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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In this issue: new simplified guidance for the treatment of acute **paracetamol overdose** with intravenous acetylcysteine is now in place. The new guidance includes an updated treatment nomogram, and all patients with a timed plasma paracetamol level on or above a single treatment line joining the points of 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion should receive acetylcysteine, regardless of risk factors for hepatotoxicity See article A1 for further information.

Also this month: clinicians should be aware that oseltamivir (**Tamiflu**) 12 mg/mL oral suspension is no longer available. From early October 2012 it will be replaced by a **6 mg/mL** suspension, and a new dosing dispenser, calibrated in mL, will be introduced at the same time. Until October 2012 there will be no Tamiflu oral suspension products available in the UK; however, Tamiflu hard capsules remain available and these can be used to prepare a suspension if needed (see article A2)

There have been reports of acute pancreatitis occurring with the antidiabetic drugs dipeptidylpeptidase-4 inhibitors ('**gliptins**'). Prescribers of these medicines should inform their patients of the symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and discontinue treatment if pancreatitis is suspected (article A3).

See article S1 for news on life-threatening complications of severe skin reactions, including five cases of necrotising fasciitis, which have been reported in patients treated with **panitumumab.** Treatment must be withheld or discontinued if such complications develop.

And finally: **levofloxacin** may only be considered in the treatment of acute bacterial sinusitis, chronic bronchitis, pneumonia, or skin/soft-tissue infections when other medicines cannot be prescribed or have been ineffective. See article S2 for more information.

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Drug safety advice

A1 Paracetamol overdose: new guidance on treatment with intravenous acetylcysteine

New simplified guidance on treating paracetamol overdose with intravenous acetylcysteine is as follows:

- All patients with a timed plasma paracetamol level on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion should receive acetylcysteine (Parvolex or generics) based on a new treatment nomogram, regardless of risk factors for hepatotoxicity (see Figure 1 below)

- Where there is doubt over the timing of paracetamol ingestion including when ingestion has occurred over a period of one hour or more – 'staggered overdose' – acetylcysteine should always be given without delay (the nomogram should not be used)

- Administer the initial dose of acetylcysteine as an infusion over 60 minutes to minimise the risk of common dose-related adverse reactions

- Hypersensitivity is no longer a contraindication to treatment with acetylcysteine

Paracetamol overdose can result in liver damage which may be fatal. Intravenous acetylcysteine is the antidote to treat paracetamol overdose and is virtually 100% effective in preventing liver damage when given within 8 hours of the overdose. After this time efficacy falls substantially, affording only a very limited window of time in which to successfully prevent serious hepatotoxicity.

New simplified guidance on the treatment of acute paracetamol overdose with acetylcysteine is now in place, following an evidence-based review by the Commission on Human Medicines (CHM).

Review findings

Previously, healthcare professionals treating paracetamol overdose were advised to assess for risk factors of hepatotoxicity such as chronic alcohol consumption, co-medications and poor nutritional intake. This resulted in two lines on the treatment nomogram – one for patients with risk factors and one for those without. The CHM review found that the evidence base to support the use of risk factors was poor and inconsistent, and that many of the risk factors for hepatotoxicity were imprecise and difficult to determine with sufficient certainty in clinical practice. By removing the need to assess risk factors for hepatotoxicity, the approved indication for acetylcysteine is greatly simplified to a single line on the paracetamol overdose treatment nomogram (figure 1).

In the past there were also a substantial number of reports of administration errors with intravenous acetylcysteine, some of which had the potential to result in significant harm. A major contributory factor for these errors was the complex dosing regimen for intravenous acetylcysteine. The CHM recommended a number of measures to reduce the incidence of administration errors, most notably the introduction of weight-based dosage tables for adults and children to remove the need to calculate the dose.

The majority of common dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine. Sufficient evidence of efficacy is available to support extending the time of the initial infusion from 15 minutes to 60 minutes in order to reduce the incidence of adverse reactions.

There are now no specific contraindications to acetylcysteine in the treatment of paracetamol overdose, including known hypersensitivity to any of the ingredients in the product. Even if a patient has a history of a previous reaction to intravenous acetylcysteine, the benefits of acetylcysteine outweigh the risks in such cases, and patients should receive treatment. Any 'hypersensitivity-like' reactions ascribed to acetylcysteine are likely to be anaphylactoid in nature; ie, they are not immunologically mediated and therefore may not occur on repeated exposure.

Advice for healthcare professionals:

- All patients with a timed plasma paracetamol level on or above a single treatment line joining points of 100mg/L at 4 hours and 15mg/L at 15 hours after ingestion should receive acetylcysteine (Parvolex or generics) based on a new treatment nomogram, regardless of risk factors (see Figure 1 below)
- Where there is doubt over the timing of paracetamol ingestion including when ingestion has occurred over a period of one hour or more – 'staggered overdose' – acetylcysteine should be given without delay (the nomogram should not be used).
- Administer the initial dose of acetylcysteine as an infusion over 60 minutes to minimise the risk of common dose-related adverse reactions
- Hypersensitivity is no longer a contraindication to treatment with acetylcysteine
- New weight-based dosing tables and a technical information leaflet (TIL) to help calculate the dose of acetylcysteine and infusions to minimise the risk of dosing errors are available to download [see margin link to MHRA webpage]
- A model patient discharge leaflet for patients who have taken a paracetamol overdose but who are not treated with acetylcysteine is available to download [see margin link to MHRA webpage]

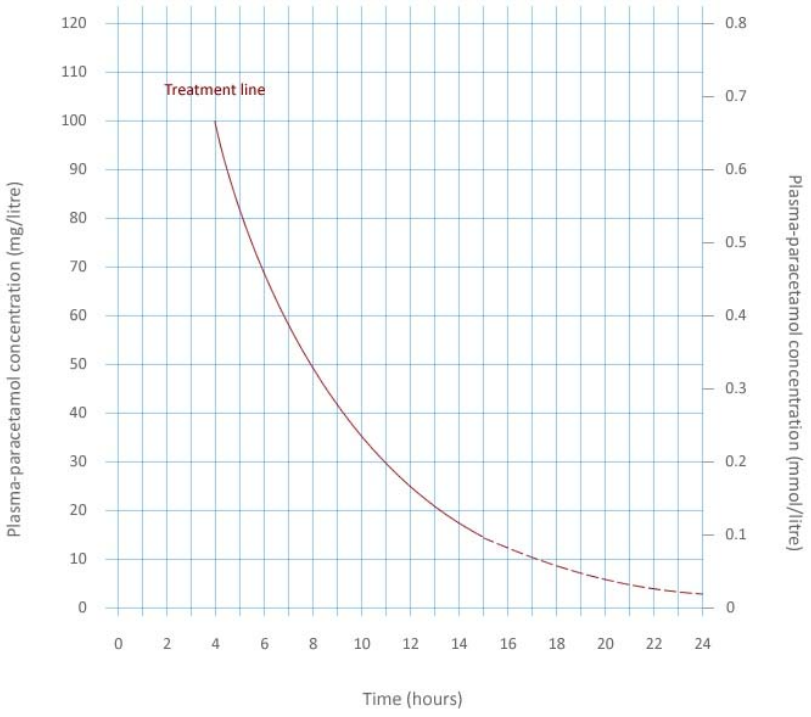
Please report serious adverse reactions to acetylcysteine or any other medicine to the MHRA through the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

Further information:

Letter sent to healthcare professionals in September 2012 [https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=101827]

MHRA webpage on new guidance for the treatment of paracetamol overdose with acetylcysteine [http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON178225]

Figure 1. New treatment nomogram for paracetamol overdose



Article citation: Drug Safety Update September 2012 vol 6, issue 2: A1.

A2 **Oseltamivir (Tamiflu): changed concentration and dosing dispenser of oral suspension from October 2012**

From early October 2012, the strength of oseltamivir (Tamiflu) oral suspension will be **6 mg/mL**. A new dosing dispenser, calibrated in mL, will be introduced at the same time. Prescriptions for Tamiflu oral suspension should state the dose in mL, and healthcare professionals should advise patients and/or carers of the changes in the dose, packaging, dose dispenser and leaflet.

The 12 mg/mL suspension is no longer available, and there will be no Tamiflu oral suspension products available in the UK until October 2012. However, Tamiflu hard capsules remain available and these can be used to prepare a suspension if needed.

Oseltamivir (Tamiflu) is licensed to treat patients aged 1 year and above with symptoms of influenza when the virus is circulating in the community. It is also licensed to prevent influenza in individuals who have been in contact with a clinically diagnosed case of influenza when the virus is circulating in the community. Tamiflu should not be given to infants aged below 12 months except during pandemic outbreaks of influenza. Tamiflu is available as hard capsules and an oral suspension.

Changes to concentration of oral suspension

The 12 mg/mL suspension which is used for children, and for those who find it difficult to swallow tablets, has been withdrawn and will be replaced in October 2012 by a more dilute 6 mg/mL suspension. The new strength will make it possible to dispense the dose with greater accuracy. At the same time, a new dosing dispenser, calibrated in millilitres will be introduced and the dosing tables in the product information will include a new column showing the volume in millilitres based on the new 6 mg/mL concentration.

Summary of Product Characteristics for Tamiflu oral suspension 6 mg/mL [http://www.medicines.org.uk/EMC/medicine/26927/SPC/Tamiflu+6+mg+ml+Powder+for+Oral+Suspension/]

In August 2012 a letter was sent to healthcare professionals informing them of the new changes. It is important for clinicians and their patients to be aware of these changes in the concentration of the oral suspension and in the way the dose dispenser is calibrated.

Letter sent to healthcare professionals in August 2012 [http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con183920.pdf]

Advice for healthcare professionals:

- Tamiflu oral suspension 12 mg/mL is no longer available. It will be replaced by a **6 mg/mL** suspension from early October 2012. Please note that from end July 2012 – early October 2012 there will be no Tamiflu oral suspension products available in the UK; however, Tamiflu hard capsules remain available in this period and these can be used to prepare a suspension
- When prescribing Tamiflu oral suspension, state the dose in millilitres (mL). The dosing tables in the Summary of Product Characteristics for the 6 mg/mL suspension include a column showing this dosage.
- Ensure that patients and/or carers are made aware that the product is different from what they may have used in the past and that the dose dispenser, carton packaging and packaging leaflet have changed.

Further information:

BNF section 5.3 Antiviral drugs [http://www.medicinescomplete.com/mc/bnf/current/3992.htm]

Please remember to report suspected adverse reactions to Tamiflu, or any medicine or vaccine, on a Yellow Card at www.mhra.gov.uk/yellowcard

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A3 Dipeptidylpeptidase-4 inhibitors ('gliptins'): risk of acute pancreatitis

There have been reports of acute pancreatitis associated with drugs in the dipeptidylpeptidase-4 (DPP-4) inhibitor class of antidiabetic agents ('gliptins'). Patients should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and encouraged to tell their healthcare provider if they have such symptoms. If pancreatitis is suspected, the DPP-4 inhibitor and other potentially suspect medicinal products should be discontinued.

DPP-4 inhibitors are indicated for the improvement of glycaemic control in adults with type 2 diabetes mellitus. Drugs of this class include Onglyza▼ (saxagliptin), Trajenta▼ (linagliptin), Galvus▼ (vildagliptin) and Januvia (sitagliptin). A number of fixed-dose combination tablets containing a DDP-4 inhibitor with metformin are also available, including Eucreas▼ (vildagliptin) and Janumet (sitagliptin).

Risk of pancreatitis

An increased risk of acute pancreatitis has been identified for all approved DPP-4 inhibitors. For most of the compounds this was detected in spontaneous post-marketing reports; for one of the newer compounds, linagliptin, a small increased number of cases compared with placebo was detected in clinical development.

See:
http://www.medicines.org.uk/EMC/default.aspx

Consequently, pancreatitis is now included in the product information for all DPP-4 inhibitors as a possible adverse reaction. The reporting rate of pancreatitis appears to be low (ranging between 1/1 000 and 1/100 patients receiving the drug) but the precise frequency is unknown as few cases have been reported in clinical trials. In most cases, pancreatitis resolved after discontinuation of treatment.

The possible mechanism leading to acute pancreatitis is not clear. Data from animal studies have been inconclusive or have not suggested a safety concern. In addition, patients with diabetes are known to have a higher incidence of pancreatitis compared with non-diabetic patients.

Further information:

NICE guidance on the treatment of type 2 diabetes [link to: http://guidance.nice.org.uk/CG87]

BNF section 6.1.2. Antidiabetic drugs [link to: http://www.medicinescomplete.com/mc/bnf/current/4163.htm]

Advice for healthcare professionals:

- Patients treated with DDP-4 inhibitors should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and encouraged to tell their healthcare provider if they have such symptoms.
- If pancreatitis is suspected, the DPP-4 inhibitor and other potentially suspect medicines should be discontinued
- Report suspected adverse reactions through the Yellow Card Scheme—see www.yellowcard.gov.uk. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, and treatment dates.

Article citation: Drug Safety Update September 2012 vol 6, issue 2: A3.

Stop press

S1 **Panitumumab (Vectibix): risk of necrotising fasciitis**

Panitumumab (Vectibix) is an epidermal growth factor receptor inhibitor used as monotherapy and in combination with oxaliplatin- and irinotecan-based chemotherapy to treat patients with non-mutated (wild-type) *KRAS* metastatic colorectal cancer.

Severe skin reactions with panitumumab use are known to be very common (≥1/10 individuals) and may be followed by life-threatening and fatal infectious complications including sepsis and cellulitis. In addition, five cases of necrotising fasciitis, three of which were fatal, have now been reported in patients treated with panitumumab in combination with chemotherapy. The cases occurred both in clinical trials and the post-marketing setting.

The main symptoms of necrotising fasciitis are: intense and severe pain which may seem out of proportion to any external signs of infection on the skin; fever, diarrhoea and vomiting and eventual unconsciousness; skin typically becoming a dark violet colour, with the formation of blisters and death of the tissue underneath.

Patients who have severe skin reactions or who develop worsening skin reactions whilst receiving panitumumab should be monitored for the development of inflammatory or infectious sequelae. If such complications develop, withhold or discontinue panitumumab, and initiate appropriate therapy promptly.

Further information:

Letter sent to healthcare professionals in August 2012 [http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con175480.pdf]

BNF section 6.1: Cytotoxic drugs [http://www.medicinescomplete.com/mc/bnf/current/4676.htm]

Article citation: Drug Safety Update September 2012 vol 6, issue 2: S1.

S2 **Levofloxacin: some indications restricted**

Levofloxacin (a fluoroquinolone antibiotic) may only be considered in the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, community acquired pneumonia or complicated skin and soft tissue infections when other medicines cannot be prescribed, or have been ineffective.

This restriction resulted from a review of overall efficacy and safety data, which suggested that the safety profile of levofloxacin was unfavourable as first-line treatment for these indications. The risks contributing to this assessment included serious hepatotoxicity, cardiac arrhythmia, severe skin reactions and tendon rupture.

Other licensed indications for oral and intravenous levofloxacin remain unchanged.

Product information for all levofloxacin products will be updated with the recommendations. Official guidance on the appropriate use of antibiotics and the prevalence of resistance (such as NICE guidance) should be considered when prescribing levofloxacin.

Further information:

British Thoracic Society Guidelines: [link to: http://www.brit-thoracic.org.uk/guidelines.aspx]

BNF section 5.1: Antibacterial drugs [http://www.medicinescomplete.com/mc/bnf/current/201584.htm]

NICE guidance: http://www.nice.org.uk/#panel3

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