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An initiative to prevent the adverse effects of metformin

● **Collaboration between clinicians and a pharmacovigilance centre results in practical benefits for patients.**

Lactic acidosis is a well-known adverse effect of *metformin*. Although rare, it can be fatal.

Metformin accumulation increases the risk of lactic acidosis. Other risk factors include: dehydration, cardiac or respiratory failure, recent myocardial infarction, liver failure, severe acute alcohol intoxication, surgery, and impaired renal function (sometimes associated with acute intercurrent disorders or nephrotoxic drugs, including imaging contrast agents) (1).

In 2009, the French regional pharmacovigilance centre in Rouen, in conjunction with a local emergency department, reviewed morbidity and mortality resulting from the adverse effects of *metformin* (2). This process is one way of improving the quality of care, through collective, systematic and retrospective analysis of deaths, complications and other potentially harmful events (3).

After implementation of this review of morbidity and mortality associated with *metformin*, the number of reports of lactic acidosis rose from 7 to 38. However, mortality fell from 43% to 23%, as did the proportion of patients requiring intensive care, from 57% before 2009 to 35% in 2011 (2).

In practice. Collaboration between healthcare professionals in the analysis and prevention of adverse effects can yield concrete improvements in medical practice and patient care.

Selected references from Prescrire's literature search

1- Prescrire Rédaction "4-1-3. Patients sous metformine" *Rev Prescrire* 2011; **31** (338 suppl. interactions médicamenteuses).

2- Gillet I et al. "Metformin: from pharmacovigilance to medical practices improvement ! A morbimortality review (MMR)" 33rd Pharmacovigilance Meeting, Dijon: 4-6 April 2012. *Fundamental Clin Pharmacol* 2012; **26** (suppl. 1): 39 (abstract 457).

3- Prescrire Editorial Staff "Analysing an adverse event in primary care: a multidisciplinary, collaborative process" *Prescrire Int* 2011; **20** (121): 274-278.

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Methylphenidate: abuse in Europe

● **In Europe, *methylphenidate* consumption is rising at an alarming rate. Reports of abuse and addiction are also increasing.**

Methylphenidate, an amphetamine-like psycho-stimulant, has been used since the 1990s in attention deficit-hyperactivity disorders and narcolepsy (1,2), as a last-resort symptomatic treatment.

The potential for abuse and addiction has long been known, with cases already reported in France and elsewhere (2,3).

The regional pharmacovigilance and pharmacodependence monitoring centres in Toulouse and Marseille, and the World Health Organization (WHO), have analysed *methylphenidate* consumption and reports of abuse and addiction recorded in the WHO database in Uppsala between 1994 and 2010.

Between 2005 and 2010, *methylphenidate* consumption rose sharply in Europe, increasing by 525% in Denmark, 222% in the Netherlands, 216% in Germany, and 167% in France, for example (4).

There appeared to be a proportional increase in reports of abuse and addiction, but the authors did not specify the number of cases.

In practice. These European data are in line with previous observations made in France (2). The risk of abuse and addiction must be taken into account when considering *methylphenidate* prescription.

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "Méthylphénidate: un amphétaminique à ne manier qu'avec beaucoup de précautions" *Rev Prescrire* 2011; 31 (330): 263.

2- Prescrire Editorial Staff "Methylphenidate: abuse and addiction" *Prescrire Int* 2012; **21** (131): 241.

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

4- Micallef J et al. "Detection and magnitude of methylphenidate abuse and misuse using Vigibase and correlation with data from drug utilisation studies" 33rd Pharmacovigilance Meeting, Dijon: 4-6 April 2012. *Fundamental Clin Pharmacol* 2012; **26** (suppl. 1): 11 (abstract 12-P193).

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Benfluorex and cardiac valve disease: long delay in publication

● **Unresponsive authorities.**

In 1998, the Italian health authorities demanded a reassessment of the cardiac toxicity of *benfluorex*. Similarly, in 1999, the French drug regulatory agency asked the pharmaceutical company, Servier, to assess the cardiovascular effects of *benfluorex* (1). A double-blind, randomised trial (Regulate), launched in 2005, included cardiac monitoring of diabetic patients treated with *benfluorex* or *pioglitazone* (2). Preliminary data were submitted to the French agency in 2009 (3), and detailed results were published in mid-2012 (2).

Among the 846 patients included, 615 underwent echocardiography at baseline and after 52 weeks.

Valvular regurgitation occurred or worsened in 82 patients on *benfluorex* and 33 patients on *pioglitazone* (27% versus 11%, p<0.0001) (2). The aortic valves were most commonly affected (42 patients treated with *benfluorex*, versus 3 treated with *pioglitazone*; p<0.0001). According to the published article, the valvular regurgitation was generally considered mild.

These cases of valve damage, reported after only one year of *benfluorex* treatment in a randomised trial, represented an important safety alert.

In practice. The ensuing *benfluorex* disaster revealed a lack of responsiveness and major shortcomings when it comes to drug safety monitoring; this scandal demonstrated that changes are needed to help protect public health (4).

Selected references from Prescrire's literature search.

1- Inspection générale des affaires sociales "Enquête sur le Mediator°" Rapport définitif, tome annexes, January 2011: 3015 pages.

2- Derumeaux G et al. "Echocardiographic evidence for valvular toxicity of benfluorex: a double-blind randomised trial in patients with type2 diabetes mellitus" *Plos One* 2012; **7** (6): 12 pages.

3- Afssaps "Commission nationale de pharmacovigilance, compte rendu de la réunion du mardi 29 Septembre 2009" 24 November 2009: 12 pages.

4- Prescrire Editorial Staff "France's Mediator° scandal: take the high road" english.prescrire.org.