Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month we update you on the interaction between statins and the antistaphylococcal agent fusidic acid. Although it has been known for some time that there is an increased risk of rhabdomyolysis when fusidic acid is used at the same time as some statins, in recent years the number and severity of case reports (some fatal) have increased. Furthermore, the mechanism of the interaction is unknown and could occur with any statin. Fusidic acid should not be given with statins—read further advice in article A1.

A recent Europe-wide review has concluded that there is a risk of extrapyramidal effects or withdrawal symptoms (or both) in newborns after maternal use of antipsychotics during the third trimester of pregnancy. Expectant mothers should be counselled about the benefits and risks of antipsychotic treatment during pregnancy. Article A2 outlines the symptoms affected newborns may show, which should be monitored and (if necessary) treated.

Also this month, read our update on the continuing effective measures to minimise the risk of misuse of pseudoephedrine and ephedrine in the potential manufacture of the class A drug methylamphetamine (article H2).

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Drug safety advice

A1 Systemic fusidic acid and interaction with statins: risk of rhabdomyolysis

Systemic fusidic acid (Fucidin) should not be given with statins because of a risk of serious and potentially fatal rhabdomyolysis. Healthcare professionals should be aware of strengthened warnings regarding this potential drug interaction

Fusidic acid and its salts (including sodium fusidate) is an antistaphylococcal agent which is used for the treatment of serious or deep-seated infections requiring good tissue or bone penetration, such as osteomyelitis. Systemic formulations include tablets, suspension, and intravenous infusion.

See Drug Safety Update, January 2008: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084705

Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin) are widely used for the prevention of cardiovascular events. We have previously highlighted in Drug Safety Update that consideration of any potential drug interaction is important because comorbidity is common in statin users.

Risk of rhabdomyolysis

It has been known for some time that there is an increased risk of rhabdomyolysis when systemic fusidic acid (Fucidin) is used at the same time as some statins. The product information for systemic fusidic acid and for simvastatin and atorvastatin lists this interaction and warns of the associated risk.

1 Burtenshaw AJ, et al. Anaesthesia 2008; 63: 656–58.
2 Magee C, et al. Am J Kidney Dis 2010; 56: e11–15.

In recent years, the number and severity of case reports[1,2] of rhabdomyolysis (including those with a fatal outcome) suspected to be due to an interaction between fusidic acid and a statin have increased.

Although the number of cases reported is small, the use of fusidic acid is low, making this a serious safety signal. The exact mechanism for this interaction is unknown and therefore could occur with some, or all, statins. Product information for systemic fusidic acid is being updated to include a strict warning against concomitant use with statins.

Advice for healthcare professionals:

- Systemic fusidic acid should not be given with statins because of a risk of (potentially fatal) rhabdomyolysis
- In patients for whom the use of systemic fusidic acid is essential, statin treatment should be temporarily discontinued throughout the duration of fusidic acid treatment
- To ensure clearance of systemic fusidic acid, statin therapy may be reintroduced 7 days after the last dose of systemic fusidic acid
- In exceptional cases where prolonged systemic fusidic acid treatment is necessary, the need for co-administration of a statin should be considered on an individual basis and only under close medical supervision
- Patients should be clearly advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain, or tenderness
- Any muscle symptoms reported in patients who are prescribed statins should be followed up

Further information:

BNF sections 5.1.7 Some other antibacterials (see http://bnf.org/bnf/bnf/61/3871.htm?q=fusidin&t=search&ss=text&p=5#_3871) and 2.12 Lipid-regulating drugs (see http://bnf.org/bnf/bnf/current/33422.htm?q=statins&t=search&ss=text&p=2#_hit)

Article citation: Drug Safety Update Sept 2011 vol 5, issue 2: A1.

A2 **Antipsychotics: use during third trimester of pregnancy and extrapyramidal effects or withdrawal symptoms in newborns**

A recent Europe-wide review has concluded that there is a risk of extrapyramidal effects or withdrawal symptoms (or both) in newborns after maternal use of antipsychotics during the third trimester of pregnancy. This conclusion is based on worldwide post-marketing case reports and information provided by the US Food and Drugs Administration

There are insufficient data to determine the size of the risk or any difference in risk between classes of antipsychotics or between individual antipsychotics.

UK product information for all antipsychotics will be updated to include consistent information about this risk.

Advice for healthcare professionals:

- Following maternal use of antipsychotics in the third trimester, examine newborns for symptoms which may include: agitation; hypertonia; hypotonia; tremor; somnolence; feeding problems; and respiratory distress
- Symptoms may vary in severity and duration, and they should be monitored and treated (if necessary) on an individual basis
- Expectant mothers should be counselled about the benefits and risks of antipsychotic treatment during pregnancy

Please report suspected adverse events related to the use of antipsychotics during pregnancy through the Yellow Card Scheme at www.yellowcard.gov.uk

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Further information:

Report from the European Pharmacovigilance Working Party: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109581.pdf

US Food and Drug Administration safety information on antipsychotic drugs and treatment during pregnancy: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm244175.htm

Summaries of Product Characteristics are available at: www.emc.medicines.org.uk

BNF section 4.2.1 Antipsychotic drugs: http://bnf.org/bnf/bnf/61/3209.htm?q=antipsychotics&t=search&ss=text&p=3

Hot topic

A UK and Europe-wide review of available efficacy and safety data has confirmed that reboxetine has benefit over placebo in its authorised indication. Efficacy was clearly shown in patients with severe or very severe depression. Like many antidepressants, there are limited efficacy data for the use of reboxetine in patients with mild to moderate-severity depression

H1 **Reboxetine: benefit-risk balance reviewed**

Reboxetine is a highly selective and potent inhibitor of noradrenaline reuptake and has only a weak effect on serotonin. It is indicated for acute treatment of depressive illness or major depression, and for maintaining clinical improvement in patients who initially respond to treatment. Reboxetine is not widely used in the UK, reflecting NICE recommendations (see http://www.nice.org.uk/CG90) that some antidepressants such as reboxetine should only be used when selective serotonin reuptake inhibitors (SSRIs) do not show an effect or are not well tolerated.

A meta-analysis has investigated the effect of possible publication bias on the overall assessment of the safety and efficacy of reboxetine.[1] The study was part of a German health technology assessment of three antidepressants, and concluded that reboxetine was “an ineffective and potentially harmful antidepressant”.[2]

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As a result of the concerns raised, the totality of safety and efficacy data for reboxetine was assessed in the UK by the Commission on Human Medicines and in Europe. This analysis included the published meta-analysis,[1] data submitted in support of the original licence application that had shown the efficacy of reboxetine, and further data submitted by the licence holder.

The published meta-analysis[1] included 13 acute-treatment trials (placebo-controlled, SSRI-controlled, or both) involving 4098 patients. Data for 3033 (74%) patients were unpublished.

Seven trials looked at remission rates and noted no significant difference between those receiving reboxetine compared with placebo (odds ratio [OR] 1.17 [95% CI 0.91–1.51], p=0.216). Eight trials investigated response rates and after exclusion of one trial (see below), the point estimate calculated from the remaining seven showed no significant difference between reboxetine and placebo (OR 1.24 [95% CI 0.98–1.56], p=0.071).

The published meta-analysis[1] had several limitations. A pivotal efficacy study was excluded from the efficacy analysis, but included in the safety assessment. The positive efficacy result was regarded by the researchers as a statistical outlier, which is not considered an adequate justification for omission of a valid study.

When data from this study and other earlier studies that formed part of the original licence application are included in an updated (unpublished) meta-analysis, reboxetine showed a benefit in treatment response over placebo in the treatment of depression: OR 1.47 (95% CI 1.10–1.97), p=0.01.

The review also explored possible reasons for the differences in the findings between the studies before and after licensing. Differences in care setting and disease severity at baseline are the most likely explanation for the difference in size of the reboxetine treatment effect. Studies in an in-patient setting and in severe depression consistently showed better efficacy results than those in out-patients. The greater effect compared with placebo seen in patients with more severe depression is also seen with other antidepressants, which is consistent with current clinical guidance (see http://www.nice.org.uk/CG90) that antidepressants are not recommended for first-line treatment of mild or moderate depression.

A thorough review of all available safety data has not identified any previously unrecognised safety concerns associated with reboxetine, and has confirmed the side-effect profile previously recognised.

Overall the balance of benefits and risks for reboxetine remains positive in its authorised indication.

Article citation: Drug Safety Update Sept 2011 vol 5, issue 2: H1.

1 Eyding D, et al. BMJ 2010; 341: c4737.

2 Bupropion, mirtazapine, and reboxetine in the treatment of depression. Translation of executive summary of the final report Bupropion, Mirtazapin und Reboxetin bei Depressionen (published by Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG, 2009). See https://www.iqwig.de/download/A05-20C_Executive_Summary_Bupropion_mirtazapine_and_reboxetine_in_depression.pdf

Further information:

BNF section 4.3.4 Other antidepressant drugs: http://bnf.org/bnf/bnf/61/60899.htm?q=reboxetine&t=search&ss=text&p=1

Continues…

Hot topic

H2 **Pseudoephedrine and ephedrine: update on managing risk of misuse**

Pseudoephedrine and ephedrine are medicines used as nasal decongestants, which are available from pharmacies. Between 2007 and 2008, we introduced restrictions on their use because of concern that medicines containing these active substances could be used in the illicit manufacture of the Class A controlled drug methylamphetamine.

Sales restrictions

Since April 2008, after public consultation and following advice from the Commission on Human Medicines (CHM) the following sales restrictions have been in place:

- It is illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction

Furthermore, the Royal Pharmaceutical Society advises that the sale and supply of these products must be made by a pharmacist or suitably trained pharmacy staff under the supervision of a pharmacist.

This information was published in the October 2008 issue of Drug Safety Update.

CHM has continually reviewed these measures and the impact on containing the potential problem of misuse.

Impact of restrictions: 2011 review

Between July 2010 and July 2011 there was one report in UK of limited misuse of these medicines. The evidence suggests that the restrictions are continuing to help manage the risk of misuse. Further information is available in our report: Pseudoephedrine and ephedrine: Managing the risk of misuse of medicines—July 2011 review).

Implementation of measures to regulate sales, together with the additional voluntary actions overseen by the profession, has made an important contribution to managing the risk of misuse. The CHM commended the pharmacy profession for their substantial contribution to managing the risk of misuse and recommended that existing levels of monitoring, education, and awareness measures by pharmacists should be maintained.

See http://www.rpharms.com/home/home.asp

See Drug Safety Update: Oct 2008 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087857; Sept 2009 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087910 ; and Sept 2010 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON093847

See July 2011 report: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON126277

Further information:

BNF section 3.10 Systemic nasal decongestants: http://bnf.org/bnf/bnf/61/20311.htm?q=pseudoephedrine&t=search&ss=text&p=1

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