**Abstract**

- Several amphetamine-like appetite suppressants are known to have cardiovascular adverse effects, in particular pulmonary arterial hypertension and cardiac valve disease.
- Is this also the case with methylphenidate, an amphetamine-like psychostimulant used in attention-deficit hyperactivity disorder (especially in children) and also in narcolepsy?
- Cases of pulmonary hypertension and heart valve disease have been reported with methylphenidate, including in children. The risk appears to be low, but epidemiological studies are needed to estimate the incidence.
- This risk should be minimised by only using methylphenidate to treat serious disorders, at the lowest effective dose. Attention should be paid to warning signs such as dyspnoea.

**Fragmentary data**

In response to our request for information, the French and British drug regulatory agencies provided us with periodic safety update reports (PSURs) and extracts from their pharmacovigilance databases concerning methylphenidate. It is not possible to determine how many recorded cases of pulmonary hypertension and heart valve disease are duplicate cases.

We found no clinical trials or pharmacological studies investigating the risk of pulmonary hypertension and heart valve disease associated with methylphenidate.

The only available data come from published cases and reports received by pharmacovigilance agencies; they are too fragmentary to accurately estimate the frequency of these disorders.

**Pulmonary hypertension at standard doses**

Various reports have shown that methylphenidate increases the risk of pulmonary hypertension.

Improvement after methylphenidate withdrawal. A 15-year-old boy developed symptoms of pulmonary hypertension after 4 days of treatment with methylphenidate 54 mg/day for attention-deficit hyperactivity disorder: in particular, he experienced mild episodes of shortness of breath at any time of the day, in the absence of physical exercise or anxiety. Eighteen months later, after he fainted and complained of shortness of breath, transthoracic echocardiography showed a pulmonary arterial pressure of 40 mmHg at rest. The symptoms improved 4 weeks after methylphenidate withdrawal, and his pulmonary arterial pressure fell to 28 mmHg.

A 58-year-old man taking methylphenidate 15 mg/day for drowsiness (an off-licence use) developed severe pulmonary hypertension about 8 years after treatment initiation. His condition improved after methylphenidate withdrawal. He had a history of left ventricular failure (without valve disorders), angina, myocardial ischaemia and hypertension.

**Some reported cases, including in children.** The periodic safety update report for Ritalin® (methylphenidate) dated 31 October 2011 mentioned a cumulative total of 10 cases of pulmonary hypertension (7 spontaneous reports and 3 published cases).

On 1 October 2012, the French database contained two reports of pulmonary hypertension (7). One case concerned a 10-year-old boy who developed pulmonary hypertension seven months after starting methylphenidate, and the other a 72-year-old man (few details specified). The summaries of these cases are brief, and the clinical details were blacked out in the report of the Pharmacovigilance Technical Committee provided by the French health products agency (ANSM) on 9 October 2012. According to this redacted report, 4 cases of pulmonary hypertension in children taking methylphenidate had been recorded worldwide. The patients all had a history of heart problems or were taking another substance known to carry this risk.

On 7 November 2014, the publicly accessible part of the British database mentioned two cases of pulmonary hypertension linked to methylphenidate.

**Heart valve disease in children**

In October 2011, periodic safety update reports for methylphenidate-based products mentioned about 15 spontaneous reports or published cases of cardiac valve damage.

On 1 October 2012, the French database contained two cases of cardiac valve disease linked to methylphenidate, but once again the clinical details were blacked out in the report of the Pharmacovigilance Technical Committee released on 9 October 2012.
Mechanisms of action of amphetamine-like drugs

Amphetamine is an indirect sympathomimetic agent. It increases the concentrations of catecholamines (epinephrine, norepinephrine and dopamine) and serotonin at interneuronal synapses by enhancing their release and reducing their reuptake. At high doses, it inhibits monoamine oxidase (MAO), an enzyme involved in the metabolism of serotonin and dopamine (1-3).

Amphetamine is a central nervous system stimulant: in the short term, it increases alertness and leads to psychomotor stimulation, reducing appetite and the need for sleep. Psychiatric effects, including psychotic disorders such as hallucinations and delusions, sometimes occur.

Tolerance is common during long-term use, resulting in a need for higher doses to achieve the same effect. Dependence (withdrawal symptoms) is also frequent (1-3).

At the peripheral level, short-term sympathomimetic effects cause: cardiac stimulation, leading to tachycardia with palpitations, stronger cardiac contraction, and cardiac rhythm disorders; as well as vasoconstriction leading to an increase in blood pressure; mydriasis; hyperthermia; and contraction in the urinary bladder sphincter, leading to difficulty urinating.

Many drugs have chemical structures and pharmacological effects similar to those of amphetamine; these amphetamine-like drugs include methylphenidate, bupropion, sibutramine, ephedrine, benfluorex and fenfluramine (1,2).

Prescrire International June 2015 / Volume 24  No 161  • Page 155

Selected references from Prescrire’s literature search.
2- Prescrire Rédaction “Méthylphénidate: abus en Europe” Rev Prescrire 2012, 32 (1349); 830.
3- Prescrire Rédaction “Ritaline” LP à 10 mg: conditionnement trop similaire à celui de Ritaline® 10 mg” Rev Prescrire 2013; 33 (357); 509.
4- Karanam MG et al. “Pulmonary arterial hypertension is usually defined as an average pulmonary arterial pressure above 25 mmHg at rest (ref 17).”

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Up to June 2011, the companies concerned had received 6 spontaneous reports of heart valve disorders linked to methylphenidate in children (7).

Uncertain mechanism of valve disease. Pharmacologically, methylphenidate has mainly amphetamine-like properties (see inset) (11). Serotonergic activity appears to play an important role in the onset of valve disorders, based mainly on studies of amphetamine-like anorectic drugs such as fenfluramine and its derivatives (6,12).

One methylphenidate enantiomer shows affinity for 5-HT2B (hydroxytryptamine 2B) serotonin receptors in vitro, but the pharmacological implications are unclear (7). Activation of serotonin receptors, particularly 5-HT2B receptors, has been suggested to account for drug-induced cardiac damage, particularly valve disease (7,11,12).

In practice

Amphetamine-like anorectic drugs have long been known to cause pulmonary hypertension and cardiac valve disease, dangers that were largely underestimated in the case of benfluorex. The scant data available in late 2014 suggest that methylphenidate increases the risk of pulmonary hypertension and, possibly, heart valve disease. The risk is probably low but cannot be precisely quantified. There are no known risk factors.

In late 2014, these serious adverse effects were not mentioned in the summaries of product characteristics for methylphenidate-based products in France (13-15), but it would be prudent to take them into account. This is yet another reason to use methylphenidate only in severe forms of attention-deficit hyperactivity disorder and narcolepsy, at the lowest effective dose. Attention should be paid to warning signs of heart valve disease and pulmonary hypertension such as dyspnoea.