Domperidone and convulsions

Introduction
Domperidone (Motilium®) is a dopamine-antagonist with anti-emetic qualities, which is approved for the Dutch market for relieve of symptoms of nausea and vomiting, epigastric feeling of ‘fullness’, an annoying feeling in the upper abdomen, regurgitation of gastric content in adults. For children it is approved to relieve symptoms of nausea and vomiting [1]. Dosing in children is guided by bodyweight. Convulsions are not described in the Dutch SmPC in the sections 4.4, 4.8, nor 4.9 [1].

Reports
Until January 4, 2008, the Netherlands Pharmacovigilance Centre Lareb received three reports of convulsions in association with domperidone.

Patient A is a male aged 59 years who underwent a highly selective vagotomy and has a slackened intestinal passage. He uses chronically domperidone 10 mg tablets four times daily for regurgitations. Maximum dose in adults is 80 mg/day [1]. He had several convulsions, which required hospitalization. Electroencephalograms did not show any epileptic activity. The patient was being treated with valproic acid and carbamazepine. After start of domperidone (latency unknown) the convulsions reappeared, despite this antiepileptic treatment. After domperidone was stopped, the convulsions did not occur anymore.

Patient B is a female toddler aged 21 months, with a weight of 12.5 kg. Because of vomiting during three days, she was given domperidone suppository 10 mg twice daily by her mother. Later on her mother increased the dose to 30 mg twice daily, because the vomiting did not improve. For children weighing between 5 and 15 kg 20 mg is the total daily dose [1]. Because of a tonic-clonic convulsion patient was admitted to hospital. On admittance, she was somnolent and had a normal body temperature. She experienced two grand-mal convulsions during hospitalization. A febrile seizure was ruled out. Electrolytes were normal, as were cerebral CT and liquor. A Rotavirus was detected in the faeces. It was concluded that patient had had an overdose of domperidone, which had caused the convulsions.

Patient C is a male infant aged 13 months, with a weight of 9 kg. One week before hospital admittance he suffered from an upper airway infection (fever, coughing, abnormal crying), for which he received amoxicillin. Three days later patient developed diarrhoea three to four times a day. His appetite decreased, he started vomiting and his micturition diminished. Amoxicillin was stopped and domperidone suppository 10 mg TID was started. For children weighing between 5 and 15 kg 20 mg is the total daily dose [1]. His fluid intake decreased during these days. Patient was admitted to hospital because of a convulsion. Before and after the incident body temperature was normal (36.9°C). He recovered quickly after cessation of domperidone and treatment with extra fluid and ORS. There was no underlying disorder explaining the convulsion, except the high dose of domperidone.
Other sources of information

Literature
Seizures occurred in four adults receiving high doses of IV domperidone as prophylaxis for chemotherapy-induced emesis. Domperidone was given in doses of 0.6-1.8 mg/kg by slow IV infusion (0.8-2.0 mg/min) prior to cisplatin therapy. Generalized seizures occurred following total doses of 50-100 mg. One patient died during domperidone administration, with a seizure followed by cardiac and respiratory arrest [2].

According to the Informatorium Medicamentorum parenteral domperidone has been withdrawn in the Netherlands in 1985 because of convulsions, extrapiramidal disorders, and severe ventricular arrhythmias [3].

Databases
On January 4, 2008, the Lareb database contained 798 reports of convulsions, 129 reports on domperidone. The reporting odds ratio is 2.2 (95%CI 0.7-7.0).

The database of the Uppsala Monitoring Centre of the WHO contains 30 cases of domperidone and convulsions, which is also not disproportional (ROR 1.1, 95%CI 0.8-1.6).

Mechanism
The mechanism through which domperidone causes seizures is unknown. A central effect can be expected in young children, because the blood-brain barrier is not fully developed. But also in older children and adults central ADRs, like extrapiramidal symptoms, are described [4].

Domperidone is a phenothiazine like droperidol. Droperidol is a fluorinated derivative of the phenothiazines [5,6]. Droperidol is used in the emergency department (ED) for sedation, analgesia, and its anti-emetic effect. It is thought to lower seizure threshold, as phenothiazines can do [6,7].

Discussion and conclusion
Lareb received three reports of convulsions in association with domperidone. In patients B and C, the recommended dose was exceeded. Although it is stated that domperidone cannot easily cross the blood-brain barrier in adults, central ADRs are described. Central symptoms are warned for in the Dutch SmPC in the toxicology section 4.9 [1].

References

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