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EDITORIAL

Adverse Effects of Domperidone: Prolonged QuesT for Knowledge?

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Domperidone, a dopamine (D) receptor antagonist which blocks D2 receptors in the chemoreceptor trigger zone centrally and the enteric nervous system peripherally, is an anti-emetic and prokinetic medication predominantly used for treating symptomatic gastroparesis. An important recent concern regarding the safety of domperidone is whether it can prolong the QT interval, increasing the probability of developing ventricular arrhythmias with consequent cardiac death, based on publications addressing its possible cardiotoxicity [1–7]. Unlike metoclopramide, another D2 antagonist which has significant adverse effects particularly related to central nervous system and is approved by the Food and Drug Administration (FDA) as a prokinetic agent in the USA, domperidone cannot be marketed legally for clinical use in this country, but is nevertheless available through an investigational new drug (IND) application.

The decisions made by FDA regarding the safety of domperidone have wide implications for restrictions in the use of this medication in patients diagnosed with gastroparesis or suffering from nausea and vomiting of other origins. Therefore, it is important to clarify and understand the balance between the therapeutic efficacy and the reported adverse effects of domperidone.

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In the current issue of *Digestive Diseases and Sciences*, Schey et al. [8] have published an interesting article discussing the benefits and adverse effects of domperidone in gastroparesis. In their study, domperidone was prescribed at a dose of 10 mg QID or TID to 125 patients with refractory gastroparesis symptoms who were observed for symptomatic improvement and for adverse effects. Tachycardia and palpitations were observed in six and three patients, respectively, with one patient developing QT prolongation necessitating discontinuation of the medication. In total, 14 patients stopped taking the medication for different reasons. Observation of 101 patients for a mean of 2.4 months taking an average domperidone dose of 36 mg/day revealed some degree of symptomatic improvement in 69 patients, with 45 reporting at least moderate improvement.

The findings of Schey et al. [8] are in agreement with previous studies of domperidone in gastroparesis. Based on a systematic review, 64 % of the included studies reported symptomatic improvement, 60 % reported improved gastric emptying, and 67 % of the studies described a reduction of hospital admissions. No serious complications such as sudden cardiac death or serious cardiac events were described [9]. A list of previous published trials on domperidone in gastroparesis is shown in Table 1.

In the most recent publication on this topic by our research group, 64 patients received a twofold to threefold greater dose of domperidone (40–120 mg daily) than standard for 3 months to 4 years; indicated in 52 for gastroparesis and in eight for chronic nausea and vomiting. Seventy-three percent of the patients had a clinically meaningful response to domperidone with no reported serious adverse effects. Only three of the 64 patients chronically receiving domperidone at high doses reported palpitations but without any complaints of chest pain, and

Table 1 Trials on the effects of domperidone in gastroparesis

Study	Number of patients	Dose	Duration (number: duration)	Baseline cardiac evaluation	Cardiac adverse effects
Patterson [11]	48 (DG)	20 mg q.i.d.	4 W	NA	No
Farup [12]	269 (DG)	20 mg q.i.d.	269: 4 W 105: 8 W	NA	No
Silvers [13]	287 (DG)	20 mg q.i.d.	287: 4 W 105: 8 W	Yes	No
Soykan [14]	12 (IG), 3 (DG), 2 (PSG)	40–120 mg daily	17: 23.3 M (range 6–48 M)	Yes	No
Dumitrascu [15]	10 (DG), 5 (C)	10 mg t.i.d.	–	NA	No
Watts [16]	3 (DG), 15 (C)	10 mg q.i.d.	6 M	NA	No

C Control, *DG* diabetic gastroparesis, *IG* idiopathic gastroparesis, *PSG* postsurgical Gastroparesis, *NA* not assessed or reported, *M* month, *W* week

no documented QTc prolongation or cardiac dysrhythmias. In 37 of the studied patients who had a baseline and follow-up electrocardiogram (ECG), the mean QTc interval at baseline was 424 ms compared with 435 ms at study end, a nonsignificant difference, although ten of these 37 patients had a prolongation of their QT interval ranging from 453 to 509 ms. Among those, three were taking a maximum dose of 120 mg/day, five took 80 mg/day, and two took 30 mg/day, suggesting no correlation between the dose and the degree of QTc prolongation. All patients with a prolonged QT interval were asymptomatic without any documented arrhythmia. According to FDA protocol, whenever QT prolongation was identified electrocardiographically, the patients were asked to stop taking domperidone [10]. The clinically significant response to domperidone in our study (73 %) was much higher compared to Schey et al. [8] ($\sim$45 %), suggesting that a higher dose of domperidone is necessary to achieve a good symptomatic response in many of patients with gastroparesis.

The literature, mainly from Europe, indicates that domperidone is linked with sudden cardiac death or severe ventricular arrhythmias [3–5]. In order to determine the clinical value of this statistical finding, we carefully analyzed the data obtained from the source case–control studies that were the basis for the decision made by health agencies regarding the cardiotoxicity of domperidone. Although those studies claim that domperidone is a significant risk factor for sudden cardiac death, many of them have methodological weaknesses; specifically, they all are retrospective surveys based on community health and death records and on hospital registrations. Moreover, they did not sufficiently address the risk factors underlying the QT interval prolongation associated with the use of domperidone and did not closely monitor at-risk patients with serial ECGs. Furthermore, these studies potentially provide a biased effect size due to the low frequency of domperidone use among the studied cases. For instance, in van Noord et al.'s study [3], just ten subjects in the case group were taking domperidone when they died; this group was further subdivided based on dose. Therefore, the statistical validity of the performed multivariate analysis needs to be addressed. Moreover, some of these studies were performed in countries where domperidone was available without prescription, indicating that usage data could be inaccurate, an additional source for potential bias.

In De Bruin et al.'s article [5], the patients had much more severe underlying diseases compared to the controls, another possible source of bias. Another serious concern in De Bruin et al.'s study is that cisapride, which is well acknowledged to increase the risk of cardiac death, was not associated with cardiac arrest, raising doubts about the validity of these data.

The report of Schey and colleagues of Temple University [8] as well as our data [10] provides a more realistic account of the use of domperidone in gastroparesis. Due to the questionable quality of the original case–control studies addressing the cardiotoxicity of domperidone, caution is required prior to drawing any conclusions regarding cardiac concerns and domperidone. Further well-planned, prospective studies should be encouraged to investigate possible cardiac adverse effects of the drug. In the meantime, practitioners may thoughtfully continue to prescribe domperidone for appropriate gastroparesis patients who are refractory to or who are experiencing adverse events from other medications. Furthermore, we support the USA investigational new drug (IND) protocol recommendations for prescribing domperidone which are summarized thus: (1) baseline and on-treatment ECGs should be obtained in all patients to identify prolonged QT interval (QTc $>$ 450 ms in males and $>$470 ms in females); (2) domperidone should not

be administered with other medications which prolong the QT interval as well as with cytochrome P450 inhibitors which increase the circulating concentrations of domperidone in the blood; (3) patients who are receiving domperidone should be monitored for electrolyte abnormalities (e.g., hypokalemia and hypomagnesaemia), and (4) there needs to be heightened clinical awareness for possible cardiac-related symptoms and outcomes in patients receiving chronic domperidone.

We hope the article by Schey et al. [8] and our experience as well as analysis of the literature provide reasonable answers to the questions that have been raised in the literature about the cardiotoxicity of domperidone. Currently, there are phase 2 and 3 studies with two novel D2/D3 antagonists, ATC1906 and NG101, which have demonstrated no cardiac toxicity in early phase trials, and newer ghrelin agonists and 5-HT4 agonists may also provide effective and safe therapeutic options for treating gastroparesis patients.

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