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**

Volume 4, Issue 2, **September 2010**

Contents

The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medicaldevices 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.

NHS Evidence accredited provider

NHS Evidence - provided by NICE www.evidence.nhs.uk

For full details on our accreditation visit NHS Evidence [1]

Drug Safety Update brings you the latest information every month to support safer and effective use of medicines. This month, much of our advice relates to safer use in children.

Dexrazoxane (Cardioxane) is indicated for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin in patients with advanced or metastatic cancer after previous anthracycline-containing treatment. Prescribers should be aware that data on the efficacy of dexrazoxane as a cardioprotective agent in children is very limited. Furthermore, findings from clinical trials suggest an increased risk of secondary malignancies, particularly acute myeloid leukaemia and myelodysplastic syndrome (A1).

A review of published and unpublished data for inhaled and intranasal corticosteroids suggests that in addition to the known systemic effects of these medicines, a range of psychological or behavioural effects may also occur. These include psychomotor hyperactivity, sleep disorders, anxiety, depression, and aggression (particularly in children). See A4 for further information.

See also article H2 for a reminder to support the safer use of long-acting β2-agonists in the management of asthma in children younger than 12 years.

Finally this month, erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported in association with isotretinoin for severe acne. Patients starting treatment should be informed of the signs and symptoms of these serious skin eruptions and advised to stop treatment and contact their healthcare professional immediately if any of these arise (see A2).

Claire Tilstone, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Dexrazoxane: increased risk of secondary malignancies in children with haematological malignancies

A three-fold increased risk of secondary malignancies, particularly acute myeloid leukaemia and myelodysplastic syndrome, in association with the use of dexrazoxane (Cardioxane) combined with chemotherapy, has been reported from randomised clinical trials in children with Hodgkin's disease and acute lymphoblastic leukaemia. When considering treatment with dexrazoxane, prescribers should note that data on its efficacy as a cardioprotective agent in children is very limited, and that there is a possibility of inducing second tumours

Dexrazoxane

Dexrazoxane (Cardioxane) is indicated for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin in patients with advanced or metastatic cancer after previous anthracycline-containing treatment. An analogue of ethylene diamine-tetraacetic acid (EDTA), it is thought to reduce anthracycline-induced cardiotoxicity by chelation of free iron-containing cations. The drug is also an inhibitor of topoisomerase II and has cytotoxic properties. Most controlled clinical studies of dexrazoxane have been done in adult patients with advanced breast cancer.

Association with secondary malignancies

A publication [c1] in 2007 reported adverse outcomes from two clinical trials of children with Hodgkin's disease who were receiving dexrazoxane as cardioprotectant in combination with doxorubicin-containing chemotherapy. Eight patients developed acute myeloid leukaemia or myelodysplastic syndrome, six of whom were receiving treatment with dexrazoxane. There were two solid tumours (osteosarcoma and papillary thyroid carcinoma); both occurred outside the radiation field in recipients of dexrazoxane. The 4-year cumulative incidence for any second neoplasm was 3·43% (SE ±1·2%) in the dexrazoxane group versus 0·85% (±0·6%) in the non-dexrazoxane group (p=0·06).

Salzer and colleagues [c2] analysed long-term outcomes of paediatric trials in acute lymphoblastic leukaemia, including one trial in which the 10-year cumulative incidence of second malignancies was 4·2 (±2·2%) in patients who had received dexrazoxane versus 1·3 (±0·9%) in patients who had not received dexrazoxane (p=0·15).

Furthermore, three cases of acute myeloid leukaemia have been reported in France in adults with breast cancer up to August 2010. In 1985, 15 cases of acute myeloid leukaemia were reported [c3] in UK adults with gastrointestinal malignancies and psoriasis who had been treated with razoxane—a racemic mixture of dexrazoxane and levrazoxane; razoxane is no longer available.

Advice for healthcare professionals:

- Data on the efficacy of dexrazoxane as a cardioprotective agent in children is very limited
- The possibility of induction of secondary malignancies should be taken into account when considering treatment with dexrazoxane

Further information

See letter sent to healthcare professionals, August 2010 [2]

c1: Tebbi CK, et al. J Clin Oncol 2007; 25: 493–500

c2: Salzer WL, et al. Leukemia 2010; 24: 355–70

c3: Caffrey EA, et al. Br J Dermatol 1985; 113: 131–34

A2 Isotretinoin: risk of serious skin reactions

Erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported in association with isotretinoin, and may result in hospitalisation, disability, life-threatening events, or death. Patients starting isotretinoin treatment should be informed of the signs and symptoms of these serious skin eruptions and advised to stop treatment and contact their healthcare professional immediately if any of these arise

Isotretinoin (brand leader Roaccutane) is a treatment for severe acne that is resistant to adequate courses of standard antibacterial or topical therapy. Over the past 25 years in which isotretinoin has been on the market, it has been prescribed worldwide for approximately 16 million patients.

Association with serious skin reactions

The licence holder for Roaccutane identified a possible association between isotretinoin use and serious skin conditions including erythema multiforme (EM), Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) after a thorough review of the data held in their global safety database. This review identified 66 cases of severe skin reactions have been reported worldwide to date in association with isotretinoin as follows: 15 cases of SJS; 44 cases of EM (in four of which rash symptoms reoccurred when isotretinoin was reintroduced); and five cases of TEN.

Although there are other possible explanations for most of the reports, a causal association between isotretinoin and these severe skin reactions cannot be excluded.

Advice for healthcare professionals:

- Serious skin reactions (EM, SJS, and TEN) have been reported in association with isotretinoin, which may result in hospitalisation, disability, life-threatening events, or death
- Isotretinoin must be immediately discontinued and appropriate supportive care given if symptoms of EM, SJS, or TEN develop
- Patients starting isotretinoin treatment should be informed of the signs and symptoms of these serious skin eruptions and advised to stop treatment and contact their healthcare professional immediately if any of these arise

Further information

See also report from the European Pharmacovigilance Working Party, July 2010[3]

A3 Sprayable fibrin sealants: risk of life-threatening air or gas embolism

Vigilance is required during administration of sprayable fibrin sealants using an applicator attached to a pressure regulator. To avoid potentially fatal air or gas embolism, do not exceed the recommended pressure for the regulator device and ensure adequate distance from the tissue surface

Four sprayable fibrin sealants are authorised in the UK:

- Evicel ▼
- Quixil
- Tisseel Lyo
- Tisseel Ready to use

Summaries of Product characteristics are available at: European Medicines Agency [4]

Europe-wide, five cases of air embolism after spray application with a fibrin sealant have been received up to August 2010. Of these, two patients experienced life-threatening air embolism (one patient had a fatal outcome). All five reports were related to inappropriate use of the spray applicator, which was used to apply high-pressure air or gas in close proximity to tissue surfaces and large open vessels.

Evicel, Tisseel Lyo, and Tisseel Ready to Use are second-generation sprayable fibrin sealants that consist of two human plasma-derived components—human fibrinogen and human thrombin. They are indicated for use as supportive treatment in surgery where standard surgical techniques are insufficient for improvement of haemostasis, and as suture support for haemostasis in vascular surgery.

Quixil is a first-generation sprayable fibrin sealant that also consists of human fibrinogen and human fibrin. The fibrinogen component of Quixil is different to the other fibrin sealants in that it contains tranexamic acid, which inhibits the degradation of fibrin.

Product information for all sprayable fibrin sealants has been updated to include advice on prevention of air or gas embolism.

Advice for healthcare professionals:

To prevent life-threatening air or gas embolism during application of a fibrin sealant using a spray applicator, it is important that the following advice is adhered to:

- The regulator pressure should not exceed 2.0–2.5 bars for Quixil and 1.4–1.7 bars for Evicel, Tisseel Lyo, and Tisseel Ready to Use
- Do not spray closer than 10–15 cm from the tissue surface
- Changes in blood pressure, pulse rate, oxygen saturation, and end tidal CO_2 should be monitored during application because of the possibility of occurrence of air or gas embolism
- Follow manufacturer's instructions for use of accessory tips when used with these products

See letter for healthcare professionals, August 2010 [5]

Reporting of suspected adverse reactions

Healthcare professionals are reminded to report all suspected adverse reactions to fibrin sealants promptly via the Yellow Card Scheme (see www.yellowcard.gov.uk [6]).

Published September 13, 2010; Drug Safety Update Volume 4, Issue 2. Crown copyright 2010

A4 Inhaled and intranasal corticosteroids: risk of psychological and behavioural side effects

Psychological and behavioural side effects may occur in association with use of inhaled and intranasal formulations of corticosteroids

Inhaled corticosteroids are used for the prevention of asthma. Intranasal corticosteroids are used in the management of hayfever, allergy, and some nasal conditions.

We have previously reminded healthcare professionals that psychiatric side effects can occur with all systemic steroids (See Drug Safety Update September 2007 [7], p 9).

A review of data for inhaled and intranasal corticosteroids suggests that in addition to the known systemic effects of these medicines, a range of psychological or behavioural effects may also occur. These include psychomotor hyperactivity, sleep disorders, anxiety, depression, and aggression (particularly in children).

See www.mhra.gov.uk/drugsafetyupdate

Affective disorders may be more frequently reported in patients with asthma or allergy than in patients without these conditions; however, treatment with inhaled and intranasal corticosteroids is also widespread in these patient groups, as is treatment with some substances known to be associated with behavioural and sleep disorders (such as β-receptor agonists).

Advice for healthcare professionals:

- All patients (or their carers) should be informed of the important benefits of steroid treatment, and should be advised of these safety issues
- All patients (or their carers) who receive steroids should receive a Patient Information Leaflet and be encouraged to read it
- Patients should keep using their steroid medication, but should seek medical advice in the event of worrying symptoms or illness while taking steroids

Published September 13, 2010; Drug Safety Update Volume 4, Issue 2.

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions in the UK. See www.yellowcard.gov.uk

Y1 Yellow Cards which made a difference: protease inhibitors and lipodystrophy

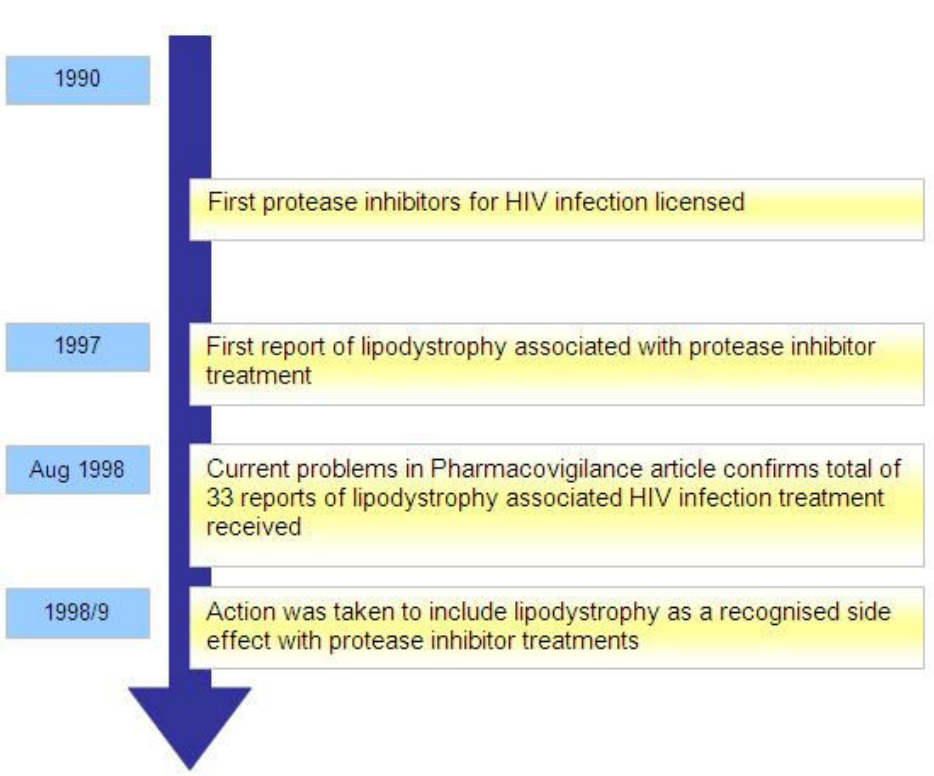
Yellow Cards: helping safeguard public health

The Yellow Card Scheme principally acts as an early warning system for identifying previously unrecognised adverse drug reactions (ADRs). However, it also provides valuable information on recognised ADRs, allowing us to identify and refine the understanding of risk factors that may affect the clinical management of patients.

The value of the scheme has been demonstrated many times and it has helped to identify numerous important safety issues. Many of the safety issues detected were not recognised as being related to treatment with a particular medicine until they were identified as a result of Yellow Cards.

Making a difference: Yellow Cards reporting lipodystrophy with protease inhibitors

In the late 1990s the first protease inhibitors for treatment of HIV infection were licensed. In 1997 we received the first reports of lipodystrophy associated with protease-inhibitor treatment. By August 1998, 33 reports of lipodystrophy associated with HIV treatment had been received (see Current problems in Pharmacovigilance, August 1998 [8]). Although not all were taking protease inhibitors, this class of drug seemed to be a strongly related factor for lipodystrophy. We asked professionals to report ADRs to all antiretroviral drugs to help further characterise the reaction and the longer-term consequences.



Continues...

As the evidence-base increased for an association between protease inhibitors and lipodystrophy, action was taken to include this as a recognised side effect in 1998–99. Lipodystrophy is now a well-recognised class effect with protease inhibitors and warnings are listed in safety information for, amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, ritonavir, saquinavir, and tipranavir. Overall, however, the benefits of protease inhibitors outweigh any risks for most patients. Combination antiretroviral therapy including a protease inhibitor delays progression of HIV infection.

Yellow Cards provided vital evidence on this emerging safety issue, and they show how the information provided by reporters is crucial. Show your support of the Yellow Card Scheme by reporting suspected adverse drug reactions for medicines and vaccines, and you can help make medicines safer.

Report online at www.yellowcard.gov.uk[6].

Published September 13,2010; Drug Safety Update Volume 4, Issue 2. Crown copyright 2010

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions in the UK. See www.yellowcard.gov.uk

Y2 New Freepost address for Yellow Cards

You maybe aware that we are moving offices in the near future (see Relocation of the MHRA head office[9]). In order to ensure that Yellow Cards continue to reach us promptly, we have set up a Freepost service at our new building. From now on, the only address information you should put on the envelope is FREEPOST YELLOW CARD; no other address details or stamps are required.

Although post sent to the old addresses will continue to be delivered via redirect, using the new address will be faster. The most efficient way to report a suspected adverse drug reaction is online at www.yellowcard.gov.uk[6]

Published September 13,2010; Drug Safety Update Volume 4, Issue 2. Crown copyright 2010

Hot topic

H1 Pseudoephedrine and ephedrine: update on managing risk of misuse

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

Sales restrictions

In April 2008, following consultation and advice from the Commission on Human Medicines (CHM), the following sales restrictions came into force:

- It became illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It became 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 became illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction

Sales restrictions
see Drug Safety Update October 2008 [10], p 6

Furthermore, the Royal Pharmaceutical Society of Great Britain advised 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.

See Drug Safety Update October 2008 [10], p 6

Successful impact of restrictions—2010 update

CHM has continually reviewed the impact of these measures, which are helping to contain the potential problem of misuse (see Drug Safety Update, September 2009 [11], p 5). Between July 2009 and July 2010, there have been no new reports of the misuse of these medicines (see Pseudoephedrine and ephedrine: Managing the risk of misuse of medicines - July 2010 update [12]).

CHM commended the pharmacy profession for their significant contribution towards helping to keep the situation under control. It noted that implementation of the measures introduced to regulate sales, together with the additional voluntary actions overseen by the profession, had so far been effective. CHM recommended that the existing levels of monitoring, education, and awareness measures by pharmacists should be maintained.

Published September 13,2010; Drug Safety Update Volume 4, Issue 2.

Hot topic

H2 Long-acting β2-agonists: reminder for use in children and adults

Following a previous review in 2007 of long-acting β2-agonists (LABA) in the treatment of adults, adolescents, and children with asthma, we have further reviewed the use of LABA, specifically in children younger than age 12 years.

All available data on the use of LABA in the treatment of asthma in children were reviewed, and it was concluded that the benefits of these medicines used in conjunction with inhaled corticosteroids (ICS) in the control of asthma symptoms in children outweigh any apparent risks.

Advice for all patients:

Prescribers are reminded to follow the advice on the management of asthma from the Commission on Human Medicines, consistent with the guideline from The British Thoracic Society [13] and Scottish Intercollegiate Guidelines Network. In particular:

- Always prescribe LABA with concomitant ICS and only when ICS alone are not sufficient to control asthma symptoms
- LABA should not be initiated in patients with rapidly deteriorating asthma
- Review LABA therapy regularly, prescribe the lowest effective dose, and stop if there is no benefit
- Stepping-down therapy should be considered when good long-term asthma control has been achieved
- LABA should not be prescribed for the relief of exercise-induced asthma symptoms in the absence of regular ICS (a short-acting β2-agonist should be used in this situation)
- Combination inhalers should be prescribed when appropriate to aid compliance in line with NICE Guidance [14]

Further advice for use in children:

Prescribers are advised that a daily dose of 24 micrograms formoterol should be sufficient for most children, particularly for younger age-groups. Higher doses should be used rarely, and only when control is not maintained on the lower dose.

Further information about LABA in asthma management is available on our website (see Asthma: Long-acting β2 agonists [15])

Published September 13,2010; Drug Safety Update Volume 4, Issue 2.

Stop press

S1 Medstream Implantable Drug Pumps: check pumps after MRI

Codman has issued a safety notice about their **Medstream Implantable Drug Pumps**. After MRI, five pumps have shut down, alarmed, and could not be reset using the physician control unit. However, they could be reset and restarted by Codman field support technicians using a technician key.

Clinicians are reminded that pumps need to be checked after any MRI exposure, and that support technicians should be contacted if there are effects that cannot be addressed using the physician control unit.

See Implants, active, infusion pumps - Codman & Shurtleff Inc - Medstream Implantable Drug Pump - updated [16]

Published September 13,2010; Drug Safety Update Volume 4, Issue 2. Crown copyright 2010

Footnotes

Citations

c1: Tebbi CK, et al. J Clin Oncol 2007; **25**: 493–500
c2: Salzer WL, et al. Leukemia 2010; **24**: 355–70
c3: Caffrey EA, et al. Br J Dermatol 1985; **113**: 131–34

URLS

1. http://www.evidence.nhs.uk/Accreditation/

2. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON090791

3. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/07/WC500095336.pdf

4. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124

5. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON093769

6. http://www.yellowcard.gov.uk/

7. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2032233&RevisionSelectionMethod=LatestReleased

8. http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007471

9. http://www.mhra.gov.uk/Aboutus/RelocationoftheMHRA/index.htm

10. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON028266&RevisionSelectionMethod=LatestReleased

11. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON057142&RevisionSelectionMethod=LatestReleased

12. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON090754

13. http://www.brit-thoracic.org.uk/clinical-information/asthma/asthma-guidelines.aspx

14. http://guidance.nice.org.uk/

15. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1016

16. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/FieldSafetyNoticesformedicaldevices/CON081780