

WHO PHARMACEUTICALS NEWSLETTER



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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In addition to the usual sections (Regulatory Matters and Safety of Medicines) this issue includes the summary of recommendations from the sixth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) that was held earlier this year in Geneva.

The thirty-second Annual meeting of National Pharmacovigilance Centres will take place at Rabat, Morocco, 2-5 November 2009. Pre-meeting events will include a training workshop in the use of MedRA (Medical Dictionary for Regulatory Activities), a workshop on strategies for identifying and preventing medication errors, and a technical briefing on pharmacovigilance to all new members joining the WHO Programme for International Drug Monitoring. We hope to see many of you at this meeting.

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Botulinum toxins Type A and Type B

Warnings to be strengthened about distant spread of toxin effects

USA. The United States Food and Drug Administration (US FDA) has notified health-care professionals that after an ongoing safety review, the manufacturers of licensed botulinum toxin products (Botox, Botox Cosmetic, Myobloc) will be required by the Agency to strengthen warnings in the product labelling and add a boxed warning regarding the risk of adverse events when the effects of the toxin spread beyond the injection site. 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.

The US FDA will also require that manufacturers develop and implement a Risk Evaluation and Mitigation Strategy (REMS), including a communication plan to provide more information on the above mentioned risk, and to explain that botulinum toxin products cannot be interchanged. The REMS would also include a Medication Guide that explains the risks to patients, their families and caregivers.

In addition, the US FDA is requiring the manufacturers to submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the signal of serious risk regarding the spread of toxin effects beyond the injection site.

In the Agency's review of postmarketing safety data,

- in the pediatric adverse event case reports, botulinum toxin products were mostly used to treat muscle spasticity in cerebral palsy, which has not been approved. The reported cases of spread of botulinum toxin effect beyond the site of injection were described as botulism or involved symptoms. Serious case reports described hospitalizations involving ventilatory support and reports of death;
- the majority of the adult case reports of distant spread of toxin effects occurred following use of botulinum toxin for the treatment of spasticity (an unapproved use) or cervical dystonia. Some cases resulted in hospitalization, including placement of a gastric tube or mechanical ventilation. Although there were several deaths in adults, it is not possible to attribute them to the botulinum toxin because the patients also suffered from complications due to their pre-existing conditions.

Reports in WHO Global ICSR database, Vigibase: Botulinum toxin Type A

Number of reports: 752
Number of events:
Eyelid ptosis 203
Diplopia 60
Constipation 14
Dysphagia 249

Death 22
Botulism 32
Muscular weakness 185
Facial palsy 49
Speech disorder 48
Dyspnoea 133
Respiratory depression 4
Pneumonia aspiration 18

Botulinum toxin Type B

Number of reports: 79
Number of events:
Eyelid ptosis 8
Constipation 17
Dysphagia 43
Death 3
Botulism 1
Muscular weakness 6
Facial palsy 1
Speech disorder 4
Dyspnoea 10
Pneumonia aspiration 4

(See WHO Pharmaceuticals Newsletter No.2, 2009, No.1, 2009 and No. 2, 2008 for similar information issued in Australia, Canada and the USA, respectively).

Reference:

Follow-up to the early communication about an ongoing safety review, US FDA, 30 April 2009 (www.fda.gov).

Ceftriaxone

Updated recommendations concerning the interaction with calcium-containing products

USA. The US FDA has notified health-care professionals of an update to an earlier alert (September 2007) that addresses the interaction of ceftriaxone (broad-spectrum cephalosporin antibiotic marketed as Rocephin and generics) with calcium-containing products, based on previously reported fatal cases in neonates. The manufacturer of ceftriaxone conducted two *in*

vitro studies using neonatal and adult plasma to assess the potential for precipitation of ceftriaxone-calcium when ceftriaxone and calcium-containing products are mixed in vials and in infusion lines. Based on the results from these studies, the US FDA has recommended the following:

- Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (28 days of age and under). Ceftriaxone should not be used in neonates (28 days of age and under) if they are receiving (or are expected to receive) calcium-containing intravenous products.
- In patients aged over 28 days, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group.
- Ceftriaxone and calcium-containing products may be used concomitantly in patients aged over 28 days, using the precautionary steps above because the risk of precipitation is low in this population. The US FDA had previously recommended, but no longer recommends, that in all age groups, ceftriaxone and calcium-containing products should not be administered within 48 hours of one another.

(See WHO Pharmaceuticals Newsletter No. 4, 2007 for revisions to the prescribing information in the USA).

Reference:

Information for Healthcare Professionals, US FDA, 21 April 2009 (www.fda.gov).

Chromic Phosphate P32

Risk of acute lymphocytic leukaemia

Canada. Health-care professionals have been alerted about the risk of acute lymphocytic leukaemia associated with chromic phosphate P 32 (Phosphocol® P 32). This product is authorized for intracavitary instillation for the treatment of peritoneal or pleural effusions caused by metastatic disease.

According to Health Canada and the company, two children (9 and 14 years) with haemophilia developed acute lymphocytic leukaemia approximately 10 months after intra-articular injections of chromic phosphate P 32 (Phosphocol® P 32) (0.6 and 1.5 mCi total dose). The product is not indicated in the treatment of haemarthroses.

The Canadian Product Monograph will be updated to include the above warning as well as post-marketing reports of radiation injury (necrosis and fibrosis) to the small bowel, caecum and bladder following peritoneal administration of the product.

Reference:

Advisories, Warnings and Recalls, Health Canada, 30 March 2009 (www.hc-sc.gc.ca).

Cough and cold medicines

Advisory on use in children

Canada(1). Health Canada has advised the public that certain over-the-counter cough and cold medicines should not be used in children under 6 years

of age, following a review of additional data. The Agency also says that cough and cold medicines marketed for use in children will require enhanced labelling and packaging and that it is working with manufacturers to revise the labelling of these products.

New Zealand(2). In

December 2007, the Medicines Adverse Reactions Committee (MARC) reviewed the safety and efficacy of cough and cold medicines in children and recommended that these products should be contraindicated in children under two years of age, based on limited evidence for efficacy in this age group, an absence of evidence-based dosing, and evidence of significant toxicity in overdose. The product packaging will be amended to include the warning that these products must not be used in children under two years of age. The affected products are those containing bromhexine, brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, ipecacuanha, oxymetazoline, phenylephrine, pholcodine, promethazine, pseudoephedrine, triprolidine and xylometazoline. Medsafe and MARC are continuing to review the safety and efficacy of cough and cold medicines in children over two years of age.

(See WHO Pharmaceuticals Newsletters No.2, 2009 for advice on use of over-the-counter cough and cold medicines for children in Kenya and the UK).

References:

(1) Canadian Adverse Reaction Newsletter Volume 19, Issue 2, Health Canada, April 2009 (www.hc-sc.gc.ca).

(2) *Prescriber Update Vol. 30, No.2, May 2009*
(www.medsafe.govt.nz)

Dietary supplements

Warning about potential risks with Hydroxycut

USA. The US FDA has alerted the public and health-care professionals about dietary supplement products named Hydroxycut that are associated with serious liver injuries, and warned consumers not to take these products. They contain a variety of ingredients and have been marketed for weight-loss, as fat burners, as energy-enhancers, as low carbohydrate diet aids, and for water loss. The products have been recalled by the company.

The Agency has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes to liver damage requiring liver transplants. One death due to liver failure has been reported. Other health problems reported include seizures, cardiovascular disorders, and rhabdomyolysis.

The US FDA continues to investigate the potential relationship between Hydroxycut dietary supplements and liver toxicity or other adverse events.

Reference:

Media release, US FDA, 1 May 2009 (www.fda.gov).

Erlotinib

New safety information on cases of gastrointestinal perforation, Stevens-Johnson syndrome and corneal perforation

Canada and USA. Health-care professionals have been notified of new safety information regarding the use of erlotinib (Tarceva). The product is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. Erlotinib (Tarceva) monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

The information comes from routine pharmacovigilance activities involving clinical trials, spontaneous reports and literature. Cases of gastrointestinal perforation (including fatalities), cases of bullous, blistering and exfoliative skin conditions suggestive of Stevens-Johnson syndrome and Toxic epidermal necrolysis, which in some cases were fatal, and cases of corneal perforation or ulceration have been reported in patients treated with the product. Prescribers have been advised that treatment with erlotinib should be interrupted or discontinued in patients developing any of these adverse reactions.

The Canadian Product Monograph is being reviewed by Health Canada in conjunction with the manufacturer regarding the above mentioned safety concerns and will be updated accordingly. The US prescribing information has been changed to include the new information in the WARNINGS AND PRECAUTIONS sections.

References:

(1) *Advisories, Warnings and Recalls, Health Canada, 11 May 2009*
(www.hc-sc.gc.ca).

(2) *Media release, US FDA, 8 May 2009* (www.fda.gov).

Etanercept

Risk of histoplasmosis and other invasive fungal infections

Canada. Health-care professionals have been alerted about the risk of invasive fungal infections in patients taking etanercept (Enbrel). The product is a soluble form of a fully human tumour necrosis factor (TNF) receptor protein authorized for the treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and plaque psoriasis. The Boxed Warning and Warnings and Precautions (Infections) sections of the Canadian Product Monograph have been revised to include information regarding the risk of invasive fungal infection, including histoplasmosis.

According to Health Canada and the company, there have been reports of serious pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis infections, sometimes with fatal outcomes, in patients taking tumour necrosis factor- α blockers (TNF blockers), including etanercept (Enbrel). For a patient taking a TNF blocker who presents with signs and symptoms of systemic illness, such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, health-care professionals have been advised to ascertain if the patient has lived or worked in or traveled to areas of endemic mycoses. If so, appropriate empiric antifungal treatment may be initiated while a diagnostic workup is being performed. The TNF blocker

should be stopped until the infection has been diagnosed and adequately treated.

**Reports in WHO Global ICSR database, Vigibase:
Etanercept**

Fungal infectious disorders: 507

Most reported reactions:

Candidiasis 44

Oral candidiasis 52

Vulvovaginal candidiasis 35

Coccidioidomycosis 23

Fungal infection 202

Fungal skin infection 13

Onychomycosis 11

Vulvovaginal mycotic infection 32

Acute pulmonary histoplasmosis 12

Pneumocystis jiroveci pneumonia 11

(See WHO Pharmaceuticals Newsletter No.3, 2008 and No.6, 2004 for risk of infections in children in the USA and for reports of infections in Canada, respectively).

Reference:

Advisories, Warnings and Recalls, Health Canada, 23 April 2009
(www.hc-sc.gc.ca).

Hydroxyzine hydrochloride

Alert on skin necrosis and ulcer

Japan. The Ministry of Health, Labour and Welfare (MHLW), Japan has alerted health-care providers about skin necrosis and ulcer following injection of hydroxyzine hydrochloride. The medicine is indicated for anxiety, tension, depressed mood in neurosis, anaesthetic premedication and prevention of preoperative or postoperative nausea/vomiting, and has been marketed since 1966. From April 1994 to September 2008, there were 45 cases of injection site reactions reported in association with the medicine. Out of these, nine serious cases

of skin necrosis and ulcer at the injection site that required necrectomy or skin graft were identified.

Following an expert review, MHLW requested relevant companies to revise package inserts of hydroxyzine hydrochloride. The revision includes adding a description of injection site skin necrosis/ulcer in the "clinically significant adverse reactions" section, and in the "important precautions" section, the instruction to apply gentle pressure to the injection site and not knead strongly after intramuscular injection.

Reference:

Pharmaceuticals and Medical Devices Safety Information No.256, MHLW, March 2009
(www.pmda.go.jp/english/).

Salicylate containing oral gels

New advice on use in children

UK(1). The Medicines and Healthcare products Regulatory Agency (MHRA) has sent a letter to health-care professionals, stating that the Commission on Human Medicines (CHM) has recommended that topical oral pain relief products containing salicylate salts should be contraindicated in children and young people under the age of 16 years.

The MHRA has reviewed the safety of oral topical salicylate-containing products after publication of a case report of suspected Reye's syndrome associated with use of a dental gel that contained choline salicylate in a 20-month-old child. The review concluded that the symptoms were not consistent with Reye's

syndrome and were more likely to reflect salicylate toxicity, but nevertheless, substantial systemic levels of salicylate were achievable after overuse of salicylate-containing dental gels. Up to April 2009, the Agency has received three suspected serious adverse drug reaction reports in association with the use of topical oral gels in children containing choline salicylate. In all cases, Reye's syndrome was suspected but in none of the cases was Reye's syndrome confirmed. The CHM concluded that these products should be contraindicated in children and young people under the age of 16 years in line with other oral salicylate-containing preparations, as a precautionary measure to remove the theoretical risk of Reye's syndrome if these products are overused.

Ireland(2). After the announcement of the restriction of use of salicylate-containing products for oral use in children in the UK, the Irish Medicines Board (IMB) has issued an Advisory, stating that following its own review, the Board has concluded that the risk-benefit for the use of salicylate-containing products in children is positive when used according to their approved conditions of use. The Board has advised parents and care-givers that oral gels containing choline salicylate should be applied very sparingly and only at the frequency indicated in the product information, and that these products are intended for short-term use only. The IMB states that the risk associated with the short-term use of these products, which are indicated for the treatment of infant teething, is extremely low and that it has received no reports of adverse reactions in children with these products. The Board says that the risk of toxicity is associated with

incorrect use or over-dosing, and emphasizes the importance of the correct use of these products.

References:

(1) Advisory, Warning and Recall Notices, *IMB*, 23 April 2009

(www.imb.ie).

(2) Safety warnings and messages for medicines, *MHRA*, 23 April 2009

(www.mhra.gov.uk).

Testosterone gel products

Boxed warning about secondary exposure

USA. The US FDA has announced that it is requiring manufacturers of two prescription topical testosterone gel products (AndroGel 1% and Testim 1%) to include a boxed warning on the products' labels about the risk of virilisation in children and women after secondary exposure. As of 1 December, 2008, the Agency has received reports of eight cases of secondary exposure (through contact with another person being treated with the products) to testosterone in children ranging in age from nine months to five years. Of the fully reviewed cases, adverse events reported in these children included inappropriate enlargement of the genitalia, premature development of pubic hair, advanced bone age, increased libido and aggressive behaviour. The products are approved for use in men who either no longer produce testosterone or produce it in very low amounts, and applied once daily, to the shoulders or upper arms. Precautions in the current labels instruct users to wash their hands after using

the product and to cover the treated skin with clothing.

The US FDA has recommended precautions to minimize the potential for secondary exposure, including that children and women should avoid contact with testosterone application sites on the skin of men who use these products. The Agency is also requiring that the manufacturers of these products develop a Medication Guide as part of a Risk Evaluation and Mitigation Strategy to ensure that the benefits of these products continue to outweigh their potential risks.

Reference:

Media release, *US FDA*, 7 May 2009 (www.fda.gov).

Trastuzumab

Risk of oligohydramnios in pregnant women

Canada. Health-care professionals have been notified of new safety information that cases of oligohydramnios during the second and third trimesters have been reported in pregnant women receiving trastuzumab (Herceptin) in the post-marketing setting. The product is a recombinant DNA-derived humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2). Over-expression of HER-2 protein is observed in 25-30% of primary breast cancers. Trastuzumab has been shown, both in in vitro assays and in animals, to inhibit the proliferation of human tumour cells that over-express HER-2. The product is authorized for the treatment of patients with early stage breast cancer, whose tumours over-express

HER-2, following surgery and after chemotherapy, and in the treatment of patients with metastatic breast cancer whose tumours substantially over-express HER-2.

A review was conducted of six reports of oligohydramnios reported between 2004 and August 2008. In three cases, a decrease in amniotic fluid level was diagnosed seven weeks after the start of trastuzumab, and a causal relationship to trastuzumab could not be ruled out. In addition, it has been concluded that the fetal outcome is not different than in women who have not been exposed to trastuzumab. Based on this, the recommendation remains that trastuzumab (Herceptin) should not be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. If trastuzumab is administered during pregnancy, monitoring of the amniotic fluid is recommended.

The Canadian Product Monograph has been updated to include the post marketing cases of oligohydramnios and provides the information on reproductive toxicity under Special Populations, Pregnant Women. However, there are no adequate and well-controlled studies in pregnant women and it is not known whether trastuzumab (Herceptin) can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

Reference:

Advisories, Warnings and Recalls, Health Canada, 24 April 2009 (www.hc-sc.gc.ca).

Aliskiren

Risk of angioedema and acute renal failure

UK. The MHRA has alerted that angioedema can occur as a rare and serious adverse event of treatment with aliskiren (Rasilezt). The Agency has also warned about the risk of acute renal failure with the use of the product and the risk associated with the concomitant use of aliskiren and non-steroidal anti-inflammatory drugs (NSAIDs). Aliskiren (Rasilezt) is the first of a new class of medicines that directly inhibit renin, and is used for the management of high blood pressure.

According to the Agency, there have been reports of acute renal failure in patients with risk factors for renal dysfunction, including hypovolaemia, heart disease, liver disease, or kidney disease. There is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. In addition, NSAIDs may reduce the antihypertensive effect of aliskiren. In some patients with compromised renal function (eg, dehydrated or elderly patients), aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible when treatment is stopped.

Health-care professionals have been advised that aliskiren (Rasilezt) should not be used in patients who have previously had angioedema after using it. Aliskiren should be used with caution in patients taking NSAIDs, or in patients who may be at increased risk of acute renal failure or with risk factors for kidney dysfunction.

(See WHO Pharmaceuticals Newsletter No.2, 2009 for related contraindication and warning added to the product information in Europe).

Reference:

Drug Safety Update, MHRA, Volume 2, Issue 10, May 2009
(www.mhra.gov.uk).

Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists

Recommendations on use during breastfeeding

UK. The MHRA has issued an advice about use of Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists in breastfeeding mothers. These medicines are licensed for a range of conditions including hypertension. The Agency says that although the levels of ACE inhibitors transferred to an infant via breastfeeding are unlikely to be clinically relevant, there are insufficient data to exclude a possible risk of profound neonatal hypotension, particularly in preterm babies. With regard to angiotensin II receptor antagonists, no data on the use of the medicines are available, and the effects of potential exposure on a nursing infant are unknown.

Health-care professionals have been advised of the following:

- ACE inhibitors (captopril, enalapril, or quinapril): use in breastfeeding is not recommended in the first few weeks after delivery because of the possibility of profound neonatal hypotension; preterm babies may be at particular risk. Use may be considered

when the infant is older, if an ACE inhibitor is necessary for the mother; careful follow-up of the infant for possible signs of hypotension is recommended.

- ACE inhibitors (ramipril, lisinopril, fosinopril, trandolapril, moexipril, or perindopril) and all angiotensin II receptor antagonists: use in breastfeeding is not recommended. Alternative treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby.

With regard to use in pregnancy, the MHRA has reminded that ACE inhibitors and angiotensin II receptor antagonists should not be used at any stage of pregnancy unless absolutely necessary. Angiotensin II is essential for normal kidney development, and the use of ACE inhibitors and angiotensin II receptor antagonists in late pregnancy has been associated with adverse effects on the kidney and other congenital anomalies.

Reference:

Drug Safety Update, MHRA, Volume 2, Issue 10, May 2009
(www.mhra.gov.uk)

Antiepileptics

Risk of decreased bone mineral density

UK. The MHRA has alerted about adverse effects of antiepileptics on bone. Carbamazepine, phenytoin, primidone and phenobarbital are known to cause osteomalacia, and the product information for these drugs contains information about this risk. Osteoporosis is also recognized with carbamazepine.

According to the MHRA, the available data suggest that long-term treatment with carbamazepine, phenytoin, primidone and sodium valproate is associated with decreased bone mineral density that results in an increased risk of developing osteopenia, osteoporosis and fractures in the following, at-risk patients: those who are immobilised for long periods; those who have inadequate sun exposure; and those with inadequate dietary calcium intake. The Agency has advised health-care professionals that vitamin D supplementation should be considered for at-risk patients who receive long-term treatment with primidone, phenytoin, carbamazepine, phenobarbital or sodium valproate.

At present there are insufficient data to support an association between decreased bone mineral density, osteopenia, osteoporosis and osteomalacia, and other antiepileptic drugs.

Reference:

Drug Safety Update, MHRA, Volume 2, Issue 9, April 2009
(www.mhra.gov.uk).

Antipsychotics

Adverse metabolic effects

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has warned that all antipsychotics, in particular some atypical antipsychotics, are associated with adverse effects on weight, blood glucose, and lipid concentrations, mentioning that schizophrenia itself is associated with several adverse metabolic effects. While the effects of antipsychotics on weight gain may be responsible for the increased risk of diabetes

and hyperlipidaemia, a direct effect on glucose metabolism may also occur.

The Agency says that clozapine and olanzapine are considered to cause adverse metabolic effects more frequently than other agents. Prescribers have been advised that, where possible, patients with high baseline risk factors for diabetes should be prescribed an antipsychotic with lower risk of adverse metabolic effects.

Reference:

Prescriber Update Vol. 30, No. 2, May 2009
(www.medsafe.govt.nz).

Atypical antipsychotics

Risk of agranulocytosis

Canada. Health Canada has warned about the risk of agranulocytosis associated with atypical antipsychotics. Atypical antipsychotics are indicated for the management of symptoms of schizophrenia and other related psychotic disorders. Antipsychotics clozapine, olanzapine, quetiapine, risperidone and ziprasidone have been marketed in Canada.

Granulocytopenia and agranulocytosis have been shown to occur in association with clozapine. Recent evidence suggests that olanzapine, quetiapine, risperidone and ziprasidone may also be associated with an occurrence of agranulocytosis, but not to the extent of clozapine.

As of 30 November 2008, Health Canada received 69 reports of granulocytopenia, neutropenia and agranulocytosis suspected of being associated with the use of olanzapine, quetiapine and risperidone. No report was identified with ziprasidone,

which was marketed in January 2008. There were 14 cases of agranulocytosis, six cases of severe neutropenia, 45 cases of neutropenia and four cases of granulocytopenia. Concomitant medical conditions (e.g. cancer, lupus, Tourette syndrome, depression and cardiovascular disease) or concomitant use of other medications (e.g. typical and atypical antipsychotics, antidepressants, anticonvulsants, anti-inflammatory and antineoplastic drugs), or both, were reported in many of these cases.

Reference:

Canadian Adverse Reaction Newsletter Volume 19, Issue 2, Health Canada, April 2009
(www.hc-sc.gc.ca).

Bevacizumab

Eye-related adverse reactions with unauthorized use

New Zealand. Medsafe has warned that an increase in eye-related adverse reactions has been identified following the administration of bevacizumab (Avastin) into the vitreous humour. Bevacizumab (Avastin) is approved for the treatment of metastatic colorectal cancer in combination with fluoropyrimidine based chemotherapy and advanced and/or metastatic renal cell cancer in combination with interferon alfa-2a.

In New Zealand, there have been five reports of eye-related adverse reactions such as eye inflammation, endophthalmitis, blurred vision and the presence of "floaters", following intraocular administration of bevacizumab (Avastin). Medsafe has reminded prescribers that the intraocular use of bevacizumab for the treatment of neovascular age-related

macular degeneration is not approved.

(See WHO Pharmaceuticals Newsletter No.1, 2009 for reports of eye inflammation in Canada).

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Cefaclor

Serum sickness-like reactions in children

Australia. Health-care professionals have been reminded of the risk of serum sickness-like reactions (SSLR) associated with the use of cefaclor (a cephalosporin antibiotic). According to the *Australian Adverse Drug Reactions Bulletin*, about 10 reports per year are received of cefaclor-related SSLR in children. SSLR are characterized by a variety of rashes, which include urticaria or erythema multiforme, with or without angioedema, accompanied by arthritis/arthralgia, with or without fever. The reactions are rare but occur more often after a second or subsequent course of treatment. Onset time is often a few days after cefaclor is commenced and signs and symptoms typically subside a few days after the drug is ceased. However, onset may also be delayed and occur 7-21 days after stopping cefaclor. Children are more susceptible than adults, but the underlying reasons are not clear.

The Bulletin emphasizes that if cefaclor must be prescribed to a child, the parents and care-givers should be advised to remain alert for the development of new or worsening symptoms that might indicate a hypersensitivity

reaction to the drug and to contact their doctor immediately if there are concerns.

(See WHO Pharmaceuticals Newsletters No.3 and No.4, 1997 for reports of serum sickness-like reactions in Canada).

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009
(www.tga.gov.au).

Clopidogrel

Interim advice on concurrent use of proton pump inhibitors

Ireland. The Irish Medicines Board (IMB) has issued interim advice about the use of clopidogrel, following the publication of reports suggesting that it is less effective in some patients (including those taking proton pump inhibitors) than it is in others, resulting in an increased risk of acute myocardial infarction. Differences in effectiveness may be due to genetic differences in the way the body metabolizes clopidogrel, or due to co-administration of drugs that can interfere with the metabolism of clopidogrel, (Clopidogrel is an antiplatelet drug authorized for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or acute coronary syndrome, or those at risk of these problems).

The IMB says that evaluation of all available data is currently under way and has advised health-care professionals to be aware of interaction between clopidogrel and proton pump inhibitors (PPIs) and the potential to increase cardiac events such as acute myocardial infarction; Health-care providers

should continue to prescribe clopidogrel because of demonstrated benefits in preventing blood clots, but they should re-evaluate the need for starting or continuing treatment with a PPI (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) in patients taking clopidogrel. (See WHO Pharmaceuticals Newsletter No.2, 2009 about an ongoing review in the USA, on the impact of genetic factors and other medications on the effectiveness of clopidogrel).

Reference:

Advisory, Warning and Recall Notices, IMB, 12 May 2009
(www.imb.ie).

Corticosteroids

Risk of avascular necrosis

New Zealand. Medsafe has warned about the risk of avascular necrosis (AVN) associated with corticosteroids. Prescribers are advised to be alert to symptoms of joint pain in patients using corticosteroids and to consider stopping or interrupting corticosteroid treatment if AVN is confirmed.

The Centre for Adverse Reactions Monitoring (CARM) has received a number of reports of AVN in association with corticosteroid use that involve major joints such as hips, knees and ankles, often with bilateral involvement. The reports involve patients who were prescribed corticosteroids for asthma, immunosuppression in transplant recipients, polymyalgia rheumatica, rheumatoid arthritis, eczema, and cerebral oedema. Medsafe explains that AVN usually occurs with high doses of corticosteroids over a period of a few weeks to several years. Other known risk factors for AVN include alcoholism, infections,

hyperbaric events, marrow infiltrating diseases, coagulation defects, sickle cell anaemia and some autoimmune diseases.

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Flecainide

Risk of cardiac adverse events

New Zealand. Medsafe has reminded prescribers of the risk of inducing 1:1 atrioventricular conduction, with a consequent paradoxical increase in ventricular rate, when flecainide (Tambacor™) is used to treat atrial flutter. This reaction is more likely to occur with the use of intravenous flecainide. Flecainide is indicated only in patients without structural heart disease for the prevention, rapid control, or short-term prophylaxis of supraventricular and ventricular arrhythmias.

According to Medsafe, there have been reports of patients treated with flecainide for tachycardia due to atrial flutter who have developed a paradoxical increase in the ventricular rate. This increase has been attributed to the induction of 1:1 atrioventricular conduction following the slowing of the atrial rate. A paradoxical increase in the ventricular rate may also occur in patients with atrial fibrillation who receive flecainide. The Agency emphasizes that flecainide is not recommended for use in patients with chronic atrial fibrillation.

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Immunoglobulin

Severe adverse reactions with intravenous immunoglobulin

Australia. Health-care professionals have been alerted about severe adverse reactions associated with intravenous immunoglobulin. Intravenous immunoglobulin, normal (human) (IVIG) is a plasma derived product used to treat a variety of deficiencies and disorders with an immune (or presumed immune) etiology.

According to the *Australian Adverse Drug Reactions Bulletin*, there have been 356 reports of adverse reactions associated with IVIG in Australia. Of these reports, IVIG was the sole suspected agent in 319 (90%). Serious reactions are described in 125 (35%), including five with fatal outcome that is due to stroke/myocardial infarction, myocardial infarction, convulsions, hepatic and renal failure, and respiratory failure, respectively. In the fatal cases, patients generally had thrombogenic risk factors such as hypertension, obesity, increasing age, or past history of stroke. Many of the adverse reaction reports describe symptoms which may be consistent with a hypersensitivity reaction. These include 71 reports of rash, urticaria and/or pruritus, 33 of which also describe oedema and/or respiratory disorder, as well as an additional 14 reports with descriptions of 'anaphylaxis' or 'anaphylactoid reaction'. In addition, there have been reports describing pyrexia (58), chills (41), haemolysis or anaemia (32), meningitis (20), neutropenia (12), hepatic disorders (11) and renal failure/impairment (8).

Health-care professionals have been advised to assess whether there are any pre-existing thrombogenic risk factors before and during the use of IVIG and monitor all patients closely during infusion. A slow infusion rate of IVIG should be considered for all patients with risk factors.

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009
(www.tga.gov.au).

Isotretinoin

Risk of teratogenicity

New Zealand. Medsafe has reminded prescribers of indications and the risk of teratogenic effects of isotretinoin. Isotretinoin is an oral retinoid indicated for the treatment of severe forms of nodulo-cystic acne, in particular cystic acne and acne conglobata.

Medsafe is aware that isotretinoin exposure has been responsible for a number of pregnancy terminations in recent years. If exposure to isotretinoin occurs during pregnancy, there is a high risk of a deformed infant or fetal death, even if the exposure is only for a short period. As a result of its teratogenicity, isotretinoin is contraindicated in women of childbearing potential unless an extensive list of conditions for prescribing are met. Medsafe is currently assessing the risk mitigation strategies used by the manufacturers of isotretinoin products in New Zealand.

(See *WHO Pharmaceuticals Newsletter No.2, 2007 for a risk management programme in the USA*).

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Lignocaine with Chlorhexidine

Risk of anaphylaxis

Australia. Health-care professionals have been reminded of the risk of anaphylaxis associated with the use of lignocaine with chlorhexidine gel, even when applied topically. It has been advised that users of local anaesthetic preparations should check which products contain chlorhexidine. Lignocaine 2% gel with chlorhexidine (0.05%) is an anaesthetic/antiseptic/disinfectant combination used as a lubricant for urology procedures and examination, and as symptomatic treatment of painful urethritis. Since 1990, the Therapeutic Goods Administration (TGA) has received 19 reports of suspected adverse reactions to lignocaine with chlorhexidine gel. Eleven of these were of anaphylaxis, some of them life threatening (no fatalities).

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009
(www.tga.gov.au).

Methylthionium chloride

Update on CNS toxicity with serotonergic antidepressants

UK. The MHRA has provided an update on the risk of central nervous system (CNS) toxicity associated with an interaction between methylthionium chloride (formerly called

methylene blue) and a serotonergic drug. Methylthionium chloride is approved for the management of drug-induced methaemoglobinaemia in adults.

Since the previous advice based on the review of 27 reports of CNS toxicity in the January 2008 issue of *Drug Safety Update* (see *WHO Pharmaceuticals Newsletter No.1, 2008*), additional cases of CNS toxicity have been reported in association with methylthionium. Five of the new cases involved parathyroid surgery. A further new case of CNS toxicity involved the use of methylthionium for the management of uncontrollable hypotension during cardiac surgery. In all those cases, the patients were being treated with either a selective serotonin reuptake inhibitor (SSRI) antidepressant or clomipramine. Use of methylthionium chloride is not approved in visualisation in surgical procedures or in the management of intractable hypotension.

The Summary of Product Characteristics for methylthionium chloride now mentions the possibility of CNS toxicity when used in patients who are being treated with serotonergic drugs. Features of toxicity include confusion, disorientation, agitation, expressive aphasia, altered muscle tone in limbs, hypoxia, ocular symptoms and depressed level of consciousness.

In view of the new reports, the MHRA has strengthened the advice for health-care professionals, including emphasis on approved indication. It is also advised that intravenous methylthionium chloride should be avoided in patients who have been treated recently with serotonergic antidepressants, including

SSRIs, clomipramine and venlafaxine.

Reference:

Drug Safety Update, MHRA, Volume 2, Issue 9, April 2009
(www.mhra.gov.uk)

Non-steroidal anti-inflammatory drugs

Interaction with over the counter medicines

New Zealand. Medsafe has emphasized the risk of interaction between Non-steroidal anti-inflammatory drugs (NSAIDs) and over-the-counter (OTC) medicines and the importance of advising patients about their use of OTC medicines when prescribing NSAIDs. According to *Prescriber Update*, the Centre for Adverse Reactions Monitoring (CARM) has identified four reports of serious adverse reactions with NSAIDs, including gastrointestinal bleed (requiring transfusion), gastric, duodenal and colonic ulcers, acute renal failure and haematemesis. The reports were in patients who had taken OTC ibuprofen in addition to prescribed diclofenac or, in patients who had taken excessive doses of OTC ibuprofen for extended periods.

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Non-steroidal anti-inflammatory drugs

reminder on Risk of renal failure and impairment

UK. The MHRA has alerted health professionals about the risk of renal failure associated with the use of non-steroidal

anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, saying that the Agency continues to receive case reports of renal failure in NSAID users. Prescribing information for NSAIDs includes warnings about renal impairment and renal failure, and advises that the risk of renal failure is highest in those with existing renal impairment.

According to the MHRA, in patients with conditions that cause renal hypoperfusion, prostaglandin production may be increased to maintain adequate renal blood flow. The adverse renal effects associated with NSAIDs are mainly mediated via inhibition of prostaglandin-induced vasodilation and can result in reduced renal blood flow. Patients with conditions such as hypovolaemia, congestive heart failure, liver cirrhosis, or multiple myeloma are at particular risk. Contributing risk factors include the current administration of medicines such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptors antagonists, and diuretics. NSAIDs may also produce direct toxic effects on the kidney. Adverse renal effects are generally reversible on discontinuation of NSAID treatment.

Health-care professionals have been advised to avoid the use of NSAIDs if possible with patients at risk of renal impairment or renal failure (particularly elderly people), and to consider other concomitant disease conditions or medicines that may precipitate reduced renal function when prescribing NSAIDs.

Reference:

Drug Safety Update, MHRA, Volume 2, Issue 10, May 2009
(www.mhra.gov.uk).

Phosphate containing laxatives

Risk of hyperphosphataemia and kidney damage

New Zealand. Medsafe has advised about the increased risk of acute renal failure associated with the use of oral phosphate containing laxatives prior to colonoscopy. According to the Agency, adverse reaction reports include end stage renal failure (requiring dialysis) and renal failure resulting in death. A review by the Medicines Adverse Reactions Committee concludes that significant risks exist, particularly renal damage and electrolyte imbalances such as hyperphosphataemia, hypokalaemia and hypocalcaemia, and renal damage typically takes the form of phosphate nephropathy.

Medsafe explains that risk factors for the development of renal damage following colonoscopy include prior dehydration and co-morbid conditions such as hypertension, congestive cardiac failure, diabetes mellitus, liver and renal impairment. Medicines that may predispose patients to phosphate nephropathy include non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics.

Medsafe has advised that, in order to reduce the risk of dehydration and hyperphosphataemia, patients should be encouraged to drink large quantities of fluid during bowel preparation. In addition, products containing alternative active ingredients should be considered for bowel preparation in patients at risk, the elderly and others unlikely to be able to maintain hydration.

(See WHO Pharmaceuticals Newsletter No.1, 2009 for alert on risk of acute phosphate nephropathy associated with the use of oral sodium phosphate products in the USA).

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Red yeast rice extract

Risk of myalgia

New Zealand. Medsafe has notified prescribers that there has been a report of chest pain, myalgia, elevated creatine kinase levels, and abnormal liver function tests in an individual who had taken a combination of red yeast rice extract, saw palmetto (*Serenoa repens*), coenzyme Q10 and multivitamins. Red yeast rice extract is an extract of red yeast (*Monascus purpureus*) grown on rice. It contains lovastatin, which is a naturally-occurring statin and can cause severe muscle problems (myalgia) leading to kidney impairment. The risk of myalgia is increased in patients taking other medicines such as itraconazole, ketoconazole and other statins, according to *Prescriber Update*.

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Selective serotonin reuptake inhibitors

Interaction with dextromethorphan

New Zealand. Medsafe has reminded prescribers of the potential interaction between selective serotonin reuptake inhibitors (SSRI) and

dextromethorphan, commonly included in cough and cold products, and pharmacists to ask about concomitant medicines when recommending cough and cold products. The Centre for Adverse Reactions Monitoring (CARM) has received a report of a patient taking citalopram who experienced a serotonin syndrome-type reaction following the use of an OTC medicine containing dextromethorphan. Medsafe explains that serotonin syndrome is a dose-dependent toxic state caused by excess serotonin within the central nervous system and is characterised by mental, autonomic and neuromuscular changes. Clinical features include confusion, agitation, hyperactivity sweating, tachycardia, ataxia, hypertonia and tremor.

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz).

Sodium valproate

Fetal malformations

Australia. Health-care professionals have been reminded that women of child-bearing age prescribed sodium valproate for any indication should be informed about the potential risks of the drug, including teratogenesis, and should be strongly advised, and periodically reminded, to maintain adequate contraception while taking this drug. Sodium valproate is well known to cause fetal malformations. Teratogenic risk appears to be dose-dependent and increases markedly at doses greater than 1100 mg/day in the first trimester.

According to the *Australian Adverse Drug Reactions Bulletin*,

since 1980, there have been 72 reports of babies born with malformations from mothers taking sodium valproate during pregnancy, including 18 of spina bifida, four of myelomeningocele and 13 of multiple malformations mainly involving the central nervous system. In most of these cases, sodium valproate was being used to treat epilepsy. Two recent reports describe fetal spina bifida and myelomeningocele in babies born to mothers taking sodium valproate for bipolar disorder.

Reference:

Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009
(www.tga.gov.au).

Varenicline

Reports of psychiatric reactions

New Zealand. Varenicline (Champix), which is used for smoking cessation, has been monitored by the Intensive Medicines Monitoring Programme (IMMP) since its introduction in New Zealand in 2007. In the interim analysis of results for 3389 patients in the first year of marketing (1 April 2007 to 31 March 2008), the IMMP identified 293 reports (for 284 patients) with 538 adverse events occurring while the patient was taking varenicline. The most frequently reported adverse events were psychiatric effects, with a total of 169 events (31% of all events). The most common psychiatric adverse events reported were depression (22 events), insomnia (22), sleep disturbance (13), fatigue (12), vivid/strange dreams (10), nightmares (10), and anxiety (9). There have also been four reports of depersonalization, four reports of mood swings, four of panic

attacks, and two of hypomania/mood elevation. According to the IMMP, out of the 22 reports of new-onset depression while taking varenicline, 15 were assessed as having a 'probable' relationship (i.e. there was evidence of positive dechallenge) with varenicline and seven were assessed as having a 'possible' relationship. Three of the patients who experienced depression while taking varenicline also reported suicidal ideation and in two cases this resolved on cessation of the medicine. A further 10 patients experienced a worsening or recurrence of existing depression while taking varenicline.

In addition, the IMMP identified six reports with symptoms which appear to be withdrawal effects following cessation of varenicline. Two patients experienced a withdrawal depression and one of these patients also experienced anxiety. In the other patients, withdrawal symptoms included agitation, mood swings, cravings, night sweats, insomnia, and taste disturbance. Prescribers have been alerted to risk of psychiatric reactions and withdrawal effects associated with varenicline and to advise patients accordingly. Prescribers are also reminded that patients may also experience psychiatric symptoms for many other reasons, including nicotine withdrawal.

(See *WHO Pharmaceuticals Newsletter No.1, 2009 for reports of psychiatric events with varenicline in Australia and Ireland, as well as reports in the WHO Global ICSR database*).

Reference:

Prescriber Update Vol. 30, No.2, May 2009
(www.medsafe.govt.nz)

Advisory Committee on Safety of Medicinal Products (ACSoMP) Recommendations from the Sixth Meeting, March 2009, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. Following is a summary of the recommendations from the Sixth Meeting.

Global Awareness of Medicine Safety

A CD-ROM is being prepared for different stakeholders in PV. The key message which is common for all is the concept of risk-benefit balance, and the fact that this can change as more information becomes available. As a new framework for action, three phases are proposed. Phase 1 is social marketing, phase 2 is identifying a medium for disseminating any developed messages, and phase 3 is creating social networking through patient's participation. Governments need to be made aware of this situation as well as the cost-effectiveness of having a PV system. Piloting the materials for the next stage of this work will help refine the key messages.

Recommendations/action

The Committee suggested that the CD-ROM should be piloted in order to assess its utility.

Developing a set of impact indicators specific to pharmacovigilance

Bench-marking and outcome assessment in pharmacovigilance was discussed in this session, which covered the rationale for PV indicators, broad and specific objectives, characteristics, types of indicators, data sources, and process of developing indicators. Structural indicators, process indicators and outcome (impact) indicators were discussed and the Committee agreed that both core and supplementary indicators should be developed.

Recommendation/action

A sub-group was assigned to continue developing a set of practical indicators for developing countries. A draft will be developed and discussed at the Annual Meeting of the National PV centres in Morocco in November. The final draft will be resubmitted to the next meeting of ACSoMP in 2010.

Developing a guideline for acute safety issues management

This session dealt with the management of acute safety issues by regulatory authorities. The major considerations were the evidence for decision-making after signal detection; analytical and methodological challenges; the optimal design and organization of a signal detection system; signal detection and public health; and risk communication. Several questions were posed including how people in developing countries react when regulatory decisions are made in developed countries with impact on their work; what is the basis of the decision and how do they prepare themselves for any potentially embarrassing public health crisis? The International Programme on PV suffers if acute safety issues are not handled properly.

Discussion

There are two issues to be considered separately. One is how and when to take action on an acute drug safety issue and the other is communicating i.e. sharing of information when action is taken so that others can understand and make their own decision. There is a need for a protocol to help in dealing with acute safety issues taking into consideration the limitation of the WHO ICSR (Individual Case Safety Reports) database in providing all the needed information. WHO should provide some guidance. National governments and regional agencies also have to assume some responsibilities. Confidentiality agreements regarding information exchange could be made by all members of the WHO International Drug Monitoring Programme, rather than bilaterally or in specific regions. Members agreed that ACSoMP can take the lead in designing a protocol on how and when to take action relating to an acute drug safety issues. However, when it comes to information sharing between regulators, the appropriate forum is the International Conference for Drug Regulatory Authorities (ICDRA).

Recommendations/ action

A recommendation should be made from ACSoMP to the planning committee for the next ICDRA to include a session on information sharing between regulators. A guideline for the management of acute safety issues will be prepared.

The International Network of Safe Medication Practice Centres

The International Medication Safety Network (IMSN) is a growing network of countries that are working together to promote safe medication practices. The group representing the network presented a case on why PV centres should be concerned with medication error reports. Medication errors are a system issue, and involve different regulatory bodies. There may be a reluctance to report medication errors because of litigation and punitive measures. There is a need to create an environment that will encourage reporting to understand "what caused the error" and "how to prevent the error" rather than "who caused the error".

Recommendations/action

A training workshop and / or a group activity should be organized at the Annual meeting of national PV Centres in Morocco, to share common concerns and objectives, and to facilitate collaborations between IMSN and PV networks.

Collaboration with the Expert Committee on the Selection and Use of Essential Medicines

A comprehensive draft guideline on safety information to be included with an application for inclusion (or deletion) of a medicine to (from) the WHO Model List of Essential Medicines (EML) was presented in this session. It outlined the difficulties involved in writing a new safety guideline, the structure of the proposed guideline and typical shortcomings of current applications. General issues were also mentioned including sources of information, general advice on the handling of safety information, drug administration, adverse drug reactions (ADRs) and references. It was considered whether every application for inclusion of a medicine on the EML should be accompanied by a risk management plan for the medicine involved. If so, these risk management plans should include suggestions for the management of any adverse drug reaction already known to be associated with the use of the specific medicine. It was also suggested that Cohort Event Monitoring (CEM) studies should accompany the deployment of any new medicine being proposed for mass administration in order to ensure that potential problems are quickly identified before large numbers of people are affected.

Recommendations/action

The current applications do not contain sufficient information to provide an adequate safety assessment. The safety component of most applications submitted to ACSoMP for assessment meet neither the proposed guidelines nor the current requirements. There is a need to establish new guidelines for the safety review of EML applications, both for applicants and for reviewers. ACSoMP will provide guidance and leadership in the development and adoption of these guidelines. The principles of the new guideline on safety evaluation of products proposed for inclusion in the EML should be complete, up-to-date, thorough, and scientifically valid,. These principles should be involved for all safety assessments for the EML. These views should be presented to the forthcoming meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines.

Opening access to signals

A paper was presented on opening the WHO ICSR database to the public and on the wider distribution of the 'Signal' document. In principle opening the WHO database to the public and consumers was agreed. However, the narrative should be excluded (in order to protect patient confidentiality) and a new caveat statement should be drafted. It was also agreed that publication in the scientific media was a way of promoting the PV activities spearheaded by WHO/UMC. The Committee also agreed that it would be acceptable to provide information with no narratives to academia to help with research provided there is declaration of interests and the usual caveats inserted. The paper will be revised accordingly and presented at the next meeting of the national PV centres. The subject of making the 'Signal' document more available will be discussed further.

A Global Strategy for best practice in pharmacovigilance

The broad outline of a global strategy for best practice in pharmacovigilance was presented. It is part of the overall WHO strategy for the next 5 years. The UMC 4-year plan should be aligned with it. The main objectives will be to provide an advocacy tool for stakeholders, to develop a plan for a health-systems approach to PV and to build cost-effective PV systems with broad scope to respond to questions for several health areas. The Committee was requested to discuss specific strategy elements and help identify a core group to lead the development of the strategy.

Recommendations/action

A sub-group of ACSoMP will develop the document further. This will then be circulated to other members of the Committee before finalizing the paper for presentation at the National PV Centres Meeting in November.

Leishmaniasis

The safety monitoring of drugs used in the leishmaniasis elimination programme in India, Nepal and Bangladesh was described including the assessment of the risk of preventable ADRs using surrogate markers, risk minimization including use of checklists of precautions and contraindications, use of patient cards, training of health-care workers and supervision, analysis of ADRs, and evaluation of PV activity. There are serious safety concerns about miltefosine an important drug which brings tremendous advantage in controlling the disease. The disease control programmes should work closely with the PV people to develop risk management and risk minimization plans.

Chagas Disease

WHO activities in the area of Chagas disease were presented. In 2007, WHO and Bayer Healthcare agreed on distributing 500 000 tablets free of charge of nifurtimox per year for Chagas disease. Chagas disease, which used to be found only in Latin America, is now present in other regions of the world including Europe and the Western Pacific mainly because of population movement. For example, in 2008, around 150 patients were diagnosed in Geneva with Chagas disease in the period of six months. There are two drugs available for Chagas disease: nifurtimox and benznidazole, both developed in the 1960s. In Bolivia, deaths have been reported in children related to the wrong use of nifurtimox. For benznidazole, WHO is in contact with a public Brazilian laboratory Laboratório Farmacêutico do Estado de Pernambuco - LAFEPE, manufacturer of the drug. WHO is trying to assist with the distribution of benznidazole and nifurtimox, both of which are in the WHO Essential Medicines List.

Even though nifurtimox and benznidazole were developed in the 60s, the available information on their safety is limited. It is important not only to implement PV but also to consider what kind of operational research needs to be implemented to ensure the collection, analysis and dissemination of safety information on these products, to patients and to health-care providers alike. Further discussions are necessary to determine optimal PV systems in these settings.

Vaccines

A dedicated vaccine safety specialist has been appointed at the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) to strengthen the signal detection process and improve the tools used for reporting vaccines. Activities are being undertaken to address key safety challenges with new vaccines, i.e. quality of safety data in individual countries, capacity to respond to crises, and quality of data at "global level" for signal detection and risk assessment. These include routine capacity strengthening, developing a global crisis management plan and strengthening a Global Network for the Post-marketing Surveillance (PMS) of newly pre-qualified vaccines. The Global Network for PMS of newly pre-qualified vaccines will provide data for these pre-qualified vaccines and will support the vaccine prequalification system with safety data in the post-marketing phase.

Other collaboration of the WHO vaccines and medicines safety departments and the UMC includes the development of a vaccine dictionary (part of the WHO Drug Dictionary) and an ATC classification for vaccines. The Global Advisory Committee on Vaccine Safety (GACVS) continues to provide support and oversight on all activities related to vaccine safety and acts as an independent advisory committee to the WHO. A member of ACSoMP serves on GACVS to ensure collaboration and sharing of information.

Malaria

A presentation was made on the rationale and need for PV of ACTs, collaboration between the malaria and medicines safety programmes in WHO, challenges at country, regional and global levels, and the way forward. The move to deregulate ACT as over-the-counter (OTC) medicines (thereby removing a barrier to treatment access) is a big challenge especially since home-based care is involved. The way forward is to promote risk management plans, to empower consumers, and to strengthen integration between PV and public health programmes.

The Affordable Medicines Facility for Malaria (AMFm) which seeks to lower the net cost of ACTs will expand availability to this effective treatment. This increase in availability should be accompanied by an expansion in the safety monitoring systems for these medicines in all settings and under all conditions of use. The first phase of the AMFm will be immediately rolled out in 11 countries, providing both a challenge and an opportunity to develop PV systems or to strengthen existing ones.

There are various initiatives by different organizations in the area of PV of antimalarials in particular, and tropical diseases in general. These activities should be coordinated and members suggested that WHO takes a leading role in coordinating these initiatives which involve several different players. ACSOMP should be informed of all the safety studies being undertaken so that it can provide independent scientific and technical advice to WHO and member countries. Future plans in WHO include a meeting with MMV (Medicines for Malaria Venture) and some other partners to try to develop a joint protocol and guidelines for the PV of antimalarials. Such joint meetings would ensure harmonization in the safety monitoring of antimalarials.

Recommendations/action

An ACSOMP member will help WHO by coordinating various ongoing initiatives in Africa.

HIV/AIDS

Methods to improve safety of antiretroviral medicines in the public health context, pharmacovigilance for ARVs including gaps and needs, and a pilot project for improving the safety of antiretrovirals (ARVs) were presented. There are different toxicities expected of drugs used for post-exposure prophylaxis of HIV and for drugs used in the management of patients living with HIV/AIDS. As more and more people stay on treatment, toxicities become an important issue to address. There is a need to identify the gaps in ART programmes including the need for additional definitions and newer methodologies for capturing data relating to toxicity on ARVs. Towards this, a pilot project that is being funded by the Bill and Melinda Gates Foundation will establish internationally agreed reporting tools, strengthen PV capacity in some countries, support key studies, and to coordinate the analysis of safety data on ARVs.

Discussion

Switching of patients from first to second line regimen has huge cost implications. The safety data on ARVs is very limited regarding second line regimen. For example, the pharmacokinetic details of protease inhibitors in children are not known. It is important to learn the reasons why patients are switched from first to second line ART. Subjective reasons possibly dominate the switching of patients and this must be avoided. Guidelines on management of adverse events and treatment limiting toxicities should be developed and disseminated to all countries. Given the issues of co-morbidity and drug interactions, collaboration with other programmes is important to ensure the safe use of ARVs.

Review of specific medicines - artesunate+amodiaquine (ASAQ)

Based on the paper "draft proposal for action", the safety issues on ASAQ were discussed. A meeting with DNDI and Sanofi-Aventis had been held as a result of which a Risk Management Plan for ASAQ has been produced by Sanofi-Aventis. Sanofi-Aventis is currently carrying out studies in Cote d'Ivoire on the real-life safety of its fixed dose combination of ASAQ. The weakness of the Sanofi-Aventis study design was discussed by ACSOMP. It appears several groups are planning to undertake active PV but without good planning. There are difficulties in proper engagement of some of the key personnel and organizations. Other drugs administered at the same time as ASAQ should also be considered.

Recommendations/action

ACSOMP members will review the Risk Management Plans submitted by Sanofi-Aventis and offer suggestions to WHO. In addition, a Consultant, currently reviewing some adverse events reported with ASAQ, will be requested to write a paper outlining the safety profile of ASAQ.

PV in Drugs of Dependence

E-mail discussions had been carried out about the use of pharmacovigilance data for the assessment of dependence and abuse potential of drugs of dependence. It was concluded that PV is one tool out of many for evaluating drug dependence liability and that a distinction should be made between ADRs from clinical trials and spontaneous reporting; that terms should not be defined too exactly as various terms can exist in parallel; it was

agreed that the DDD is the best standard to be used as the unit and it was agreed that various drug classes should be approached separately.

A presentation on “opioids, safety surveillance and risk management”, elaborating key challenges in the review of post-marketing safety information on opioids in the USA was also made. The challenges for drugs with abuse potential include the fact that we are not necessarily looking to identify something new. In addition quantifying the known adverse events including those which indicate abuse is very difficult. Geographic clustering of abuse and abuse potential may occur but reporting practices are variable. Many reports are based on active ingredients and not on specific products used. The intended patient is often not the person who experiences the harm. Understanding prescribing decisions is very hard in the post-approval setting. The number of persons at risk is often unknown. Information is not always available in a timely manner. There are also several important factors that are difficult to ascertain in spontaneous reports, including medication theft, overuse of prescribed medication, abuse/dependence/addiction, overdose, non-prescription use etc.

It is important to understand the abuse potential of new formulations. Definitions related to abuse potential should be broadened, to include also non-opioids. The legal classification for products is also an important issue to be tackled.

Hot topics of current interest

a) Dietary supplement

A dietary supplement has been associated with reports of serious adverse events. The product was sold for pain relief on the Internet. The Medical Products Agency (MPA) in Sweden has detected that the product contains nimesulide. Four cases of liver damages including one fatality were reported in Sweden in relation to the product. The MPA intends to seek information from the European Union (EU) about experience from other member countries. The information is available on the MPA website at www.mpa.se.

b) Intermittent Preventive Treatment of malaria in Infants (IPTi)

A brief summary on IPTi and the various policy processes was given. It was discussed whether ACSoMP should be involved in policy debates and assessment of safety in these areas. The absence of a strong input from the safety team on some of these issues came up for discussion.

Recommendations/action

ACSoMP, as set out in the terms of reference for this Committee, should take a lead in issues that have implications on the safety of medicines, to guide and advise WHO in these matters.

c) Update on Gardasil

An update on the safety issues of Gardasil was provided. GACVS has carried out a review of the safety of Gardasil but there is no evidence or etiological basis for any of the safety concerns highlighted. A knowledge of the background rates of the conditions involved will help. GACVS will revisit the issue. The whole Gardasil issue brings to the fore the importance of data and information sharing between regulatory authorities.

d) Rotavirus vaccine

Current issues related to rotavirus vaccine and reports of Kawasaki disease were presented. Three spontaneous reports of Kawasaki disease in Germany were reported in association with RotaTeq vaccine in 2008. The number of reported cases was not more than expected. Review of the cases does not suggest a causal relationship at present. No signal has yet arisen from post-marketing studies. It is important to highlight the wrong association of Kawasaki disease with rotavirus vaccine.

e) Cough and Cold preparations

The Medicines and Healthcare Products Regulatory Agency (MHRA) has reviewed antitussives, expectorants, decongestants and antihistamines. The data showed no robust evidence of efficacy. The expert advisory committee concluded that the risk benefit balance is unfavourable in children under six. The MHRA has taken regulatory action to contraindicate OTC cough and cold medicines containing these ingredients in children under six years. In addition, certain combinations that are illogical have been contraindicated in children under 12. The assessment reports will be published on the MHRA website.

Ethics in observational studies

The need for code of ethics for epidemiological and observational studies is being recognized globally. There are few documents discussing ethics in PV. The CIOMS document and the Indian Council of Medical Research (ICMR) document identify risks of epidemiological or observational studies, such as preventive intervention being denied. In New Zealand, public health investigations approved by competent authority and post-marketing surveillances using spontaneous reporting and prescription event monitoring are exempt from review by the ethics committee, whereas the guidelines (Volume 9A) governing medicinal products in the EU recommends that non-interventional post-authorization safety studies should be referred to an ethics committee. According to ICMR, informed consent is waived for research on publicly available information, research on anonymized biological samples and others. Ethical committee approval should be sought in all settings especially for CEM in countries where there are vulnerable populations. Individual consent may not be necessary or possible. A guidance document on ethics is needed, one that takes into consideration national and even local issues – CIOMS has developed a document on this.

In preparing a study protocol, it is important to think ahead and decide what data will be collected, for how long and how the data will be used immediately and in the future. The assumption that something is “for the public health good” should not prevent investigators from seeking ethical approval.

Internet Connectivity in Africa

A presentation on the WHO initiative called Africa Health Infoway (AHI) was made. Improving internet connectivity in Africa is the objective. The expected deliverables include health facilities being able to have access to health information, telemedicine, eLearning, disease surveillance, etc. Since WHO does not have a mandate for establishing infrastructure for the internet, a collaboration has been initiated between WHO and the International Telecommunications Union to set this up. There are also partnerships with regional organizations like the African Union Commission through which funding is being sought from the EU and other donors.

Discussion

There are several initiatives aimed at improving IT infrastructure in Africa, including an initiative called telemedicine task force, which involves the European Space Agency, the EU, African Union, WHO and others. This initiative proposes the use of satellite technology for e-health. ACSoMP asked for updates on the progress of this work. ACSoMP also asked how it can play an advocacy role and whether a letter from the Committee will help in advocacy. The utility of this project need to communicated to senior management, policy makers, donors etc.

Recommendations/ action

WHO medicines safety unit will cooperate with Africa Health Infoway in the following ways.

- An advocacy letter from ACSoMP will be sent to the Programme
- The PV programme tools (VigiFlow and CEMFlow) will be incorporated into the AHI plan
- Priority list of countries (to be supported by this initiative) will be identified
- Promotion of Africa Health Infoway in all workshops

Review of existing definitions

There is a lot of support on the concept of reviewing the existing definitions in pharmacovigilance. This topic was discussed at the Annual Meeting of National Centres in 2008. Signals and Adverse Reactions/Adverse Events are top priorities. During the last year, the CIOMS Working Group on Signal Detections has been moving on with new definitions. There are many people engaged in revision of definitions. ACSoMP was requested to give a firm view and guidance on whether and how WHO should lead this activity.

Discussion

WHO should take this activity forward because it has the mandate and the convening capacity to coordinate activities for developing global norms and standards. But it will be important to have the various stakeholders on board. Led by ACSoMP, the WHO Programme for International Drug Monitoring should prepare a set of definitions that are needed and relevant for the Programme.

Recommendations/ action

A concept paper will be drafted for the next Annual Meeting of National Centres in November. Uppsala Monitoring Centre will take the lead, supported by two other members of the ACSoMP

