

WHO PHARMACEUTICALS NEWSLETTER



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:

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News & Issues

Three items in this issue have received much media attention: nelfinavir, nimesulide and rosiglitazone. Roche undertook a worldwide withdrawal of nelfinavir amidst concerns that some batches of the product were contaminated with a genotoxic substance. WHO issued a Statement for general information and an Information Exchange System Alert for the attention of global regulatory authorities.

Nimesulide on the other hand is an old issue revisited. In May 2007 the Irish Medicines Board withdrew the drug in the country on receiving six new reports of nimesulide-associated liver failure. It may be recalled that in 2003 the EMEA had adopted a positive opinion for nimesulide, that the drug had a favourable benefit-risk profile. This decision was based on a review of all available evidence at that time. Clearly a more critical reappraisal is needed now, given the current information. It is also of interest that the Irish reports were received from a liver transplant clinic. This is (arguably) the first time that adverse reaction reports have been received from this sector of health care.

A meta-analysis suggesting a significant risk of myocardial infarction with rosiglitazone has raised comments. Critics are discussing the reliability of meta-analysis in general and in particular, the absence of primary or time-to-event data in the current analysis. While the debate continues, rosiglitazone will have to be kept under close surveillance.

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Antidepressant medications

Black box warning update about increased risks of suicidality

USA. The United States Food and Drug Administration (US FDA) is advising all manufacturers to update their labels for all of their antidepressant products. The black box warnings in the labels for these products will now include warnings about increased risks of suicidality (suicidal thinking and behaviour) in the early treatment period (first one to two months) in young adults aged 18 to 24 years. The labelling changes will also include language stating that scientific data did not show an increased risk of suicidality in adults older than 24 and that adults 65 years of age and above taking the antidepressants have a decreased risk of suicidality.

Results of individual placebo-controlled scientific studies are reasonably consistent in showing a slight increase in suicidality with most antidepressants in the early phase of treatment. Therefore the proposed labelling changes will apply to the entire category of antidepressants.

In 2004, the US FDA directed all manufacturers of all antidepressants to include a 'black box' warning about an increased risk of suicidality in children (see WHO Pharmaceuticals Newsletter No. 6, 2004). Later, in 2005, the Agency began a comprehensive review of 295 individual antidepressant trials that included over 77 000 adult patients with major depressive disorder (MDD) and other psychiatric disorders, to examine the risk of suicidality in adults receiving antidepressants.

The present updates to the boxed warning follows the US FDA's Psychopharmacologic Drug Advisory Committee's conclusions that the labels should indicate both the increased risk of

suicidality in younger adults using antidepressants, and the apparent beneficial effect in older adults treated with the antidepressants. The current update is also intended to remind health-care professionals that the disorders themselves are the most important cause of suicidality.

Reference:

FDA News. U.S. Food and Drug Administration, 2 May 2007 (www.fda.gov).

Desmopressin nasal spray

Primary nocturnal enuresis (PNE) no longer an approved indication

UK. Primary nocturnal enuresis (PNE, bedwetting) is no longer an approved indication of desmopressin nasal spray products (Desmospray). This measure was requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA) because, according to the Agency, the nasal formulations were associated with a majority of the adverse drug reactions occurring in PNE patients while the oral formulations had a more favourable risk-benefit profile. Rare, serious ADRs associated with nasal desmopressin included hyponatraemia, seizures and water intoxication. Nasal desmopressin is still approved in cranial diabetes insipidus and multiple sclerosis related nocturia.

Reference:

Letter to health-care providers from MHRA, 18 April 2007 (www.mhra.gov.uk).

Gadolinium-based contrast agents

Boxed warning about risk of nephrogenic systemic fibrosis

USA. The US FDA has asked manufacturers to include a boxed warning on the product labelling of all gadolinium-based contrast agents which are used to enhance the quality of magnetic resonance imaging (MRI). The warning will state that patients with severe kidney insufficiency who receive these agents are at risk for developing a debilitating and potentially fatal disease known as nephrogenic systemic fibrosis (NSF). In addition, the label will also state that patients just before or just after liver transplantation or those with chronic liver disease are also at risk for developing NSF with these agents if they are experiencing kidney insufficiency of any severity. Patients with NSF develop thickening of the skin and connective tissues that inhibits their ability to move and may result in broken bones. Other organs are at risk as well. The cause of NSF is not known and there is no consistently effective treatment of this condition. (See WHO Pharmaceuticals Newsletter No. 4, 2006 for reports of gadodamide-associated NSF in Canada).

Reference:

FDA News. U.S. Food and Drug Administration, 23 May 2007 (www.fda.gov).

Nelfinavir (Viracept) Marketing authorization suspended due to possible contamination with genotoxic substance

Europe. The European Medicines Agency (EMA) has recommended that the marketing authorization for nelfinavir (Viracept) should be suspended (1). Nelfinavir is an antiretroviral medicine used to treat HIV-1 infected adults, adolescents and children of three years of age and older. Viracept has also been suspended from the list of WHO prequalified products (2).

The current suspension follows an earlier Press Release from the EMA (3) that nelfinavir was being recalled by the company Roche due to the presence of ethyl mesylate in some batches of the product. Ethyl mesylate is a genotoxic substance. As the contamination may have affected all strengths and presentations of Viracept, the company has undertaken a worldwide recall of this medicinal product. All packs of Viracept currently available on the market are being recalled. Packs of the product that patients may have at home are to be returned to the pharmacy.

Patients receiving Viracept have been directed to contact their doctor immediately for advice on appropriate treatment alternatives.

WHO has also issued various communications on the subject (4, 5).

The EMA has now outlined a specific action plan to follow-up patients who were exposed to the contaminated product (1). The Agency:

1. has requested the company (Roche) to carry out studies in animals in order to establish precisely which doses of ethyl mesylate may be toxic to humans,

2. has asked Roche to identify the group of patients who have been exposed to batches of contaminated Viracept with a view to establishing appropriate follow-up and monitoring of these patients.

The EMA's Committee for Medicinal Products for Human Use (CHMP) has also advised that the following groups should be followed up:

1. patients exposed to high levels of the contaminant in batches of Viracept released since March 2007,
2. all pregnant women who have ever been exposed to Viracept,
3. all children who have ever been exposed to Viracept, including those exposed in utero.

The EMA will review the situation as data from these measures become available.

References:

1. *Press Release. European Medicines Agency, EMA/275367/2007, 21 June 2007.* (www.emea.europa.eu).
2. *Suspension of Viracept from the list of WHO prequalified products. WHO Prequalification Programme, 21 June 2007* (<http://mednet3.who.int/prequal>).
3. *Press Release. European Medicines Agency, EMA/251283/2007, 6 June 2007* (www.emea.europa.eu).
4. *WHO Statement on Roche's Viracept recall. WHO Prequalification Programme, 14 June 2007.* (<http://mednet3.who.int/prequal>).
5. *WHO Information Exchange System Alert No. 114, 11 June 2007* (<http://www.who.int/medicines/publications/drugalerts/en/index.html>).

Nimesulide- containing products for oral use

Marketing suspended in Ireland due to reports of liver failure

Ireland. The Irish Medicines Board (IMB) has announced the suspension of the marketing and sale of nimesulide-containing medicinal products for oral use available in Ireland, with immediate effect (1). The suspended products include Aulin (100 mg tablets and granules), Mesulid (100 mg tablets and granules) and Mesine (100 mg tablets). The IMB decision was based on new information from a National Liver Transplant Unit that six patients required liver transplant following treatment with nimesulide.

Nimesulide is a non-steroidal anti-inflammatory medicine authorized in many countries for the treatment of acute pain, the symptomatic treatment of painful osteoarthritis and for primary dysmenorrhoea. Liver damage is a serious and rare damage known to occur with nimesulide and the IMB had previously issued advice to health-care professionals regarding this risk. The IMB has received 53 liver-related adverse reaction reports with nimesulide since the product was first approved for use in Ireland in 1995.

The IMB has notified the medicines regulatory authorities throughout Europe of the six new cases of nimesulide associated liver failure and has initiated a referral for a full safety review of nimesulide-containing products by the EMA.

WHO has issued an Information Exchange System Alert for wider dissemination of the IMB decision to suspend oral

nimesulide-containing products from the Irish market (2).

In 2003 the Committee for Proprietary Medicinal Products (CPMP) made a referral to the EMEA that the benefit-risk profile of nimesulide-containing products for systemic topical use is favourable (see WHO Pharmaceuticals Newsletter No. 4, 2003).

In the WHO database there are a total number of 320 reports of liver and biliary system disorders in patients who received nimesulide. Of these, 18 cases have been shown to have a clear association with nimesulide use.

Reference:

1. Press Release from the Irish Medicines Board, 15 May 2007 (www.imb.ie).
2. WHO Information Exchange System Alert No. 113, (www.who.int/medicines/publications/drugalerts).

Tizanidine

Concomitant use with fluvoxamine or ciprofloxacin contraindicated

USA. Tizanidine is a centrally acting α -2 adrenergic agonist. It is used to treat the spasms, cramping, and tightness of muscles caused by medical problems such as multiple sclerosis, spastic diplegia, back pain, or certain other injuries to the spine or central nervous system. Acorda Therapeutics, in consultation with the US FDA has issued a 'Dear health-care professional' letter warning that tizanidine should not be used concomitantly with the potent CYP1A2 inhibitor drugs fluvoxamine and ciprofloxacin. This contraindication is based on the fact that both fluvoxamine and ciprofloxacin are potent inhibitors of the enzyme CYP1A2, an enzyme needed for the metabolism of tizanidine. Acorda warns that the interaction between tizanidine and either fluvoxamine or ciprofloxacin is

characterized by dangerously high serum levels of tizanidine and is most likely due to the inhibition of CYP1A2 by fluvoxamine or ciprofloxacin. Although there are no clinical studies evaluating the effect of other CYP1A2 inhibitors on tizanidine, other CYP1A2 inhibitors may lead to substantial increases in tizanidine blood concentrations. Therefore, concomitant use of tizanidine with other CYP1A2 inhibitors such as zileuton, other fluoroquinolones, antiarrhythmics (amiodarone, mexiletine, propafenone and verapamil), cimetidine, famotidine, oral contraceptives, acyclovir and ticlopidine should ordinarily be avoided. The product label for tizanidine has been updated with this contraindication.

References:

'Dear health-care professional' letter from Acorda Therapeutics, 5 March 2007 (www.fda.gov).

Trimethobenzamide Suppository drug products not approved

USA. The US FDA has announced that suppository products of trimethobenzamide are not approved to treat nausea and vomiting in adults or children. The Agency has asked the responsible companies to stop manufacturing and distributing these products which are marketed under various names (Tigan, Tebamide, T-Gen, Trimazide and Trimethobenz). The US FDA warns that there is no evidence of effectiveness of suppository trimethobenzamide in nausea and vomiting. Consumers are urged to contact their health provider regarding alternative products approved to effectively treat nausea and vomiting: these are available in a variety of dosage forms, including tablets, capsules,

solutions, injectables and suppositories.

The Agency adds that several oral capsules and injectable products containing trimethobenzamide have been approved by FDA and are not affected by the current action. Any company wishing to market a product containing trimethobenzamide in suppository form must now obtain an approved new drug application prior to marketing.

Reference:

FDA News. U.S. Food and Drug Administration, 6 April 2007 (www.fda.gov).

Bevacizumab Tracheo-esophageal fistulas if given with concurrent chemotherapy and radiation in SCLC patients

USA, UK. Genentech (in the USA) and Roche (in the UK) have written to health-care professionals that tracheo-esophageal (TE) fistula occurred in patients with limited stage small cell lung cancer (SCLC) in a study combining concurrent chemotherapy and radiation plus bevacizumab (Avastin) in these patients. Bevacizumab is not indicated in SCLC.

The patients in the study received four cycles of concurrent irinotecan, carboplatin, radiation therapy, and bevacizumab followed by maintenance bevacizumab for up to six months. The letters note that there were two confirmed serious adverse events of TE fistula (one fatal) reported amongst the first 29 patients enrolled in the study. A third fatal event was also reported in which TE was suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase.

The letters advise that health-care providers should permanently discontinue bevacizumab in patients with TE fistula or any grade 4 fistula; that limited information is available on the continued use of bevacizumab in patients with other fistulae; and that in cases of internal fistula not arising in the gastro-intestinal tract, discontinuation of bevacizumab should be considered.

References:

1. 'Dear health-care provider' letter from Genentech, April 2007 (www.fda.gov).

2. 'Dear Health-care provider' letter from Roche, 8 May 2007 (www.mhra.gov.uk).

Citrus aurantium (bitter orange)

Reports of adverse cardiovascular effects

Canada. Between 1 March 2004 and 31 October 2006, Health Canada received 21 domestic reports of adverse reactions suspected of being associated with *Citrus aurantium* (bitter orange). Of these, 15 reports were of cardiovascular adverse reactions, 10 of which were serious and included one report of myocardial infarction. According to Health Canada, synephrine, an alpha-adrenoceptor agonist found in bitter orange, can have serious adverse effects on heart rate and blood pressure; these effects are significantly potentiated by caffeine. Synephrine is found in various natural health products that are promoted for weight loss. Health Canada cautions that the following people may be particularly at risk of adverse reactions from synephrine-containing products:

- those with heart conditions, Central Nervous System (CNS) disorders, diabetes mellitus, enlarged prostate, glaucoma, hypertension, phaeochromocytoma, thyroid disease or known risk factors for cardiovascular disease
- those receiving caffeine-containing products, monoamine oxidase inhibitors, thyroid hormones or medications to control blood pressure or heart rate
- underweight people.

Reference:

Canadian Adverse Reactions Newsletter, Vol. 17(2): 2, April 2007 (www.hc-sc.gc.ca).

Clozapine Reports of myocarditis

Australia. Clozapine, an antipsychotic drug, was approved in Australia in 1993. 116 cases of suspected myocarditis associated with the use of clozapine had been reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) during 1993-2003. A boxed warning in the product label for clozapine alerts prescribers to the risk of myocarditis and cardiomyopathy with the product. ADRAC warns that potentially fatal myocarditis may develop early after the commencement of clozapine treatment, often within the first 28 days. Initial symptoms may be non-specific such as tachycardia, fever and flu-like symptoms. According to ADRAC, if myocarditis is confirmed, clozapine should be discontinued.

Reports in the WHO database:
Myocarditis - 436

Reference:

Australian Adverse Drug Reactions Bulletin, Vol. 26(3): 10, June 2007 (www.tga.gov.au).

Metformin Risk factors for lactic acidosis

Sweden. The Medical Products Agency (MPA) in Sweden is drawing attention to the risk factors for the development of lactic acidosis in patients receiving metformin for type 2 diabetes mellitus. The MPA lists various causes of impaired renal function among those risk factors that predominate but adds that additional factors include alcoholism, advanced age and impaired liver function in patients receiving metformin. The MPA has received a total of 52 reports of lactic acidosis and an additional eight reports of acidosis as a diagnosed adverse reaction associated with metformin.

Reports in the WHO database:
Lactic Acidosis - 1514

Reference:

Reactions Weekly, No. 1148: 2,
21 April 2007

(<http://reactions.adisonline.com>).

Oseltamivir Update on behavioural effects

Japan. Since the launch of oseltamivir (Tamiflu) in February 2001, over 1000 cases of side effects have been reported to health authorities in Japan. Of the 1000 reports, there were 128 cases involving various types of unusual behaviour. In the group of 128, there were eight deaths, with five occurring in adolescents. According to information from the Ministry of Health, Labour and Welfare (MHLW), the majority of deaths involved falls from high places. Only 28 of the 128 cases (including three deaths) involved adults (≥ 20 years); the highest incidence of unusual behaviour occurred in the 10–19 year age group, for which restrictions for use were announced recently. There were 43 cases in children aged < 10 years, although there were no deaths. Close monitoring in patients in this age group is recommended for 48 hours after the administration of the first oseltamivir (Tamiflu) dose (see WHO Pharmaceuticals Newsletter No. 2, 2007).

Reports in the WHO database:
Personality disorders - 26
Death - 22

Reference:

Reactions Weekly, No. 1149: 4,
28 April 2007.

(<http://reactions.adisonline.com>).

Pioglitazone Long-term treatment associated with increased incidence of fractures in women

Switzerland, Canada, France. The manufacturers of pioglitazone (Eli Lilly in Canada, Takeda in France and Switzerland) have written to health-care professionals about the increased incidence of fractures in women receiving long-term treatment with pioglitazone for type 2 diabetes mellitus. Pioglitazone belongs to the thiazolidinedione (TZD) group of antidiabetic medicines. An analysis of the pioglitazone clinical trial database, with a special focus on fractures reported as adverse events, has shown that significantly more pioglitazone-treated female patients experienced at least one event of bone fracture than patients treated with non-TZD comparator drugs (other diabetes medicines such as metformin or sulfonyl ureas or placebo). The majority of the fractures involved distal lower limb: ankle, foot (fibul and tibia), or distal upper limb (hand, forearm and wrist). Currently, there is no known explanation for these events. There was no increased risk of fracture identified in men. Health-care professionals are advised to carefully consider the risk of fracture in the care of female patients with type 2 diabetes who are currently being treated with pioglitazone or when initiation of pioglitazone is being considered. (See WHO Pharmaceuticals Newsletter No. 2, 2007 for related communications in the USA).

Reports in the WHO database:
Fracture - 17

References:

1. 'Dear health-care professional' letter from Takeda, 5 April 2007 (www.swissmedic.ch).

2. 'Dear health-care professional' letter from Eli Lilly, 18 April 2007

(www.hc-sc.gc.ca).

3. 'Dear health-care professional' letter from Takeda, 19 April 2007

(www.afssaps.fr).

Quetiapine Pancreatitis and thrombocytopenia

Canada. Between 1 December 1997 and 31 October 2006, Health Canada received 615 reports of adverse drug reactions suspected of being associated with the use of quetiapine. Nine reports involved cases of pancreatitis and eleven involved cases of thrombocytopenia. Quetiapine (Seriquel) is an atypical antipsychotic drug indicated for the management of symptoms of schizophrenia and the acute management of manic episodes associated with bipolar disorder.

In five of the nine reported cases of pancreatitis, quetiapine was the only suspect drug. Acute pancreatitis typically presents as an acute inflammation of the pancreas and usually results from gallstones or alcohol abuse. Drug-induced pancreatitis is less common. Elderly patients taking multiple medications, HIV-positive patients, cancer patients and patients receiving immunomodulatory agents are at risk of drug-induced pancreatitis. In the majority of the patients, drug-induced pancreatitis resolves without long-term morbidity. But in some it can lead to fatal complications. Quetiapine was the only suspect drug in six of the eleven reported cases of thrombocytopenia. In one of these six cases the patient was rechallenged one month after the drug was stopped. According to Health Canada, although relatively rare, drug-induced thrombocytopenia may

be associated with risks of morbidity and mortality.

Reports in the WHO database:
Pancreatitis - 3
Thrombocytopenia - 90

Reference:

Canadian Adverse Reactions Newsletter, Vol. 17(2): 1, April 2007 (www.hc-sc.gc.ca).

Rituximab

Three cases of progressive multifocal leukoencephalopathy

Sweden. The Swedish Medical Products Agency (MPA) is advising of three fatal cases of progressive multifocal leukoencephalopathy (PML) in patients treated with rituximab. Two of the cases of PML with a fatal outcome were reported in patients with systemic lupus erythematosus (SLE) who had received Rituximab (MabThera). The third case was reported in a patient with vasculitis who had received the drug (MabThera). These patients had received immunosuppressive therapy previously or were currently receiving such treatment. The Agency notes that these cases were associated with rituximab treatment outside of approved indications and that a causal relationship between rituximab use and PML has not been established.

Reference:

Reactions Weekly, No. 1148: 3, 21 April 2007 (<http://reactions.adisonline.com>).

Rosiglitazone

Issues of cardiac safety

Canada, Europe, USA. An article in the New England Journal of Medicine (NEJM) (1) has generated significant public attention on the cardiac safety of rosiglitazone (Avandamet, Avandaryl, Avandia), a drug approved to treat type 2 diabetes. The article, based on

an analysis of data retrieved from 42 clinical studies, showed a small increased risk for myocardial infarction and cardiovascular death among approximately 15 500 patients treated with rosiglitazone. Health Canada, EMEA and the US FDA have issued different statements referring to the article:

US FDA (2): Safety data from controlled clinical trials have shown that there is a potentially significant increase in the risk of heart attack and heart-related deaths in patients taking rosiglitazone (Avandia). However, other published and unpublished data from long-term clinical trials (of Avandia) provide contradictory evidence about the risks in patients treated with this product. The Agency has been monitoring several heart-related adverse events based on signals from previous controlled clinical trials of rosiglitazone (Avandia) alone and in combination with other drugs and from postmarketing reports. The Agency has updated the product's labelling to reflect all new data. The most recent labelling change for rosiglitazone (Avandia) included a new warning about a potential increase in heart attacks and heart-related chest pains in some individuals using rosiglitazone (Avandia). This new warning was based on the result of a controlled clinical trial in patients with existing congestive heart failure. The US FDA's analyses of all available data are ongoing. Results of the analyses will be made public as soon as possible. The Agency will present the issue of cardiovascular risk with rosiglitazone and with other drugs in this class to an Advisory Committee at the earliest opportunity. In the meantime, prescribers and their patients are advised to consult together to make individualized treatment decisions.

EMEA (3): The EMEA in a Press Release has reminded physicians that when rosiglitazone was first authorized in the European Union in 2000, it was contraindicated in patients with a history of cardiac failure. Since then the Agency has closely monitored rosiglitazone for cardiovascular effects (cardiac failure and other cardiac disorders including myocardial infarction). The EU rosiglitazone product information was updated in September 2006 with information about the risk of ischaemic events. Prescribers are reminded to adhere to the restrictions for use in patients with cardiac disease as set out in the product information. Patients are advised not to stop treatment with rosiglitazone and to discuss the medication with their doctor at their next regular visit.

Canada (4): GlaxoSmithKline, in consultation with Health Canada, has written to health-care professionals that:

- conclusions in the NEJM article require confirmation
- analysis of all available data is ongoing and will be communicated when completed
- in Canada, rosiglitazone (Avandia) is not approved for use with insulin therapy, with the combination of metformin and a sulfonylurea and in patients with pre-diabetes
- rosiglitazone (Avandia) is contraindicated in patients with New York Heart Association (NYHA) Class III and IV cardiac status
- rosiglitazone (Avandia) should be used with caution in any patient with NYHA Class I and II cardiac status
- all patients should be monitored for signs and symptoms of fluid retention, oedema and rapid weight gain, and that
- the dose of rosiglitazone (Avandia) used in combination with a

sulfonylurea should not exceed 4 mg daily.

Reports in the WHO database:
Cardiovascular disorders - 2

References:

1. Nussen SE, Wolski K. *Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine, 356: 2457-71, 2007.*
2. FDA News. U.S. Food and Drug Administration, 21 May 2007 (www.fda.gov).
3. Press release. EMEA, 23 May 2007 (www.emea.europa.eu).
4. 'Dear health-care professional' letter from GlaxoSmithKline, 1 June 2007 (www.hc-sc.gc.ca).

Vinca alkaloids Should only be given intravenously

France. The French Agency for the safety of health-care products (AFSSAPS) is reminding health-care professionals that vindesine, vincristine and vinblastine are to be given only by the intravenous route and NOT by the intrathecal route. Vindesine, vincristine and vinblastine are vinca alkaloids that are widely used as chemotherapeutic agents in cancer patients. Between 2000 - 2006, the Agency received seven reports of administration errors when vinca alkaloids were given by the intrathecal route. Six of these errors were reported in adult patients and one in a child of 23 months. The patients died in all seven of these cases. AFSSAPS, in consultation with a group of experts made of clinicians and hospital pharmacists has prepared a list of recommendations for the safe administration of vinca alkaloids. Some of the recommended measures include:

- administering vincristine in a diluted volume (e.g. 50 ml normal saline) via

a minibag, as an intravenous perfusion of 5 - 10 minutes

- where cancer patients receive vincristine by the iv route and a second chemotherapeutic agent by the intrathecal route, to ensure enough time interval between the two treatments to prevent inadvertent intrathecal administration of the vinca alkaloid
- reading out loud the label instructions to the other health professional in the treatment room (physician to nurse, physician to physician) before administering the injection.

Reports in the WHO database:
Medication error - 38
Death - 318 (since 1969)

Reference:

Letter to health-care professionals. Afssaps, May 2007
(www.afssaps.sante.fr).

Pharmacovigilance training

The WHO pharmacovigilance team is organizing a course for the safety monitoring of antimalarial in Africa. Participants will receive training in an active surveillance method. A 'training of consultants' is also being organized towards creating a pool of experts in order to build pharmacovigilance capacity in Africa. A short report from both these will be included in the next issue of the newsletter.

(see Feature, page 8).

Building pharmacovigilance capacity: a multi-method approach

Should we support courses that bring together people from around the world? Or, should we focus on building pharmacovigilance capacity, one country at a time? It is obvious that both methods have their advantages. Offering a 'generic course' that teaches the broad principles of pharmacovigilance to participants from different parts of the world allows global interaction and helps establish, to the extent possible, harmonious first principles and attitudes to the profession. However, the broad assumption here would be that all participants come from similar backgrounds and have similar needs of pharmacovigilance in practice. Besides, depending on where the course would be offered, it could also be rather expensive to support attendance. This and a need to ensure fair geographic representation at these courses would limit attendance to one or two per country. It is harmonized capacity building but at a slow pace.

A national course, tailored for the specific needs of a country, could roll out pharmacovigilance in a much bigger scale within one country. One national course could at once train as many as fifty participants or more (cost and other factors allowing); it could address specific pharmacovigilance needs in the country and training could be customized to introduce / reinforce safety surveillance in specific disease treatment programmes that are relevant to the country, for example, in malaria or in HIV/AIDS treatment programmes. These courses would, however, lack the richness of inter-country exchange and sharing.

A third could be a synthesis of the two approaches: a training that builds capacity in a group of countries with very similar disease burdens and pharmacovigilance interests. This would help build a regional pool of expertise for groups of countries to exploit and share resources across borders.

The WHO Programme for International Drug Monitoring has adopted all of the above methods to promote global pharmacovigilance.

The pharmacovigilance training in September 2006 for Drug Regulatory Authorities in Gaborone was an effort towards national capacity building in Botswana. Ten drug regulatory staff attended the week-long course and were trained in the basic principles of pharmacovigilance, reporting systems, adverse drug reactions (ADR) database, tools for ADR data management, causality assessment, signal detection, preventing and managing ADRs, cohort-event monitoring and communications in pharmacovigilance. Practical details of setting up a pharmacovigilance system and liaising with public health programmes such as HIV/AIDS were discussed. Working groups compared various national reporting forms and designed one for Botswana.

In February 2007, a pharmacovigilance training course was organized for Francophone countries. The training was offered in French and organized by the national pharmacovigilance centre in Rabat, Morocco with financial support from WHO and the USAID. Participants came from Algeria, Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Madagascar, Mali, Morocco, Sao Tomé-et-Principe, Senegal, Togo and Tunisia. This was the first time that WHO had offered a pharmacovigilance course in French - it helped identify ongoing efforts in Francophone Africa and has also resulted in many more Francophone African countries joining the WHO Programme for International Drug Monitoring.

About the same time in February 2007, Burundi, Democratic Republic of Congo, Mozambique, Zambia and Zanzibar met in Zambia, in an intensive follow-up of a course offered in 2003 for introducing pharmacovigilance in countries set to introduce artemisinin-based combination therapies (ACTs) in Africa. Countries identified three broad recommendations at this meeting:

- to prioritize and strengthen pharmacovigilance activities.
- to advocate pharmacovigilance issues at regional level through the regional economic bodies such as SADC, CEEAC, EAC, COMESA.
- to integrate national ADR forms and guidelines for spontaneous reporting in Malaria Case Management training manuals and guidelines.

Later, in May 2007 the Uppsala Monitoring Centre offered its two-week biennial course. Twenty-four participants from around the world attended the first eight-day Module on an Introduction to ADRs and Spontaneous ADR reporting. Most of the twenty-four participants then stayed on, joined by other participants for one of two second module options, either a) Introduction to pharmacoepidemiology, or b) Effective Communications in pharmacovigilance. As in previous years, feedback from the course evaluation has been very positive.

WHO is currently preparing for two training programmes, in two successive weeks, in Ghana. The objectives are twofold:

1. The first week will be devoted to teaching three countries in Africa (Ghana, Nigeria and the United Republic of Tanzania) the basic principles of cohort event monitoring, an active surveillance method for collecting ADR reports. Developing a final protocol to collect information on ADRs in the malaria programme will be a key deliverable.
2. The second week will be on teaching consultants about the more advanced problems that may arise in pharmacovigilance. Creating a pool of experts to act as 'consultants on call' for African countries will be the key deliverable for this week.

At least in the next few years the WHO pharmacovigilance programme is more likely to lean towards training courses that support resource sharing and regional collaborations. Africa will be the focus of several of these exercises. African countries with relatively well established pharmacovigilance systems are expected to take the lead in fostering regional co-operations in Africa.