Drug Safety Update

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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The Department of Transport has introduced a new offence of driving with certain drugs above specified limits in the blood; this is likely to come into force on 2nd March 2015. Anyone found to have any of these drugs in their blood above the specified limits will be guilty of an offence, whether their driving was impaired or not. However, there is a medical defence for people taking the drugs for medical reasons, if their ability to drive was not impaired—see article A1.

Also, some newly issued vials of intravenous dantrolene (Dantrium intravenous) may contain crystals of undissolved dantrolene sodium following reconstitution. New advice is to draw up the reconstituted solution with a filter needle to prevent these crystals from being administered to patients. There may be a residual increased risk of injection site reactions as some crystals may remain present after filtration; heightened vigilance is therefore required—see article A2.

We also take this opportunity to remind you of the risks of life-threatening harm from accidental exposure to transdermal fentanyl "patches". Children are at particular risk as they may touch, suck, chew, or swallow a patch that has not been disposed of properly. We therefore remind you to provide clear information to patients and caregivers regarding the risk of accidental patch transfer and ingestion of patches, and the need for appropriate disposal of patches—see article S1.

Maria Root, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Drugs and driving: blood concentration limits to be set for certain controlled drugs in a new legal offence

The Department of Transport has introduced a new offence of driving with certain controlled drugs above specified limits in the blood; this is likely to come into force on 2nd March 2015. The list of drugs includes some licensed medicines. Anyone found to have any of these drugs in their blood above the specified limits will be guilty of an offence, whether their driving was impaired or not. However, there is a medical defence for people taking the drugs for medical reasons, if their ability to drive was not impaired. Advise patients to continue taking their medicines as prescribed

A new offence of driving with certain controlled drugs* above specified limits in the blood is expected to come into force on 2nd March 2015.† These drugs include some prescribed medicines. Anyone found to have any of the drugs above specified limits in their blood will be guilty of an offence, whether their driving was impaired or not. A preliminary, non-specific roadside test may be used to detect if an individual has any of the drugs in their body. To identify the particular drug taken and quantify blood levels, a blood sample will be taken at a police station and sent for forensic analysis.

*Controlled drugs are defined in the Misuse of Drugs Act 1971

†Dependent upon the regulations being approved before Parliament is dissolved on 30 March 2015 prior to the General Election of 7 May 2015.

The legislation provides a statutory "medical defence" for people taking the drugs for medical reasons, **if their driving was not impaired**. The conditions of the medical defence state that the individual is not guilty of an offence if:

- the medicine was prescribed, supplied, or sold to treat a medical or dental problem, and
- it was taken according to the instructions given by the prescriber or the information provided with the medicine.

The individual may need to provide written evidence to satisfy the points above (eg, the tear-off section of a prescription or the medicine's patient information leaflet).

If the individual's driving is impaired, they can be found guilty of an offence under the current law, which has no statutory medical defence and will not change.

Drugs included in the new offence that might be used for medicinal purposes:

- Cannabis (tetrahydrocannabinol, THC)
- Cocaine
- Morphine
- Diamorphine
- Methadone
- Ketamine
- Amphetamine‡
- Flunitrazepam§
- Clonazepam
- Diazepam
- Lorazepam
- Oxazepam
- Temazepam

‡Whilst amphetamine will not be included in the current regulations to go before Parliament in 2014, it is expected to be included later in 2015 once a limit has been agreed

§Not currently licensed in the UK

Although only a few benzodiazepines and opioids are included in the list above, all benzodiazepines and opioids can impair driving ability. The risk of driving impairment is increased if the medicine is taken with alcohol. Warnings on the risks of driving impairment are already in the patient information leaflet.

Advice for healthcare professionals:

- Any condition that requires medicinal treatment may itself pose a risk to driving ability if left untreated. Therefore it is important to advise patients to continue their treatment.

Advice to give to patients taking any medicine:

- Continue taking your medicine as prescribed
- Check the leaflet that comes with your medicine for information on how your medicine may affect your driving ability
- It is against the law to drive if your driving ability is impaired by this medicine
- Do not drive while taking this medicine until you know how it affects you (especially just after starting or changing the dose of the medicine)
- Do not drive if you feel sleepy, dizzy, unable to concentrate or make decisions, or if you have blurred or double vision

Further information:

Information leaflet to give to patients http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con437439.pdf

Guidance document from the Department for Transport: https://www.gov.uk/government/collections/drug-driving.

Article citation: Drug Safety Update volume 7 issue 12, July 2014: A1.

A2 Intravenous dantrolene: risk of skin and injection site reactions from undissolved crystals—use a filter needle when drawing up reconstituted dantrolene solution and remain vigilant

Some newly issued vials of intravenous dantrolene may contain crystals of undissolved dantrolene sodium following reconstitution. Draw up the reconstituted solution with a filter needle to prevent these crystals from being administered to patients. There may be a residual increased risk of injection site reactions due to crystals that may not have been removed by filtration; heightened vigilance is therefore required

Intravenous dantrolene (Dantrium intravenous) is indicated for the treatment of malignant hyperthermia, a rare and potentially fatal condition induced by inhalational anaesthetics and depolarising neuromuscular blockers. Dantrium intravenous is the only product licensed in the EU for this indication.

Due to a manufacturing problem, visible crystals of undissolved dantrolene sodium have been seen in some newly issued vials following reconstitution.

Emergency measures

Emergency measures have been put in place until a definitive solution to the manufacturing problem is found. The measures apply to newly issued stock only.

Newly issued packs of intravenous dantrolene are being supplied with one filter needle per vial of dantrolene (BD Blunt Fill Needle with 5 micron filter 18 G 40 mm). Once reconstituted, draw up the dantrolene solution with the filter needle provided to minimise the risk of administering crystals to patients. This advice applies immediately to all newly issued packs of intravenous dantrolene until further notice.

Instruction leaflets have been included in all newly issued dantrolene packs along with the filter needles. Stickers with the same information were sent in a letter to healthcare professionals in June (see further information below). When refilling emergency toolkits for malignant hyperthermia, place the dantrolene pack with the leaflet and filter needle in the toolkit and stick the sticker onto a clearly visible surface of the toolkit.

Existing stock (ie, vials supplied without a filter needle) does not require filtering.

Extension of expiry date of existing stock

In January 2014, the Department of Health and the licence-holder contacted Trust Pharmacists to extend the shelf life of some intravenous dantrolene batches (see further information below). This was to prevent a stock shortage while the manufacturing problem was being resolved.

Trusts that are currently using batches with an extended shelf life should continue to use them. The licence-holder will contact these trusts before the extended expiry date to advise on when to replace these batches and to remind trusts to use the filter needle provided when using the new stock.

Risk of skin reactions
Dantrolene is associated with injection site reactions including redness, rash, swelling, localized pain, thrombophlebitis, and tissue necrosis. This risk may be increased by the crystals from affected vials. Although using filter needles should reduce this risk, be vigilant for the development of injection site reactions.

Dose
Filtration does not reduce the amount of intravenous dantrolene in solution and will not affect efficacy. Intravenous dantrolene should be administered as currently recommended.

The product information states that the initial dantrolene dose should be 1 mg/kg. If the physiological and metabolic abnormalities persist or reappear, this dose may be repeated up to a cumulative dose of 10 mg/kg. If a relapse or recurrence occurs, dantrolene should be re-administered at the last effective dose.

Advice for healthcare professionals:

- When refilling emergency toolkits for malignant hyperthermia, place the dantrolene pack with the instruction leaflet and filter needle provided into the toolkit and stick the sticker onto a clearly visible surface of the toolkit

Administration
- Use the filter needle provided when drawing up reconstituted dantrolene solution
- Use one filter needle per vial
- Administer the solution immediately once reconstituted

Skin reactions
- Be vigilant for skin and injection site reactions

Dose
- Filtration does not reduce the amount of intravenous dantrolene in solution and will not affect efficacy
- Give an initial dose of 1mg/kg of dantrolene
- If malignant hyperthermia persists or reappears, repeat this dose up to a cumulative dose of 10 mg/kg. If a relapse or recurrence occurs, re-administer dantrolene at the last effective dose

Advice for Trusts using batches with an extended shelf life
- Trusts that are using batches with an extended shelf life should continue to use them

Further information

Letter sent to healthcare professionals in June 2014
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con428393.pdf

Letter sent to healthcare professionals in January 2014
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con437441.pdf

Article citation: Drug Safety Update volume 7 issue 12, July 2014: A2.

Stop press

S1 **Transdermal fentanyl "patches": reminder of potential for life-threatening harm from accidental exposure, particularly in children**

Drug Safety Update article September 2008
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087796

Accidental exposure to transdermal fentanyl can occur if a patch is swallowed or transferred to another individual (see Drug Safety Update article September 2008). A recent EU-wide review emphasised the need for safe handling of patches. To date, we have received three Yellow Card reports of describing accidental contact with or transfer of fentanyl patches.

Children are at risk as they may touch, suck, chew, or swallow a patch that has not been disposed of properly. Also, children have a lower threshold for fentanyl overdose than adults. Two of the three Yellow Card reports we have received to date concerned children.

Further information

Letter sent to healthcare professionals in June 2014
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con428394.pdf

Information leaflet to give to patients and caregivers
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con437440.pdf

We therefore remind you to provide clear information to patients and caregivers regarding risk of accidental patch transfer and ingestion of patches, and need for appropriate disposal of patches. Advise patients and caregivers to follow the instructions on the patch carton and in the accompanying leaflet. If a patch is transferred to another person, it should be removed and the individual should get medical help immediately. If a patch is swallowed, the individual should get medical help immediately

Please report any cases of accidental exposure where harm has occurred or suspected side effects via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

Article citation: Drug Safety Update volume 7 issue 12, July 2014: S1.

S2 **Administration errors with drugs for infusion: ensure appropriate checking procedures are in place**

Take care to ensure that checking procedures are in place to reduce the risk of administration errors with drugs for infusion.

We have recently received reports of mannitol being administered instead of sodium chloride (saline) and vice versa. Mannitol is an osmotic diuretic used to decrease a patient's fluid status. Saline is used to hydrate a patient and restore their fluid status. No adverse events resulted from the reported drug administration errors. However, confusing these drugs may cause the opposite of the intended effect, which may be life-threatening and require additional medical treatment. This confusion may occur in high-risk clinical environments where mannitol and saline are both commonly used (eg, intensive or intermediate care units).

Take care to ensure that solutions for infusion are carefully checked before administration. This includes checking that:

- the container with the correct drug name has been selected
- the container is not damaged
- the solution is clear and free of particles
- the drug has not passed its expiry date.

Please report medication errors where harm has occurred via the Yellow Card Scheme. If harm has not occurred, report through the National Reporting and Learning System (NRLS) or, if the NRLS is not available, on a Yellow Card (www.mhra.gov.uk/yellowcard).

Article citation: Drug Safety Update volume 7 issue 12, July 2014: S2.

Other information from the MHRA

O1 Medicines learning modules

We have updated our popular learning module on opioids. The changes cover recent concerns about transdermal patches. We have also revised a few of the self-assessment questions.

The Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom has re-approved the module for continuing professional development (CPD) – up to 2 CPD points are available for this module.

Over 90% of survey respondents learned something new from the opioids module or re-learned something that had forgotten. Here is what health professionals said about the module:

> "I found the format easy to use and convenient … the questions helped consolidate what I had learnt and were relevant to my work"
> —Community pharmacist

> "Very useful for something which I come across every day"
> —Foundation programme trainee doctor

> "Well summarised; adequate information for a refresher for an already established doctor"
> —General practitioner

> "Very good, took me the recommended time allowed which was good as well."
> —Nurse prescriber

> "Good content as I am an autonomous clinician administering morphine to patients as a paramedic. The differing interactions between opioids and other drug groups and the consequences of opioid withdrawal will assist me greatly."
> —Paramedic

The Education page on our website has more information about MHRA's learning modules. Here you will find links to medicines learning modules on:

- Antipsychotics
- Benzodiazepines
- Selective serotonin reuptake inhibitors (SSRIs)

The Education page also includes links to the pharmacovigilance module produced in close collaboration with BMJ Learning and to frequently asked questions about medicines learning modules.

Article citation: Drug Safety Update volume 7 issue 12, July 2014: O1

Opioids learning module:
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Opioids-learning-module/index.htm

Education page:
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/index.htm

Antipsychotics:
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Antipsychoticslearningmodule/Antipsychotics%20learning%20module

Benzodiazepines
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Benzodiazepineslearningmodule/index.htm

SSRIs
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/SSRIlearningmodule/index.htm

Pharmacovigilance module
http://learning.bmj.com/learning/module-intro/pharmacovigilance-adverse-drug-reactions.html?moduleId=10042344&locale=en_GB

Frequently asked questions
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/FAQsforthelearningmodules/index.htm

Correction

Last month we reported that we had received 13 reports of serious side effects in premature infants who were treated with chlorhexidine solution and that another 16 cases had been identified in the medical literature (Drug Safety Update volume 7 issue 11, June 2014: S2). A subsequent re-evaluation of the cases has identified one duplicated case and one literature case already recorded in our database. The article has now been updated as follows:

"We have received **14** reports of serious side effects in premature infants who were treated with chlorhexidine solution…Another **14** cases were identified in the medical literature."

Chlorhexidine solutions: risk of chemical burn injury to skin in premature infants
Drug Safety Update volume 7 issue 11, June 2014: S2
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON428307