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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An analysis of pooled results from clinical trials of the antibiotic tigecycline versus comparator drugs in a range of infections has shown numerically higher mortality rates in patients receiving tigecycline. Therefore, doctors are advised to use tigecycline only when other antibiotics are unsuitable. See article A1 for further information.

The licensed indication for stavudine for the treatment of HIV has been restricted to use only in individuals for whom there are no other appropriate treatment alternatives, and only for the shortest period possible in these individuals. This restriction is due to an increased risk of potentially severe adverse effects compared with alternative HIV treatments—see article A2 for further information.

People with schizophrenia are three times more likely to die prematurely from natural causes (mainly cardiovascular disease) compared with people without mental health disorders. Furthermore, some atypical (second-generation) antipsychotics are associated with metabolic adverse effects. Given that these patients have an increased baseline risk of cardiovascular morbidity and mortality, identification and management of metabolic adverse effects during atypical antipsychotic treatment is important. See our Hot topic this month for further advice.

There have been rare reports from outside the UK of thromboembolic events with the use of Vivaglobin (normal immunoglobulin solution for subcutaneous injection). Where possible, healthcare professionals should use alternative appropriate therapy for patients with risk factors for thromboembolism. Prescribers should be vigilant for signs of arterial or venous thromboembolism, and note that Vivaglobin should only be given subcutaneously (not intravenously). See article S1 for further information.

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Drug safety advice

A1 Tigecycline (Tygacil▼): increased mortality in clinical trials – use only when other antibiotics are unsuitable

An analysis of pooled results from clinical trials of tigecycline (Tygacil▼) versus comparator drugs in a range of infections has shown numerically higher mortality rates in patients receiving tigecycline. Therefore, doctors are advised to use tigecycline only when other antibiotics are unsuitable.

Tigecycline is a glycylcycline antibiotic approved for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections.

Results of pooled analysis

The licence holder for tigecycline completed a pooled analysis of results from all phase 3 and phase 4 trials in the approved indications (complicated skin and soft tissue infections and complicated intra-abdominal infections). Death occurred in 2.3% (52 of 2216) patients receiving tigecycline and 1.5% (33 of 2206) patients receiving comparator drugs.

A larger analysis adding results from trials of tigecycline use in unapproved indications (diabetic foot infections, nosocomial pneumonia, and treatment of resistant pathogens) also showed numerically higher overall mortality rates in patients treated with tigecycline versus those treated with active comparators.

The cause of these findings is unknown. The possibility that tigecycline has a poorer efficacy and/or safety profile than the comparator drugs cannot be excluded. Patients who develop superinfections, particularly nosocomial pneumonia, seem to be at particular risk of having a poor outcome, including death.

Advice for healthcare professionals:

- Tigecycline is approved only for treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections
- Tigecycline should only be used in situations where it is known or suspected that other drugs are unsuitable
- Numerically higher mortality rates have been reported in patients treated with tigecycline in clinical studies in approved and unapproved indications, compared with patients treated with other antibacterial agents
- Patients who develop superinfections, particularly nosocomial pneumonia, seem to be at particular risk of having a poor outcome. Patients should be closely monitored for the development of superinfections. If medically indicated, they should be switched to alternative antibiotic treatment which has been shown to be efficacious in the treatment of the specific infection present
- Report suspected adverse reactions with tigecycline through the Yellow Card Scheme—see at www.yellowcard.gov.uk. When reporting, please provide as much information as possible, including information about medical history, concomitant medication, and dates of treatment and reaction onset

Further information:

See letter for healthcare professionals sent March 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON111795

BNF section 5.1.3 Tetracyclines: http://bnf.org/bnf/bnf/current/129712.htm?q=tygacil&t=search&ss=text&p=1#_129712

Article citation: Drug Safety Update April 2011; vol 4, issue 9: A1.

A2 Stavudine (Zerit): use only when there are no appropriate alternatives, and for the shortest possible time

An increased risk of potentially severe adverse effects in patients receiving stavudine compared with alternative HIV treatments means that stavudine should only be used when there are no appropriate alternatives, and for the shortest possible time

Stavudine (Zerit) is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in combination with other antiretroviral products for the treatment of HIV-1 infection in adults and children. Zerit was first authorised in 1996. Its use has declined over time, and is currently used only in approximately 160 patients in the UK.

Side effects with stavudine

Similar to some other NRTIs, stavudine has a toxic effect on mitochondria, which can result in various serious side effects—particularly lactic acidosis, lipoatrophy, and peripheral neuropathy.

A recent review of stavudine worldwide safety data (including case reports, clinical studies, and published literature) found that cases of potentially fatal lactic acidosis have been reported[1], both within the first few months of stavudine treatment and also substantially later. An increased risk of lipoatrophy compared with other NRTIs has also been identified. The incidence and severity of lipoatrophy seems to be cumulative over time, and is often not completely reversible on stopping stavudine[2].

Peripheral neuropathy also occurs frequently, reported in up to 20% of patients treated with stavudine. Patients at particular risk are those with a history of neuropathy, excessive alcohol intake, renal impairment, or patients receiving isoniazid concomitantly[3,4].

On the basis of these safety concerns, the balance of benefits and risks of stavudine is considered to be favourable only in a small and highly selected group of patients. Therefore, the licensed indication for stavudine has been restricted to use only in individuals for whom there are no other appropriate treatment alternatives, and only for the shortest period possible in these individuals.

Advice for healthcare professionals:

- Only treat patients with stavudine when no suitable alternatives are available
- Use stavudine for the shortest possible time
- Switch all other patients, including those starting and those continuing stavudine, to appropriate alternative therapy as soon as possible
- Frequently assess patients taking stavudine for evidence of mitochondrial toxicity, and discontinue treatment if appropriate, if toxicity occurs
- Warn patients of the potential serious adverse effects that can be associated with short-term and long-term use of stavudine, and the need to report any signs of these reactions to their physician

1 Lactic Acidosis International Study Group. AIDS 2007; 21: 2455–64

2 Riddler SA, et al, for the AIDS Clinical Trials Group Study A5142 Team. N Engl J Med 2008; 358: 2095–2106

3 Cherry CL, et al. Neurology 2006; 66: 867–73

4 Smyth K, et al. Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993–2006. HIV Medicine 2007; 8: 367–73

Further information:

Q&A document on EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/human/000110/WC500102227.pdf

Letter for healthcare professionals sent March 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON111795

BNF section 5.3.1 HIV infection: http://bnf.org/bnf/bnf/current/57191.htm?q=zerit&t=search&ss=text&p=1#_57191

Article citation: Drug Safety Update April 2011; vol 4, issue 9: A2.

Hot topic

H1 **Atypical (second-generation) antipsychotics: reminder to monitor and manage weight, glucose, and lipid levels**

People with schizophrenia are three times more likely to die prematurely from natural causes (mainly cardiovascular disease) compared with people without mental health disorders[1,2]. Schizophrenia also seems to be associated with modifiable and non-modifiable risk factors for cardiovascular morbidity and mortality (eg, smoking, poor diet, sedentary lifestyle, and family history of cardiovascular disease).

Some atypical (second-generation) antipsychotics are associated with significant weight gain (>7% of baseline), dyslipidaemia, and hyperglycaemia (metabolic adverse effects). Individual atypical antipsychotics differ in their propensity for metabolic adverse effects: available data suggest that clozapine, olanzapine, and quetiapine are especially implicated[3].

An analysis of baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study confirms that people with schizophrenia are undertreated for metabolic disorders[4]. Given that people with schizophrenia are at an increased baseline risk of cardiovascular morbidity and mortality, the following are needed during atypical antipsychotic treatment to support the physical health of the patient in the long term:

- early identification of modifiable risk factors
- monitoring for further development of metabolic adverse effects
- management of metabolic adverse effects

Although the available data do not support a similar association between typical (first-generation) antipsychotics and metabolic adverse effects, the increased risk associated with schizophrenia means that the physical wellbeing of all patients should be assessed, monitored, and treated according to relevant clinical guidelines.

NICE guidance on schizophrenia[5] gives further information about physical health screening for people with schizophrenia (see Chapter 9, sections 9.2.3.6 – 9.2.3.10).

Advice for healthcare professionals:

NICE guidance

- GPs and primary healthcare professionals should monitor the physical health of people with schizophrenia at least once a year. Focus on cardiovascular disease risk assessment as described in NICE clinical guideline 67—lipid modification[6], but bear in mind that people with schizophrenia are at a higher risk of cardiovascular disease than the general population

- People with schizophrenia at increased risk of developing cardiovascular disease and/or diabetes (eg, those with elevated blood pressure, raised lipid levels, smokers, increased waist measurement) should be identified at the earliest opportunity. Their care should be managed using the appropriate NICE guidance for prevention of these conditions[6–9]

- Treat people with schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance

1 Brown S, et al. Br J Psychiatry 2010; 196: 116–21

2 Hennekens CH. J Clin Psychiatry 2007; 68: 4–7

3 Rummel-Kluge C, et al. Schizophr Res 2010; 123: 225–33

4 Nasrallah HA, et al. Schizophr Res 2006; 86: 15–22

5 National Institute for Health and Clinical Excellence. Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). Clinical guideline 82. 2009 www.nice.org.uk/CG82

6 National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline 67. 2008. www.nice.org.uk/CG67

7 National Institute for Health and Clinical Excellence. Type 1 diabetes: diagnosis and management of type I diabetes in children, young people and adults. Clinical guideline 15. 2004. www.nice.org.uk/CG15

8 National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes (update). Clinical guideline 66. 2008. www.nice.org.uk/CG66

9 National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention identification, assessment and management of overweight and obesity in adults and children. Clinical guideline 43. 2006. www.nice.org.uk/GC43

Further information:

Metabolic and lifestyle issues and severe mental illness—new connections to well-being? Expert Consensus Meeting, Dublin, 14–15 April 2005, consensus summary. Journal Psychopharmacol 2005; 19 (suppl 6): 118–22.

Foley DL and Morely KI. Systematic review of early cardiometabolic outcomes of the first treated episode

of psychosis. Arch Gen Psychiatry, published online Feb 7, 2011. doi:10.1001/archgenpsychiatry.2011.2

Mackin P and Thomas SHL. Atypical antipsychotic drugs. BMJ 2011; 342: d1126.

Summaries of Product Characteristics and Patient Information Leaflets for atypical antipsychotics are available via the Electronic Medicines Compendium: www.medicines.org.uk/emc

BNF section 4.2.1 Antipsychotic drugs: http://bnf.org/bnf/bnf/current/65561.htm?q=atypical%20antipsychotics&t=search&ss=text&p=3#_hit

Further advice

- Encourage and educate patients as appropriate to maintain a healthy diet and regular exercise
- Any decision to change antipsychotic drugs should be based on a careful assessment of the potential benefits and on the risks of destabilising their mental state

Article citation: Drug Safety Update April 2011; vol 4, issue 9: H1.

Stop press

S1 **Vivaglobin solution for subcutaneous injection: rare risk of thromboembolic events**

Vivaglobin 160 mg/mL (human normal immunoglobin solution for subcutaneous injection) is licensed as replacement therapy for adults and children with primary immunodeficiency syndromes, myeloma, or chronic lymphatic leukaemia.

There have been rare and unexpected reports from outside the UK of thromboembolic events such as stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism in association with Vivaglobin use.

Investigations revealed pro-coagulant activity of some batches. The affected batches are no longer being distributed by the manufacturer (although some may still be in use), and only batches with low pro-coagulant activity will be distributed in future. A supply shortage is not envisaged and alternative treatments are available.

Advice for healthcare professionals:

- Where possible, use an appropriate alternative therapy for patients at increased risk of thrombosis.
- Vivaglobin is not indicated for intravenous use. Do not infuse Vivaglobin intravenously and make sure that no vessel is damaged during subcutaneous injection.
- Be extra vigilant for signs of a thromboembolic event in patients who receive Vivaglobin, particularly if they have pre-existing risk factors.
- Patients should be advised to seek immediate medical attention if first symptoms of a thromboembolic event occur, such as shortness of breath, pain and swelling of a limb, focal neurological deficits, chest pain, or other manifestations.
- Report any suspected adverse reactions with Vivaglobin through the Yellow Card Scheme at www.yellowcard.gov.uk

Further information:

See letter for healthcare professionals sent March 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON111795

BNF section 14.5.1 Normal immunoglobin for subcutaneous use: http://bnf.org/bnf/bnf/61/129302.htm?q=Vivaglobin&t=search&ss=text&p=1

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