Extrapyramidal disorders with domperidone

See also p. 43

● **Parkinsonism, dystonia, tremor, acute or tardive dyskinesia. Often starting after the first dose of domperidone.**

The Regional Pharmacovigilance Centre in Amiens, France identified 174 cases of extrapyramidal disorders linked to *domperidone* that were recorded between 1985 and 2015 in the French national pharmacovigilance database; 126 sufficiently well documented cases were analysed (1).

The extrapyramidal disorders reported were: parkinsonism (41 patients), dystonia (37 patients), acute dyskinesia (36 patients), tremor (22 patients), worsening of pre-existing Parkinson's disease (7 patients), and tardive dyskinesia (3 patients).

Almost half of the patients affected were under 18 years of age, and about one-quarter were aged over 75 (1).

Domperidone had been used for nausea or vomiting in 41 patients, gastroesophageal reflux disease in 14 patients, and gastritis in 4 patients; the indication was not specified for the 67 other patients (1). The average dose was 32 mg per day (it was only in 2014 that the French Health Products Agency (ANSM) recommended that adults should take no more than 30 mg per day) (1,2).

In 76 of the 126 reported cases, the extrapyramidal adverse effects were serious, including 53 patients (42%) who were hospitalised or whose hospitalisation was prolonged, and one patient who suffered disability or incapacity. About three-quarters of the patients for whom the time to onset was reported developed the disorders within 24 hours after initiating *domperidone*. The disorders persisted in 15 patients (12%), although their duration was not specified (1).

Domperidone is related to neuroleptics such as *risperidone* (see p. 43 of this issue). Its harm-benefit balance is unfavourable, given its minor efficacy as an antiemetic and its serious adverse effects, including QT prolongation, ventricular arrhythmia, cardiac arrest, and sudden cardiac death (2-4).

It was long thought that *domperidone* did not enter the central nervous system, and it was used in patients with Parkinson's disease to relieve the peripheral adverse effects of dopaminergic drugs, such as nausea (2). Yet it provokes extrapyramidal disorders such as dystonia, tardive dyskinesia and neuroleptic malignant syndrome (3).

In practice Given its limited efficacy and severe adverse effects, *domperidone* is a neuroleptic antiemetic agent to avoid, including in Parkinson's disease.

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1- Radoubé F et al. "Domperidone induced extrapyramidal disorders: an observational study from the French pharmacovigilance database" 37th Pharmacovigilance Meeting [conference], Nancy: 19-21 April 2016. *Fundam Clin Pharmacol* 2016; **30** (suppl.1): 65 (abstract PS-081) (full version: 1 page).

2- Prescrire Rédaction "Dompéridone et morts subites en France (suite)" *Rev Prescrire* 2014; **34** (369): 555.

3- "Domperidone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 25 May 2016: 11 pages.

4- Prescrire Editorial Staff "Metoclopramide, domperidone: sudden cardiac death, ventricular arrhythmia" *Prescrire Int* 2016; **25** (175): 238-240.

Tramadol: fatal overdoses in children

An overdose of the opioid analgesic *tramadol* can provoke serious disorders, including respiratory depression. It is metabolised by the cytochrome P450 isoenzyme CYP2D6, yielding a metabolite that is more active than *tramadol*. This means that patients who have higher CYP2D6 activity than others (ultrarapid metabolisers) can develop symptoms of overdose even with doses consistent with the summary of product characteristics (SPC) (1,2).

In 2016, the French Health Products Agency (ANSM) published a review of serious adverse effects reported with *tramadol* between 2011 and 2015 involving children or adolescents (3). 85 cases were analysed, corresponding to 241 adverse effects. An overdose was reported in 46% of cases, either intentional or due to a medication error (3).

Four children died, two of whom had received an overdose.

In 11 other cases, the adverse effects were life-threatening. An overdose was noted in 10 of these cases, 4 of which resulted from a medication error. And a 5-year-old boy who had undergone tonsillectomy and adenoidectomy developed respiratory depression after receiving 8 drops of *tramadol*, consistent with the dose of 1 mg/kg stated in the French SPC (3,4). He was shown to be an ultrarapid CYP2D6 metaboliser. High concentrations of O-desmethyltramadol, a metabolite that is more potent than *tramadol*, were measured in his urine.

A search of the French database of medication errors identified 36 error reports involving *tramadol* in children from January 2011 to January 2016. These errors caused adverse effects in 26 children,

which were serious in 13 cases. *Tramadol* oral solution was implicated in 15 errors, including 5 dose preparation errors due to confusion between the number of drops per dose stated in the SPC and the number of drops per kg of body weight (3,5).

In practice *Tramadol* is difficult to use in children, with a risk of overdose related to ultrarapid metabolism of the drug by certain individuals and to the high concentration of the drug present in oral liquid forms. The *tramadol* oral solutions available in France in mid-2016 contain 2.5 mg of *tramadol* per drop, while a usual dose is 1 mg to 2 mg per kg (2,6-8). The dosing devices are droppers, which can lead to errors when counting the number of drops.

If *tramadol* is chosen despite its dangers, it is prudent to write down the number of drops to be given at each administration when prescribing or dispensing this drug. It is important to make sure that this information has been understood and communicated to the child's parents and carers.

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1- Prescrire Rédaction "5-1-4. Patients sous opioïde" *Rev Prescrire* 2015; **35** (386 suppl. Interactions médicamenteuses).
2- Prescrire Editorial Staff "Weak opioid analgesics. Codeine, dihydrocodeine and tramadol: no less risky than morphine" *Prescrire Int* 2016; **25** (168): 45-51.
3- ANSM "Réunion du comité technique de pharmacovigilance, compte rendu de la séance du 16 février 2016. Suivi national de pharmacovigilance des spécialités à base de tramadol, focus pédiatrique" 26 February 2016: 6 pages.
4- Orliaguet G et al. "A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol" *Pediatrics* 2015; **135** (3): 3 pages.
5- ANSM "Lettre à *Prescrire*" 27 September 2016: 6 pages.
6- ANSM "RCP Contramal 100 mg/ml solution buvable" 8 February 2016 + "RCP Topalgic 100 mg/ml solution buvable" 26 February 2016: 14 pages.
7- Sanofi-Aventis "Topalgic 100 mg/ml-Conditionnement, lot 00659H" packaging examined on 6 September 2016.
8- Grunenthal "Contramal 100 mg/ml-Conditionnement, lot 00236H" packaging examined on 6 September 2016.

Hormonal contraceptive + enzyme inducer: unintended pregnancies

● **In France, 78 unintended pregnancies linked to loss of efficacy of a hormonal contraceptive mediated by an enzyme-inducing drug.**

The Regional Pharmacovigilance Centre in Tours, France identified 78 unintended pregnancies that were linked to a drug interaction with a hormonal contraceptive and recorded in the French national pharmacovigilance database (1). The women affected had a median age of 30 years. The median time from initiation of the implicated drug to the start of pregnancy was 56 days (range: 28 days to 266 days). The pregnancies were discovered after a median gestation of 9.5 weeks, based on the last menstrual period (range: 5 weeks to 18 weeks). Twenty-three women (30% of cases) had an elective abortion (1).

The contraceptives most frequently involved were *ethinylestradiol + levonorgestrel* combinations (32 cases) and the *etonogestrel* implant (16 cases).

In 46 cases, the risk of interaction was mentioned in the French summary of product characteristics (SPC) for the enzyme-inducing drug. The drug implicated was *rifampicin* in 13 cases, *carbamazepine* in 12 cases, and *efavirenz* in 6 cases (1).

Hormonal contraceptives are metabolised by the cytochrome P450 system. Enzyme-inducing drugs can reduce their contraceptive efficacy (2,3). The main enzyme-inducing drugs are: antiepileptics such as *carbamazepine*, *fosphenytoin*, *phenobarbital*, *phenytoin*, *primidone* and *rufinamide*; the antibiotics *rifabutin* and *rifampicin*; the antiretrovirals *efavirenz*, *etravirine*, *lopinavir*, *nevirapine* and *ritonavir*; *St John's wort*, a plant used as an antidepressant; the antiandrogen *enzalutamide*; and *bosentan* a vasodilator used in pulmonary hypertension. Chronic alcohol consumption also causes enzyme induction (2,3).

Some enzyme-inducing drugs can also provoke malformations, in particular antiepileptics and *efavirenz* (3,4).

In practice When considering prescribing or dispensing an enzyme-inducing drug to a woman, it is important to discuss contraception. If she is using a hormonal method, i.e. the pill, an implant or a vaginal ring, there is a very real risk of pregnancy through loss of its contraceptive effect. Both the prescription and her method of contraception will need to be reviewed.

▶ Translated from *Rev Prescrire* **November 2016**
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3- Prescrire Rédaction "11-1. Patients infectés par le HIV" *Rev Prescrire* 2015; **35** (386 suppl. Interactions médicamenteuses).
4- Pescrire Editorial Staff "Carbamazepine, phenytoin, lamotrigine and topiramate: uncertain risk of birth defects" *Prescrire Int* 2009; **18** (104): 254-255.