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Methylphenidate: pulmonary hypertension and heart valve disease

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.**

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Amphetamine-like appetite suppressants such as *fenfluramine* and *benfluorex* were taken off the market because of cardiovascular adverse effects, in particular pulmonary hypertension and cardiac valve damage (1).

Methylphenidate, another amphetamine-like drug, is used in two very different indications: attention-deficit hyperactivity disorder in children and some forms of narcolepsy. Its adverse effects include cardiovascular and neuropsychiatric disorders, growth retardation in children, addiction and a risk of abuse (2,3). We reviewed the literature for reports of pulmonary hypertension and cardiac valve disease linked to *methylphenidate*.

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* (**a**). 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 pharmacoepidemiological 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 (**b**). The symptoms improved 4 weeks after *methylphenidate* withdrawal, and his pulmonary arterial pressure fell to 28 mmHg (4).

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 (5).

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) (6).

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) (7,8). 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 (7). 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 (7).

On 7 November 2014, the publicly accessible part of the British database mentioned two cases of pulmonary hypertension linked to *methylphenidate* (9).

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 (6,10).

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 (7).

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.

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).

Selected references from Prescrire's literature search.

1- "Noo-analeptiques". In: "Pharmacologie clinique. Bases de la thérapeutique" Giroud JP et al. Expansion scientifique française, Paris, 1988: 1274-1281.

2- "Miscellaneous sympathomimetic agonists". In: Brunton LL et al. "Goodman & Gilman's. The Pharmacological Basis of Therapeutics", 12th ed., McGraw-Hill Medical, New York 2011: 297-300.

3- "5-Hydroxytryptamine (Serotonin) and dopamine". In: Brunton LL et al. "Goodman & Gilman's. The Pharmacological Basis of Therapeutics", 12th ed., McGraw-Hill Medical, New York 2011 : 335-360.

a- Periodic Safety Update Reports for a given drug are produced by the company that owns or exploits marketing authorisation. It includes pharmacovigilance data collected worldwide during the period in question and provided to health authorities at various intervals, for example every 6 months for the first 2 years after market approval, annually for the following two years, and then once every 3 years (ref 16).

b- Pulmonary hypertension is usually defined as an average pulmonary arterial pressure above 25 mmHg at rest (ref 17).

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Benfluorex. EU marketing authorisation finally withdrawn" *Prescrire Int* 2010; **19** (109): 206.

2- Prescrire Rédaction "Méthylphénidate: abus en Europe" *Rev Prescrire* 2012; **32** (349): 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- Karaman MG et al. "Pulmonary arterial hypertension in an adolescent treated with methylphenidate" *J Child Adolesc Psychopharmacol* 2010; **20** (3): 229-231.

5- "Respiratory, thoracic and mediastinal disorders". In: Shire Pharmaceuticals "Equasym/Metadate (methylphenidate HCL). Periodic Safety Update Report. Report No: 03. Reporting period: 11 Oct 2010 to 10 Oct 2011": 1 page.

6- "App.3.4.1: Cumulative summary tabulation HCP report" and "App.3.4.2: Cumulative summary tabulation HCP report". In: Novartis "Ritalin (methylphenidate). Periodic Safety Update Report 10 (PSUR 10). Period covered by this report: 1 Nov 2010 - 31 Oct 2011": 6 pages.

7- Centre régional de pharmacovigilance Reims Champagne - Ardennes "Mise à jour données de pharmacovigilance. Méthylphénidate. Comité technique du 9 octobre 2012" 17 July 2013. ansm.sante.fr accessed 12 September 2013: 160 pages.

8- ANSM "Lettre à *Prescrire*" 14 June 2013: 3 pages.

9- MHRA "Methylphenidate. Drug Analysis Print". 7 November 2014. www.mhra.gov.uk accessed 3 December 2014: 40 pages.

10- "Appendix 5: Cumulative Tabulation". In: "OROS Methylphenidate Hydrochloride Periodic Safety Update Report. 11 October 2010 to 10 October 2011": 3 pages.

11- "Miscellaneous sympathomimetic agonists". In: Brunton LL et al. "Goodman & Gilman's. The Pharmacological Basis of Therapeutics" McGraw-Hill Medical. 12th edition, 2011: 297-300.

12- Prescrire Editorial Staff "Drug-related cardiac valve disease" *Prescrire Int* 2013; **22** (144): 292-295.

13- ANSM "RCP-Ritaline" 28 November 2014: 8 pages.

14- ANSM "RCP-Concerta" 28 November 2014: 10 pages.

15- ANSM "RCP-Quasym LP" 24 February 2014: 14 pages.

16- Prescrire Editorial Staff "Telithromycin: review of adverse effects" *Prescrire Int* 2014; **23** (154): 264-266.

17- Prescrire Rédaction "L'hypertension artérielle pulmonaire. Grave quand elle est symptomatique" *Rev Prescrire* 2004; **24** (256): 843-846.