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. 1, 2007

News & Issues

In early February, WHO met in Lusaka with five African countries in a follow-up meeting to a workshop conducted in 2003 in Zambia to assess progress and barriers in implementing pharmacovigilance activities for the safety monitoring of artemisinin combination products in the malaria programmes in these countries. A pharmacovigilance training course was organized from 12 to 23 February in Morocco. The course was offered in French, to help launch a national pharmacovigilance programme in 13 countries in Francophone Africa. The WHO Advisory Committee on Safety of Medicinal Products will meet from 26 to 27 February, to discuss current issues and concerns in pharmacovigilance. We will bring you a summary of all these events in the next issue of the newsletter.

In capturing adverse reactions to medicines, national pharmacovigilance centres design a reporting form that best meets the centre's needs. Would a 'generic reporting form' help harmonize efforts and improve the quality of data captured? Indeed, is it even possible to design such a generic adverse reaction reporting form? What are the constraints we are likely to face in designing such a generic form? Sten Olsson, WHO Collaborating Centre for International Drug Monitoring, Sweden discusses some of these issues in his article (page 7).

In the next issue, we hope to introduce a Letters section. Here we will include, if appropriate, various comments from our readers, either on specific items in the newsletter or on other issues of medicine safety. We hope that this will allow even better interaction with our readers. We invite you to send your letters with comments to pals@who.int.
But we caution that we may not be able to publish every letter.

We hope that you will find useful the usual sections on Regulatory Matters and Safety of Medicines.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of medicines

Feature

Aprotinin injection

Use limited to patients at increased risk of blood loss during heart surgery

USA. The safety warnings have been strengthened and the approved use limited to specific situations for aprotinin injection (Trasylol), a product used before heart surgery to reduce bleeding and the need for blood transfusions. The label now specifies that aprotinin (Trasylol) should only be given to patients who are at an increased risk of blood loss and blood transfusion in the setting of coronary bypass graft surgery, when patients undergo cardiopulmonary bypass. The label also has the new warning that aprotinin increases the possible risk for kidney damage. These measures follow a United States Food and Drug Administration (US FDA) conducted safety review triggered by the results of two published research studies: one study reported an increase in the possibility of kidney damage, heart attack and stroke in patients treated with aprotinin compared to those treated with other drugs, while the second study showed only an increase in the possibility of kidney damage compared to other drugs. The Agency has also received the results of an additional safety study from Bayer, (Marketing Authorization Holder for Trasylol) that suggest, in addition to serious kidney damage, an increased risk of death, congestive heart failure and strokes with the product. According to the US FDA, these results are being reviewed and may result in other actions, including additional changes to the labelling.

Reference:
FDA News. U.S. Food and Drug Administration, 15 December 2006 (www.fda.gov).

Buflomedil

Higher dose tablets withdrawn due to risk of suicide

France. Agence française de sécurité sanitaire des produits de santé (Afssaps) has decided to withdraw buflomedil 300 mg tablets from the market and to strengthen the summary of product characteristics (SPC) for buflomedil 150 mg.
The agency undertook a benefit-risk evaluation of buflomedil (used chiefly to treat peripheral vascular disease), following the results of two enquiries about cardiovascular and neurological toxicity in accidental or voluntary buflomedil overdoses. The agency says that neurological and serious cardiac adverse events occurred within 15–90 minutes in cases of suicide with buflomedil and, because of a narrow therapeutic index, the clinical manifestations of buflomedil overdose are serious. The overdose cases are difficult to manage and often have fatal outcomes, adds the agency; the majority of voluntary overdose cases occurred with 300 mg dose of buflomedil. According to Afssaps, the toxic dose of 3 g can easily be reached with buflomedil 300 mg tablets; therefore, the benefit-risk for buflomedil 300 mg is considered negative. The agency has decided to recall batches of buflomedil 300 mg tablets from the market, and to include the following information in the SPC for buflomedil 150 mg:

- indicated for improvement of symptoms of peripheral occlusive arterial disorders or Raynaud's disease only;
- contraindicated in patients with severe renal failure (creatinine clearance <30 mL/min);
- dose adaptation in patients with moderate renal failure (creatinine clearance between 30 and 90 mL/min) and low body weight (<50 kg);
- control of creatinine clearance before and during treatment; and
- information about low therapeutic range of buflomedil.

(Reports in the WHO database: Neurologic disorder - 1 report from 1999)

Reference:
Reactions 1131: 2, 9 December 2006.

Heparin

Delayed onset of heparin-induced thrombocytopenia

USA. The US FDA has informed health-care professionals that Baxter has revised the warnings section of the labelling for heparin sodium injection to highlight the potential of delayed onset of heparin-induced thrombocytopenia (HIT), and to highlight that HIT may develop into heparin-induced thrombocytopenia and thrombosis (HITT). Furthermore, the Agency states that thrombotic events could be the initial presentation of HITT, which can happen up to several weeks after heparin discontinuation, and that patients should be evaluated for HIT and HITT if they present with thrombocytopenia or thrombosis after heparin discontinuation.

Reference:
MedWatch Internet posting, 8 December 2006 (www.fda.gov).

Methadone

Risk of QT prolongation and Torsades de pointes

France. Afssaps, the Regulatory Agency in France, has issued a letter of information to health professionals and care-givers working with patients of drug

abuse. Methadone is used in the treatment of opioid dependence and for analgesia in moderate to severe pain. The letter warns about the evidence of QT-prolongation and torsades de pointes associated with the use of methadone. The Agency advises that these adverse effects were usually observed in patients at risk of QT prolongation or in those receiving a high dose of methadone (>120 mg/day). The Summary of Product Characteristics for methadone has been revised with this information. ECG monitoring is recommended in patients with risk factors for QT prolongation including:

- history of QT-prolongation, congenital or acquired;
- family history of sudden death;
- methadone dose >120 mg/day
- use of other medications known to prolong QT-interval, induce hypokalaemia, bradycardia, or inhibit the metabolism of methadone.

The interactions and contraindications sections of the SPC for methadone have been modified with details of medicines to be avoided as concomitant treatment, needing special clinical and ECG monitoring or favouring methadone dose reduction. The full list can be accessed from Afssaps home page on the internet (www.afssaps.sante.fr).

(Also see WHO Pharmaceuticals Newsletter, No. 5, 2005, for previous information from New Zealand).

Reports in WHO database: Arrhythmia - 32 (since 1986)

***Reference*:**
Lettre d'information aux medicines prescripteurs, cardiologues, pharmaciens et acteurs de soins auprès de patients usagers de drogue. Afssaps, 2 January 2007 (www.afssaps.sante.fr).

Quinine

Consumers cautioned against off-label use in treating leg cramps

USA. The US FDA is cautioning consumers against off-label use of quinine in leg cramps, citing serious safety concerns, including deaths, associated with quinine products. Quinine is used in treating malaria. Only one quinine product (Qualaquin) is approved by the US FDA in treating certain types of malaria without complications. However, the Agency notes that there are multiple unapproved products containing quinine in the US market and has ordered the responsible firms to stop marketing these. Quinine is a drug with a narrow therapeutic window, with a small margin between effective and toxic doses. But the Agency advises that because malaria is life-threatening, the risks associated with quinine use are justified for that condition; but it should not be used to treat or prevent leg cramps. Quinine drugs are associated with serious side effects such as cardiac arrhythmias, thrombocytopenia and severe hypersensitivity reactions. There is also the potential for serious interactions with other drugs. The US FDA notes that since 1969 it has received 665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths.

Reference:
FDA News. U.S. Food and Drug Administration, 11 December 2006 (www.fda.gov).

Rituximab

Fatal PML following off-label use in systemic lupus erythematosus (SLE)

Switzerland, USA. Roche Pharma, in collaboration with Swissmedic, the Swiss regulatory agency (1) and the US FDA (2) are informing health-care professionals of two fatal cases of progressive multifocal leukoencephalopathy (PML), a viral infection of the central nervous system in patients treated with rituximab (Rituxan, Genentech, US; MabThera, Roche Pharma, Switzerland). These two patients received rituximab for the treatment of systemic lupus erythematosus (SLE). SLE is not an approved indication for rituximab; rituximab is approved only in the treatment of patients with non-Hodgkins lymphoma and in patients with rheumatoid arthritis whose disease no longer responds to other common treatments and works by blocking the effect of specific immune cells in the blood known as B cells for up to six to nine months. PML appears to be a risk in patients treated with rituximab for any reason. There have been 23 confirmed cases of PML in patients with lymphomas who received rituximab. The majority of these patients had also received other drugs known to affect the immune system. Physicians and patients are advised to be aware of the risk of PML in patients treated with rituximab. Patients who experience signs of PML such as major changes in vision, balance or coordination, or who experience confusion should promptly contact their physician. The product label is being updated with this information on PML.

(Post-marketing reports of bowel obstruction and gastrointestinal perforation had led to a previous revision of the rituximab product label. See WHO Pharmaceuticals Newsletter No. 6, 2006)

References:
1. Lettre au médecin. Roche Pharma (Schweiz), le 24 janvier 2007 (www.swissmedic.ch)
2. FDA News. U.S. Food and Drug Administration,

18 December 2006
(www.fda.gov)

Sodium phosphate oral solution

Electrolyte and renal function disturbances in the elderly

France. Ferring and Casen Fleet Laboratories, in consultation with Afssaps, have revised the product monograph for sodium phosphates oral solution (Fleet® Phospho-Soda®), advising prior evaluation of risk factors and caution when using the product in the elderly. Sodium phosphates oral solution is used as a purgative as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for X-ray or endoscopic examination. The product has been associated with rare but severe and potentially fatal cases of electrolyte disturbances in the elderly. Gastroenterologists and nephrologists are reminded to pay special attention while using the product in special populations including the elderly, individuals with asymptomatic renal insufficiency, patients with a history of acute myocardial infarction or unstable angina, etc. Very rare cases of nephrocalcinosis (deposits of calcium phosphate tubules in the kidney) leading to acute or chronic renal insufficiency have also been associated with use of this product, particularly in elderly patients who were on anti-hypertensives or other medications (e.g. diuretics or other products known to cause dehydration). When considering the use of sodium phosphates oral solution in patients at risk, it is important to evaluate the baseline electrolyte levels before and after administration and to ensure sufficient fluid replacement to prevent dehydration and serious electrolyte problems.

Reference:
Lettre destinée aux gastro-entérologues et nephrologues ville et hospitaliers. Laboratoire Casen Fleet et Laboratoire Ferring SAS France, 13 décembre 2006 (www.afssaps.sante.fr).

Topical anaesthetic creams

Pharmacies warned to cease compounding standardized versions

USA. The US FDA is warning five pharmacies to cease compounding and distributing standardized versions of topical anaesthetic creams, which are marketed for general distribution rather than responding to the special requirements of individual patients. Such creams contain high doses of local anaesthetics including lidocaine, benzocaine, prilocaine and tetracaine. The Agency warns that exposure to high concentrations of local anaesthetics can lead to reactions such as irregular heartbeats and seizures. According to the FDA, two deaths have been linked to anaesthetic creams compounded by two of the five pharmacies receiving warning letters. The Agency says their warning serves as a general warning to firms that produce standardized versions of anaesthetics.

Reference:
FDA News. U.S. Food and Drug Administration, 5 December 2006 (www.fda.gov).

Cough and cold medications

Deaths in infants reviewed

USA. According to a recent report , during 2004 - 2005, an estimated 1 519 children aged less than two years were treated in the Emergency Departments in the United States for adverse events, including overdoses, associated with cough and cold medications. The Centers for Disease Control and Prevention (CDC) and the National Association of Medication Examiners (NAME) have determined cold and cough medications to be the underlying cause of three deaths (infants aged ≤6 months) in 2005; all three infants had high levels of pseudoephedrine (a nasal decongestant) in postmortem blood samples. One infant had received both a prescription and an over-the-counter cough and cold combination medication at the same time. The dosages at which cough and cold medications cause illness or death in children aged <2 years are not known. Nor do approved dosing recommendations exist for prescribing cough and cold medications for this age group. The US FDA advises that because of the risks of toxicity, absence of dosing recommendations, and limited medications that may have been given to these children, to avoid overdose from multiple medications that contain the same ingredient. Besides these recommendations, public health officials have taken additional safety measures including

- an enforcement action to stop the manufacture of unapproved carbinoxamine-containing medications that were inappropriately labelled for use in children despite safety concerns associated with the use of carbinoxamine in children aged <2 years;
- an act that banned over-the-counter sale of cold medications that contain pseudoephedrine etc (although this act was enforced to inhibit access to pseudoephedrine, and thus the manufacture of methamphetamine);
- replacing pseudoephedrine with other nasal decongestants in many of the cough and cold preparations.

Reference:
Morbidity and Mortality Weekly Report, 12 January 2007, 56(01): 1-4 (www.cdc.gov/mmwr).

3,4 diamino-pyridine (DAP)

Not for treating fatigue in multiple sclerosis patients

France. Based on its evaluation of the benefit-risk profile of 3,4 diaminopyridine, Afssaps, the symptoms of Lambert-Eaton myasthenic syndrome in those patients with no other treatment alternatives.

Reference:
Letter to health-care professionals (in French). Afssaps, 11 December 2006 (www.afssaps.sante.fr).

Gefitinib

No survival advantage; increased risk of tumour haemorrhage

Canada. AstraZeneca Canada has issued a `Dear Health-care Professional' letter highlighting Health Canada-endorsed safety information regarding the lack of survival benefit and an increased incidence of tumour haemorrhage associated with the use of gefitinib (Iressa) in patients with squamous cell cancer of the head and neck. The letter describes the top-line results from a trial that examined the efficacy and safety/tolerability of gefitinib (Iressa) 250 mg and 500 mg versus methotrexate in a refractory unselected population of 486 patients with recurrent squamous cell carcinoma of the head and neck (SCHNN). In summary, the results suggest:

- a potential new toxicity finding of tumour haemorrhage in gefitinib (Iressa) recipients: tumour haemorrhage occurred in 8.9% and 11.4% of gefitinib (Iressa) 250 mg and 500 mg