



Translated from *Rev Prescrire* March 2012; 32 (341): 196-197

## Domperidone: ventricular arrhythmia and sudden death (continued)

### Abstract

● **Domperidone**, a “hidden” neuroleptic, is used for symptomatic treatment of gastroesophageal reflux disease, despite its uncertain efficacy. The intravenous form was withdrawn from the market in the 1980s following deaths due to cardiac arrhythmias. QT prolongation leading to cardiac arrhythmias, including life-threatening torsades de pointes, has also been attributed to oral *domperidone*.

● In 2010, two case-control studies, one Canadian and one Dutch, showed that patients who died suddenly or had severe ventricular arrhythmias were statistically significantly more likely than controls to have been exposed to *domperidone*.

● In practice, given its uncertain efficacy and a disproportionate risk of sudden death and severe ventricular arrhythmia, *domperidone* should not be used.

*Rev Prescrire* 2012; 32 (341): 196-197.

**D**omperidone is a “hidden” neuroleptic used for symptomatic treatment of gastroesophageal reflux, nausea and vomiting (1,2). QT prolongation leading to cardiac arrhythmias, including life-threatening torsades de pointes, has been attributed to *domperidone* (1,3,4).

In 1986, ventricular arrhythmias, that were sometimes fatal, led to market withdrawal of injectable *domperidone*. However, oral forms remained on the market.

*Domperidone* is metabolised by cytochrome P450 isoenzyme CYP 3A4. Co-administration with drugs that inhibit this isoenzyme, such as macrolides and azole antifungals, can lead to *domperidone* accumulation causing QT prolongation and cardiac arrhythmias (5-7).

A Dutch case-control study conducted in 2005 showed that patients who died suddenly due to cardiac causes were four times more likely than controls to have been exposed to *domperidone* (2,8).

In late 2008, QT prolongation and ventricular arrhythmias were added to the summaries of product characteristics (SPCs) for products containing this neu-

roleptic. These warnings were reinforced in 2011 (9-11), following publication of two new case-control studies in 2010 (12,13).

**Troubling Dutch data.** A case-control study examined a Dutch general practice database including patients aged 18 years or over, between 1996 and 2007 (12).

Cases were patients who either died due to cardiac causes preceded by abrupt loss of consciousness within one hour after acute symptom onset, or patients who died unexpectedly and who had been stable during the previous 24 hours, with no evidence of a non-cardiac cause. 1304 cases of sudden death and 62 cases of severe ventricular arrhythmia were matched with respectively 13 480 and 634 controls based on age, sex and date of onset.

The risk of sudden death was about four times higher among patients taking *domperidone* (odds ratio (OR) = 3.7, 95% confidence interval (95%CI): 1.7 to 8.1), and daily doses above 30 mg were associated with an 11-fold increase in the risk (OR = 11.4, 95%CI: 2 to 65) (a,b)(12).

**Another study in Canada.** A Canadian case-control study using a database for the province of Saskatchewan examined whether sudden death and severe ventricular arrhythmia were linked to exposure to *domperidone*, proton pump inhibitors or other drugs (13).

Between 1990 and 2005, among the 83 212 patients listed in the database, 1559 patients who died suddenly due to cardiac causes and 49 patients who developed severe ventricular arrhythmia were matched with 6428 controls.

Average age was 79 years, 53% of patients were women, and 22% were diabetic. The relative risk of sudden death or severe ventricular arrhythmia was about 1.5 times higher among patients taking *domperidone* than among those taking a proton pump inhibitor (OR = 1.44, 95%CI: 1.1 to 1.9) or no medication (OR = 1.6, 95%CI: 1.3 to 2) (a)(13).

**In practice: do not use domperidone.** It is unacceptable to expose patients with simple gastroesophageal reflux or nausea and vomiting to a risk of severe ventricular arrhythmia and sudden death. *Domperidone* should therefore be

avoided. If lifestyle measures fail to control gastroesophageal reflux, patients may be prescribed an antacid (taking care to avoid drug interactions) or a proton pump inhibitor (7).

In addition, *domperidone* must not be used to increase milk production in breastfeeding women (14). It is better to discuss non-drug solutions with patients.

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a- The odds ratio is the ratio between the probability that an event (e.g. a disease) will occur and the probability that the same event will not occur (ref 15).

b- According to the French SPC, the daily dose for adults and children over 12 years of age is 10 to 20 mg of *domperidone* 3 or 4 times per day, with a maximum dose of 80 mg per day (ref 10).

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