No. 1, 2002

EDITORIAL

In November 2001 the 24th Annual Meeting of the National Centres participating in the WHO Programme for International Drug Monitoring met in Dunedin, New Zealand. Once again this was a most successful event with an agenda including such topics as BSE, How regulation affects medical practice, Benefit risk assessment and Pharmacovigilance and public health. In this issue you will find some excerpts from the report which is now available on request from WHO. These include a few of the Drugs of current interest which were discussed during the meeting and which we consider need to be publicised more widely. The other is the discussion article on the controversial analgesic metamizole sodium. We are publishing a personal opinion as to why it is still on the market in Brazil and the article provides a compelling argument for continuing postmarketing studies on older generic drugs.

Herbal medicines continue to be in the forefront for monitoring safety. WHO is in the process of developing Guidelines for Safety Monitoring of Herbal Medicines and in the future training courses will be offered to all interested parties.

WHO took part as an observer in the ICH meeting in Brussels in February where the topic of pharmacovigilance was once again on the agenda. New ICH guidelines on Periodic Safety Update Reports (PSURs) and case management and definitions will be developed. These guidelines should be of value to all countries.

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ARISTOLOCHIA

More products cancelled

Aristolochic acid is a toxin that can cause cancer, changes in human cells and end-stage kidney failure. The previous issue of the WHO Pharmaceuticals Newsletter (WHO Pharmaceuticals Newsletter Nos. 2 & 3, 2001) had published a summary of the American and Canadian alerts for products containing Aristolochic acid. The following section reports additional regulatory actions.

Australia. The product Longdan Qiegan Wan – 'Wetness Heat' Pill has been cancelled from the Australian Register of Therapeutic Goods following the detection of Aristolochic acid by Therapeutic Goods Administration (TGA) laboratory testing.

Canada. Health Canada has advised consumers about additional products that could contain Aristolochic acid. In previous warnings Health Canada requested manufacturers, importers and retailers to stop sale and remove from the shelves all products labelled to contain Aristolochia, Aristolochic acid, Stephania, Clematis, Akebia, Cocculus, Asarum or Mu Tong. This request is now being extended to include Bragantia, Diploclisia, Menispermum, Sinomenium, Vladimiria souliei and Soussurea lappa since these herbs may be used interchangeably with Aristolochia in traditional Chinese medicine.

***Reference**:*

1. *Therapeutic Goods Administration Media Release, 7 Dec 2001. Available from URL: http://www.health.gov.au*
2. *Health Canada Advisory, 5 Oct 2001. Available from URL: http://www.hc-sc.gc.ca*

CAPECITABINE

Interaction with anticoagulants

USA. FDA and Roche have added a black box warning and strengthened the precautions section in the label for capecitabine (Xeloda). Capecitabine is indicated in the treatment of colorectal and breast cancer. The labelling additions advise patients to have their anticoagulant response (international normalised ratio – INR or prothrombin time) monitored frequently if they are on concomitant capecitabine and oral coumarin-derived anticoagulant therapy. This warning follows the demonstration of a clinically important capecitabine (Xeloda)-warfarin interaction leading to significant increases in prothrombin time. The patient package insert has also been revised to reflect this new safety information.

Reference:

Media Release, 1 Nov 2001. Available from URL: http://www.fda.gov/medwatch/safety

DROPERIDOL

Strengthened warning section about cardiac arrhythmias

USA. The FDA has strengthened the warnings and precautions sections in the labelling for droperidol, a sedative used as a preanaesthetic medication in treating anaesthesia-induced nausea and for sedating agitated patients. The FDA action follows reports of QT prolongation and/or torsades de pointes at or below recommended doses of droperidol. Specific changes to the droperidol labelling include a black box warning intended to increase the physician's focus on the potential for cardiac arrhythmias during administration, and to consider use of alternative medications for patients at high risk for cardiac arrhythmias. Akorn Pharmaceuticals, the proprietary manufacturer of droperidol (Inapsine) has issued a letter advising healthcare professionals about these safety concerns.

Reference:

1. *'Dear Healthcare Professional' letter from Akorn Pharmaceuticals, 4 Dec 2001. Available from URL: http://www.fda.gov/medwatch/safety*
2. *FDA talk paper, 5 Dec 2001. Available from URL: http://www.fda.gov*

FLUTICASONE PROPIONATE

New advice for prescribing

UK. Prescribing advice for inhaled fluticasone propionate (Flixotide) has been updated to minimise the risk of systemic adverse effects that occur at high doses, the UK MCA has announced in Current Problems. The updated information includes the following new guidelines, which are to be included in the product information for all inhaled preparations of fluticasone propionate.

- The starting dosage should reflect the severity of the disease.
- The dosage should be gradually reduced to the lowest dosage at which the patient's asthma is effectively managed.
- Patients with mild asthma should start fluticasone propionate at a dosage of 100µg twice daily, while those with moderate-to-severe asthma should initially receive 250−500µg twice daily.
- More importantly, dosages > 500µg twice daily should only be prescribed to patients with severe asthma in whom an additional clinical benefit is expected and demonstrated by either an improvement in pulmonary function and/or symptom

control, or a reduced requirement for oral corticosteroids. Furthermore, only a consultant physician, or a general practitioner with appropriate experience in the management of asthma, should initiate such a dosage.

Reference:
Current Problems in Pharmacovigilance 27: 10, Aug 2001.

INFLIXIMAB

Clinical alert: worsening congestive heart failure

Canada, Europe, USA. Infliximab is a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease. Schering Canada and Centocor have issued a 'Dear Healthcare Professional' letter for infliximab (Remicade) through Health Canada's website warning about the use of the drug in patients with congestive heart failure (CHF)[(1)]. The letter advises that

- Infliximab therapy should not be initiated in patients with CHF
- Existing infliximab recipients with CHF should discontinue treatment if their CHF is worsening
- Treatment discontinuation should be considered for existing infliximab recipients with stable CHF and, if a decision is made to continue treatment, close monitoring of cardiac function should be undertaken.

The letter is based on the preliminary results of an ongoing phase II trial assessing the use of infliximab in patients with moderate to severe CHF which demonstrated higher incidences of mortality and hospitalisation for worsening heart failure in patients treated with the higher dose of 10mg/kg. Centocor will continue to acquire follow-up data from the study to provide more definitive recommendations to healthcare professionals in the future. The above safety information has also been disseminated via the website of the US FDA[(2)]. The European Agency for the Evaluation of Medicinal Products (EMEA) reinforced the above concerns through its public statements issued first in October 2001 and later, again in February 2002[(3,4)].

Reports in WHO-file: cardiac failure 10.

Reference:

1. *Media Release, 23 Oct 2001. Available from URL: http://www.hc-sc.gc.ca*
2. *'Dear Healthcare Professional' letter from Centocor, 18 Oct 2001. Available from URL: http://www.fda.gov/medwatch*
3. *EMEA Public Statement (CPMP/3257/01), 24 Oct 2001. Available from URL: http://www.emea.eu.int*
4. *EMEA Public Statement (CPMP/32/02), 1 Feb 2002. Available from URL: http://www.emea.eu.int*

INFLIXIMAB

Risk of infections

Worldwide. In the post-marketing spontaneous reporting for infliximab (Remicade), infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Up to the middle of 2001, 202 deaths had been reported. Nearly 50% of these were associated with infections. Up to 31 October 2001 approximately 130 cases of active tuberculosis with extra-pulmonary location were reported worldwide in patients treated with infliximab (Remicade). A 'Dear Healthcare Professional' letter from Centocor, the Marketing Authorisation Holder for infliximab (Remicade) was posted on the US FDA's website in October 2001 detailing labelling revisions for infliximab (Remicade) about tuberculosis (TB) and other serious infections including histoplasmosis, listeriosis and pneumocystosis reported with the use of infliximab. Centocor has added a black box warning about these opportunistic infections and revised the Warnings and Adverse Reactions sections in the product label. Centocor advises physicians to review the revised labelling for infliximab and to carefully assess the risks and benefits of initiating treatment with infliximab in patients who have lived in endemic regions.

The latest EMEA Public Statement on Infliximab issued in February 2002 also informs health professionals about the risk of infections including tuberculosis in patients undergoing treatment with inflixmab. The statement advises that:

- infliximab is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses or opportunistic infections;
- patients should be closely monitored for infections including tuberculosis before, during and after infliximab (remicade) therapy, in accordance with local recommendations;
- treatment with infliximab (remicade) must be discontinued if the patient develops serious infections or sepsis and that before starting treatment with infliximab all patients must be evaluated for both active and inactive (latent) tuberculosis. If active tuberculosis is diagnosed, infliximab therapy must not be initiated; if inactive (latent) tuberculosis is diagnosed, prophylactic anti-tubercular therapy must be started before initiating infliximab therapy.

The statement also informs patients that while infliximab (Remicade) continues to be an effective and safe medicine, it increases the risk of getting infections, including tuberculosis. Patients should inform their physician if they have had TB or

have been in close contact with a TB patient. In addition, patients receiving infliximab should report symptoms such as shortness of breath, swelling in the feet etc. as these may be signs of heart failure. In general, patients with a severe infection and/or moderate or severe heart failure may not be treated with infliximab.

Reports in WHO-file: infection (various kinds) 46; sepsis 39

Reference:

1. *'Dear Healthcare Professional' letter from Centocor, 5 Oct 2001. Available from URL: http://www.fda.gov/medwatch*
2. *EMEA Public Statement (CPMP/32/02), 1 Feb 2002. Available from URL: http://www.emea.eu.int*

ITRACONAZOLE

High dose regimens may precipitate heart disorders

UK. The UK Medicines Control Agency (MCA) has highlighted that long courses and high-dose regimens of itraconazole (Sporanox) may predispose patients to heart disorders. Also, elderly patients, those with pre-existing heart disorders or risk factors for heart failure, and those receiving concomitant calcium channel antagonists may also be at an increased risk, the agency says. Since the licensing of oral formulations of itraconazole in the UK in 1989, 1 report of heart failure that was suspected to be induced by the agent has been received by the MCA. Meanwhile, worldwide, 75 spontaneous reports of suspected oral itraconazole-induced heart failure, and 63 reports of oedema suggestive of heart failure with oral itraconazole, have been made. Supportive evidence of a negative inotropic effect of itraconazole has been provided by some of these reports. IV formulations of itraconazole, which have been marketed in the UK since earlier this year, were associated with asymptomatic reductions in left ventricular function in a recent study, the agency reports.

The agency says that while the available evidence suggests that the risk of heart failure with short courses of itraconazole is low in healthy, young patients, prescribers should exercise caution when prescribing the drug to at-risk patients. Amendments to the product information of all itraconazole formulations have been made to reflect this information.

Reports in WHO file: cardiac failure 30, cardiac failure right 5, oedema 86, oedema peripheral 209, oedema generalized 10

***Reference**:*

Current Problems in Pharmacovigilance 27: 11-12, Aug 2001.

LEVO-NORGESTREL

Emergency contraception to be made available over the counter

New Zealand. New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) has indicated that the emergency contraception containing levo-norgestrel is to be made available for sale over-the-counter by Registered nurses and pharmacists. Emergency contraception, often referred to as the morning after pill, is used to prevent pregnancy within 72 hours of unprotected sexual intercourse. This decision will make emergency contraception more readily available to women with the aim of reducing the number of unintended pregnancies and abortions. The Ministry of Health is working with the Nursing Council and Pharmaceutical Society to ensure the systems are in place to allow this over-the-counter sale by late 2001, early 2002. The emergency contraceptive pill has already been made available over-the-counter in a number of countries including France, the United Kingdom, Norway and parts of Canada.

Reference:

Media Release, 5 Oct 2001. Available from URL: http://210.48.125.104/moh.ns

LIPOKINETIX

Reports of liver injury

USA. The FDA has received multiple reports of persons who developed liver injury or liver failure while using Lipokinetix, a dietary supplement (for promoting weight loss) marketed by Syntrax Innovations Inc. Lipokinetix contains phenyl-propanolamine (PPA), caffeine, yohimbine, diiodothyronine, and sodium usniate. The US FDA has advised consumers to immediately stop using the product and to consult their physician if experiencing symptoms of nausea, weakness or fatigue, fever, abdominal pain, or any change in skin colour. The FDA has also alerted physicians to the possible health risks with Lipokinetix.

Reference:

1. *CFSAN warnings and safety info webpage, 20 Nov 2001. Available from URL: http://www.cfsan.fda.gov*
2. *'Dear Healthcare Professional' letter, 20 Nov 2001. Available from URL: http://www.fda.gov/medwatch/safety*

KAVA – KAVA

Piper methysticum and concerns of liver injury

Germany, Switzerland, UK, USA. Products containing herbal extracts of Kava-kava (Piper methysticum) have been implicated in cases of serious liver toxicity, including hepatitis, cirrhosis and liver failure in Germany and Switzerland. Regulatory authorities in Germany and elsewhere in the European Union are reviewing the evidence carefully before deciding on the appropriate regulatory action. (For specific regulatory actions taken in Switzerland please refer to the

section under 'Drugs of Current Interest'). The Medicines Control Agency (MCA), UK in the meanwhile has encouraged the voluntary move by several UK companies to suspend the marketing of the product as a precautionary measure. The US FDA is investigating whether the use of kava-containing dietary supplements in the US poses similar public health concerns. At least one report of hepatic failure requiring liver transplantation in a previously healthy young female has been received by the agency.

Reference:

1. *MCA press releases, 21 Dec 2001. Available from URL: http://www.mca.gov.uk*
2. *FDA letter, 19 Dec 2001. Available from URL: http://www.fda.gov/medwatch/safety*

TOLCAPONE

Renewal of suspension of marketing authorisation

Europe. Tolcapone (Tasmar) is indicated for the adjunctive treatment of Parkinson's disease. In August 1997 the European Commission granted Roche Registration Limited a marketing authorisation for tolcapone (Tasmar). The scientific committee of the European Agency for the Evaluation of Medicinal Products suspended Roche's marketing authorisation for tolcapone (Tasmar) in 1998 due to increasing concerns over reports of severe hepatotoxicity. The suspension order was later renewed in the years 1999 and 2000. On 19 September 2001, having reviewed the evidence submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, and with a prospective trial over comparable treatment in progress, the committee has recommended renewal of the suspension of the marketing authorisation for a further year. This suspension could be re-evaluated when the results of the prospective study become available.

Reference:

EMEA Press Release CPMP/2986/01, 26 Sept 2001. Available from URL: http://www.csmwm.org/safety_issues.htm

TOPIRAMATE

Warning about ocular syndrome (acute myopia and secondary angle closure glaucoma)

Canada, USA. The warnings and precautions sections in the label of topiramate (Topamax) tablets and sprinkle capsules have been strengthened to include information about an ocular syndrome that can occur in patients receiving topiramate. A post-marketing surveillance in over 825, 000 patients has revealed that topiramate, an adjunctive therapy for adults and paediatric patients with seizure disorders, can produce secondary angle closure glaucoma characterised by ocular pain, acute myopia and increased ocular pressure. As on 17 August 2001, 23 cases of the ocular syndrome had been reported in patients receiving topiramate, including 1 case in a paediatric patient. The primary treatment of the ocular syndrome is discontinuation of topiramate. If left untreated, serious sequelae, including permanent vision loss, may occur. Janssen-Ortho Inc., Canada and Ortho-McNeil Pharmaceutical, Inc. U.S.A. have sent out letters briefing healthcare professionals about additions on the ocular effects in the product label for topiramate (Topamax). In the 'Precautions-information for Patients' section, patients receiving topiramate have been advised to seek immediate medical attention if they experience blurred vision or periorbital pain.

Reports in WHO-file: vision normal 34, blindness 3, blindness temporary 2, glaucoma 10, diplopia 5, eye pain 2, myopia 1

Reference:

1. *'Dear Health Professional' letter by Janssen-Ortho Inc., Canada, 13 Sept 2001. Available from URL: http://www.hc-sc.ca/*
2. *'Dear Health Professional' letter by Ortho-McNeil Pharmaceutical Inc., U.S.A., 26 Sept 2001. Available from URL: http://www.fda.gov/medwatch/safety/*

BLOOD PRODUCT INFUSIONS

Risk of fatal acute lung injury

USA. The US FDA has issued a 'Dear Colleague' letter outlining the risk of transfusion-related acute lung injury (TRALI) with the use of blood products, particularly those that contain plasma. The agency notes that since the first report of TRALI resulting in death in 1992, 45 more reports of fatal TRALI have been received by the Centre for Biologics Evaluation and Research. TRALI is now believed to be the third commonest cause of infusion-related deaths. Also, the number of nonfatal cases of TRALI associated with blood products reported to MedWatch, or as Biological Product Deviation reports, is on the increase, the agency says, but adds that this may be due to 'better recognition and reporting of events'. Also, the agency points out that the full scope of TRALI is not known, due to misdiagnosis and/or under-reporting.

The majority of the fatal cases of TRALI involved transfusions of fresh frozen plasma, the agency says, with whole blood, packed RBC, cryoprecipitate, platelet concentrates, apheresis platelets and occasional IV immunoglobulin transfusions also typically implicated. Furthermore, donors most frequently linked with cases of fatal TRALI were multiparous women and were antihuman-lymphocyte antigen-positive or antigranulocyte antibody-positive; 1 or both of these antibody types have been evident in 89% of reported cases of TRALI. Characteristics of transfusion recipients that may predispose to TRALI include surgery, active infection, massive transfusion and cytokine therapy that activates pulmonary endothelium and primes the patient's WBCs. It has been hypothesised that TRALI is a combination of 2 independent insults, namely, the patient's clinical status and the presence of anti-WBC antibodies.

Reference:
Media Release, 13 Aug 2001. Available from URL: http://www.fda.gov

CLOZAPINE, OLANZEPINE, QUETIAPINE, RISPERIDONE

Atypical antipsychotics and glucose metabolism disorders

Canada. Based on reports of atypical antipsychotic-associated glucose metabolism disorders received by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), the Canadian Bureau of Licensed Product Assessment suggests that glucose metabolism monitoring may be useful in some patients upon the initiation and titration of antipsychotics, with continued monitoring on a regular basis thereafter. As at 7 June 2001, the CADRMP had received 37 reports of suspected glucose metabolism disorders associated with use of clozapine, olanzapine, quetiapine and risperidone (see table). The affected patients were aged 11–78 years and had been receiving treatment for between 118 days and 6.5 years (≤ 5 months in 17 cases). They were receiving treatment with clozapine 100–775 mg/day (n = 17), olanzapine 7.5–30 mg/day (10), quetiapine 300–700 mg/day (3) and risperidone 1–6 mg/day (7).

Of the 37 reported cases, 10 cases of ketoacidosis were reported, among which 3 fatalities occurred. Also, among the 35 reports in which hyperglycaemia was noted, 24 were considered to be new-onset diabetes mellitus. In one of these reports, the patient developed diabetes 2 weeks after an overdose of risperidone. In the 2 reports received of hypoglycaemia, the patients had a history of diabetes.

Clozapine, olanzapine, quetiapine and risperidone were launched in Canada in 1991, 1996, 1997 and 1993, respectively.

Glucose metabolism-related adverse reactions reported in association with antipsychotics in Canada*

Type of reaction	Number of reported cases			
	Clozapine	Olanzapine	Quetiapine	Risperidone
Diabetes mellitus	*8*	*2*	*1*	*1*
Diabetic ketoacidosis	*5***	*3*	*2*	*0*
Diabetic coma	*0*	*2*	*0*	*0*
Hyperglycaemia	*4*	*3*	*0*	*3*
Hypoglycaemia	*0*	*0*	*0*	*2*
Labile blood glucose level	*0*	*0*	*0*	*1*

* Only the most significant adverse reaction term is included for each report.
** One of these cases also involved diabetic coma.

Reference:
Canadian Adverse Drug Reaction Newsletter 11: 2-4, Oct 2001.

DESOGESTREL/ GESTODENE ORAL CONTRA-CEPTIVES

Low risk of venous thromboembolism

Europe. The EMEA Committee for Proprietary Medicinal Products (CPMP) has published the outcome of its assessment on the risk of venous thromboembolic events (VTE) associated with the use of so called 'third generation' combined oral contraceptives (COCs) containing the progestins desogestrel or gestodene. The

CPMP assessment is the result of an ongoing review which began in 1995 based on epidemiological studies and studies on blood clotting mechanisms. All available information up to mid-September 2001 has been taken into account. The conclusions are as follows. While there appears to be a small increase in the risk of VTE with the use of contraceptives containing desogestrel or gestodene (relative risk in the range of 1.5 to 2.0 versus levonorgestrel containing contraceptives), especially in the first year that a woman starts using the oral combined contraceptive, the overall balance of benefits and risks remains favourable, as with all combined oral contraceptives. As such there is no reason for women currently using any brand of a COC to stop taking it on the basis of these findings. Contraindications for the use of combined oral contraceptives include a history of or existing VTE diseases and a history of or recent myocardial infarction or stroke. Known risk factors to take into account while prescribing combined oral contraceptives include obesity, the post-partum period, recent surgical operation and family history of venous thrombosis.

The CPMP, after having considered all options of safety measures, recommends amendment of the relevant sections of the prescribing information of national marketing authorisations to reflect the outcome of

DIGOXIN

Increased toxicity following P-glycoprotein inhibition

Australia. The potential for P-glycoprotein to cause drug interactions has been highlighted by the Australian Adverse Drug Reactions Advisory Committee (ADRAC). The committee says that it is now known that P-glycoprotein transports digoxin, but is inhibited by clarithromycin, and several case reports have been published in which blood digoxin concentrations have been increased during treatment with this agent and concomitant macrolide antibacterials.

ADRAC says that it has received 2 reports of digoxin toxicity in patients who were receiving digoxin 250 µg/day and concomitant roxithromycin. One report involved a 76-year-old woman who developed symptoms of digoxin toxicity 4 days after starting roxithromycin 300 mg/day. The second report involved an 80-year-old woman who developed malaise, vomiting and confusion 9 days after roxithromycin was added to her treatment regimen which included digoxin. Her digoxin concentration was 6.3 nmol/L. The digoxin dosage in both patients was high for their age, and this may have put them at greater risk of toxicity, notes ADRAC.

ADRAC says that both the above cases are consistent with

substrates for this glycoprotein include cyclosporin, fluoroquinolones, quinidine and ranitidine, while inhibitors include diltiazem, verapamil and macrolide antibacterials.

Reference:

Australian Adverse Drug Reactions Bulletin 20: 11, Aug 2001. Available from URL: http://www.health.gov.au

DTaP VACCINE BOOSTERS

Extensive limb swelling

Australia. Extensive limb swelling appears to occur with equal frequency with diphtheria, tetanus and pertussis vaccines that contain whole cell pertussis antigens (DTwP) and acellular pertussis antigens (DTaP), reports the Australian Adverse Drug Reactions Advisory Committee (ADRAC). Between November 1997 and June 2001, ADRAC received 331 reports of adverse reactions associated with DTaP vaccine administration. Of these, 103 described reactions at the injection site in children aged ≥ 18 months, while only 37 such reactions were reported in children aged < 18 months.** Among the 103 reports in children in the older age group, 48 reports described extensive limb swelling or included at least 1 measurement of swelling > 10cm. From these 48 reports, it was deduced, based on the patients' ages, that 37 and 11 were associated with a fourth and fifth DTaP vaccine