



Long-acting injectable olanzapine: post-injection syndrome

● **36 cases in France, including coma, hypertension and arrhythmia.**

Long-acting injectable *olanzapine* is used as maintenance treatment for patients with schizophrenia sufficiently stabilised with oral *olanzapine*: for example, patients who have difficulty taking an anti-psychotic every day. It is administered by intramuscular injection every two to four weeks (1).

It mainly exposes patients to a group of disorders referred to as *olanzapine* post-injection syndrome, which includes: symptoms of sedation (ranging from mild sedation to coma) or delirium (including disorientation, agitation, anxiety, cognitive impairment); extrapyramidal symptoms; dysarthria; ataxia; aggression; dizziness, weakness, hypertension and convulsions (2). These symptoms are consistent with *olanzapine* overdose through intravenous absorption (2).

The Montpellier, Dijon, Marseille and Reims Regional Pharmacovigilance Centres analysed the cases of *olanzapine* post-injection syndrome linked to long-acting injectable *olanzapine* recorded in the French pharmacovigilance database since its market introduction (3). They analysed serious cardiovascular effects in particular, with coma, hypertension above 180 mm Hg, or tachycardia above 150 bpm (3).

The 36 cases analysed involved patients aged 25 to 70 years, 30 of whom were men (3). In more than

half of cases, the disorders developed within 30 minutes after the injection and on average after 46 minutes (the range was not reported). Ten patients were comatose. Four patients were intubated. Cardiovascular disorders were observed in 18 patients: tachycardia in 4 cases, hypertension in 5 cases, tachycardia with severe hypertension in 5 cases, hypotension in 2 cases and atrial fibrillation in 2 cases. No sequelae were reported (3).

In practice The disorders that occur within minutes or hours after injection of long-acting *olanzapine* require serious consideration when weighing the harms of treatment against the expected benefits. If long-acting injectable *olanzapine* is chosen despite these risks, the EU summary of product characteristics (SPC) recommends monitoring of the patient in a healthcare facility by qualified personnel for at least 3 hours after each injection (2).

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1- Prescrire Editorial Staff "Long-acting injectable olanzapine. Inadequate assessment and a risk of overdose" *Prescrire Int* 2010; **19** (107): 114.

2- EMA "SPC-Zypadhera 210 mg" 13 April 2016: 93 pages.

3- Bergdoll E et al. "Olanzapine long-acting injection: post-injection delirium/sedation syndrome and cardiovascular disorders" 37th Pharmacovigilance Meeting, Nancy: 19-21 April 2016. *Fundam Clin Pharmacol* 2016; **30** (suppl 1): 80 (abstract PS-148).

Methylphenidate: cardiac disorders



Methylphenidate is an amphetamine used in children with attention deficit hyperactivity disorder, and in certain patients with narcolepsy. Although it has been in use since the 1960s, its cardiovascular adverse effects are poorly documented (1-3).

A large study was conducted using South Korea's national health insurance database (4). During the period 2008-2011, 114 647 patients aged 17 years or younger were prescribed *methylphenidate* for attention deficit hyperactivity disorder. 1224 of these children experienced a first cardiovascular event, at an average age of about 12 years. The events included 864 cases of arrhythmia, 396 cases of hypertension, and 52 cases of myocardial infarction. The authors compared the incidence of these disorders during periods of *methylphenidate* treatment versus the incidence during periods without treatment.

After adjustment for a number of factors, the incidence of arrhythmia was higher during treatment, with a relative risk (RR) of 1.6 (95% confidence interval (95CI): 1.5 to 1.7). The risk of myocar-

dial infarction also appeared higher during *methylphenidate* treatment (RR 1.3; 95CI: 0.9-2.0). The difference reached statistical significance during week 2 of treatment (RR 2.5; 95CI: 1.5-4.2).

There was little difference in the incidence of hypertension: RR 1.1 (95CI: 0.9-1.2).

The risk of valve disorders or pulmonary arterial hypertension was not studied.

In practice As *methylphenidate* is an amphetamine, these results are consistent with its foreseeable adverse effects. The risk of cardiac disorders with *methylphenidate*, including in children aged 17 or younger, has a considerable impact on its harm-benefit balance.

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1- Prescrire Editorial Staff "Methylphenidate: cardiac risks" *Prescrire Int* 2006; **15** (84): 138.

2- Prescrire Editorial Staff "Methylphenidate: pulmonary hypertension and heart valve disease" *Prescrire Int* 2015; **24** (161): 154-155.

3- Prescrire Editorial Staff "Methylphenidate tablets" *Prescrire Int* 1997; **6** (31): 126-130.

4- Shin JY et al. "Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder

(ADHD): nationwide self controlled case series study" *BMJ* 2016; **353**; i2550: 8 pages.

Benfluorex: adverse effects reviewed, 1976–2015



In 2016, the French Health Products Agency (ANSM) published a review of the adverse effects reported between 1976 and spring 2015 with the amphetamine *benfluorex* (1-3).

It includes in particular:

- 11 cases of pleural fibrosis, sometimes with heart valve disease or pulmonary hypertension;
- 6743 cases of heart valve disease, usually involving several valves, mainly the aortic and mitral valves, with regurgitation. 69 patients died following valve replacement surgery;
- 1273 cases of pulmonary arterial hypertension, with a median latency time from initiation of *benfluorex* to diagnosis of about 9 years.

In practice In late 2005, the ANSM reported being aware of 17 cases of pulmonary arterial hypertension and no cases of heart valve disease (4). So

many wasted years and so much preventable suffering.

All we can do in 2016 is help the victims, avoid drugs that are more dangerous than useful, and be watchful for signals of drug toxicity.

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1- ANSM "Point d'information - Benfluorex (Mediator): bilan du suivi de pharmacovigilance" 9 May 2016: 2 pages.

2- ANSM "Mediator, Benfluorex Mylan, Benfluorex Qualimed. Valvulopathies. Suivi national de pharmacovigilance. Bilan des cas rapportés jusqu'au 30/04/2015" 23 November 2015: 18 pages.

3- ANSM "Rapport d'expertise. Suivi national de pharmacovigilance sur le risque d'hypertension artérielle pulmonaire sous benfluorex" 17 November 2015: 15 pages.

4- Prescrire Editorial Staff "What matters most to the French regulatory agency: public health, or the health of drug companies?" *Prescrire Int* 2005; **15** (81): 34-36.

NSAIDs in children: gastrointestinal bleeding



In 2016, an Italian team published a retrospective study on a series of 51 children hospitalised in eight paediatric units between 2005 and 2013. They had undergone gastrointestinal endoscopy for gastrointestinal bleeding associated with the use of a nonsteroidal anti-inflammatory drug (NSAID) (1). Their median age was 7.8 years (5 months to 18 years).

Ibuprofen was the NSAID most frequently implicated (69% of cases). The NSAID was used for pain in 57% of cases and for fever in 41% of cases. The median exposure to the NSAID before bleeding was 4 days. The NSAID had been used at appropriate doses in half of the cases.

33.3% of the children had haematemesis, 31.3% had abdominal pain, 25% had anaemia and 8% melaena, and 1.9% had nausea and vomiting. The children with haematemesis were younger on average than the children who had other symptoms.

On gastrointestinal endoscopy, 62% of the children were found to have gastric lesions, 33% duodenal lesions and 15% oesophageal lesions.

In practice This study shows that NSAIDs can provoke gastrointestinal bleeding in children, even when used for only a few days. *Paracetamol* is a better choice as first-line treatment for both pain and fever, in children as well as in adults, taking care not to exceed the maximum daily dose.

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1- Cardile S et al. "Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children" *World J Gastroenterol* 2016; **22** (5): 1877-1883.