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

Welcome to the first issue of Drug Safety Update for 2010. We start with some new advice for the antiepileptic drug phenytoin, regarding an increased risk of Stevens-Johnson syndrome associated with the presence of the *HLA-B*1502* genetic variant in patients of Thai or Han Chinese ethnic origin. Phenytoin should be avoided in individuals with increased susceptibility when alternative therapy can be given (p 2).

For professionals involved in imaging, we have the latest advice to support safer use of gadolinium-containing contrast agents in light of the serious and life-threatening risk of the condition, nephrogenic systemic fibrosis in some patients (p 3).

Also this month, patient information for methylphenidate products is being enhanced. Further information is on p 5, along with a reminder of key points for safer use. Furthermore, a recent review including all preclinical data has looked at the possible cytogenetic effect of methylphenidate. Overall, there is no strong evidence that methylphenidate causes chromosome damage, and the evidence provides no clear basis for suspecting an increased risk of cancer with this treatment.

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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.

Phenytoin: risk of Stevens-Johnson syndrome associated with *HLA-B*1502* allele in patients of Thai or Han Chinese ethnic origin

Keywords: phenytoin, antiepileptic, Stevens-Johnson syndrome, SJS

Presence of the *HLA-B*1502* allele may be associated with an increased risk of developing SJS in individuals of Thai and Han Chinese ethnic origin when treated with phenytoin. If these patients are known to be *HLA-B*1502*-positive, phenytoin should be avoided when alternative therapy can be given. Use of phenytoin should only be considered if the benefits are thought to outweigh the risks

Phenytoin (brand leader Epanutin) is a commonly used antiepileptic drug. Phenytoin is one of the most common causes of antiepileptic-related cutaneous adverse reactions, including life-threatening Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[1] A recent study[2] has shown a significant association between the human leukocyte antigen (HLA) allele *HLA-B*1502* and phenytoin-induced SJS in patients of Thai or Han Chinese ethnic origin.

Healthcare professionals should be aware of the risk of SJS in patients of Thai or Han Chinese ethnic origin and the association with *HLA-B*1502* genetic variant when prescribing phenytoin. In these individuals with increased susceptibility, phenytoin should be avoided when alternative therapy can be given. However, available data are too limited to recommend screening of patients of Thai or Chinese ethnic origin for presence of the *HLA-B*1502* allele before starting phenytoin treatment.

1 Arif H, et al. *Neurology* 2007; **68:** 1701–09.
2 Locharernkul C, et al. *Epilepsia* 2008; **48:** 1015–18.

See the April 2008 issue of Drug Safety Update (p 5) for information and advice on the risk of carbamazepine-induced SJS associated with presence of *HLA-B*1502* in those of Han Chinese, Hong Kong Chinese, or Thai origin
www.mhra.gov.uk/mhra/drugsafetyupdate

Further information on the recent study

Locharernkul and co-workers'[2] study included ten patients of Thai ethnic origin who had epilepsy and SJS induced by antiepileptic treatment; all tested positive for *HLA-B*1502* and had only been taking a single medicine. Of these, six had taken carbamazepine and four phenytoin. 50 antiepileptic-tolerant patients with epilepsy were recruited as controls and defined by the absence of allergic reactions on therapy for more than 3 months. Eight of 45 controls in the phenytoin-tolerant group tested positive for *HLA-B*1502*. Comparison of the frequency of *HLA-B*1502* in patients with phenytoin-associated SJS with that of the phenytoin-tolerant group showed a significant association (p=0·005).

When the phenytoin-tolerant group was used as control, the presence of *HLA-B*1502* had a 33% (95% CI 14–61%) positive predictive value for phenytoin-associated SJS, and its absence had a negative predictive value of 100% (91–100%). In the test for phenytoin-associated SJS, the *HLA-B*1502* allele has 100% (51–100%) sensitivity and 82% (69–91%) specificity.

*HLA-B*1502* prevalence

The prevalence of *HLA-B*1502* is estimated at between 8·2% and 9% of the Thai population.[2,3] The prevalence is similar in Han Chinese (8·6%).[4]

The prevalence of *HLA-B*1502* is extremely low in the Caucasian population (1–2%).[4] However, no conclusions can be drawn at present on the risk association between phenytoin-induced SJS and the presence of this allele in this population. Adequate information about risk association for patients of other ethnic origin is currently not available.

3 Pimtanothai N, et al. *Tissue Antigens* 2002; **59:** 223–25.
4 Chung WH, et al. *Nature* 2004; **428:** 486.

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Advice for healthcare professionals:

- *HLA-B*1502* may be associated with an increased risk of developing SJS in individuals of Thai or Han Chinese ethnic origin when treated with phenytoin. If these patients are known to be *HLA-B*1502*-positive, phenytoin should be avoided when alternative therapy can be given. Use of phenytoin should only be considered if the benefits are thought to outweigh the risks
- In the Caucasian and Japanese population, the frequency of *HLA-B*1502* is extremely low, and thus it is not possible at present to conclude on risk association. Adequate information about risk association in other patients of other ethnic origin is currently not available

Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis

Keywords: Gadolinium-containing contrast agents, nephrogenic systemic fibrosis, NSF

Gadolinium-containing contrast agents are associated with a varying degree of risk of nephrogenic systemic fibrosis. See advice below to minimise risk in the following vulnerable groups: patients with renal impairment; patients in the perioperative liver transplantation period; infants, neonates, and the elderly; and women who are pregnant or breastfeeding. High-risk gadolinium-containing contrast agents are contraindicated in patients with severe renal impairment, patients in the perioperative liver-transplantation period, and in neonates

See http://www.emea.europa.eu/pdfs/human/press/pr/73981809en.pdf

The European Committee for Medicinal Products for Human Use (CHMP) has reviewed the risk of nephrogenic systemic fibrosis (NSF) with gadolinium-containing contrast agents.

On the basis of current evidence, the risk classification is as follows:

High risk—Omniscan (gadodiamide), OptiMARK (gadoversetamide), Magnevist (gadopentetic acid)

Medium risk—MultiHance (gadobenic acid), Primovist (gadoxetic acid), Vasovist (gadofosveset)

Low risk—Gadovist (gadobutrol), ProHance (gadoteridol), Dotarem (gadoteric acid)

Nephrogenic systemic fibrosis

NSF, previously called nephrogenic fibrosing dermopathy (NFD), is a serious and life-threatening condition characterised by the formation of connective tissue in the skin which becomes thickened, coarse, and hard, sometimes leading to contractures and joint immobility. Patients with NSF can have systemic involvement of other organs including the lungs, liver, muscles, and heart.

Nine gadolinium-containing contrast agents are authorised in the EU to aid MRI of the body and of the blood vessels (magnetic resonance angiography, MRA)—see box above.

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The risk of NSF with these agents has been kept under close review since the association was first observed in January 2006.[1] In August 2007, Drug Safety Update advised healthcare professionals that the risk of NSF was highest with Omniscan and OptiMARK, and that there was also evidence to suggest that Magnevist should not be used in patients at greater risk (ie, those with severe renal dysfunction).

In the recent review, the CHMP has considered: the risk of NSF in patients with renal impairment; risk in patients in the perioperative liver-transplantation period; use in infants, neonates, and the elderly; use during pregnancy and lactation; the need for screening of renal function before use and dose restrictions; measures to accurately record the agent used; and what further studies are required.

1 Grobner T. *Nephrol Dial Transplant* 2006; **21:** 1104–08. Erratum 2006; 21: 1745.

See Drug Safety Update August 2007, p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

Advice for healthcare professionals:

The following risk-minimisation measures should be used for gadolinium-containing contrast agents:

Renal-function monitoring

- Renal function should be tested in all patients receiving high-risk agents, and is generally advisable for patients receiving medium-risk or low-risk agents. It is particularly important to screen patients aged 65 years or older

Renal impairment

- For patients with **severe** renal impairment (glomerular filtration rate [GFR] <30 mL/min/1·73m^2), use of a high-risk agent is contraindicated. If use of a medium-risk agent cannot be avoided or if it is necessary to use a low-risk agent, a single lowest dose possible can be used and should not be repeated for at least 7 days
- For patients with **moderate** renal impairment (GFR 30–59 mL/min/1·73 m^2), if it is necessary to use a high-risk agent a single lowest dose possible can be used and should not be repeated for at least 7 days

Perioperative liver-transplantation period

- Use of a high-risk agent is contraindicated. If use of a medium-risk agent cannot be avoided or if it is necessary to use a low-risk agent, a single lowest dose possible can be used and should not be repeated for at least 7 days

Neonates

- Use of a high-risk agent is contraindicated. For medium-risk or low-risk agents, use a single lowest possible dose and do not repeat for at least 7 days

Infants

- Use a single lowest dose of agent possible and do not repeat for at least 7 days

Breastfeeding

- Discontinue for at least 24 hours after use of a high-risk agent. The decision of whether to continue or suspend breastfeeding for 24 hours after use of a medium-risk or low-risk agent should be at your discretion in consultation with the mother

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Pregnancy

- Use of any gadolinium-containing contrast agent is not recommended unless absolutely necessary

Haemodialysis

- There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis

Recording of the agent used

- When they become available, peel-off tracking labels found on the vials, syringes, or bottles should be stuck onto the patient record to accurately record the name of the gadolinium contrast agent used. The dose used should also be recorded

Reporting of suspected adverse reactions

- Please report to us on a Yellow Card any suspected adverse reactions, including NSF, to gadolinium-containing contrast agents (see www.yellowcard.gov.uk)

Hot topic

Methylphenidate: new patient information

Methylphenidate is a stimulant treatment for children aged 6 years or older and adolescents with attention-deficit hyperactivity disorder (ADHD).

Patient information

The design and content of the Patient Information Leaflets for methylphenidate products are being updated with the latest guidance on safe and effective use for patients and carers.

This includes a tear-off section for children and adolescents who are taking methylphenidate. This tear-off section includes the most important messages written in an engaging style for children and adolescents. The leaflets have been tested with adults, children, and adolescents, and the key messages for safe use have been readily found and easily understood. Youngsters very much appreciated having their own specially drafted section. Examples of these leaflets can be found at http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

Reminder for healthcare professionals

Updated guidance from the MHRA on the safer use of methylphenidate recommends that patients should have careful ongoing monitoring during treatment, and that the need for long-term treatment is re-evaluated at least yearly.

Reminder for healthcare professionals to support safer use of methylphenidate

The product information for prescribers of methylphenidate has recently been updated with guidance to support safer use:

- Treatment with methylphenidate should be supervised by a specialist in childhood or adolescent behavioural disorders
- Diagnosis should be made according to DSM-IV (Diagnostic and statistical Manual of Mental Disorders, 4th edition) criteria or ICD-10 (International

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Hot topic *Cont.*

See Drug Safety Update March 2009, p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

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Classification of Diseases 10th revision) guideline, and should be based on a complete history and evaluation and not solely on the presence of one or more symptom(s)

- Children and adolescents should have rigorous pretreatment screening, including a complete history and relevant examination (including psychiatric disorders or symptoms, cardiovascular status, height, and weight)
- Patients should be monitored regularly during methylphenidate treatment, including: blood pressure and pulse; height, weight, and appetite; onset or worsening of psychiatric symptoms (such as depression, suicidal thoughts, hostility, anxiety, agitation, psychosis, or mania); and symptoms suggestive of heart disease (which should prompt specialist cardiac evaluation)
- Treatment should be interrupted at least yearly to determine whether continuation is needed

Studies of cytogenetic effect of methylphenidate

In 2005, a small study[1] suggested significant damage to chromosomes in children with ADHD treated with methylphenidate. The study had important methodological limitations that reduced its reliability.[2,3] Concerns about the potential for methylphenidate to cause genetic damage and cancer prompted several further in vitro, in vivo, human, and pharmacoepidemiological studies investigating this issue.[4–9]

These important new studies have been assessed and included in a review by the MHRA of all relevant data on this issue to date. Most of the in vitro and in vivo studies did not show any clear evidence of the potential for methylphenidate to increase the risk of mutations, cause malignancies, or cause chromosomal damage that can lead to the formation of cancers.

Importantly, several further studies[4–6,8] of humans after the initial El-Zein study[1] with improved design all failed to replicate the preliminary findings: they did not show any chromosomal damage associated with methylphenidate treatment for ADHD.

The Commission on Human Medicines advised on the review, concluding that overall there is no strong evidence from a range of data sources that methylphenidate causes chromosomal damage, and that the evidence provides no clear basis for suspecting an increased risk of cancer with this treatment.

Conclusions

The benefits of methylphenidate continue to outweigh the risks when used to treat ADHD in children aged 6 years or older and adolescents. The longer-term safety of methylphenidate remains under close review, and the results of ongoing studies to characterise the known or potential risks of ADHD medicines will be evaluated when available.

1 El-Zein RA, et al. *Cancer Lett* 2005; **230:** 284–91.
2 Preston RJ, et al. *Cancer Lett* 2005; **230:** 292–94.
3 Jacobson-Kram D, et al. *Cancer Lett* 2008; **260:** 216–18.
4 Witt KL, et al. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 1375–83.
5 Tucker JD, et al. *Mutat Res* 2009; **677:** 53–58.
6 Walitza S, et al. *Toxicol Lett* 2009; **184:** 38–43.
7 Morris S, et al. *Mutat Res* 2009; **673:** 59–66.
8 Ponsa I, et al. *Mutat Res* 2009; **666:** 44–49.
9 Oestreicher N, et al. *Pharmacoepidemiol Drug Saf* 2007; **16:** 1268–72.

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