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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In patients treated with tamoxifen for breast cancer, concomitant use of potent inhibitors of the CYP2D6 drug-metabolising enzyme may be associated with variability in clinical response. Therefore, use of drugs that inhibit this enzyme should be avoided whenever possible in patients treated with tamoxifen for breast cancer (see article A1).

Several cases of inadvertent overdose have been reported with the new memantine pump device for Alzheimer's disease. The medication errors resulted from confusion between doses delivered by this pump device compared with doses delivered by the dropper. Healthcare professionals should be aware that there are differences in dose delivery between the pump device and dropper device for memantine (article A2).

Finally this month, a review of all relevant data for a risk of oesophageal cancer in association with oral bisphosphonates has concluded that there is insufficient evidence to confirm a link (see article for H1 further information).

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Drug safety advice

A1 Tamoxifen for breast cancer: drug interactions involving CYP2D6, genetic variants, and variability in clinical response

CYP2D6 genetic polymorphisms and concomitant use of potent CYP2D6 inhibitors may be associated with variability in clinical response in patients treated with tamoxifen for breast cancer. Therefore, concomitant use of medicines known to be potent CYP2D6 inhibitors should be avoided whenever possible in patients treated with tamoxifen.

Tamoxifen is a selective oestrogen-receptor modulator indicated for palliative and adjuvant treatment of oestrogen-receptor-positive breast cancer in premenopausal and postmenopausal women. Tamoxifen is a prodrug, and the formation of the active metabolite, endoxifen, is mediated by the CYP2D6 enzyme. Several articles have recently been published regarding the potential effect of *CYP2D6* genetic variants on clinical response to tamoxifen treatment in patients with breast cancer.

In patients with inherited non-functional alleles of the *CYP2D6* gene ('poor metabolisers') or in patients concomitantly treated with CYP2D6 enzyme inhibitors, concentrations of the tamoxifen metabolites that most strongly bind to the oestrogen receptor may be reduced.

Effect of tamoxifen in patients treated with potent CYP2D6 inhibitors

A population-based cohort study on SSRI antidepressants and breast-cancer mortality in women receiving tamoxifen found that the risk of death from breast cancer increased with the length of concomitant treatment with paroxetine—a potent inhibitor of CYP2D6, but not with other SSRIs. The proportion of time on tamoxifen with overlapping use of paroxetine of 25%, 50%, and 75% was associated with 24%, 54%, and 91% increases in the risk of death from breast cancer, respectively.[1]

A more-recent study [2] found no evidence for decreased efficacy with the co-administration of CYP2D6 inhibitors and tamoxifen, but given the strong mechanistic model and overall weight of evidence it is recommended that strong CYP2D6 inhibitors should be avoided whenever possible in patients taking tamoxifen. Examples of such drugs include **paroxetine**, **fluoxetine**, **bupropion**, **quinidine**, and **cinacalcet**.

Association of *CYP2D6* polymorphism status with poor clinical outcome

The evidence linking various poor metaboliser genotypes and tamoxifen treatment outcomes is mixed and inconclusive. Therefore there is no current recommendation for genetic testing before treatment with tamoxifen.[3-12]

Advice for healthcare professionals:

- Concomitant use of drugs that are potent inhibitors of the CYP2D6 enzyme should be avoided whenever possible in patients treated with tamoxifen for breast cancer
- Current data for the effect of genetic polymorphisms are insufficient to support recommending genotyping of patients

1 Kelly CM, et al. BMJ 2010; 340: c693.

2 Dezentje VO, et al. J Clin Oncol 2010; 28: 2423–29.

3 Schroth W, et al. JAMA 2009; 302: 1429–36.

4 Goetz MP, et al. Breast Cancer Res Treat 2007; 101: 113–21.

5 Goetz MP, et al. J Clin Oncol 2005; 23: 9312–18.

6 Schroth W, et al. J Clin Oncol 2007; 25: 5187–93.

7 Bonanni B, et al. J Clin Oncol 2006; 24: 3708–09.

8 Newman WG, et al. Clin Cancer Res 2008, 14: 5913–18.

9 Nowell SA. Breast Cancer Res Treat 2005; 91: 249–58.

10 Wegman P, et al. Breast Cancer Res 2005; 7: R284–90.

11 Wegman P. Breast Cancer Res 2007; 9: R7.

12 Abraham JE, et al. Breast Cancer Res 2010; 12: R64.

Further information is available in a report from the September 2010 meeting of the **European Pharmacovigilance Working Party**

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097444.pdf

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A2 **Memantine pump device (Ebixa): risk of medication errors**

Several cases of administration error resulting in overdose with the new memantine pump device have been reported. The medication errors resulted from confusion between doses delivered by the new pump device and doses delivered by the dropper. Four actuations of the pump device is equivalent to 40 drops delivered by the dropper device. Healthcare professionals should be aware that there are differences in dose delivery between the pump device and dropper device for memantine

Memantine (Ebixa) is indicated for the treatment of patients with moderate to severe Alzheimer's disease, and tablets and an oral solution have been available since 2002. A pump device was introduced in March 2010 and replaces memantine oral solution administered by a dropper, which is being phased out by February 2011.

Risk of medication errors and accidental overdose

A **letter was sent to healthcare professionals** in October 2010 with information on this risk.

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON099712

Further information for patients can be found in the memantine Patient Information Leaflet.

Up to Aug 9, 2010, seven cases of administration errors with the pump device have been reported worldwide. One patient was admitted to hospital and recovered, and two patients experienced somnolence, which is listed in the Summary of Product Characteristics as a possible adverse reaction associated with overdose. The remaining patients did not report any side effects.

The medication errors resulted from confusion between doses delivered by the new pump device and doses delivered by the dropper. Dosing for memantine devices is as follows:

Pump device:

- One actuation of the pump device delivers 0.5 mL of solution, corresponding to 5 mg memantine. The maximum daily dose is 20 mg (ie, four pump actuations)

Old dropper device (being phased out):

- The dropper device delivers 0.5 mg/drop and the maximum daily dose of 20 mg is achieved with 40 drops

Healthcare professionals should be aware of the correct use and administration of memantine pump device as outlined in the Summary of Product Characteristics. Healthcare professionals should also advise patients and their carers to carefully read the Patient Information Leaflet for memantine oral solution delivered by a pump device.

Advice for healthcare professionals:

- There are differences in dose delivery between the pump device and dropper device for memantine
- One actuation of the pump device delivers 0.5 mL of solution, corresponding to 5 mg memantine. The maximum daily dose is 20 mg or four pump actuations, whereas 40 drops could be given with the dropper
- Please be vigilant regarding dose delivery for memantine products, particularly during the transition period from the dropper device to the new pump device. We request that you also advise patients and their caregivers:
    - how to use the new pump device to deliver the prescribed dose
    - to carefully read the Patient Information Leaflet for memantine oral solution delivered by a pump device

Reporting of suspected adverse reactions

Please report any suspected adverse reactions associated with the use of memantine on a Yellow Card (www.yellowcard.gov.uk). Patients and caregivers can also report any

suspected reactions to us via the Yellow Card Scheme.

Article citation: Drug Safety Update Nov 2010 vol 4, issue 4: A2.

Hot topic

There is insufficient evidence to confirm a link between oral bisphosphonate use and an increased risk of oesophageal cancer. Patients should be advised to carefully follow the instructions in the Patient Information Leaflet on how to take the medicine and report any symptoms of oesophageal irritation to their doctor

H1 **Oral bisphosphonates: oesophageal cancer risk—insufficient evidence of a link**

Oral bisphosphonates are used to treat osteoporosis, Paget's disease, and bone-related cancers. There is clear evidence that nitrogen-containing bisphosphonates (ie, alendronic acid, ibandronic acid, and risedronate) can cause oesophageal irritation and reactions. After reports of oesophageal cancer in association with oral bisphosphonates, we collaborated with the Cancer Epidemiology Unit at the University of Oxford to conduct a study to assess this issue.[1]

The results from this study suggest a small increase in the risk of oesophageal cancer in patients who had taken oral bisphosphonates for more than 5 years compared with a group who had not taken oral bisphosphonates. The incidence rate of oesophageal cancer over 5 years in men and women aged 60–79 years in the general population is 0.5 women per 1000 and 1.5 men per 1000. In this study, the incidence increased with 5 years' of bisphosphonates use to one woman per 1000, and three men per 1000. By contrast, other studies have not reported a link.[2-4]

These studies were considered as part of a Europe-wide review of oral bisphosphonates and oesophageal cancer. This review concluded that given the limitations of the study by Green and colleagues [1] and a lack of supporting evidence from other studies, there is insufficient evidence to confirm a link between oral bisphosphonate use and oesophageal cancer. The limitations of the study included little available information for risk factors for oesophageal cancer (such as smoking, alcohol consumption, social deprivation, and previous oesophageal reactions). Furthermore, patients receiving oral bisphosphonates are more likely to be monitored for oesophageal reactions than those not receiving bisphosphonates, which may result in an increased detection of oesophageal cancer in patients receiving bisphosphonates.

Information and advice for healthcare professionals and patients to minimise risk of oesophageal adverse reactions with oral bisphosphonates:

- Alendronate and oral ibandronate should not be given to patients with abnormalities of the oesophagus and/or other factors which delay oesophageal emptying such as stricture or achalasia. Risedronate should be used with caution in such patients
- Alendronate, oral ibandronate, and risedronate should be used with caution in patients with active or recent upper gastrointestinal problems
- In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate and oral ibandronate on an individual basis

Advice for patients:

- Patients should be advised about the importance of adhering to dose instructions. Tablets should be swallowed whole with at least 200 mL water on an empty stomach immediately after getting up in the morning. Patients should stay fully upright for at least 30 minutes or 1 hour after taking the tablet and before taking any food, drink, or other medicine as outlined in the product information

1 Green J, et al. BMJ 2010; 341: c4444.

2 Cardwell CR, et al. JAMA 2010; 304: 657-663.

3 Abrahamsen B, et al. N Engl J Med 2009; 360; 1789.

4 Solomon DH, et al. N Engl J Med 2009; 360; 1789-1790.

Further information:

Bisphosphonate product information

http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/Bisphosphonates/index.htm

Questions and answers on the study by Green and colleagues

http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/Bisphosphonates/Questionsandanswersonthestudybygreenandco-workers2010onoralbisphosphonatesandoesophagealcancer/index.htm

See also report from the **European Pharmacovigilance Working Party**, October 2010

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500098462.pdf

- Patients should be advised to stop taking the tablets and to seek medical attention if they develop any symptoms of oesophageal irritation such as difficulty or pain on swallowing, chest pain, or new or worsening heartburn

Article citation: Drug Safety Update Nov 2010 vol 4, issue 4: H1.

Hot topic

H2 **Tiotropium: safety studies of Spiriva Respimat▼**

Tiotropium is a long-acting muscarinic receptor antagonist that is licensed as a prescription-only medicine for maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). Two formulations are available as the brand name Spiriva: a capsule containing 18 micrograms tiotropium delivered via a HandiHaler taken once daily; and a soft-mist Respimat inhaler that delivers 2·5 micrograms tiotropium per actuation taken as two puffs once a day at the same time of the day.

Recent safety analyses for Spiriva Respimat▼

The MHRA has previously highlighted the conflicting findings of a number of recent studies on the safety of inhaled anticholinergic drugs. Although some published studies have suggested an increased risk of cardiovascular death, myocardial infarction, or stroke associated with use of these medicines, a large 4-year placebo-controlled randomised double-blind trial concluded that tiotropium delivered via HandiHaler was associated with a non-significantly decreased risk of all-cause mortality, myocardial infarction, or stroke compared with placebo.

A recently completed safety study that compared Spiriva Respimat▼ with placebo in patients with COPD found that lung function, COPD exacerbations, and quality of life were improved by 5 micrograms Respimat, but a numerical increase was seen in all-cause mortality compared with placebo. A retrospective pooled analysis of three 1-year and one 6-month placebo-controlled trials with Spiriva Respimat including 6096 patients found a non-significant numerical increase in all-cause mortality in patients treated with Spiriva Respimat: 68 patients using Spiriva Respimat died (incidence rate [IR] 2.64 cases per 100 patient-years) compared with 51 deaths in patients on placebo (IR 1.98 cases per 100 patient-years)—rate ratio 1.33 (95% CI 0.93–1.92) for the planned treatment period. In a posthoc analysis of different patient subgroups, a significant excess in mortality was observed in patients with known cardiac rhythm disorders. By contrast, pooled analysis of studies longer than 4 weeks that included 17 014 patients assigned to Spiriva HandiHaler or placebo showed a rate ratio for all-cause mortality of 0.85 (95% CI 0.75–0.97).

There were differences between the Respimat and HandiHaler study populations at baseline, including smoking status, gender, and disease severity, and the causes of death varied across studies. The underlying reasons for the apparent difference in the risk of all-cause mortality between the HandiHaler and Respimat devices are unclear, and may be a chance finding. Further studies are ongoing to investigate these differences.

Information and advice for healthcare professionals:

- Recent analyses found that Spiriva Respimat was associated with a non-significant increase in all-cause mortality compared with placebo. By contrast,

Spiriva HandiHaler was associated with a decrease in all-cause mortality compared with placebo. The underlying reasons for the apparent difference are unclear, and may be a chance finding; further studies are ongoing
- Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders
- Patients with COPD who use tiotropium should be reminded not to exceed the recommended once-daily dose of:
    - one Spiriva HandiHaler 18-microgram capsule, or
    - two puffs Spiriva Respimat 2.5 micrograms
- Please remember to report suspected adverse reactions to Spiriva HandiHaler or Spiriva Respimat on a Yellow Card at www.yellowcard.gov.uk

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Other information from the MHRA

O1 **Patient Information Leaflet of the month: Spiriva and Spiriva Respimat▼**

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for supporting safer use of the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this initiative, we are publishing a series of examples of best practice on our website.

The latest example in the series are the leaflets for Spiriva and Spiriva Respimat▼ to coincide with the Hot topic this month on tiotropium. The leaflet has been designed to highlight the key information and uses good navigation tools. In testing the leaflet was well received by patients.

Patient information leaflet (PIL) of the month

http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

Article citation: Drug Safety Update Nov 2010 vol 4, issue 11: O1.