HSA Health Sciences Authority

Adverse Drug Reaction news

Published by the Centre for Drug Administration, HSA and the HSA Pharmacovigilance Advisory Committee

Oseltamivir and neuropsychiatric events

Monitor patients on oseltamivir for signs of unusual behaviour

Oseltamivir (Tamiflu®, Roche) is an antiviral agent licensed by HSA in October 2000 for the treatment of uncomplicated acute illness due to influenza infection (influenza A & B) in adults and children ≥ 1 year old who have been symptomatic for no more than two days and for the prophylaxis of influenza in adults and children ≥ 13 years old.

Recent post-marketing reports of CNS disorders[1,2]

The Health Sciences Authority (HSA) has reviewed the data from the 103 post-marketing reports of neuropsychiatric adverse events suspected to be associated with oseltamivir received between August 2005 to July 2006. These include events such as delirium with prominent behavioural disturbances (n=60) and suicidal events (n=6) including self-injury and suicidal ideation.

The majority of the cases were reported from Japan (92%) and were predominantly for the treatment of influenza (97%). These were primarily among paediatric patients (67%) with an age range of 1.5 to 17 years old. There were three deaths: a 14 year-old boy and two adults who fell to their deaths. The patients who died were healthy before contracting influenza and receiving oseltamivir. Most of the adverse events occurred during the first day of oseltamivir use (1 to 2 doses).

Our assessment of the reports was that many of the cases lacked sufficient detail for causality assessment and largely originated from one country. Therefore, it is unclear at the present time whether these events were the outcomes of the direct adverse effect of the drug, genetic differences in metabolic handling of oseltamivir, an unusual manifestation of influenza infection in Japanese patients, higher usage of oseltamivir in Japan or a coincident period of intensive monitoring of adverse events in Japan or a combination of any of these possible factors. Additionally, many events such as convulsions, delirium and depressed levels of consciousness are complications of viral encephalitis secondary to influenza making a direct causal link to Tamiflu® administration very difficult.

Nonetheless, considering the rapid temporal relationship of adverse event to the use of oseltamivir, and cases which reported positive de-challenge (n=65) where there was rapid and full recovery from neuropsychiatric adverse effects once oseltamivir was discontinued and/or lack of positive neuro-imaging findings in the reviewed reports (n=25), the local prescribing information of Tamiflu® will be updated to warn of the potential for the occurrence of neuropsychiatric adverse events. In addition, it also advised that patients with flu, particularly children may be at an increased risk of self-injury and confusion shortly after taking Tamiflu® and should be closely monitored for signs of unusual behaviour.

Local situation

HSA has received three adverse drug reactions suspected with use of oseltamivir. They are one report of hepatitis, and another of nausea and urticaria. There is also one report of a middle-aged male who committed suicide by falling to his death. He was prescribed oseltamivir at 75mg twice a day for flu and the adverse event was reported to have occurred on the 7th day. The causality however could not be established as it was reported that the patient was also taking other medications.

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Eptifibatide and increased risk of bleeding in impaired renal function

Consider a lower infusion dose of 1mcg/kg/min for patients with CrCl between 30 – 50ml/min

Recent literature reports suggest an increased risk of bleeding in patients with impaired renal function when administered infusion doses of eptifibatide similar to those in patients with normal renal function.

Background

Eptifibatide (Integrilin®, Schering-Plough) reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein IIb/IIIa receptors and is currently licensed by HSA for use in unstable angina or non-Q-wave myocardial infarction (UA/NQMI) and for patients who are managed with standard medical therapies and/or with percutaneous coronary intervention (PCI). It is intended for use with aspirin and heparin. Eptifibatide is also indicated as an adjunct to percutaneous transluminal coronary angioplasty for the prevention of abrupt closure of the treated coronary vessel and related acute ischaemic cardiac complications.[1]

The local recommended dosing regimen for UA/NQMI is an intravenous bolus of 180mcg/kg followed by continuous infusion of 2mcg/kg/min for up to 72 hours. For PCI, an intravenous bolus of 180mcg/kg is administered together with a continuous infusion of 2mcg/kg/min for a maximum of 18 – 24 hours post-PCI. In both cases, a second bolus dose of 180mcg/kg is to follow 10 minutes after the first bolus. Eptifibatide is contraindicated in patients with severe renal impairment or creatinine clearance (CrCl) < 30ml/min.[1]

Safety updates

A study on eptifibatide published in 2004 demonstrated that at an infusion rate of 2mcg/kg/min in patients with moderate (30 – 50ml/min) or severe renal impairment (CrCl < 30ml/min), the clearance rate of eptifibatide was about 50% lower and steady-state plasma levels was almost 2-fold higher compared to those with normal renal function. The authors recommended a dose reduction of eptifibatide from 2mcg/kg/min to 1mcg/kg/min in patients with ≤ 50ml/min.[2]

Another recently published study evaluated the correlates of bleeding events among eptifibatide-treated patients undergoing PCI. The bleeding rates were 2.9% (N=527) in patients with CrCl > 50ml/min and 20% (N=15) in patients with CrCl ≤ 50ml/min who received the standard eptifibatide infusion dose of 2mcg/kg/min, and 0% (N=18) in patients with CrCl ≤ 50ml/min who received a reduced dose of 1mcg/kg/min (p=0.017). The incidence of blood transfusions was also significantly increased in patients with CrCl ≤ 50ml/min on standard eptifibatide infusion dose compared to those who received reduced-dose eptifibatide (26.7% vs 0%; p=0.009).[3]

Dosing recommendations in other countries

The package inserts of eptifibatide in the different countries carry varying dosage recommendations for renal impairment. In the US, the approved infusion dose of eptifibatide is 1mcg/kg/min for patients with CrCl < 50ml/min when used for acute coronary syndrome and PCI. However, the dosing of eptifibatide in the UK Summary of Product Characteristics (equivalent of a package insert) recommends 2mcg/kg/min for patients with mild to moderate renal impairment (serum creatinine between 175 – 350 micromol/L) and contraindicates the use in patient with severe renal impairment or CrCl < 30ml/min.

Local situation and action

To date, HSA has not received any local reports of bleeding events associated with eptifibatide. However, in view of the pharmacokinetic handling of eptifibatide in renally impaired patients and available evidence[3] of efficacy of the lower dose in these patients, HSA is working with the product licence holder to amend the local package insert of Integrilin® to reflect an infusion dose of 1mcg/kg/min for patients with CrCl between 30 – 50ml/min when used for both acute coronary syndrome and PCI ■

References

1. *Product information: Integrilin®, Singapore, 2004.*
2. *Clin Ther 2004; 26:290-8.*
3. *J Am Coll Cardiol 2006; 47:2374-9.*

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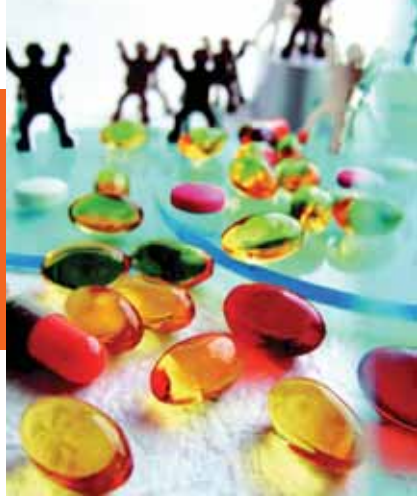
■ *Oseltamivir & neuropsychiatric events* ■

HSA will continue to closely monitor this emerging safety concern and update our healthcare professionals as and when necessary. All healthcare professionals are encouraged to report all serious adverse effects especially neuropsychiatric adverse events suspected to be associated with oseltamivir to the Pharmacovigilance Unit of HSA. ■

References

1. *Tamiflu® Adverse Event Review by the FDA Paediatric Advisory Committee. http://www.fda.gov/ohrms/dockets/ac/06/briefing20064254b_09_01_Tamiflu%20AE%20Review%202006%20Redacted_D060309_092.pdf*
2. *US FDA Medwatch 2006 Safety Alerts. http://www.fda.govmedwatch/safety/2006/safety06.htm#tamiflu*

Life-threatening cases of serotonin syndrome with SSRI/SNRI-triptan combination



HSA would like to remind healthcare professionals of the potential risk of developing serotonin syndrome in patients taking 5-hydroxytryptamine receptor agonists (triptans) and Selective Serotonin Re-uptake Inhibitors (SSRIs) or Selective Norepinephrine Re-uptake Inhibitors (SNRIs). SSRIs are known to increase serotonin levels and possibly cause serotoinin syndrome when used concomitantly with serotonergic agents such as triptans.

In July 2006, the US Food and Drug Administration alerted healthcare professionals and the public of this potentially life-threatening interaction. The FDA reviewed 27 reports of serotonin syndrome reported from 1998 to 2002 in association with concomitant SSRI or SNRI and triptan use. Two cases were life-threatening and 13 required hospitalisation. It was found that some of the cases occurred in patients who had previously used both drugs concomitantly without experiencing serotonin syndrome.

The reported signs and symptoms of serotonin syndrome were highly variable and included respiratory failure, coma, mania, hallucinations, confusion, dizziness, hyperthermia, hypertension, sweating, trembling, weakness and ataxia. In eight cases, recent dose increases or addition of another serotonergic drug to a SSRI/triptan or SNRI/triptan combination were temporally related to symptom onset. The median time to onset of symptoms was one day, with a range of ten minutes to six days.

HSA has not received any local ADR reports associated with this interaction and serotonin syndrome. However, healthcare professionals are reminded to consider the following when prescribing SSRIs/SNRIs or triptans:

1. To weigh potential risk versus benefit of prescribing concomitant SSRI/SNRI and triptan therapy and discuss the possibility of serotonin syndrome with the patient when prescribing both concomitantly;
2. To keep in mind that triptans are often used intermittently and that SSRIs, SNRIs or triptans may be prescribed by a different healthcare professional;
3. To be alert to the highly variable signs and symptoms of serotonin syndrome. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucination, coma), automatic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea);
4. To observe patient on concomitant therapy carefully, particularly during treatment initiation and dose increases.

Healthcare professionals are also encouraged to report suspected adverse reaction of this nature to the Pharmacovigilance Unit of HSA ■

Examples of locally available products

Triptans

Eletriptan (Relpax®),
naratriptan (Naramig®),
rizatriptan (Maxalt®),
sumatriptan (Imigran®),
zolmitriptan (Zomig®)

SSRIs

Citalopram (Cipram®),
escitalopram (Lexapro®),
fluoxetine (Deprexin®, Fluoxone®, Fluxetin®, Fluxil®, Foxtin®, Magrilan®, Proctin®, Prodep®, Prozac®, Zactin®),
fluvoxamine (Faverin®),
paroxetine (Seroxat®),
sertraline (Zoloft®)

SNRIs

Duloxetine (Cymbalta®),
venlafaxine (Efexor®)

References

1. *FDA public health advisory, July 2006. http://www.fda.gov/cder/drug/advisory/SSRI_SS200607.htm*
2. *Information for healthcare professionals – Venlafaxine (Effexor®), July 2006. http://www.fda.gov/cder/drug/InfoSheets/HCP/venlafaxineHCP.htm*

Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety updates from April to September 2006. Details of the updates are listed at **http://www.hsa.gov.sg/cda/labelchanges**. Please note that there might be some lag time in the availability of the package insert which reflects the latest change(s).

1. Albendazole (Zentel®, GSK) Caution in the elderly with hepatic dysfunction & renal impairment. New ADRs: elevations of hepatic enzymes (rare), erythema multiforme & SJS (very rare).

2. Atenolol, nifedipine (Nif-ten®, AstraZeneca) Contraindicated in treatment of acute attacks of angina, secondary prevention of myocardial infarction, malignant hypertension, unstable angina, during or within 1 month of a myocardial infarction. Caution in obstructive airway disease & liver dysfunction. May intensify effect of insulin & oral antidiabetics. Bioavailability of nifedipine may increase if taken with grapefruit juice.

3. Bupropion (Wellbutrin®, GSK) Caution in severe hepatic cirrhosis & clinical circumstances associated with increased risk of seizures e.g. severe hepatic cirrhosis, excessive use of alcohol or sedatives, diabetes treated with hypoglycaemics or insulin, & use of stimulants or anorectics. Patients with depression may have worsening of their depressive symptoms. Interacts with CYP2D6 inhibitors. Minimise consumption of alcohol because of adverse neuropsychiatric events (rare) or reduced alcohol tolerance.

4. Busulphan (Myleran®, GSK) Co-administration of metronidazole & high-dose Myleran® is not recommended due to risk of toxicity (metronidazole increases the trough levels of busulphan by ~80%). Itraconazole reduces clearance of busulphan by ~20%. Monitor closely for toxicity with weekly measurements of blood counts. Common ADRs: secondary acute leukaemia, idiopathic pneumonia syndrome (with high dose use), & interstitial pneumonitis (with long term use).

5. Caffeine, ergotamine (Cafergot®, Novartis) May cause myocardial ischaemia or infarction even in patients with no history of coronary heart disease. Uncommon & rare ADRs include vertigo, cyanosis, bradycardia, tachycardia, gangrene, myalgia, absence of pulse & ergotism.

6. Ciprofloxacin (Ciprobay®, Bayer) Contraindicated with tizanidine (can result in hypotension, somnolence & drowsiness). Interacts with polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids & highly buffered drugs (e.g. didanosine) containing magnesium, aluminium or calcium & methotrexate. New ADRs: confusion, dysaesthesia, hypoaesthesia, vertigo, hypotension, arthritis, muscle cramps, agranulocytosis, pancytopenia, bone marrow depression, serum sickness-like reaction, psychotic reactions, hyperesthesia, intracranial hypertension, impaired hearing, pancreatitis, liver necrosis, SJS, TEN, tendonitis, & exacerbation of myasthenia gravis.

7. Diflucortolone, isoconazole (Travocort®, Schering) Contraindicated in tuberculous or syphilitic processes such as rosacea, perioral dermatitis & post-vaccination skin reactions.

8. Doxorubicin (Adriblastina®, Pfizer) Children & adolescents are at an increased risk for developing delayed cardiotoxicity with doxorubicin. Females at greater risk than males. Recommend periodic follow-up cardiac evaluations. May impair fertility. New ADR: Palmar plantar erythrodysaesthesia.

9. Eletriptan (Relpax®, Pfizer) Should not give without prior evaluation to patients at risk of cardiac & coronary artery disease due to association with vasospasm. Rarely, myocardial ischaemia/infarction. If symptoms of ischaemic heart disease occurr, take no further dose & carry out appropriate evaluation. New ADRs: hypertension, syncope & ischaemic colitis (rare).

10. Entacapone (Comtan®, Novartis) Isolated cases of rhabdomyolysis & neuroleptic malignant syndrome (following abrupt reduction or discontinuation of entacapone & other dopaminergic medications) reported.

11. Epoprostenol (Flolan®, GSK) Contraindicated in congestive heart failure arising from severe left ventricular dysfunction & not to use chronically in patients who develop pulmonary edema during dose-ranging. Interacts with other anticoagulants, tissue plasminogen activator, NSAIDs & other drugs affecting platelet aggregation. New ADRs include (very commonly) sepsis, septicaemia; (commonly) decreased platelet count, tachycardia; & very rarely agitation.

12. Flavoxate (Urispas®, IDS Pharmaceutical) Patients with galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption should not take Urispas®.

13. Gadobutrol (Gadovist®, Schering AG) Not to be used in patients with uncorrected hypokalaemia. Caution in history of arrhythmias & congenital QT syndrome.

14. Galantamine (Reminyl®, J&J) New ADRs: asthenia, atrial arrhythmias, palpitations, depression, paresthesia, tinnitus, transient ischaemic attack or cerebrovascular accident.

15. Hydrochlorothiazide, valsartan (Co-Diovan®, Novartis) Very rarely, hydrochlorothiazide-induced pulmonary edema with granulocytic infiltration & IgG deposition in alveolar membranes. New ADR terms include chest pain, erectile dysfunction, paraesthesia, & blurred vision.

16. Iopromide (Ultavist®, Schering AG) The contraindication in "manifest hyperthyroidism" was changed to "uncontrolled thyrotoxicosis". Special warnings include thyroid dysfunction, elderly & patients in very poor state of health, bronchial asthma. Special precautions (specific to IV) include renal impairment, cardiovascular disease, CNS disorders, pheochromocytoma, myasthenia gravis, autoimmune disorders, alcoholism & thromboembolic events.

Interacts with beta-blockers & interleukin-2. New ADRs: arrhythmia, vasodilatation, vasovagal reactions & more rarely, thyrotoxic crisis, cardiac arrest, heart failure, thromboembolic events, respiratory arrest & SJS.

17. Lantanoprost, timolol (Xalacom®, Pfizer) Precautions include aggravation of Prinzmetal's angina, aggravation of peripheral & central circulatory disorders, hypotension, cardiac failure resulting in death, severe respiratory reactions, bradycardia, & spontaneous hypoglycaemia or diabetes. May mask symptoms of hypoglycaemia & hyperthyroidism. May increase muscle weakness in myasthenia gravis or myasthenic symptoms.

18. Lidocaine (Xylocaine®, AstraZeneca) Caution in acutely ill patients, sepsis, severe liver disease, cardiac failure & when used concurrently with anti-arrhythmic class III drugs.

19. Lisinopril (Zestril®, AstraZeneca) Caution in mitral valve stenosis, renal impairment (CrCl <80ml/min), angioedema associated with tongue edema, anaphylactoid reactions in haemodialysis patients dialysed with high flux membranes, anaphylactoid reactions during low-density lipoproteins apheresis with dextran, hepatic failure, neutropenia, diabetics, & concurrent lithium therapy. New ADRs: neutropenia, lymphadenopathy, autoimmune disease, hypoglycaemia, allergic alveolitis/eosinophilic pneumonia, hepatic failure & pemphigus.

20. Metformin (Glucophage®, Merck) Contraindicated in patients with CrCl<60ml/min.

21. Nifedipine (Adalat LA®, Bayer) Phenytoin reduces the bioavailability of nifedipine. Fluoxetine, ritonavir & saquinavir may increase plasma conc. of nifedipine.

22. Nimodipine (Nimotop®, Bayer) Interacts with neuroleptics, antidepressants, zidovudine, rifampicin & grapefruit juice.

23. Ondansetron (Zofran®, GSK) Very rarely, transient ECG changes including QT prolongation. Monitor patient with signs of subacute intestinal obstruction. Interact with phenytoin, carbamazepine, rifampicin & tramadol. New ADR terms include anaphylaxis, movement disorders, dizziness during rapid IV administration, transient visual disturbances & blindness.

24. Risperidone (Risperal®, J&J) Under caution: (1) Findings in placebo-controlled trials: a) significantly higher incidence of cerebrovascular adverse events with risperidone vs placebo; b) in elderly patients with dementia, mortality was increased vs placebo c) concomitant use with furosemide resulted in a higher incidence of mortality in elderly patients with dementia. (2) patients with Parkinson's disease or dementia with Lewy bodies as both groups may be at increased risk of NMS & may exhibit increased sensitivity to Risperdal® (e.g. confusion, obtundation). (3) renal & hepatic patients should start with halved doses & slower titration.

Very rarely, pituitary adenomas. Interacts with fluoxetine, paroxetine & topiramate. Reversible extrapyramidal symptoms observed in neonate following use during last trimester.

25. Serratiopeptidase (Danzen®, Luen Wah) New ADRs: SJS, TEN, anaphylactic symptoms, hepatitis & jaundice.

26. Zoledronic acid (Zometa®, Novartis) Infrequently, severe & occasionally incapacitating bone, joint or muscle pain. Time to onset: 1 day to several months after starting therapy. Very rarely, hypotension has led to syncope or circulatory collapse in patients with underlying risk factors.

Other products with labelling changes include Adefovir (Hepsera®, GSK), Alfuzosin (Xatral®, Sanofi-Aventis), Atazanavir (Reyataz®, BMS), Atomoxetine (Strattera®, Eli Lilly), Azathioprine (Imuran®, GSK), Azelaic acid (Skinoren®, Schering), Basiliximab (Simulect®, Novartis), Bupivacaine (Pfizer), Clobetasol (Dermovate®, GSK), Cyproterone (Androcur®, Schering), Dexketoprofen (Ketesse®, Pharmaforte), Domperidone (Domper®, Yung Shin), Doxycycline (Vibramycin®, Pfizer), Etonorgestrel (Implanon®, Organon), Formoterol (Foradil®, Novartis), Fusidic acid (Fucidin®, Leo Pharma), Hydroxyurea (Hydrea®, BMS), Leflunomide (Arava®, Aventis), Nicotinic acid (Niaspan®, Merck), Melphalan (Alkeran®, GSK), Omeprazole (Losec® / Losec Mups®, AstraZeneca), Pregabalin (Lyrica®, Pfizer), Progestogen (Primolut N®, Zuellig), Ranitidine (Zantac®, GSK), Ropinrole (Requip®, GSK), Ropivacaine (Naropin®, AstraZeneca), Saquinavir (Invirase® / Fortovase®, Roche), Sildenafil (Viagra®, Pfizer), Tadalafil (Cialis®, Eli Lilly), Vardenafil (Levitra®, Bayer) ■

Raloxifene and risk of venous thomboembolism / fatal stroke

Results from the RUTH study raises safety concerns

Raloxifene (Evista®, Eli Lilly) is a selective oestrogen-receptor modulator (SERM) that binds to the oestrogen receptor, leading to oestrogen-agonist effects in some tissues and oestrogen-antagonist effects in others. The drug was approved in Singapore in 1999 and is licensed for the treatment and prevention of osteoporosis in postmenopausal women.

In July 2006, The New England Journal of Medicine published the results of the Raloxifene Use for the Heart (RUTH) Study, designed to investigate possible cardioprotective effects of raloxifene in the elderly. The results suggest that raloxifene did not demonstrate to protect women against heart disease and could be associated with excess deaths from stroke.

The RUTH study

RUTH was an international, multicentre, randomised, double-blind, placebo-controlled trial. The two primary objectives were to determine the effect of raloxifene as compared with placebo on the incidence of coronary events (i.e. death from coronary causes, nonfatal [including silent] myocardial infarction, or hospitalisation for an acute coronary syndrome other than myocardial infarction) and invasive breast cancer.

A total of 10,101 postmenopausal women (mean age, 67.5 years) with coronary heart disease (CHD) or multiple risk facts for CHD were randomly assigned 60mg of raloxifene or placebo and followed for a median of 5.6 years and the median exposure to the study drug was 5.05 years.

Primary outcomes

There was no significant difference between raloxifene and placebo group in the risk of primary coronary events (533 vs 553 events; hazard ratio, 0.95; 95% confidence interval, 0.84 to 1.07). Compared to placebo, raloxifene reduces the risk of invasive breast cancer (40 vs 70 events; hazard ratio, 0.56; 95% confidence interval, 0.38 to 0.83; absolute risk reduction, 1.2 invasive breast cancers per 1,000 women treated for one year); the benefit was primarily due to a reduced risk of oestrogen-receptor-positive invasive breast cancers.

Secondary outcomes

The overall incidence of stroke did not differ significantly between the treatment groups, but raloxifene was associated with an increased risk of fatal stroke (59 vs 39 events; hazard ratio, 1.49; 95% confidence interval, 1.00 to 2.24; absolute risk increase, 0.7 per 1,000 woman-years) and venous thromboembolism (VTE) (103 vs 71 events; hazard ratio, 1.44; 95% confidence interval, 1.06 to 1.95; absolute risk increase, 1.2 per 1,000 woman-years).

Raloxifene reduced the risk of clinical vertebral fractures (64 vs 97 events; hazard ratio, 0.65; 95% confidence interval, 0.47 to 0.89; absolute risk reduction, 1.3 per 1,000).

There was no significant difference between the treatment groups in the rates of death from any cause or overall death from cardiovascular events.

With these results, the authors concluded that raloxifene did not significantly affect the risk of CHD. The benefits of raloxifene in reducing the risks of invasive breast cancer and vertebral fracture should be weighed against the increased risk of venous thromboembolism and fatal stroke.

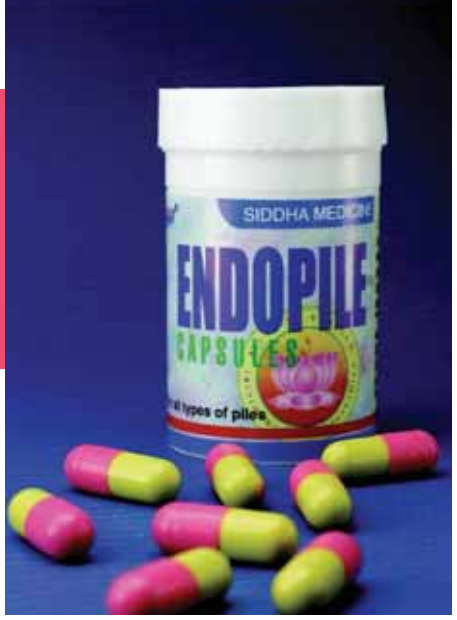
Local situation

HSA has not received any serious report of VTE or stroke suspected to be associated with raloxifene. The ADR reports submitted pertain to non-serious skin reactions, headache and insomnia.

HSA is working with the product licence holder to amend the local package insert of Evista® to reflect the conclusions of the RUTH study ■

Presence of heavy metals in traditional Indian medicines –

A case of lead poisoning with ayurvedic medicine, Endopile®



Local case report

A 31 year-old female patient was reported to have developed symptoms of lead poisoning after the consumption of a traditional Indian medicine, Endopile® for one month. She presented with abdominal pain, nausea, vomiting, anaemia with basophilic stippling and Burton's Line (a bluish line on the free border of the gingiva). Upon hospitalisation, she was found to have a blood lead level of 4.78µmol/L (normal upper limit: 0.4mg/L or 1.93 µmol/L[1]).

Endopile® is produced by two firms in India, Santhigiri Ayurveda and Siddha Vaidyasala. It is available as a yellow and pink capsule. The product is indicated for the treatment of piles and related symptoms and labelled to contain herbal ingredients.

Laboratory analysis of Endopile® capsules conducted by HSA found the product to contain lead at more than 100 times the permissible limits (limit is 20ppm) and mercury at 8 times the permissible limits (limit is 0.5ppm). HSA has since taken actions to recall the affected batch of product from the local market.

Presence of heavy metals in traditional medicines

As certain branches of traditional medicine believe in using small amounts of heavy metal to treat specific ailments, it is not uncommon to find traces of heavy metals in traditional medicines such as Ayurvedic medicine. According to the principles of Ayurvedic medicine, heavy metals are used in a detoxified state in these medicinal products because of their reputed therapeutic properties. However, should the detoxification process not be strictly followed during manufacturing, it is possible for the resulting product to contain high levels of heavy metals.[2]

The presence of heavy metals such as lead, arsenic and mercury in traditional medicines has been reported worldwide with numerous literature published on this topic.[3-7] For instance, the December 2004 issue of the Journal of the American Medical Association (JAMA) reported a study of commercially available Ayurvedic medicinal products sold in the Boston area, USA which found that 14 out of 70 (20%) of these products contained potentially harmful levels of lead, mercury and/or arsenic.[8]

Conclusion

With the increasing popularity of the use of traditional medicines, healthcare professionals need to be vigilant of the possible adverse effects arising from the consumption of such products. A thorough medication history inclusive of the patient's use of traditional medicines is important when evaluating a suspected adverse drug reaction. All healthcare professionals are encouraged to report suspected adverse reactions to traditional medicines to the Pharmacovigilance Unit of the HSA ■

Signs & symptoms of lead poisoning[9]

Acute phase: Metallic taste, gastro-intestinal irritation, nausea, persistent vomiting, abdominal pain, diarrhoea, malaise, anorexia at acute phase.

Chronic phase: Avitaminosis, loss in weight, foul mouth odour, black gum line (Burton's line), severe colic, anaemia, basophilic stippling, jaundice, encephalitis, increase in reticulocytes, coproporphyrins in urine, constipation alternating with diarrhoea, possible hepatic, kidney or pulmonary damage, central nervous system damage, mental aberration, arthralgia, wrist or foot drop, peripheral neuritis, collapse, coma, death.

References

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