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Domperidone: QT prolongation in infants

● ***Domperidone*** **is a "hidden" neuroleptic, mainly used for symptomatic treatment of gastroesophageal reflux. It can prolong the QT interval, thus predisposing patients to life-threatening cardiac arrhythmia such as torsades de pointes.**

● **A French study of 31 newborns and infants receiving *domperidone* showed statistically significant QTc prolongation.**

● **In practice, these data confirm that *domperidone* should not be used to treat mild regurgitation in infants.**

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Regurgitation is very frequent in infants. Recurrent regurgitation is rarely harmful and generally disappears spontaneously after the first year of life. Infantile regurgitation is known as physiological gastroesophageal reflux (**a**)(1).

Several drugs are used for symptomatic treatment of gastroesophageal reflux in infants, despite their poorly documented efficacy. One of these drugs, *domperidone*, is a "hidden" neuroleptic used to stimulate gastrointestinal motility (1,2).

Neuroleptics are known to lengthen the QT interval and create a risk of torsades de pointes, a potentially life-threatening form of ventricular tachycardia (3,4).

A study conducted by a French team has yielded new information on the cardiac risks of *domperidone* therapy in infants.

QTc prolongation in newborns and infants

Over a one-year period in a French neonatal unit, 31 newborns and infants aged 2 to 42 days who had gastroesophageal reflux of unspecified severity were given an ECG before and after *domperidone* administration (5). They were divided into three groups based on their gestational age: less than 32 weeks of gestation, 32 to 36 weeks, and 37 weeks or more.

The mean daily *domperidone* dose of 1.3 mg/kg/day was administered in 3 or 4 oral intakes, 15 to 20 minutes before meals. The first ECG was performed before initiation of *domperidone* treatment and the second ECG a median of two days later. The QT interval was measured three times on each ECG, and then corrected for the heart rate to obtain the QTc. The three readings were averaged for each QTc interval.

The QTc interval rose by an average of 14 ms during treatment with *domperidone*, a statistically significant increase. Nearly half of patients had an increase of more than 12 ms.

Domperidone was withdrawn in one case when the QTc increased by 45 ms, to 450 ms, 48 hours after treatment initiation (**b**). The QTc interval had returned to its initial value within a week.

No cases of ventricular arrhythmia were recorded.

The mean QTc prolongation was higher in infants with a gestational age between 32 and 36 weeks than in those with a gestational age of 37 weeks or more: 26 ± 14.4 ms versus 19.1 ± 23.7 ms, respectively ($p<0.05$). After adjustment for gestational age, plasma potassium concentrations near the upper limit of normal were statistically significantly associated with QTc prolongation.

Domperidone known to induce serious cardiac arrhythmia

Domperidone has the same dose-dependent adverse effects as neuroleptics used in psychiatry, including extrapyramidal disorders and cardiac arrhythmia (**c**)(1,2).

QT prolongation and torsades de pointes have been reported with oral *domperidone* in both adults and infants (6,7).

Cases of ventricular arrhythmia, some of which were fatal, led to market withdrawal of injectable *domperidone* in 1986 (6).

The risk of QTc prolongation and ventricular arrhythmia has been mentioned in the French summary of product characteristics for oral *domperidone* since late 2008 (8).

In practice: avoid using domperidone

Despite its inherent weaknesses, this unblinded and uncontrolled observational study confirms the risk of cardiac arrhythmia associated with *domperidone*.

In practice, physiological gastroesophageal reflux is transient and harmless, and does not justify exposing newborns and infants to the adverse effects of *domperidone*, especially its potentially severe cardiac effects.

Lifestyle measures should be tried first for infants with physiological gastroesophageal reflux: they include adjusting the infant's position before and after meals, thickening the formula and slowing its delivery rate, and timing meals appropriately (1).

a- Pathological gastroesophageal reflux is rare and carries a risk of oesophagitis (ref 1). Omeprazole, a proton pump inhibitor, can be used to treat ulcerative or erosive oesophagitis. Metoclopramide, like domperidone, exposes patients to the adverse effects of neuroleptics. Surgical treatment can be envisaged in the rare cases in which oesophagitis is recurrent or refractory to treatment.

b- A QTc interval above 450 milliseconds is considered pathological in infants less than 6 months old (ref 5).

c- In 2004, the US Food and Drug Administration warned breast-feeding women not to use domperidone to increase their milk production (domperidone, like other neuroleptics, increases prolactin secretion). Domperidone is excreted in breast milk, thus exposing breastfed newborns and infants to its arrhythmogenic effects (ref 9).

Selected references from Prescrire's literature search.

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2- Prescrire Rédaction "6-1-5. Patients sous modificateur de la motricité" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).

3- Prescrire Rédaction "19-1. Patients psychotiques" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).

4- Prescrire Rédaction "Fiche 8. Torsades de pointes médicamenteuses en bref" *Rev Prescrire* 2009; **29** (314 suppl. interactions médicamenteuses).

5- Djeddi D et al. "Effect of domperidone on QT interval in neonates" *J Pediatr* 2008; **153** (5): 663-666.

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8- Prescrire Rédaction "Dompéridone: troubles cardiaques ajoutés dans les RCP de ce neuroleptique" *Rev Prescrire* 2009; **29** (313): 821.

9- Hampton T "FDA warns against breast milk drug" *JAMA* 2004; **292** (3): 322.