WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

The aim of the 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.

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This Newsletter is also available on our Internet website:
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This issue records, in addition to other regulatory news, the revision to the package information for antidepressants in Japan; an approval for the use of colchicine in familial Mediterranean fever in the United States of America; and updated safety information for mycophenolic acid. The risk of hearing impairment with isotretinoin, a review of the abnormal behaviour and sudden death with oseltamivir and an increased risk of bleeding with warfarin and aspirin combination are some of the issues discussed under Safety of Medicines. Under Feature there are three items: a brief note on a newly-funded three year project in New Zealand, to scope and pilot a medication error reporting and prevention system; a brief review of reports of acute generalized exanthematous pustulosis (AGEP) with paracetamol in the WHO database for a potential signal;and a summary of adverse drug reaction reports in Sweden with influenza A (H1N1) vaccine.

Several regulatory authorities have licensed H1N1 swine flu pandemic vaccines for their countries. WHO advises all countries administering these vaccines to conduct intensive monitoring for their safety and to report all adverse events. The WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) and Swissmedic (Swiss Agency for Therapeutic Products) have developed a new software tool, PaniFlow, for reporting adverse events following immunization. For additional details of this tool visit the UMC website at www.who-umc.org.

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Safety of Medicines

Feature

Antidepressants

Warning about aggression

Japan. The Ministry of Health, Labour and Welfare (MHLW), Japan have warned patients treated with antidepressants, their families and caregivers to pay due attention to any changes in the patient condition during the course of treatment. This warning came following a review of adverse reactions including hostility and aggression associated with selective serotonin reuptake inhibitors (SSRIs) (fluvoxamine maleate, paroxetine hydrochloride hydrate, and sertraline hydrochloride), serotonin and noradrenaline reuptake inhibitors (SNRIs) (milnacipran hydrochloride), tricyclic antidepressants (amitriptyline hydrochloride, amoxapine, imipramine hydrochloride, clomipramine hydrochloride, dosulepin hydrochloride, lofepramine hydrochloride, nortriptyline hydrochloride and trimipramine maleate), tetracyclic antidepressants (setiptiline maleate, maprotiline hydrochloride and mianserin hydrochloride), trazodone hydrochloride and sulpiride.

With regard to adverse reaction reports with SSRIs and SNRIs (reported to the MHLW until the end of March 2009), there have been a total of 39 cases of harmful behaviour to others including injury and potential events, identified from the clinical course; seven cases associated with fluvoxamine maleate, 26 cases with paroxetine hydrochloride hydrate, two cases with sertraline hydrochloride, and four potential cases with milnacipran hydrochloride. However, causality was considered unknown in 35 of the 39 cases.

With regard to adverse reaction reports with tricyclic antidepressants, tetracyclic antidepressants, trazodone hydrochloride and sulpiride (reported until 15 May 2009), there have been a total of 13 cases of harmful behaviour to others including injury and potential events. For 10 out of the 13 cases, causality was considered unknown or it was evaluated that the SSRIs administered concomitantly had a greater effect.

In many cases of the reports reviewed, it was considered that patients with co-morbid disorders such as a depressed state of manic depressive psychosis or schizophrenia developed excitement, aggression or irritability, or exacerbated co-morbid disorders when prescribed antidepressants.

In light of the above findings, marketing authorization holders have been required to revise package inserts of antidepressants, except sulpiride, to include a precaution of careful administration to patients with manic depressive psychosis or an organic brain disorder, those predisposed to schizophrenia, or those with highly impulsive co-morbid disorders. The following statements will also be added to the package inserts: episodes of anxiety, irritation, excitement, panic attack, irritability, hostility, aggression, and impulsivity have been reported; in patients with these symptoms or behavior, exacerbation of underlying disease and harmful behaviour to others have been reported, though causality with the drugs is not clear. For sulpiride, the reported adverse reactions were considered to be the effect of concomitant SSRIs.

References:

Pharmaceuticals and Medical Devices Safety Information No.258, MHLW, June 2009.
(http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-258.pdf)
Pharmaceuticals and Medical Devices Safety Information No.260, MHLW, August 2009.
(http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-260.pdf).

Botulinum toxin Type A and Botulinum toxin Type B

Changes to the prescribing information and established drug names

USA. The US Food and Drug Administration (US FDA) has notified health-care professionals that on 31 July 2009, the Agency approved the following revisions to the prescribing information of the botulinum toxin products (Botox, Botox Cosmetic and Myobloc).

- A Boxed Warning highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from the injection site after local injection.
- A Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide to help patients understand the risks and benefits of botulinum toxin products.
- Changes to the established drug names to reinforce individual potencies and prevent medication errors. The new drug name to replace "botulinum toxin type A" is OnabotulinumtoxinA (marketed as Botox and Botox Cosmetic). The one to replace " botulinum toxin type B" is RimabotulinumtoxinB (marketed as Myobloc).

The US FDA approved the other botulinum toxin product in this class, AbobotulinumtoxinA (marketed as Dysport), on

29 April 2009 and this product also includes the Boxed Warning and REMS.
Botulinum toxin products have been approved for temporary improvement in the appearance of glabellar lines, treatment of strabismus, blepharospasm, cervical dystonia and primary axillary hyperhidrosis.

(See WHO Pharmaceuticals Newsletter No. 3, 2009 for warnings about distant spread of toxin effects in the USA as well as reports in WHO Global ICSR database).

Reference:
Safety Information, US FDA 3 August 2009 (www.fda.gov).

Clopidogrel

Potential interaction with proton pump inhibitors

Canada (1). Health-care professionals have been warned about the potential interaction of proton pump inhibitors (PPIs) with clopidogrel (Plavix). This potential interaction could lead to a reduction in the level of clopidogrel's active metabolite and therefore, the therapeutic response to clopidogrel may be affected. Clopidogrel is an antiplatelet medicine that is used to prevent atherothrombotic events.

A letter for health-care professionals from Sanofi-aventis Canada Inc. and Bristol Myers Squibb Canada Co. explains that clopidogrel is a pro-drug metabolized by the liver, partly by cytochrome P450 2C19 (CYP2C19), before it can be biologically active in preventing atherothrombotic events. PPIs are used to prevent and treat peptic ulcer and gastroesophageal reflux and may inhibit, to some degree, the activity of CYP2C19. Recent reports in the literature, mainly for omeprazole, suggest a potential interaction with PPIs through CYP2C19 that may reduce the efficacy of clopidogrel. Although the evidence for CYP2C19 inhibition varies within the class, the effect is possibly related to all members of the PPI class.

Health-care professionals have been advised that administration of PPIs or of other drugs that inhibit CYP2C19 should be discouraged in patients taking clopidogrel (Plavix). They have also been recommended to continue to prescribe clopidogrel (Plavix), because this medicine has demonstrated benefits in preventing life-threatening atherothrombotic events that could lead to myocardial infarction or stroke. The Canadian Product Monograph will be revised to include the new safety information.

New Zealand (2). The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has required the clopidogrel data sheets to be updated, to include information about genetic factors influencing clopidogrel metabolism, specifically in patients with genetically reduced CYP2C19 function. The information discouraging the use of concomitant medicines that inhibit CYP2C19 metabolism, e.g. omeprazole, will also be included as a precaution.

Until further data are available, Medsafe recommends that health-care professionals continue their current prescribing practices for clopidogrel. Medsafe also recommends that an H2-receptor blocker and/or antacid be considered instead of a proton pump inhibitor in patients requiring concomitant treatment with a proton pump inhibitor, where possible.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for a public statement in Europe on the possible interaction between clopidogrel and proton pump inhibitors).

References:
(1) Advisories, Warnings and Recalls, Health Canada 20 August 2009 (www.hc-sc.gc.ca).
(2) Prescriber Update Vol. 30 No.3, August 2009 (www.medsafe.govt.nz).

Codeine and dihydrocodeine-containing medicines

New advice on OTC analgesics to minimize the risk of addiction

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced a package of measures to minimize the risk of overuse and addiction associated with over the counter (OTC) medicines containing codeine and dihydrocodeine (DHC). This follows recent advice from the Commission on Human Medicines (CHM).

The Patient Information Leaflet and labels will state that these products can cause addiction or overuse headache if used continuously for more than three days. In particular, the warning statement "Can cause addiction. For three days use only" will be positioned clearly and prominently on the front of the pack. All indications related to colds, flu, coughs and sore throats, and references to minor painful conditions will be removed. The remaining list of indications will be for the short term treatment of acute, moderate pain which is not relieved by paracetamol,

ibuprofen or aspirin alone. The pack size and advertising will be also regulated. These measures will affect all OTC solid dose medicines containing codeine or DHC including brands, generics and effervescent forms.

Reference:
Safety warnings and messages for medicines, MHRA 2 September 2009 (www.mhra.gov.uk).

Colchicine

New safety information about drug interactions

USA. Oral colchicine has been used for many years as an unapproved drug with no FDA-approved prescribing information, dosage recommendations, or drug interaction warnings.The Agency is notifying health-care professionals that it has now approved the first single-ingredient oral colchicine product (Colcrys) for the treatment of familial Mediterranean fever (FMF) and acute gout flares; the FDA is also sharing information on two previously uncharacterized safety concerns associated with the use of colchicine that were identified during the drug application review by the Agency.

The US FDA analysis has revealed cases of fatal colchicine toxicity reported in certain patients taking standard therapeutic doses of colchicine and concomitant medications that interact with colchicine, such as clarithromycin. The Agency says that these reports suggest that drug interactions affecting the gastrointestinal absorption and/or hepatic metabolism of colchicine play a central role in the development of colchicine toxicity. In addition, the data supporting the safety and efficacy of the product (Colcrys) in acute gout flares demonstrated that a substantially lower dose of colchicine was as effective as the higher dose traditionally used. Moreover, patients receiving the lower dose experienced significantly fewer adverse events compared to the higher dose.

Based on the above, the US FDA has included important safety considerations in the approved prescribing information of the colchicine product (Colcrys). Health-care professionals are advised not to use P-glycoprotein or strong CYP3A4 inhibitors in patients with renal or hepatic impairment who are currently taking colchicine. Patients are advised to consult the Medication Guide for important safety information.

Reference:
Safety Information, US FDA, 30 July 2009 (www.fda.gov).

Etanercept

Risk of uveitis

New Zealand. Medsafe states that a review of spontaneous post-marketing reports indicated that there may be a risk of uveitis associated with the use of etanercept. Etanercept (Enbrel) is a tumour necrosis factor (TNF) inhibitor indicated for the treatment of rheumatoid arthritis, ankylosing spondylitits, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis. The datasheet of etanercept (Enbrel) has been updated to include uveitis as an uncommon adverse reaction.

Reference:
Prescriber Update Vol. 30, No.3 August 2009 (www.medsafe.govt.nz).

Etravirine

Revisions to the prescribing information

USA. The US FDA and Tibotec Therapeutics have notified health-care professionals of revisions to the WARNINGS AND PRECAUTIONS section of the prescribing information for etravirine (Intelence), used in the treatment of HIV-1 infection in combination with other antiretroviral agents. There have been post-marketing reports of cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, as well as hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. Health-care professionals are advised to immediately discontinue the treatment with etravirine (Intelence) when signs and symptoms of severe skin or hypersensitivity reactions develop.

Reports in WHO Global Individual Case Safety Reports (ICSR) database, VigiBase:
Etravirine

Number of events:
Stevens Johnson syndrome: 5
Drug hypersensitivity syndrome: 3
Allergic reaction: 3

Reference:
Safety Information, US FDA 27 August 2009 (www.fda.gov).

Fosamprenavir

Potential association of myocardial infarction

Canada. Health-care professionals have been notified of a potential association

between myocardial infarction and exposure to fosamprenavir (PRTELZIR®) in HIV-infected patients. Fosamprenavir is a protease inhibitor used in combination with low-dose ritonavir and other antiretrovirals in the treatment of HIV-1 infection.

According to the Important Safety Information letter from GlaxoSmithKline Inc., a nested case-control study conducted in the French Hospital Database on HIV has reported an association between exposure to fosamprenavir and an increased risk of myocardial infarction (Odds Ratio 1.55 per additional year of exposure; 95% Confidence Interval, 1.20-1.99). This may be related to the propensity for this drug class to raise blood lipids. Health-care professionals are advised to check triglyceride and cholesterol levels prior to initiating therapy with fosamprenavir and at periodic intervals during therapy, as well as to initiate appropriate clinical management of lipid disorders, as required. The company notes that combination antiretroviral therapy is associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat distribution. HIV infection itself has been associated with lipid disorders and ischaemic heart disease. The Canadian Product Monograph will be revised to include the new safety information.

Reference:
Advisories, Warnings and Recalls, Health Canada 22 July2009 (www.hc-sc.gc.ca).

Leukotriene inhibitors: montelukast, zafirlukast and zileuton

Revisions to the prescribing information

USA. The US FDA has announced an update to the Precautions section of the prescribing information for the leukotriene inhibitors, montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR), to include information about neuropsychiatric events reported in patients using these products. The reported neuropsychiatric events include agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), and tremor.

This announcement is an update to the original March 2008 early communication and January 2009 follow-up communication about the ongoing safety review for these leukotriene inhibitors. Montelukast is used to treat asthma, and the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose), and to prevent exercise-induced asthma. Zafirlukast and zileuton are used to treat asthma.

The US FDA recommends that patients and health-care professionals should be aware of the potential for neuropsychiatric events with these medications.

Reports in WHO Global ICSR database, VigiBase:

A total of 2358 reports for montelukast, zafirlukast and zileuton and psychiatric disorders.
Of these reports, 648 reports concern suicide attempt.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for previous information on neuropsychiatric events with leukotriene inhibitors in Canada and the USA).

Reference:
Safety Information, US FDA 28 August 2009 (www.fda.gov).

Mycophenolic acid

Revisions to the prescribing information

USA. The US FDA and Novartis Pharmaceuticals Corporation have notified health-care professionals that cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (MMF) in combination with other immunosuppressive agents. MMF is metabolized to mycophenolic acid. Mycophenolic acid (Myfortic) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.The WARNINGS and ADVERSE REACTIONS sections of the prescribing information for mycophenolic acid (Myfortic) have been revised to reflect this new safety information about PRCA.

PRCA is a type of anaemia in which there is a selective reduction of red blood cell precursors. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin (pallor). In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for

reports of pure red cell aplasia with mycophenolate mofetil in Canad and in the Netherlands).

Reference:
Safety Information, US FDA 3 September 2009 (www.fda.gov).

Promethazine hydrochloride injection

Risk of severe tissue injury, including gangrene

USA. The US FDA has notified health-care professionals that a Boxed Warning is being added to the prescribing information for promethazine hydrochloride products to warn of the risks of severe tissue injury, including gangrene, requiring amputation following intravenous administration of promethazine. Perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration of the drug may result in irritation and tissue damage, including gangrene. The Boxed Warning will indicate that due to the risks of intravenous injection, the preferred route of administration is deep intramuscular injection and that subcutaneous injection is contraindicated. Promethazine hydrochloride injection is approved for a variety of uses including allergic reactions, sedation, motion sickness, nausea, and vomiting associated with anesthesia and surgery, and as an adjunct to analgesics for control of postoperative pain.

In addition to the Boxed Warning, a revision will be made to the Dosage and Administration section to increase the visibility and accessibility of specific recommendations for the maximum concentration (25 mg per ml) and rate of administration (25 mg per minute) when intravenous administration of promethazine is required.

The US FDA advise health-care professionals to be alert for signs and symptoms of potential tissue injury including burning or pain at the site of injection, phlebitis, swelling, and blistering.

Reference:
Safety Information, US FDA 16 September 2009 (www.fda.gov).

Sodium phosphate products

Removal of purgative use from label

Canada. Health Canada has informed the public that over-the-counter oral sodium phosphate products are no longer indicated for bowel cleansing and should only be used as a laxative. In March 2009, Health Canada warned the public not to use over-the-counter oral sodium phosphate products as bowel cleansers as they may cause serious adverse effects, including electrolyte disturbances and kidney damage. While no longer indicated for use as purgatives, Health Canada says that these products are still considered to be safe and effective for laxative use.

Health Canada received 54 adverse reaction reports in association with oral sodium phosphate products, of which 31 case reports involved kidney dysfunction, including 28 reported as serious. Other adverse reactions included gastrointestinal symptoms, cardiovascular and neurological problems, and allergic reactions.

(See WHO Pharmaceuticals Newsletter No. 1 and 3, 2009 for warnings on risk of phosphate nephropathy in the USA and New Zealand, respectively).

Reference:
Advisories, Warnings and Recalls, Health Canada 5 August 2009 (www.hc-sc.gc.ca)

Tumour necrosis factor blockers

Increased risk of lymphoma and other malignancies

Canada, USA. Health Canada and the US FDA have notified health-care professionals that there is an increased risk of lymphoma and other cancers associated with the use of tumour necrosis factor (TNF) blockers in children and adolescents, following the review conducted by the US FDA. In addition, new safety information related to the occurrence of leukemia and new-onset psoriasis in patients treated with TNF blockers were identified. TNF blockers (adalimumab, etanercept, infliximab etc)are used for the treatment of immune system diseases including juvenile idiopathic arthritis (JIA), rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn disease, and ankylosing spondylitis. The prescribing information, including the Boxed Warning, and Medication Guide for TNF blockers will be revised to reflect this new safety information.

Reports in WHO Global ICSR database, VigiBase:

A total of 37 reports for adalimumab, etanercept and infliximab and neoplasm in children up to 16 years of age.
A total of 254 reports for adalimumab, etanercept and infliximab and leukaemia in all age groups.

References:
(1) Advisories, Warnings and Recalls, Health Canada 20 August 2009 (www.hc-sc.gc.ca)
(2) Safety Information, US FDA, 4 August, 28 August 2009 (www.fda.gov).

Allopurinol

Serious skin reactions

Singapore. The Health Sciences Authority (HSA) has alerted health-care professionals about recent reports of death associated with the use of allopurinol in Singapore. Allopurinol is used for the treatment of hyperuricaemia and is known to cause serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that lead to significant morbidity and mortality.

With regard to the reports of death, HSA says that four fatal cases associated with allopurinol were reported to the HSA over the first five months of 2009. Of these reports, three patients developed TEN and the fourth patient developed hypersensitivity syndrome to allopurinol. They were from 68 to 80 years old and had co-morbidities such as ischaemic heart disease, chronic renal failure, diabetes and hypertension. Three of the patients were on concurrent medications, such as vancomycin, frusemide and irbesartan which were also suspected to have contributed to the serious skin conditions. In addition to these four cases, there were another 19 reports of death received over the period 1997 to 2008. Of these, 16 cases were associated with SJS, TEN or Allopurinol Hypersensitivity Syndrome (AHS).

With regard to reports of serious skin reactions, HSA has received 183 local reports associated with allopurinol from 1993 to May 2009. Majority of these reports (80%) comprised skin reactions, and almost half of them included reactions such as SJS, TEN, AHS and Erythema multiforme.

HSA explains that HLA-B*5801 allele has been identified as a genetic marker for severe cutaneous adverse reactions caused by allopurinol, based on a pharmacogenetic study.

Health-care professionals have been advised to be mindful of the local cases of serious skin reactions associated with allopurinol and to exercise caution with the use of alloprinol during treatment of hyperuricaemia and its complications, including its prophylactic use in the prevention of hyperuricaemia associated with cancer treatment.

Reference:
Adverse Drug Reaction News bulletin, Volume 11, Number 2, HSA, August 2009.

Duloxetine

Risk of serotonin syndrome

Australia. According to the Australian Adverse Drug Reactions Bulletin, there have been 108 reports of suspected adverse drug reactions associated with duloxetine until May 2009 (over 200 000 prescriptions have been dispensed). Duloxetine is a serotonin and noradrenaline reuptake inhibitor recently approved for the treatment of major depressive disorder. The commonly reported reactions include agitation (8), dizziness (10 cases), serotonin syndrome (7), suicidal ideation (10) and tremor (8).. In five of the seven cases of serotonin syndrome, there was no evidence of other risk factors, such as concomitant use of other serotonergic agents or excessive dosing. Based on the early post-market information, including a published case report, the Bulletin states that it appears that serotonin syndrome can occur with duloxetine treatment alone, even at therapeutic doses, as well as in combination with other drugs known to cause this syndrome.

(See WHO Pharmaceuticals Newsletter No. 5, 2007 for warning in the UK about risk of suicidal ideation with duloxetine).

Reference:
Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 (www.tga.gov.au).

Isotretinoin

Risk of acquired hearing impairment

Australia. Prescribers have been warned that isotretinoin has been associated with acquired hearing impairment. They have been advised that if isotretinoin-associated auditory toxicity is suspected, the medicine should be ceased and the patient should be referred for audiology assessment. The hearing impairment can be unilateral or bilateral. The symptoms may include tinnitus, impaired hearing at certain frequencies and deafness. Prescribers have also been reminded that this should not be confused with congenital hearing impairment, which is a known potential complication following fetal exposure to isotretinoin in utero. Isotretinoin is a retinoid therapy indicated for the treatment of severe cystic acne unresponsive to conventional treatments.

The Australian Adverse Drug Reactions Bulletin says that there have been 609 adverse event reports for isotretinoin dating back to 1982. These include two cases of unilateral

hearing loss, one case of hearing loss at low frequencies and two cases of tinnitus. Isotretinoin was the sole suspect in all five cases. The ages ranged from 14 to 46 years of age, and duration of therapy ranged from two to eight months, where reported. In all cases, the outcomes were unknown.

Reference:
Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 (www.tga.gov.au).

Leflunomide

Risk of severe pulmonary disease including interstitial lung disease

Australia. The Adverse Drug Reactions Advisory Committee (ADRAC) has warned about reports of severe pulmonary disease including interstitial lung disease (ILD) in association with leflunomide. There were some cases that resulted in a fatal outcome because the association with leflunomide was not recognised early enough.

According to the ADRAC, in December 2006, 142 of the 699 reports with leflunomide described respiratory symptoms including 22 of ILD. In June 2009, the number of leflunomide reports has increased to 845, 196 of which describe respiratory symptoms including 39 of ILD. Of the 196 reports describing respiratory symptoms, 153 (78%) described concomitant use of methotrexate, and 23 of the 39 ILD reports involved this combination. ADRAC continues to receive reports of severe pulmonary disease associated with leflunomide. The manifestations of drug-induced pulmonary toxicity commonly include fever, cough, dyspnoea, pleurisy, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

ADRAC also states that in addition to ILD, leflunomide and methotrexate are both associated with other severe, potentially fatal adverse effects, including liver failure, Stevens-Johnson syndrome and agranulocytosis. The risks for ILD and other severe toxicities would be, at the least, additive when these drugs are used concomitantly.

Prescribers are advised that patients taking leflunomide, methotrexate or a combination of these should be monitored closely and informed about the possible early warning signs of toxicity, including ILD. If ILD develops, discontinuation of these therapies and implementation of a washout with cholestyramine (as recommended in the leflunomide Product Information) may be appropriate.

(See WHO Pharmaceuticals Newsletter No. 1, 2007 for related information in Australia and No. 4, 2004 for warning on risk of interstitial lung disease in Canada).

Reference:
Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 (www.tga.gov.au).

Methaemoglobinaemia

New Zealand. Medsafe has informed prescribers that a number of medicines have been associated with the development of methaemoglobinaemia. Signs and symptoms of methaemoglobinaemia include headache, fatigue, cyanosis, tachypnoea, dyspnoea, tachycardia, altered levels of consciousness, myocardial infarction and diffuse hypoxic brain injury. Severe cases have resulted in death.
Risk factors for developing methaemoglobinaemia include the following:
- topical or injectable administration of local anaesthetics such as benzocaine, lidocaine (lignocaine), prilocaine and tetracaine (amethocaine)
- use of amylnitrite (and other nitrites and nitrates), chloroquine, dapsone, primaquine, or sulphonamides
- age (children under three months of age have a higher risk due to being more susceptible to oxidant stress.)
- systemic infection
- anaemia
- presence of congenital methaemoglobinaemia or G6PD deficiency.

Reference:
Prescriber Update Vol. 30, No.3, August 2009 (www.medsafe.govt.nz).

Natalizumab

Reports of progressive multifocal leukoencephalopathy

USA. The US FDA informed health-care professionals that the Agency continues to receive reports of progressive multifocal leukoencephalopathy (PML) in patients receiving natalizumab (Tysabri). Natalizumab (Tysabri) is indicated for the treatment of relapsing forms of multiple sclerosis (MS) and for moderate to severely active Crohn disease.

According to the US FDA, from July 2006 to 8 September 2009, 13 reported cases of PML related to natalizumab (Tysabri) were confirmed worldwide in patients being treated for MS with monotherapy with this product.

There have been no post-marketing reports of PML in patients treated with natalizumab (Tysabri) for Crohn disease. Less than 2% of natalizumab (Tysabri) use in the United States has been in patients with Crohn disease. The US FDA states that the risk for developing PML appears to increase with the number of natalizumab (Tysabri) infusions received. The overall rate of developing PML with natalizumab (Tysabri) therapy in patients who have received at least one infusion remains below one per 1000 patients. Based on available data from and outside of the United States, the current rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1000 patients. At this time, the US FDA is not requiring changes regarding PML to the prescribing information.

(See WHO Pharmaceuticals Newsletter No. 2, 2009 and No. 5&6, 2008 for warnings on PML in Canada and Europe and No. 4, 2006 for the risk management programme for natalizumab in the USA.)

Reference:
Safety Information, US FDA 17 September 2009 (www.fda.gov).

Nitrous oxide

Reminder of neurological and haematological effects

New Zealand. Medsafe has informed prescribers that prolonged use of nitrous oxide has been associated with neurological and haematological side effects such as megaloblastic anaemia and myelopathy due to inactivation of vitamin B12. Neurological symptoms can occur without any overt haematological changes. Nitrous oxide is a medical gas used widely in surgical anaesthesia. Prescribers are advised to check vitamin B12 levels in those with risk factors for vitamin B12 deficiency prior to using nitrous oxide and to seek specialist advice if necessary. Prescribers are also advised not to use nitrous oxide continuously for more than 24 hours or more frequently than every four days without clinical supervision and haematological monitoring.

(See WHO Pharmaceuticals Newsletter No. 1, 2009 for similar warnings in the UK.)

Reference:
Prescriber Update Vol. 30, No.3 August 2009 (www.medsafe.govt.nz).

Omalizumab

Review of the possible association with cardiovascular problems

Canada. Health Canada has informed health-care professionals and the public that it is conducting a safety review of the potential association between omalizumab (Xolair) and an increased risk of cardiovascular problems. The product is indicated for the treatment of asthma in persons aged 12 years and older who have moderate to severe persistent asthma, who react to airborne allergens, and whose symptoms are not adequately controlled with inhaled corticosteroids. At this time, Health Canada recommends that patients should not stop taking omalizumab (Xolair) without first speaking to their doctor.

The review comes following the interim findings of an ongoing study in the United States to assess the long-term safety profile of omalizumab (Xolair). The interim data suggest a disproportionate increase in cardiovascular problems among patients treated with omalizumab (Xolair) relative to patients not treated with the medicine. The problems reported include heart attacks, abnormal heart rhythms, heart failure, fainting, mini-strokes, and blood clots.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for early communication about possible cardiovascular and cerebrovascular events in the USA.)

Reference:
Advisories, Warnings and Recalls, Health Canada 13 August 2009 (www.hc-sc.gc.ca).

Orlistat

Early communication about an ongoing safety review

USA. The US FDA has notified health-care professionals and patients that it is reviewing new safety information regarding reports of liver-related adverse events in patients taking orlistat. Orlistat is marketed in the United States as a prescription product (Xenical) and as an over-the-counter (OTC) product (Alli). The prescription product (orlistat 120 mg) is indicated for obesity management in conjunction with a reduced caloric diet, and to reduce the risk of regaining weight after prior weight loss. The OTC product (orlistat 60mg) is indicated for weight loss in overweight adults, 18 years and older, in conjunction with a reduced-calorie and low-fat diet.

Between 1999 and October 2008, 32 reports of serious liver injury, including six cases of liver failure, in patients using orlistat were submitted to the US FDA. The most commonly

reported adverse events described in the 32 reports of serious liver injury were jaundice, weakness, and abdominal pain. Hospitalization was reported in 27 of the 32 cases.

The US FDA is not advising health-care professionals to change their prescribing practices with orlistat. The Agency says that consumers currently taking orlistat should continue to take it as prescribed or as directed.

Reference:
Safety Information, US FDA 24 August 2009 (www.fda.gov).

Oseltamivir phosphate

A review on causality for abnormal behaviour and sudden death

Japan. The Ministry of Health, Labour and Welfare (MHLW), Japan has informed the public of the results of a review on the causal relationship between oseltamivir phosphate (Tamiflu) and abnormal behaviour or sudden death.

With regard to the possibility of oseltamivir phosphate (Tamiflu) increasing the risk of abnormal behaviour associated with influenza, some epidemiological studies showed no statistically significant difference between patients treated with oseltamivir phosphate (Tamiflu) and those not treated with the medicine, when the target population was limited to teenage patients who exhibited serious abnormal behaviour. However, it was considered impossible to draw a definite conclusion on the causality between oseltamivir phosphate (Tamiflu) and abnormal behaviour, based only on the results of these studies, given various limitations of the studies in data collection and analysis.

The subcommittee also stated that the analysis of the epidemiological studies submitted to them showed more clearly that abnormal behaviour may develop with the infection of influenza itself, regardless of oseltamivir phosphate (Tamiflu) administration. Moreover, no serious adverse events in teenagers including deaths due to falling over/falling off associated with oseltamivir phosphate (Tamiflu) were reported since the implementation of preventive safety measures in March 2007. These measures included the following.
- oseltamivir phosphate (Tamiflu) should not be used in patients aged 10 through 19 years except when a patient is considered high-risk based on complications and past medical history, etc.
- when oseltamivir phosphate (Tamiflu) is administered to children and adolescents, it is required to explain to the patients or their families that, after initiation of treatment with this medicine, 1) abnormal behaviour may occur and 2) caregivers should be careful not to let those patients alone, at least for two days, if they are treated at home, as preventive measures to avoid rare accidents;
- since it has been reported that similar symptoms may occur due to influenza encephalopathy, the same explanation is required as above.

Based on its review the Subcommittee has concluded that the measures being taken for oseltamivir phosphate (Tamiflu) are still valid, and that health-care providers, patients and their families should be kept alerted.

With regard to the risk of sudden death, it was considered that the results of non-clinical studies and clinical studies did not provide clear evidence for the causality between oseltamivir phosphate (Tamiflu) administration and sudden death.

Reference:
Pharmaceuticals and Medical Devices Safety Information No.259, MHLW, July 2009 (http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-259.pdf).

Warfarin and aspirin combination

Increased risk of bleeding

New Zealand. Medsafe has warned of an increased risk of bleeding associated with the use of a combination of warfarin and aspirin. Medsafe describes that the adverse events included major bleeding events such as subdural haematoma and intra-cerebral haemorrhage, and that some of these events occurred in patients with an INR within the therapeutic range who were also taking low dose aspirin (100 mg to 150 mg each day). Warfarin was prescribed in these patients for anticoagulation in the presence of atrial fibrillation and in patients with prosthetic heart valves.

Medsafe states that for many of the therapeutic indications for warfarin, the evidence does not suggest that a combination of aspirin and warfarin is more effective than warfarin alone. The literature indicates that there is an increased risk of major bleeding events when warfarin and aspirin are used in combination.

Reference:
Prescriber Update Vol. 30, No.3 August 2009 (www.medsafe.govt.nz).

Pilot medication error system by the New Zealand Pharmacovigilance Centre

Desireé Kunac, , New Zealand Pharmacovigilance Centre

The New Zealand Pharmacovigilance Centre (NZPhvC) has recently secured funding to scope and pilot a medication error reporting and prevention system. This will be developed by the NZPhvC in collaboration with Medsafe (New Zealand's medicines regulator), the Quality Improvement Committee (a Ministerial expert advisory committee), with input from stakeholders and interested parties.

The NZPhvC is well established as the national centre responsible for monitoring Adverse Drug Reactions (ADRs) to medicines, vaccines, and complementary medicines in New Zealand (NZ); however, there is currently no parallel coordinated national mechanism for medication error recognition and prevention. Sources of medication error data exist in NZ, but a lack of standardised reporting and communication of data means valuable opportunities to learn from errors and improve patient outcomes are currently being lost. Data on medication errors in NZ largely comes from hospital based practice and little is known about errors originating in the community setting, an area that this project seeks to include.

Given the considerable contribution of medication errors to patient harm and the emerging potential role of pharmacovigilance centres in identification of these events, the NZPhvC is keen to advance medication safety in NZ. To this end, the NZPhvC has developed a proposal to establish centralised reporting and monitoring functions for medication errors alongside the existing ADR programmes integrating and optimising medicine safety monitoring initiatives. .

The aim of this three-year project is to strengthen NZ's capacity to reduce and prevent harmful medication errors and to share the learning from voluntarily reported medication errors originating across all healthcare settings, but with special attention to the primary care setting.

The project will involve scoping, developing, then piloting a medication error reporting system with recommendations for implementation and national roll-out of the piloted system. The project will be developed within a collaborative framework providing greater opportunities to share and learn from failures in the medication use system, national coordination of efforts to reduce patient harm, and opportunities to share data internationally.

FEATURE

Paracetamol and acute generalized exanthematous pustulosis

Pär Hallberg, MD, PhD, Sweden
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Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare skin disorder which is typically drug-induced, occurring within 1-2 days after drug intake (1-3). Other causes include acute infections with enteroviruses, and mercury. The condition is characterized by an acute episode of sterile pustules over erythematous-oedematous skin, accompanied by an episode of fever. The main triggering drugs are antibiotics, mainly beta-lactam ones. Other medications, such as antifungal agents, non-steroidal anti-inflammatory drugs, antiarrhythmic, anticonvulsant and antidepressant drugs, may also be responsible. Histologically, the condition is characterized by the existence of vasculitis, associated with non-follicular subcorneal pustules. It is usually self-limiting and resolves spontaneously with discontinuation of the offending drug, although treatment with corticosteroids may be required.

In March 2009, there were seven reports of the drug-event combination paracetamol-acute generalized exanthematous pustulosis (AGEP) in VigiBase. This figure was significantly higher than expected based on general reporting patterns, and prompted a detailed assessment of the seven cases.

Review of 7 cases in the WHO Global Individual Case Safety Reports (ICSR) database, VigiBase:

Characteristics of the 7 cases are outlined in table 1.

Country	Reporter	Age (years)	Gender	Drug	Reaction
Morocco	Physician	37	Female	Paracetamol(S)	Acute generalized exanthematous pustulosis
United States		47	Female	Hetastarch(C) Neostigmine(C) Ondansetron(C) Atropine(C) Remifentanil(C) Morphine(C) Thiopental(C) Droperidol(C) Ringer-lactate(C) Cisatracurium(C) Suxamethonium (C) Nefopam(S) Clindamycin(S) Paracetamol(S) Cimetidine(S) Gentamicin(S) Metronidazole(S)	Rash pustular Fever Acute generalized exanthematous pustulosis

Singapore	General practitioner	19	Male	Naproxen(S) Paracetamol(S)	Angioedema Acute generalized exanthematous pustulosis
Singapore	General practitioner	23	Male	Mefenamic acid(S) Paracetamol(S) Ibuprofen(S)	Rash erythematous Rash Acute generalized exanthematous pustulosis
Singapore	General practitioner	45	Female	Paracetamol(S)	Rash erythematous Rash erythematous Rash Acute generalized exanthematous pustulosis
Singapore	General practitioner	37	Male	Paracetamol(S) Metoclopramide(S)	Acute generalized exanthematous pustulosis
United States		5	Male	Paracetamol(S) Loratadine(S)	Acute generalized exanthematous pustulosis

Table 1. Reports of acute generalized exanthematous pustulosis where paracetamol was suspected as causative agent.

None of the reports included a narrative, which makes it difficult to assess the possible role of paracetamol. Of note is that 4/7 reports originated from Singapore. All were reported by health care professionals except for one case where reporter type was unknown. The cases involved relatively young patient, including one 5-year old child. Time to onset was known only for two cases – one and two days.

Literature review

A total of 7 cases of AGEP associated with treatment with paracetamol were found in a search of PubMed on April 9, 2009.

De Coninck et al described a 28-year-old Bangladesh man with AGEP induced by paracetamol (4). The patient presented with an erythematous and pustular eruption after taking 1 tablet of paracetamol for a sore throat. After intravenous administration of propacetamol hydrochloride (which is a prodrug of paracetamol), the rash became worse, showing a toxic epidermal necrolysis-like appearance and the patient suffered from severe haemodynamic disturbances. After discontinuation of propacetamol hydrochloride, the eruption cleared within 2 days. Prick testing performed in the patient revealed a positive reaction for propacetamol hydrochloride.

A second case was reported by Mashiah et al (5), concerning a case of AGEP provoked by a patch test with paracetamol.

A third case was reported by Halevy et al (6), concerning a patient with AGEP which occurred 3 days after ingesting paracetamol and bromhexine. Both were immediately stopped and the rash resolved rapidly. To determine the offending drug responsible for AGEP, an in vitro drug-induced

interferon (IFN)-gamma release test was performed using an ELISA technique. Increased IFN-gamma release was observed following *in vitro* challenge of the patient's lymphocytes with paracetamol or bromhexine (110% and 157% increase, respectively). *In vitro* challenge with paracetamol or bromhexine in a control patient, treated with paracetamol and bromhexine, did not induce an increase in IFN-gamma. The authors concluded that the patient may have had polysensitivity to both drugs.

A fourth and fifth case of AGEP associated with the use of paracetamol were described by Leger et al (7). Lastly, one case each was reported by Roujeau et al and Mensig et al (8,9).

Discussion

Although a proper assessment of causality between paracetamol and AGEP is not possible for the 7 cases in the Global Individual case safety Reports (ICSR) database, VigiBase due to the limited data available, the signal is substantiated by the presence of multiple case reports in the literature. It is likely that AGEP induced by paracetamol, if true, is very rare given the great cumulative exposure of the drug world-wide. AGEP is not labelled for paracetamol-containing products in Sweden or the UK. Holders of marketing authorisation for paracetamol-containing products are advised to review their safety databases for cases of AGEP and to consider the inclusion of AGEP in the product labels.

* As of 2009-09-01 there were 9 reports in VigiBase, from 5 countries, where paracetamol is reported in suspected connection to acute generalized exanthematous pustulosis.

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FEATURE

Summary of the information published on the Medical Products Agency (MPA) website (Oct 29, 2009) regarding adverse drug reaction reports in Sweden with Pandemrix – the influenza A (H1N1) vaccine

Published October 29, 2009

As of today, about 1.4 million doses of Pandemrix have been distributed in Sweden. In total, about two hundred adverse drug reaction (ADR) reports have been received by the MPA from Health Care Professionals and between 400-500 reports from consumers. The ADR reporting pattern does not deviate from what has been seen in the clinical trials. However, there is particular reason to follow reports of allergic reactions.

It should be remembered that all ADR reports should be considered as part of a larger pattern in which one single report rarely means that an adverse reaction was caused by the vaccine. It is important to stress the following:

- **The reports describe reactions that have occurred in close connection to when the vaccine was given.**
- **The reaction can thus be caused by the vaccine, but can also be signs of illness the patient suffered from regardless of the vaccination.**
- **Causality assessment can only be made after the report has been carefully assessed.**

Since the vaccination campaign began, the MPA has published summaries of adverse events reported with Pandemrix. MPA will continue to review and assess all reports, but the published compilations will mainly focus on reports relating to unknown and serious suspected adverse reactions, while the presentation of reports on the known side effects are reported only briefly.

Reports from Health-care Professionals

Almost 200 reports have been received from health-care professionals.
The majority of the adverse events are expected and known reactions such as **soreness, redness and pain at the injection site** and in the arm, and **flu-like symptoms** such as fever, shivering, fatigue, moderate/severe headaches, body aches and malaise. Experiences from certain vaccination sites point to the fact that these expected reactions have been very common. In a fewer number of reports, symptoms of nausea, vomiting, stomach pain, diarrhoea, dizziness, rashes and insomnia are reported. All these reactions are known from the studies performed on Pandemrix. Also a number of allergic reactions have been reported (see below).

Comments on some case reports

About 20 reports of the suspected adverse reactions have been identified as serious and with a causal relationship to the vaccination. **Allergic adverse reactions** represent the majority of these reports, see table below. Besides these, facial palsy (one case), paresthesia (three cases), sensibility disorder (one case), hypertension (one case), and absence attacks (one case) were reported.

Allergic reactions / allergic symptoms reported in relation to administration of Pandemrix
Included in SWEDIS data base 12 Oct - 27 Oct, 2009

	Related	(of which were serious)	Not related
Allergic reaction	10	(3)	2
Anaphylactic reaction	5	(5)	1
Angiooedema	5	(3)	0
Urticaria	6	(2)	0
Exanthema	2	(0)	1
Flush	3	(0)	0
Swollen tongue	2	(0)	1
Dyspnoea	7	(2)	1
Cough	1	(0)	0
TOTAL no of symptoms (patients)	41 (37)	(15)	6

In total, 41 reports of allergic reactions/symptoms in **37** patients were considered to be **related** to the vaccination. Allergic reactions considered **not related** were reported in **6** patients.

Four of the five patients with anaphylactic reactions had a known allergy to certain foods or medicines. In all cases the reactions occurred within one hour after the vaccination. In two of the patients, hypotension was reported, and four patients reported dizziness, tingling, oedema of the lips and throat, and moderate difficulty breathing. None of the patients developed anaphylactic shock. All patients recovered after treatment with adrenaline, corticosteroids and antihistamines. Allergic reactions such as anaphylaxis, angioedema and urticaria are not specified in the product information for Pandemrix.

Two of the patients who were diagnosed with "allergic reaction" had previously known egg allergy. One of these patients had a strong reaction directly after the vaccination, but the symptoms were relieved quickly with adrenaline, cortisone and antihistamine treatment. The other patient had a transient urticarial reaction.

Deaths reported

Five reports of death have been received all of which have had a temporal association with vaccination. The time between the vaccination and the death has varied between 12 hours and 4 days. These five patients had previously known chronic diseases such as cardiovascular disease, diabetes, renal failure, dystrophic muscle disease and senile dementia. All patients were on chronic medical treatment. Three of the patients were >74 years, the two others between 54 and 65. Autopsy result is available for the

first reported case. This showed that the patient suffered from generalized atherosclerosis and previous heart attacks. The other reports are still under investigation and autopsy results are awaited. From what has emerged so far for these cases, there is nothing to support a causal association between the vaccination and the death.

In assessing the number of reported deaths, it is important to take into account that in Sweden on average 200-250 deaths occur per day and at present a large proportion of the population, particularly the elderly and other risk groups, are being vaccinated. The majority of deaths occurring daily in Sweden are older people with complications of chronic diseases.

Experience from consumer reporting

Since the vaccination campaign with Pandemrix began, the MPA has received more than 450 consumer reports. Still a large majority, about 90% of reports, describe non-severe, expected and known reactions. The potentially serious cases are similar to the ones previously reported (such as events of transient flu-like symptoms, severe pain at the injection site, pain in arm and adjacent muscles).). Despite the fact that an adverse reaction is known and judged as non-serious, symptoms may of course still be perceived as troublesome to the individual. Some patients have reported that the reactions to this influenza vaccine differ from their experience with previous seasonal flu vaccinations, such as more pronounced pain in the injection arm and stronger flu-like symptoms.