Sudden Cardiac Death and Ventricular Arrhythmias Associated with Domperidone: Evidence Supporting Health Canada's Warning

On March 2, 2012, Health Canada issued a warning about the potential risk of sudden cardiac death and sudden ventricular arrhythmia associated with domperidone, particularly for patients older than 60 years of age and those taking more than 30 mg of domperidone per day.[1] Clinicians should consider the evidence supporting this warning when they are weighing the risks and benefits of domperidone therapy for their patients.

Domperidone, a peripheral dopamine antagonist, has been used since the late 1970s as an antiemetic and for symptomatic management of gastrointestinal dysmotility.[2,3] Its global regulatory status is highly variable, ranging from available without a prescription in many European countries to not approved for use in the United States. In most countries, such as Canada, a prescription is required. Domperidone, particularly the IV product that was removed from the Canadian market in the 1980s, is well recognized for its association with QTc prolongation, sudden cardiac death, and sudden ventricular arrhythmia.[4] For this reason, domperidone should be used with caution in patients with QTc prolongation, electrolyte abnormalities, or congestive heart failure.

The Health Canada warning was based on 2 observational studies published in 2010.[2,4] A Dutch case–control database study was the basis of the warning associating dose with sudden cardiac death.[2] That study evaluated the association between sudden cardiac death or sudden ventricular arrhythmia and domperidone use. A total of 1366 cases (62 involving sudden ventricular arrhythmia and 1304 sudden cardiac deaths) were matched to 14 114 controls by index date, sex, age, and type of practice. None of the patients who experienced sudden ventricular arrhythmia were using domperidone at the time of the event. The multivariable analysis controlled for QTc-prolonging drugs and medical conditions, smoking, alcohol use, CYP3A4 drug interactions, physician visits, and insurance type. Among the 1304 patients with sudden cardiac death, only 10 were using domperidone at the time of the event, which translates to a statistically nonsignificant increased risk of sudden cardiac death (odds ratio [OR] 1.99, 95% confidence interval [CI] 0.80–4.96). When these 10 patients were further stratified by daily dose (< 30 mg, 30 mg, and > 30 mg), the multivariable analysis showed an increased risk of sudden cardiac death for patients taking more than 30 mg per day (OR 11.4, 95% CI 1.99–65.2). The wide CI should raise some doubt as to the validity of this finding from a small subgroup. Furthermore, domperidone is available without a prescription in the Netherlands, which is potentially an important source of bias.

The second part of the Health Canada warning, associating age with a composite outcome of sudden cardiac death or sudden ventricular arrhythmia, was based on a nested case–control study involving a Canadian provincial database (mean age 79.4 years, 53% women, 22% with diabetes mellitus).[4] A total of 1608 cases of sudden cardiac death or sudden ventricular arrhythmia were identified. Each user of domperidone at the time of the event was matched with up to 4 non-users who were taking proton pump inhibitors (PPIs), to reduce confounding by indication. Controls were matched on the basis of index date, age, sex, and diabetes status. The study controlled for the following potential confounding factors: drugs and medical conditions known to prolong QTc interval, recent ventricular arrhythmias, health care utilization, and CYP3A4 drug interactions. Domperidone dose and QTc measurements were not captured. The adjusted multivariable analysis described an increased risk of the composite outcome in current domperidone users relative to users of neither drug (OR 1.59, 95% CI 1.28–1.98) and relative to PPI users (OR 1.44, 95% CI 1.12–1.86). A stratified analysis without adjustment for the aforementioned covariates concluded that patients older than 60 years of age had an increased risk of sudden cardiac death or sudden ventricular arrhythmia (OR 1.64, 95% CI 1.31–2.05), whereas the result for those 60 years of age or younger was nonsignificant (OR 1.10, 95% CI 0.35–3.47).

A systematic review published in 2008 assessed the efficacy of domperidone for diabetic gastroparesis.[5] The review included 28 trials of poor methodologic quality. The most commonly reported adverse effect was related to prolactin; no cardiac adverse events were reported. No primary studies addressing this question of safety have been published since 2008, other than the 2 aforementioned articles.[2,4]

Given that domperidone dose titration is based on symptomatic control, abiding by Health Canada's warning has created challenges for the treatment of diabetic gastroparesis. Alternative agents for this indication include erythromycin, cisapride, prochlorperazine, and ondansetron, each of which has its own cardiac risks.[6] Although the restrictions proposed by this warning may result in better screening and monitoring of risk factors

(particularly among elderly patients), they will also likely prevent some patients from receiving an effective dose of domperidone. Although the Health Canada warning represents an important aspect of postmarketing surveillance and ongoing patient safety, it is important that clinicians be aware of the evidence supporting such warnings if they are to make responsible decisions.

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Competing interests: Brian Hutton has received personal fees from Amgen Canada for teaching services and methodologic advice related to network meta-analysis (outside the scope of this submission). No other competing interests declared.