) drugs to be *avoided by congenital long QT patients*, defined as "drugs to be avoided for use in patients with diagnosed or suspected congenital long QT syndrome."<sup>20</sup>

Following the administration of **intravenous** domperidone for prophylactic antiemetic therapy during cytotoxic chemotherapy, the following reports of cardiotoxicity exist:

- Two sudden deaths (2 mg/kg infusion).<sup>21</sup>
- One sudden death (200 mg bolus).<sup>22</sup>
- Four cases of cardiac arrest (20-50 mg infusion or bolus); all patients were hypokalemic.<sup>23</sup>
- Two cases of significant ventricular arrhythmias (20 mg slow bolus, followed by infusion of 10 mg/kg over 24 hours).<sup>24</sup>

- Six cases of QT interval prolongation which returned to normal within six hours, with no arrhythmias reported (60 mg infusion, in three patients over 5 minutes and in three patients over 15 minutes); in all six patients, there was no history of cardiovascular disease and baseline EKGs were normal.<sup>25</sup>
- One case of ventricular fibrillation and syncope, no detectable arterial BP, at least three episodes of prolonged QT interval, ventricular tachycardia and bradycardia with heart rate of 10-20 beats per minute with "torsade de point" morphology (60 mg rapid bolus over 30-45 seconds).<sup>25</sup> In this patient, a previous EKG showed a "mild" ventricular arrhythmia, but an EKG one week prior to treatment was normal. Following placement of a temporary pacemaker catheter in the right ventricle, rechallenge with 60 mg rapid bolus produced QT prolongation, episodes of ventricular tachycardia, and one short episode of ventricular fibrillation; repeat rechallenge with 60 mg infusion over 5 minutes produced QT prolongation, but no arrhythmia.
- Two cases of ventricular arrhythmias, one considered potentially life threatening (20 mg bolus over 15 minutes, followed by infusion of 10 mg/kg over 24 hours); both patients were hypokalemic.<sup>26</sup>

One case report of cardiotoxicity possibly caused by **oral** domperidone therapy exists.<sup>27</sup> A 3-month-old infant was treated with domperidone 0.6 mg/kg three times daily for severe esophageal reflux disease. Following 4 weeks of therapy, the parents reported occasional cyanosis. An EKG revealed asymmetric T waves of high voltage and PT prolongation. Domperidone was discontinued and an EKG at one month was normal.

In a study comparing domperidone 10 mg three times daily and itopride 50 mg three times daily for two weeks, for the treatment of non-ulcer dyspepsia (n=55), a pre-treatment and post-treatment EKG revealed no prolongation of the QT interval.<sup>28</sup>

### Summary:

Domperidone is used therapeutically for lactation augmentation, although it has not been approved for this indication by Health Canada. The use of this agent should only be considered after other alternatives for stimulation of lactation have been explored. The AZCERT inclusion of domperidone on a list of drugs with the potential to cause torsades de pointes, and four review articles which list domperidone as a medication with the potential to cause QT prolongation and torsades de pointes appears to be the result of reports of cardiotoxicity following rapid administration, or high doses, of intravenous domperidone. Only one case report of cardiotoxicity following oral therapy exists, which occurred in a 3-month-old infant. In the absence of other reports of cardiotoxicity related to oral therapy, the risk of development of QT prolongation and torsades de pointes with the administration of usual therapeutic doses of oral domperidone appears to be low.

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