WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Quality Assurance and Safety: Medicines, PSM–HTP
World Health Organization,
1211 Geneva 27, Switzerland
E-mail address: pals@who.int

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring,
Stora Torget 3,
753 20 Uppsala, Sweden
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: sten.olsson@who-umc.org
Internet: http://www.who-umc.org

Contents

No. 5, 2006

News & Issues

The recently concluded twenty-ninth meeting of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring was, as always, an incredible event, bringing together over a hundred participants from 43 countries. Those of you who attended this meeting in Liège, Belgium will remember the sessions moving on well-oiled wheels, thanks to the excellent organization by Thierry Roisin and his team. This meeting will stay with us for many reasons. The topics were very relevant with several outstanding presentations. We learnt much but have become even more aware of all that needs to be done, in global networking for information sharing, towards improving patient safety, about special safety monitoring needs in pandemics, the need to build an evidence base for pharmacovigilance in resource-poor countries as well as in many other areas. We shall be reporting on these issues in the next editions of this newsletter. But things have never looked this promising; more and more countries are recognizing pharmacovigilance as an important tool towards rational use of medicines, with an ultimate impact on patient safety. With growing awareness, the resources too will follow. There is cause for optimism.

Earlier this year, WHO took the lead in establishing the International Medical Product Anti-Counterfeiting Taskforce, IMPACT. The feature article in this issue provides an overview of why this was needed and what countries can do to protect public health from this menace.

As usual, we also bring you sections covering new global drug regulatory and safety information on medicines.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

Bevacizumab

Reports of reversible posterior leukoencephalopathy syndrome (RPLS)

USA. Genentech Inc. is informing health-care providers that some cases of confirmed and possible RPLS have been reported in patients treated with bevacizumab (Avastin, an immunosuprressant) in clinical studies and in post-marketing experience at a rate of <0.1 %. RPLS is a rare brain-capillary leak syndrome associated with hypertension, fluid retention, and the cytotoxic effects of immunosuppressive drugs on the vascular endothelium. The syndrome can present as headache, seizures, visual disturbance and altered mental function and is characterized by its reversibility upon control of hypertension or other instigating factors. Magnetic Resonance Imaging is needed to confirm RPLS. And if RPLS is confirmed, bevacizumab (Avastin) should be discontinued and hypertension, if present, should be treated. The prescribing information for bevacizumab (Avastin) has been updated accordingly.

Reference:
'Dear Health-care Provider' letter from Genenetech Inc., September 2006 (http://www.fad.gov).

Dexamfetamine sulfate

Label to warn of sudden death from misuse

USA. The labelling for dexamfetamine sulfate (Dexedrine Spansule) sustained-release capsules and tablets has been updated in the US in response to a United States Food and Drug Administration (US FDA) request. The updated Boxed Warning section states that misuse of amfetamines may lead to serious cardiovascular adverse events and sudden death. The updated Warning section states the following:

- CNS stimulants have been linked with sudden death in children and adolescents with structural cardiac abnormalities or other serious heart disorders. Sudden death, stroke and myocardial infarction have been reported in adults receiving stimulants for attention-deficit hyperactivity disorder (ADHD). Stimulant drugs should not be given to patients with structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease or other serious heart disorders.
- Stimulant drugs can modestly increase mean heart rate (HR) and blood pressure (BP). Patients should be monitored for larger changes in BP and HR; caution is indicated in treating those with conditions that might be compromised by HR or BP increases. Cardiovascular (CV) status should also be assessed in patients being considered for treatment with stimulants.
- Stimulant drugs may worsen thought disorders and behaviour disturbances in patients with a pre-existing psychotic disorder. Care should also be taken when using stimulants for ADHD in patients with bipolar disorder due to concern for possible induction of mixed/manic episodes in such patients.
- Stimulant drugs may cause treatment-emergent psychotic or manic symptoms, and may lower the convulsive threshold. In addition, hostility or behavioural disorders have been reported in clinical trials, and in the post-marketing experience of some ADHD drugs, so patients starting ADHD treatment should be monitored for such symptoms.
- Consistent methylphenidate use was associated with a slowing growth rate in a study in children. It has been anticipated that chronic use of amfetamines may cause a similar growth suppression; therefore, growth should be monitored during stimulant therapy.
- Stimulant treatment has also been linked to visual disturbances.

(Reports in WHO database:
Death - 9
Myocardial infarction - 9).

Reference:
Advisories, Warnings & Recalls. United States Food and Drug Administration, 4 August 2006 (http://www.fda.gov).

Dietary supplement

Adulterated with estazolam

Canada. Canadian consumers have been warned by Health Canada not to use Salt Spring Herbals Sleep Well Dietary Supplement, as a sample has been found to contain estazolam. Health Canada advises that although there have been no reports of adverse reactions suspected of being associated with the supplement, estazolam is a sedative that can be habit-forming after only a few months of use, and serious adverse effects associated with the drug include memory loss, hallucinations, depression and confusion; other common adverse effects include dizziness and drowsiness. The agency also warns that people with a benzodiazepine allergy, or who have myasthenia gravis, sleep apnoea, are pregnant or elderly or have a history of substance abuse, should not use estazolam. Health Canada

says that consumers taking the supplement should talk to a health-care professional before they stop using it, as withdrawal symptoms are possible. Although the product is not authorized for sale in Canada, the agency advises that the product has been found on the Canadian market. The Canadian distributor has initiated a recall.

Reference:
Advisories, Warnings & Recalls. Health Canada, 30 August 2006 (http://www.hc-sc.gc.ca).

Diethylene glycol

Detected in cough syrup; fatalities reported

Republic of Panama. Several cases of acute renal failure, many of them fatal, were recently reported in Panama in patients treated with lisinopril. The Panama Ministry of Health investigated these cases and has concluded that these reactions resulted from the concomitant use of a cough syrup that contained diethylene glycol (DEG) and were not due to lisinopril as previously feared (1). DEG is a highly toxic organic solvent that causes acute renal failure and death when ingested. DEG-associated fatalities have been reported also in the past, in 1938 in the USA, when DEG had been used as a diluent for sulfanilamide and in 1998 in India, where contaminated cough syrup caused the deaths of a number of children (2). The United States Congress passed the Federal Food, Medicines & Cosmetic Act in 1938 in reaction to the DEG incident. WHO issued an Alert in 1996 (3) when several children died in Haiti after consuming DEG-contaminated paracetamol syrup. The Panama Ministry of Health is currently performing a root cause analysis of events leading to the presence of a poisonous substance such as DEG in a pharmaceutical preparation for human consumption.

References:
1. Communicado N° 15. Ministerio de Salud, Républica de Panama, 17 October 2006 (http://www.minsa.gob.pa).
2. The Safety of Medicines in Public Health Programmes; pharmacovigilance an essential tool. WHO, 2006.
3. DRS Information Exchange Service Alert No. 50. WHO, 28 June 2006.

Hydrogen peroxide

High strength peroxide not a medical product

USA. The US FDA is warning consumers against drinking high-strength hydrogen peroxide products for medicinal purposes, including a product marketed as "35 Percent Food Grade Hydrogen Peroxide," because ingestion may lead to serious health risks or death. The FDA advises consumers of these products to immediately discontinue them and to consult their health-care provider. The FDA says that high-strength hydrogen peroxide is not approved by the FDA and is therefore being illegally sold for medical indications without proven clinical value. The Agency says that it is working to prevent companies that sell these products from making illegal claims about their products, and that it has issued warning letters to two firms who are illegally selling "35 percent hydrogen peroxide" products on websites. The FDA states that this high-strength hydrogen peroxide is highly corrosive, and that hydrogen peroxide at a strength of 35% is dangerous even if handled according to manufacturer directions. Hydrogen peroxide ingestion can lead to GI ulceration or irritation, and IV administration can lead to air embolisms, blood vessel inflammation at the injection site and potential life-threatening allergies, says the FDA.
(Reports in WHO database:
Total 76
Conjunctivitis - 16
Application site reaction - 7
Vomiting - 8
Abdominal pain - 4).

Reference:
FDA News Release. United States Food and Drug Administration, 27 July 2006 (http://www.fda.gov).

Neophase Formula

Presence of undeclared active ingredient

Canada. Health Canada is advising consumers not to use Neophase Formula for Men, which is manufactured in the US by Vigor Nutriceutical Healthcare Inc, because it has been found to contain homosildenafil, a modified version of sildenafil. The Agency says that the use of this product can lead to serious health risks, particularly in patients with heart disorders, those at risk for stroke, and those using heart medications, and that the use of sildenafil-containing products has been linked with serious adverse effects including penile tissue damage, sudden loss of vision and urinary tract infections. The product is being recalled by its Canadian distributor, and consumers who may have purchased Neophase Formula for Men are advised to not use it and to consult a health-care professional if they have used it and have health concerns, says the Agency.

Reference:
Advisories, Warnings & Recalls. Health Canada, 4 August 2006 (http://www.hc-sc.gc.ca).

(Reports in WHO database:
Cardiomyopathy - 27).

Antidepressants

Update on adverse reaction reports

Finland. From 1998 to 2005, Finland's National Agency for Medicines (NAM) received 396 reports of adverse reactions (ARs) associated with antidepressants, including tricyclic antidepressants (7 reports), SSRIs (170) and other antidepressants (227). NAM advises that the reports received on SSRIs involved sertraline (51 reports), citalopram (44), paroxetine (27), fluoxetine (22), escitalopram (18) and fluvoxamine (8); about one-third of the reports involved neurological disorders, whereas other reports were related to skin disorders, digestive system disorders, oedema, serotonin syndrome, drug interactions, withdrawal symptoms and intentional overdoses. The Agency added that, among other antidepressants, the majority of AR reports were related to mirtazapine (106), venlafaxine (53) and reboxetine (20), and involved neurological disorders. Mirtazapine-related ARs also included skin disorders, oedema, leucopenia and stomatitis. Venlafaxine-associated reports included serotonin syndrome, withdrawal symptoms and QT-interval prolongation. According to NAM, seven adverse reaction reports involved neonates and all of them involved SSRIs, whereas 21 reports involved adolescents aged 15–19 years. Adverse symptoms in the neonates included seizures, somnolence, and breathing and eating difficulties.

Reference:
TABU, 4: 56, 2006. National Agency for Medicines, Finland.

Bismacine

Warning against use

USA. The US FDA is warning consumers and health-care providers against using bismacine, also known as chromacine. The Agency is investigating one report of death and several reports of injury associated with bismacine use. According to the US FDA, injectable bismacine is not a pharmaceutical, is not approved for anything, and contains high amounts of bismuth, which is not approved for use by injection. The FDA says that one person has died, one was hospitalised and others experienced serious adverse events after receiving bismacine. The Agency also states that possible effects of bismuth poisoning include renal failure and cardiovascular collapse.

Reference:
FDA News. United States Food and Drug Administration, 21 July 2006 (http://www.fda.gov).

Bisphosphonates

Additional cases of osteonecrosis of the jaw

Australia. Since the Australian Adverse Drug Reactions Advisory Committee (ADRAC) drew attention to the issue of osteonecrosis of the jaw (ONJ) associated with bisphosphonates in 2005, further Australian cases have been published. ADRAC advises that, up to June 2006, it has received 106 reports of ONJ associated with bisphosphonates; these reports involved IV zoledronic acid (n = 69), IV pamidronic acid (33), oral alendronic acid (19), oral risedronic acid (2), IV ibandronic acid (1) and IV and oral clodronic acid (1). According to ADRAC, a review of 368 published case reports of ONJ found that 94% involved patients with bony metastasis or multiple myeloma receiving IV bisphosphonates, and 60% of cases were preceded by a dental procedure.

Reference:
Australian Adverse Drug Reactions Bulletin 25(4): 14, August 2006.

CFC-free beclometasone inhalers

Dose adjustments needed with different brands

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has advised health professionals that two chlorofluorocarbon (CFC)-free beclometasone inhalers, Clenil Modulite and Qvar provide different amounts of the active drug to the lungs; Qvar is approximately twice as potent as Clenil Modulite. The Agency says that this difference should be taken into account and dosages adjusted according to the type of brand chosen. The MHRA is asking prescribers to state clearly on prescriptions which product should be dispensed by using the brand name rather than the generic name. Furthermore, pharmacists who receive a prescription with the generic name should establish whether a (CFC)-free product is required, and if so, which of the two brands should be dispensed.

Reference:
Press release. Medicines and Healthcare products Regulatory Agency, 8 August 2006 (http://www.mhra.gov.uk).

Enoxaparin

To decrease dose in renal disease

Australia. ADRAC has received 10 reports of death associated with haemorrhage after enoxaparin use in

2005–2006, giving a total of 46 since 1997. In three of the reports received in 2005, patients with chronic renal disease received inappropriate doses; two reports also implicated an incorrect dose for the patient's weight.

The Australian ADRAC advises that since the clearance of enoxaparin sodium is decreased in patients with chronic renal disease, the dosage should be decreased in such patients. ADRAC warns that low molecular weight heparins such as enoxaparin have a longer half-life than unfractionated heparins, their anticoagulant effect is not routinely monitored and, in cases of haemorrhage, their effects are harder to reverse.

ADRAC says that patients' renal function should be assessed before starting low molecular weight heparins; for those with severe chronic renal disease (glomerular filtration rate < 30 mL/min) requiring therapeutic dosages, the dosage of enoxaparin should be decreased from 1 mg/kg twice daily or 1.5 mg/kg once daily to 1 mg/kg once daily. An alternative is to use unfractionated heparin with dose monitoring by activated partial thromboplastin time. Also, unfractionated heparin is preferred in patients with unstable or deteriorating renal function. Where there is a high risk of haemorrhage,

Ibuprofen

Interaction with low-dose, non-coated aspirin

USA. The US FDA has warned health-care providers that ibuprofen can interfere with the anti-platelet effect of low dose aspirin (81 mg per day), potentially rendering aspirin less effective when used for cardioprotection and stroke prevention. It has been demonstrated in published and unpublished human *ex vivo* studies, that ibuprofen interferes with the antiplatelet activity of low dose aspirin (81 mg, immediate release) when they are ingested concurrently. The mechanism by which this occurs may be through competitive inhibition of the acetylation site of cyclooxygenase (COX) in the platelet. Both ibuprofen (reversible inhibition) and aspirin (irreversible inhibition) occupy nearby sites on COX, such that the presence of ibuprofen interferes with aspirin binding. Once the ibuprofen releases from the binding site, COX will not be inhibited because some aspirin available to bind will have been excreted. This ibuprofen interference attenuates the expected aspirin-mediated irreversible inhibition of thromboxane B2 (TXB2) production and the expected inhibition of platelet aggregation.
Health-care professionals

long-lasting effect of aspirin on platelets.

- patients who use immediate release aspirin (not enteric coated) and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least 30 minutes or longer after aspirin ingestion, or more than 8 hours before aspirin ingestion to avoid attenuation of aspirin's effect.
- recommendations about the timing of concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based upon available data.
- other nonselective OTC NSAIDs should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.
- prescribing analgesics that do not interfere with the antiplatelet effect of low dose aspirin for high risk populations.

Reference:
Healthcare Professional Sheet. United States Food and Drug Administration, 8 September 2006 (http://www.fda.gov).

Infliximab

Reports of hepatosplenic non-