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### **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.

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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 Pharma-

ceuticals, 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)<sup>(1)</sup>. 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<sup>(2)</sup>. The European Agency for the Evaluation of Medicinal Products (EMA) reinforced the above concerns through its public statements issued first in October 2001 and later, again in February 2002<sup>(3,4)</sup>.

*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. *EMA Public Statement (CPMP/3257/01), 24 Oct 2001.*  
Available from URL:  
<http://www.emea.eu.int>
4. *EMA 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,

listerosis 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 EMA Public Statement on Infliximab issued in February 2002 also informs health professionals about the risk of infections including tuberculosis in patients undergoing treatment with infliximab. 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 levonorgestrel 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 Syntrox Innovations Inc. Lipokinetix contains phenylpropanolamine (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:**

EMA Press Release CPMP/2986/01, 26 Sept 2001. Available from URL:  
[http://www.csmwm.org/safety\\_issues.htm](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, OLANZAPINE, 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 ( $\leq 5$  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 CONTRACEPTIVES

### 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 this scientific evaluation. The public assessment report is available together with information for users and health-care professionals on the website of the EMEA.

#### Reference:

1. EMEA Position Statement (EMEA/CPMP/2250/01), 28 Sept 2001.  
Available from URL: <http://www.emea.eu.int>
2. Dear Healthcare Professional Letter on 3rd Generation COCs, 28 Sept 2001.  
Available from URL: <http://www.emea.eu.int>

## 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 roxithromycin-induced P-glycoprotein inhibition resulting in increased absorption of digoxin from the gastrointestinal tract, as well as decreased renal excretion of this drug. The committee points out that P-glycoprotein is a drug transporter pump in the intestines and the kidneys; in the intestines it pumps drugs back into the intestinal lumen. ADRAC notes that prescribers should be aware of the potential for drug interactions by inhibition of P-glycoprotein. The committee advises that other common

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 dose, respectively. Also, for 7 of the 48 reports, the patient outcome was unknown and 14 were described as 'not yet recovered', while the limb swelling in the remaining cases resolved without sequelae. ADRAC estimates that the incidence of limb swelling following receipt of DTaP vaccine boosters is approximately 2%. The committee reports that, according to a recent study, the incidence of limb swelling following receipt of DTaP vaccine is also approximately 2%.



ADRAC notes that insufficient data exist to determine the risk of developing limb swelling after receipt of a fifth DTaP vaccine dose among children who experienced such a reaction after their fourth dose. However, it points out that pertussis is still present in the community. Therefore, as limb swelling following vaccination resolves without sequelae, it recommends that children who experience limb swelling following their fourth DTaP vaccine injection be offered a fifth dose, although their parents should be advised of the risks. The Australian Technical Advisory Group on Immunisation has endorsed this recommendation.

\*\* In Australia, it is recommended that children receive their fourth dose of DTaP vaccine at the age of 18 months, and their fifth dose at the age of 4 years.

**Reference:**

*Australian Adverse Drug Reactions Bulletin 20: 10, Aug 2001.*  
Available from URL:  
<http://www.health.gov.au>

## EPOETIN ALFA

### Reports of pure red blood cell aplasia

**Canada, U.K.** Epoetin alfa is used in the treatment of anaemia associated with chronic renal failure (CRF), cancer chemotherapy, autologous blood donation, and during major elective orthopaedic surgery. Cases of pure red blood cell aplasia (PRCA) have been reported in CRF patients treated with epoetin alfa (Eprex) in Canada as well as in UK. Typically, following months to years of initiation therapy, patients developed sudden worsening of anaemia unresponsive to increasing doses of epoetin alfa or any other erythropoietin and became transfusion dependent. Physicians are therefore advised to monitor clinical response to epoetin alfa. In patients developing sudden lack of

efficacy or worsening of anaemia, typical causes of non-response (e.g., iron, folate and vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss and haemolysis) should be investigated. If PRCA is suspected and no cause can be identified, testing for erythropoietin antibodies should be considered and therapy with epoetin alfa must be discontinued immediately. Patients should not be switched to another erythropoietin, other causes of PRCA should be excluded, and appropriate therapy should be instituted. Janssen-Ortho Inc., the manufacturer of epoetin alfa (Eprex) has issued a 'Dear Healthcare Professional' letter reflecting this updated safety information. The Summary of Product Characteristics (SPC) has been revised to include relevant warnings, precautions and adverse reaction statements.

*Reports In WHO-file: pure red cell aplasia 11*

**Reference:**

1. *Media Release, 19 Nov 2001.*  
Available from URL:  
<http://www.mca.gov.uk>
2. 'Dear Healthcare Professional' letter by Janssen-Ortho Inc. and Ortho Biotech., 26 Nov 2001.  
Available from URL:  
<http://www.hc-sc.gc.ca>

## GLITAZONES

### Important safety reminder

Serious hepatic and cardiovascular adverse drug reactions with rosiglitazone, an oral anti-diabetic drug were discussed in the previous issue of the newsletter (WHO Pharmaceuticals Newsletter, Nos. 2&3, 2001). The following section details more safety related information on the drug.

**Canada.** Health Canada has reminded patients that oral anti-diabetic medications belonging to a class known as thiazolidinediones or glitazones can cause fluid retention which can

progress to congestive heart failure. Patients who develop oedema, shortness of breath, weakness, fatigue or excessive weight gain should inform their physician immediately and the treatment of these patients should be re-evaluated. If the symptoms are due to congestive heart failure, the medication should be discontinued. This is consistent with the safety information provided when rosiglitazone (Avandia) and pioglitazone (Actos), two glitazone products, were launched in Canada last year. The present advisory has been issued to reinforce the safety concerns following a review of current safety information and medical literature. The advisory is in addition to letters issued by the manufacturers of these glitazones to health care professionals reminding them of the above mentioned safety issues.

**UK.** The UK Medicines Control Agency (MCA) has also issued a reminder of the key safety issues, important contraindications and precautions regarding the use of the two glitazones. Thus far, the MCA has been made aware of 249 and 17 adverse reactions associated with rosiglitazone and pioglitazone respectively; the overall number of prescriptions issued for these agents since their launch is 148, 000 and 16, 000 respectively. The most frequently reported adverse reactions are vomiting, palpitations, headache, pruritus, diarrhoea, oedema, dyspnoea, liver disorders, muscle cramps, bodyweight increase, dizziness and hypercholesterolaemia. The MCA notes that rare reports of hepatocellular dysfunction have been reported with both drugs but a causal relationship has not been established. The agency also draws attention to the fact that these drugs are contraindicated in the following patient groups:

- those with, or a history of, heart failure

- those with liver dysfunction
- those who are taking insulin.

The MCA emphasises that patients who receive either drug should have their liver enzyme levels monitored before initiation of therapy, every 2 months for the next 12 months and periodically thereafter. Patients whose ALT level increases to  $\geq 3$  times the upper limit of normal should be reassessed as soon as possible, and if this elevation persists, treatment with the drugs should be terminated.

*Reports in WHO file: cardiac failure - rosiglitazone 154, pioglitazone 84; pulmonary oedema - rosiglitazone 28, pioglitazone 11; hepatocellular damage - rosiglitazone 14, pioglitazone 13; hepatic necrosis - rosiglitazone 4, pioglitazone 5; hepatitis - rosiglitazone 46, pioglitazone 17*

**Reference:**

1. Advisory from Health Canada, 30 Nov 2001.  
Available from URL: <http://www.hc-sc.ca>
2. 'Dear Healthcare Professional' letter from Eli Lilly Canada Inc., 6 Nov 2001.  
Available from URL: <http://www.hc-sc.ca>
3. 'Dear Healthcare Professional' letter from GlaxoSmithKline, 13 Nov 2001.  
Available from URL: <http://www.hc-sc.ca>
4. Current Problems in Pharmacovigilance 27: 11, Aug 2001.

**INHALED CORTICOSTEROIDS**

**Use lowest effective dose in children**

**New Zealand.** The New Zealand Medicines Adverse Reactions Committee (MARC) recommends that prescribers evaluate the risks and benefits of the use of inhaled or intranasal corticosteroids in children, and prescribe the lowest effective dose, reports Medsafe.\* These recommendations were made in response to the findings of recent studies, which

demonstrated that growth suppression can occur with long-term exposure to such medication. Medsafe refers to 2 long-term, controlled studies that found that growth in children receiving inhaled or intranasal corticosteroids was retarded by approximately 1cm, mainly during the first year of treatment. In one of these studies, it was also found that initial growth retardation was significantly correlated with a younger age. The MARC advises prescribers to be aware of the cumulative effect of co-prescribing corticosteroids with different routes of administration. If growth retardation occurs, an alternative treatment to corticosteroids should be considered.

\*Medsafe is New Zealand's Medicines and Medical Devices Safety Authority.

**Reference:**

- Media Release, Sept 2001.  
Available from URL: <http://www.medsafe.govt.nz>

**ISONIAZID, PYRAZINAMIDE, RIFAMPICIN**

**Reports of liver disorders**

**Canada.** A number of reports of liver disorders associated with the antitubercular agents rifampicin, isoniazid and pyrazinamide have been received by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), report authors from the Canadian Bureau of Licensed Product Assessment. As at 18 May 2001, 420 reports of suspected liver disorders associated with these 3 anti-tubercular agents had been received by the CADRMP (see table). Healthcare professionals are reminded of the importance of testing for liver disorders in patients receiving any anti-tubercular regimen. The article also points out that it is essential that patients are advised to remain vigilant for the development of any symptoms

suggestive of hepatitis, and to discontinue their regimen and consult a physician at once if such symptoms occur.

**Reports of liver disorders associated with isoniazid, pyrazinamide and rifampicin received by the CADRMP\***

Anti-tubercular regimen	Total number of reports	Number of fatalities
Isoniazid	258	7
Pyrazinamide	4	0
Rifampicin	27	1
Isoniazid + pyrazinamide	1	1
Isoniazid + rifampicin	110	6
Pyrazinamide + rifampicin	1	0
Isoniazid + pyrazinamide + rifampicin	19	0

\* Canadian Adverse Drug Reaction Monitoring Program

**Reference:**

- Canadian Adverse Drug Reaction Newsletter 11: 1, Oct 2001.

**LAMOTRIGINE**

**Dispensing errors due to name confusion**

**USA.** The FDA has alerted pharmacists and healthcare professionals of continuing reports of dispensing errors due to name confusion involving antiepileptic tablets lamotrigine (Lamictal) and other medications, most commonly Lamisil, lamivudine, Ludiomil, labetolol and Lomotil. GlaxoSmithKline has developed materials and suggestions for pharmacists and physicians to help prevent dispensing errors. The materials include a 'shelf shouter' for pharmacists that will help differentiate Lamictal from other stocked merchandise. A patient-information tear sheet is also included to be given to patients when prescriptions are filled, facilitating communication between the dispenser and the patients, ensuring that patients receive the correct medication.

**Reference:**

1. 'Dear Healthcare Professional' letter by GlaxoSmithKline,

6 Dec 2001.

Available from URL:

<http://www.fda.gov/medwatch/safety>

2. 'Dear Pharmacist' letter by GlaxoSmithKline, Aug 2001.

Available from URL:

<http://www.fda.gov/medwatch/safety>

## LEVOFLOXACIN

### Reports of adverse reactions

**Belgium.** Levofloxacin (Tavanic) has been associated with a number of adverse reactions, including 12 cases of tendinitis, which have been reported to the Belgian centre for pharmacovigilance since the drug's launch in August 2000. Of the 12 reports of levofloxacin-associated tendinitis, 6 cases involved tendon rupture. Also, in 5 cases, concomitant corticosteroid therapy may have been a contributing risk factor. The mean age of the patients was 74 years, and it appears that the risk of tendinitis with levofloxacin therapy increases with age. The centre has also received 8 reports of allergic reactions with levofloxacin, including 7 of angioneurotic oedema and 1 of anaphylaxis.

*Reports in WHO file:* tendinitis 255, tendon disorder 268, tendon rupture 49, anaphylactic shock 27, anaphylactoid reaction 102, angioedema 61

**Reference:**

*Folia Pharmacotherapeutica* 28: 76, Aug 2001.

## LINEZOLID

### Reports of haematological disorders

**UK.** Since its launch in the UK in January 2001, 12 reports of haematological disorders associated with linezolid (Zyvox) have been received by the UK Medicines Control Agency (MCA). These reports have included thrombocytopenia, anaemia, leucopenia and pancytopenia. The MCA says that bone marrow suppression is a recognised

adverse effect of linezolid, and that close weekly monitoring is recommended in the following patients:

- those who receive > 10–14 days therapy
- those with existing bone marrow suppression
- those who are receiving other drugs that may adversely affect haemoglobin levels, platelet function or blood counts
- those with renal insufficiency.

The MCA advises that treatment with linezolid should be discontinued in any patient who develops significant bone marrow suppression, unless continued treatment is deemed essential; in such cases, intensive monitoring should be undertaken with appropriate management strategies implemented.

*Reports in WHO file:*

thrombocytopenia 80, anaemia 52, leucopenia 12, granulocytopenia 7, marrow depression 9, pancytopenia 16

**Reference:**

*Current Problems in Pharmacovigilance* 27: 14, Aug 2001.

## MMR vaccine

### Serology tests before giving second dose if ITP occurs

**UK.** The UK CSM has recommended that patients who develop idiopathic thrombocytopenic purpura (ITP) within 6 weeks of receiving their first dose of measles, mumps and rubella (MMR) vaccine undergo a serological evaluation prior to receiving a second dose. The second dose is recommended where the patient is not fully immune against measles, mumps and rubella infections. These recommendations, which have been published on the website of the UK MCA, were made after the CSM reviewed all the available evidence on MMR

vaccine and ITP. Particular attention was given to the risk/benefit balance associated with giving a second dose of MMR vaccine to patients who developed ITP within 6 weeks of their first dose of the vaccine. The MCA reports that, according to a recently published study, the absolute risk of developing ITP after receipt of a first MMR vaccination is 1/22 300 cases (with 2/3 ITP cases attributable to MMR vaccine); this is lower than the risk of developing ITP with wild measles (common) or rubella infections (1/3000 cases). The report also points out that the MMR vaccine product information is currently being revised to reflect the recommendations of the CSM.

*Reports in WHO file:* purpura thrombocytopenic 133

**Reference:**

*Current Problems in Pharmacovigilance* 27: 15, Aug 2001.

## NITRO-FURANTOIN

### Peripheral neuropathy

**Australia.** The awareness of nitrofurantoin-associated peripheral neuropathy, which is a well-established adverse effect of this agent, may be declining, says the Australian Adverse Drug Reactions Advisory Committee (ADRAC). A recently published case report of this complication has prompted the committee to remind prescribers to exercise caution with the use of nitrofurantoin in the elderly, patients with renal impairment, and patients who require a long period of treatment. It adds that the risk of developing peripheral neuropathy during nitrofurantoin therapy may be reduced by paying particular attention to the use of the minimum effective dose. Additionally, prescribers are advised that nitrofurantoin therapy should be discontinued if symptoms suggestive of peripheral neuropathy occur.

Of the 18 reports of nitrofurantoin-associated periph-

eral neuropathy received by ADRAC since 1978, none were reported during 1990–1997, but 3 have been reported in the last 4 years. 15 of the reports have involved elderly women, nitrofurantoin dosages have ranged from 100 to 400 mg/day (median 250 mg/day), and the duration of treatment until identification of the neuropathy ranged from 3 weeks to > 12 months. Only 4 of the affected patients had recovered at the time their case report was submitted to ADRAC.

*Reports in WHO file: neuropathy 221, neuritis 159*

**Reference:**

*Australian Adverse Drug Reactions Bulletin 20: 11, Aug 2001.*

Available from URL:

<http://www.health.gov.au>

## NONACOG ALFA

### Further studies for additional data

**Europe.** The Committee for Proprietary Medicinal Products (CPMP) at the European Medicines Evaluation Agency (EMA) is of the opinion that there are serious deficiencies in the pivotal clinical studies on the safety issues for nonacog alfa (BenefIX), a human recombinant factor IX product used in treating haemophilia B patients. The Committee considers that the benefit/risk balance for the treatment and prophylaxis of bleeding in previously treated patients is adequate but that the data on the frequency of some adverse reactions especially those linked to inhibitor formation and to allergic reactions is insufficient. The committee has therefore made recommendations to collect new efficacy and safety data from two additional clinical trials on the product in previously treated patients and to generate sufficient data on the use of nonacog alfa in children under 6 years of age including previously treated and previously untreated patients.

Immediate measures will involve:

1. Creating an intensive post-marketing surveillance for nonacog alfa that will register all new patients treated with nonacog alfa in Europe with careful monitoring for adverse reactions
2. Allowing patients already receiving nonacog alfa to carry on with the treatment with careful monitoring for any suspected adverse reactions that they may experience during the course of the treatment
3. Requiring all suspected adverse drug reactions to be reported to the Marketing Authorisation Holder or the National Health Authorities.
4. Considering alternative haemostatic measures in the case of severe allergic reaction
5. Switching patients to alternative haemostatic measures in case of severe allergic reactions or to another factor IX product if doses higher than 100 IU/kg are needed for routine prophylaxis or treatment, even in the absence of inhibitor formation.

The above information was sent out as a drug alert to all WHO Member States through the WHO Information Exchange System.

**Reference:**

1. EMEA Public Statement, EMEA/CPMP/2777/01, 4 Oct 2001.

Available from URL:

<http://www.emea.eu.int>

2. WHO Information Exchange System, Alert No.103, 1 Oct 2001.

## OPRELVEKIN

### Papilloedema in paediatric patient study

**USA.** A 'Dear Healthcare Professional' letter has been issued by Wyeth-Ayerst, USA, advising of important safety information changes for use of

oprelvekin (Neumega) in paediatric patients. The letter points out that no controlled clinical studies have established an oprelvekin dose that is safe and effective in children. As such, it is advised that children, especially those aged <12 years, only be administered the drug in controlled clinical trials, and under closely monitored conditions. The letter also says that papilloedema has been identified as a dose-limiting adverse reaction to oprelvekin in a pharmacokinetic study. In this study of 47 paediatric patients, 4 out of 16 (25%) who received oprelvekin 100 µg/kg/day developed papilloedema. Among the 9 participants who received oprelvekin 75µg/kg/day, none developed the complication; however, due to the small number of patients who received this dosage, it is reported that the true incidence may be as high as 33%. Furthermore, children aged <12 years who received oprelvekin 50µg/kg/day did not achieve a serum concentration of the drug that was considered effective. Although these data are preliminary, the letter from Wyeth-Ayerst indicated that once a full analysis has been performed, labelling changes will be made to include all available information associated with administration of oprelvekin to paediatric patients.

*Reports in WHO file: papilloedema total 4, 3 in children under 12*

**Reference:**

*Media Release, 24 Aug 2001.*

Available from URL:

<http://www.fda.gov>

## RALOXIFENE

### Reports of thromboembolic events

**Australia.** Raloxifene has been marketed in Australia since 1999 for the treatment of established post-menopausal osteoporosis. So far ADRAC has received 199 reports of suspected adverse reactions, with raloxifene implied as the drug causing those reactions in 185 cases. Many of

the adverse reactions are mild in nature including nausea, hot flushes, rashes, headache etc. and are described in the product information. The more serious effects include reports of deep vein thrombosis (DVT) and cerebrovascular disorders. ADRAC has received 7 reports of pulmonary embolism and 22 reports of DVT in association with raloxifene. The patients were females aged between 55 and 89 (median 71) years, taking the drug for osteoporosis. The reactions occurred from a few days to 8 months after the drug was started with most cases having an onset after several months of therapy. The outcome was fatal in one patient. Since raloxifene is associated with an increased risk for venous thromboembolic events (VTEs) comparable to the risk associated with hormone replacement therapy, the risk/benefit balance should be carefully considered in patients with known risk factors for VTEs. ADRAC recommends that patients be specifically advised of the increased risk of VTEs with all estrogenic compounds, including raloxifene. In addition to the VTEs there were also 7 reports of stroke and 3 reports of transient ischaemic attacks with raloxifene.

**Reference:**

*Australian Adverse Drug Reactions Bulletin*, 21 (4): 2001. Available from URL:  
<http://www.health.gov.au>

## TIAPROFENIC ACID

### Reports of cystitis

**New Zealand.** The New Zealand (NZ) Centre for Adverse Reactions Monitoring received 2 reports of cystitis associated with tiaprofenic acid (Surgam) in the year 2000, bringing the total number of such reports to 17 and prompting Medsafe\* to issue a reminder to clinicians in that country about this complication. Medsafe notes that the reporting rate for tiaprofenic acid-induced cystitis in the UK is 18/1 million

prescriptions filled, compared with 0.05–0.2/1 million prescriptions filled for other non-steroidal anti-inflammatory drugs (NSAIDs). Medsafe believes that some NZ clinicians may be unaware of this complication of tiaprofenic acid therapy. In one of the cases reported in NZ in the year 2000, the link between cystitis and tiaprofenic acid only came to light when the drug was discontinued prior to a cystoscopic examination. Medsafe says that tiaprofenic acid-induced cystitis is still under-recognised, and that the complication is rare and can occur months or years after starting treatment with the drug. Furthermore, failure to recognise the complication and discontinue treatment can lead to unnecessary surgery, permanent urinary tract damage and renal impairment. Medsafe points out that elderly patients on long-term treatment with tiaprofenic acid are particularly vulnerable to cystitis. Furthermore, it advises that tiaprofenic acid be used with caution in patients with recurrent urinary tract infections, pre-existing cystitis or any other urinary symptoms, as symptoms of drug-induced cystitis may be masked by such conditions. All patients receiving tiaprofenic acid should be advised to seek medical attention if they develop any urinary symptoms, Medsafe says. Moreover, all patients receiving long-term treatment with tiaprofenic acid should be regularly asked about urinary symptoms. If patients do develop such symptoms, the authority advises that tiaprofenic acid should be withdrawn immediately; such action usually results in resolution of the cystitis.

\* Medsafe is NZ's Medicines and Medical Devices Safety Authority.

*Reports in WHO file: cystitis 284, cystitis haemorrhagic 31*

**Reference:**

*Media Release, Sept 2001.*  
Available from URL:  
<http://www.medsafe.govt.nz>

## TRADITIONAL MEDICINES

### Adulterants/ undeclared ingredients pose safety concerns

**New Zealand.** Betamethasone in the range of 0.1mg to 0.3 mg per capsule, has been detected in Cheng Kum and Shen Loon, two herbal medicines popular for their benefits in joint pain, skin problems, colds, menopausal symptoms and dysmenorrhoea. Over exposure to betamethasone can result in typical signs of corticosteroid excess such as plethoric moon face, hypertension, easy bruising, purple abdominal striae, truncal obesity and hirsutism. The recommended daily dose of Cheng Kum is 1 to 3 capsules per day (less in children). Most people will only be exposed to a small amount of corticosteroid with this dose. However there have been reports of corticosteroid-induced side effects in patients taking Cheng Kum and Shen Loon, even in the absence of other exogenous corticosteroid consumption. The New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) has notified that the further importation of these herbal products into New Zealand will be stopped at Customs. However, because of the risk of adrenal suppression with corticosteroid use, consumers have been sent a letter advising them against abruptly discontinuing the use of these products. They should continue with the treatment and see their general practitioner as soon as possible for instructions on how they may be safely weaned off the products. The Director General of Health has reinforced these points through a privileged statement on Cheng Kum/Shen Loon under section 98 of the Medicines Act 1981. Medsafe has also issued a letter to doctors advising them to determine if patients taking Cheng Kum or Shen Loon are at risk of adrenal suppression by estimating the potential total dose of

corticosteroid (from Cheng Kum or Shen Loon plus any exogenous steroid) and duration of use, examining the patient for signs of corticosteroid excess and by ascertaining if other risk factors for adrenal suppression are present (such as Addison's disease, AIDS etc). In the event of excess exposure or the presence of a risk factor for adrenal suppression, the patient should be transferred to an equivalent dose of prednisone (reducing to zero over 2 weeks or longer) and Cheng Kum or Shen Loon should be stopped<sup>(1-3)</sup>.

**UK.** The United Kingdom's MCA continues to find potentially dangerous and illegal ingredients in traditional Chinese medicines. Recently traditional Chinese medicines have been found to include aristolochia, mercury, arsenic compounds and prescription-only steroids. The Chairman of the UK Committee on the Safety of Medicines has cautioned that the public should not take traditional Chinese medicines that are not labelled or do not include a list of ingredients in English. Representatives from the Chinese medicines sector have pledged their co-operation for improving the safety standards of traditional Chinese medicines<sup>(4)</sup>.

**Reference:**

1. 'Dear Doctor' letter from Medsafe, 14 Dec 2001. Available from URL: <http://www.medsafe.govt.nz>
2. 'Dear Consumer' letter from Medsafe, 14 Dec 2001. Available from URL: <http://www.medsafe.govt.nz>
3. Media Release (Director General of Health privileged statement under section 98 of the Medicines Act 1981 – Cheng Kum/ Shen Loon), 17 Dec 2001. Available from URL: <http://www.medsafe.govt.nz>
4. Media Release, 27 Sept 2001. Available from URL: <http://www.mca.gov.uk>

## TRAMADOL

### Precipitation of serotonin syndrome

**Australia.** Tramadol, a centrally acting analgesic, is known to inhibit the reuptake of norepinephrine and serotonin. Since its marketing in Australia in late 1998, ADRAC has received 171 reports of suspected adverse reactions. Six of these reports describe serotonin syndrome. The clinical features of serotonin syndrome include mental confusion, hypomania, agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhoea, incoordination and fever. Four of the six reports described the use of tramadol in patients who were taking antidepressants known to increase the concentration of brain serotonin. These included the selective serotonin reuptake inhibitors sertraline and citalopram, the selective monoamine oxidase inhibitor moclobemide (which releases serotonin) and a combination of the tricyclic antidepressants amitriptyline and clomipramine (norepinephrine and serotonin reuptake inhibitors). Another report involved a patient who was taking St John's wort which is also believed to increase serotonin concentrations. The other report described the use of a relatively high daily dose (400mg) of tramadol in an elderly male. Four of the six patients recovered after treatment, one required intensive care admission and had not recovered at the time the report was submitted and the outcome of another patient is unknown. ADRAC advises that caution should be exercised while using high doses of tramadol and in patients using tramadol along with medications known to increase brain concentrations of serotonin.

**Reference:**

- Australian Adverse Drug Reactions Bulletin*, 21 (4): 2001.  
Available from URL: <http://www.health.gov.au>

*Abstracted from presentations made at the 24th Annual Meeting of the National Centres Participating in the WHO International Drug Monitoring Programme*

### **Interaction of Coxibs (COX-2 inhibitors) with Warfarin**

**(Australia)**

Interactions with warfarin are among the most important and clinically relevant of interactions because of their potential to cause bleeding and other sequelae. In Australia, up to August 2001 there had been over 4 million prescriptions with celecoxib following its introduction in 1999. Of these, 2.1 million were during the last 7 months of that period. There were 2940 reports of adverse drug reactions with celecoxib within which there were 31 reports of increased INR (International Normalised Ratio) in patients taking warfarin. There were 13 cases of associated bleeding and 12 reports of bleeding with no increase in the INR. For rofecoxib, which was marketed in July 2000 there had been 0.91 million prescriptions in the same 7 month period as for celecoxib. There were 373 rofecoxib-adverse drug reaction reports including 7 reports of increased INR in patients taking warfarin, 2 with associated bleeding and 1 report of bleeding with no increase in the INR. Pharmacokinetic studies had shown an 8% increase in INR in 15 subjects taking warfarin, whilst for celecoxib there was no increase in the INR in 24 subjects. The clinical relevance of these findings is not clear and there is uncertainty whether these reports are co-incidental, or whether they represent a real interaction. In the case of celecoxib there is a plausible pharmacokinetic mechanism as it is primarily metabolised by CYP2C9, but rofecoxib is not metabolised by CYP.

**Discussion:** *It was considered that a warning on the use of coxibs with warfarin should be included since the chance of bleeding from a peptic ulcer could be worsened in the presence of an anticoagulant.*

### **Paroxetine during pregnancy**

**(Netherlands)**

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) approved for treating depression, obsessive-compulsive disorder, panic disorder, social anxiety disorder and social phobia. Animal teratogenicity studies with paroxetine do not indicate a risk to the foetus. There is insufficient information from human studies about possible risks of paroxetine use during pregnancy. Use of paroxetine by pregnant women close to delivery may have consequences. A case of neonatal intracranial bleeding has been reported to Lareb, which was associated with use of paroxetine during pregnancy. Apparently paroxetine is able to cross the placenta and bring about significant blood levels in the baby. This was demonstrated by the cases of neonatal withdrawal syndrome.

**Discussion:** *It is important that physicians are aware of the risks to neonates before prescribing paroxetine to pregnant women. Furthermore, the paediatrician should be prepared for possible problems in the newborn child when paroxetine is used during pregnancy.*

### **Severe liver reactions with Kava (Piper methysticum)**

**(Switzerland)**

Four cases of severe hepatic complications associated with a Kava root extract (acetone extract) have occurred in Switzerland between 10 August 1999 and 20 February 2000. In three of them hepatitis was

histologically confirmed. One patient with subfulminant hepatitis needed a liver transplant. Prothrombin time was increased in three and jaundice occurred in four patients. The incidence of severe hepatic complications can be estimated at around 1: 35,000 and 1: 175,000 patient months in Switzerland and on an international level respectively. CYP2D6 deficiency was shown in two patients, possibly a predisposing factor. Review of the international data reveals 9 reports including the 4 Swiss reports. 8 of these reports are with the acetone extract. Taking into account the benefits (versus risks) and the available alternatives, the acetone kava root extract was withdrawn in April 2001 in Switzerland. The alcohol extract as well as a synthetic preparation containing d-/l-Kavaine, with a seemingly much lower incidence of severe liver reactions, have remained on the market. However the kava ethanol extracts have been moved from OTC to 'pharmacy only' status in September 2001 and put under special monitoring.

**Discussion:** *The mechanism of the reactions to kava extract is unclear and may be allergic or toxic in nature. Fiji has reported that Kava is widely used in its natural form but has not experienced reports of hepatic disorder, although concomitant alcohol abuse can make signal identification difficult. These cases also highlight some shortcomings of non-drug causes of hepatic ADR reports.*

### Yasmin® and venous thromboembolism

(Netherlands)

Yasmin is drospirenone, a new chemical entity in combination with ethinylestradiol. 2 reports of venous thromboembolism and one of pulmonary embolism in a 17 year old after 6 months of Yasmin use and another of leg thrombosis in a 28 year old, 4 months after switching to Yasmin have raised concerns around this new product. There is one suspicious case of pulmonary embolism in the pre-registration dossier.

**Discussion:** *It was suggested that the pre-registration studies were not big enough to recognize venous thromboembolism and therefore there is a great need to do post market surveillance studies. These may be more effective if there is a proposal for countries to collaborate. Experiences from the UK show that Yasmin has a diuretic effect through its effect on the kidneys and that this aspect should be kept in mind both from a potential for adverse events as well as the possible marketing opportunities that may be taken advantage of.*

### Events & Announcements

- The IFAPP (International Federation of Associations of Pharmaceutical Physicians) Executive Committee is announcing the availability of four educational grants in Pharmaceutical Medicine for 2002-2003 for young physicians (under 40 years of age). All relevant information as well as the application form are available on IFAPP's web site [www.ifapp.org](http://www.ifapp.org) under 'news'.
- The Tenth International Conference of the Drug Regulatory Authorities (ICDRA) will be held in Hong Kong from 24 to 27 June 2002. The Pre-ICDRA Satellite Workshop on 'The Impact of Regulation on the Safe Use of Drugs' will be held on 23rd June 2002.



## A Reappraisal of Antipyretic and Analgesic Drugs

Dr Anthony Wong, MD, PhD, Medical Director, CEATOX, Instituto da Criança, Department of Paediatrics, Faculty of Medicine, University of São Paulo, Brazil.

Most antipyretics and analgesics are sold as prescription-free, over-the-counter (OTC) drugs in most countries. The main OTC drugs marketed worldwide are acetylsalicylic acid (ASA), metamizole, paracetamol and ibuprofen. Metamizole was first marketed in Germany in 1922 and is a member of the phenyl-pyrazolone group of drugs. It has been the center of considerable controversy as regards its safety.

### Adverse Drug Reaction (ADR) Reports with Metamizole - Facts & Flaws

An abnormally high incidence of agranulocytosis (0.86%) was reported by Discombe<sup>(1)</sup> from a retrospective study of four reports totalling 1272 subjects receiving metamizole. A survey by Huguley<sup>(2)</sup>, which added 127 subjects to that report, found an incidence of 0.79%, with a mortality rate of 0.57%. Both papers had two major flaws: 1) positive cases were compiled more than once, resulting in these extraordinary figures, and 2) the ADR figures for metamizole included reports due to aminopyrine and phenylbutazone, two other drugs also belonging to the phenyl-pyrazolone group. If these numbers were indeed true, it may be surmised that there would have been 102,000 cases of agranulocytosis, with 73,440 deaths among users per year in Germany; 144,300 cases and 103,900 deaths in Spain; and 195,000 cases and 140,400 deaths in France and Italy<sup>(3)</sup>. In other words, the death toll due

to agranulocytosis caused by metamizole alone would be several times higher than the deaths from myocardial infarction and cardiac arrhythmias combined. Sir Richard Doll referring to Huguley's paper stated that the evidence which led to the proscription of metamizole in the UK and the USA, 30 years ago was weak by modern standards<sup>(4)</sup>.

Several subsequent large-scale population studies have re-evaluated the incidence of drug-related agranulocytosis. The International Agranulocytosis and Aplastic Anaemia Study, also known as the Boston Study, surveyed a population of 22.8 million in seven European cities and Jerusalem for over 6½ years, and reported an overall incidence of 1 case per million persons per year<sup>(5)</sup>. Two reports from Brazil, by Sollero<sup>(6)</sup> and Hamerschlag<sup>(7)</sup> found an even lower risk for metamizole. In 1998 Andrade et al. conducted a meta-analysis to compare epidemiological studies from 1975 to 1995 and estimated that the excess mortality per million from community acquired cases of agranulocytosis, aplastic anaemia, anaphylaxis and serious upper gastrointestinal complications was 592 for diclofenac, 185 for ASA, 25 for metamizole, and 20 for paracetamol<sup>(8)</sup>. CIOMS IV in the same year reported the excess mortality risk for the same conditions to be: diclofenac=5.92; ASA=2.03; metamizole=0.20; and paracetamol=0.25<sup>(9)</sup>. These studies certainly suggest that the risks from adverse reactions to metamizole are similar to those posed by paracetamol, a drug widely reputed to be safe. According to the CIOMS IV conclusion "Newer methods of epidemiological studies have shown that the risk of agranulocytosis (1.7 per million) due to metamizole was exaggerated in the 70's"<sup>(9)</sup>.

The Ministry of Health in Brazil convened an international panel of experts in July 2001 to evaluate the safety of

metamizole and concluded that: "(a) There is consensus that its efficacy as an analgesic and antipyretic is unquestionable; (b) The data presented before this panel allow the participants to conclude that the risks of metamizole are similar, or even lower, than of other analgesic/antipyretic drugs available on the market; and (c) A change in the present regulatory status of metamizole would incur in negative aspects to the population, increasing the risk from the use of other drugs indicated for the same therapeutic ends"<sup>(10)</sup>.

A randomized, double blind, multinational study involving 555 children showed that metamizole and ibuprofen were significantly more effective than paracetamol in achieving normal body temperatures; metamizole produced a significantly greater temperature reduction than ibuprofen and paracetamol, and helped maintain low temperatures for a longer duration<sup>(11)</sup>. An editorial on the report from this study commented that drugs such as metamizole were perhaps unjustly deleted from our pharmacopoeia because of imprecise studies of adverse side effect; some of the older therapeutic agents such as metamizole may be identified as having clinical utility in children<sup>(12)</sup>.

### Paracetamol – Some Concerns

Paracetamol has long been heralded as a safe drug and gained wide popularity, more so after Reye's syndrome was linked to ASA. However, several recent papers have addressed concerns and questioned the drug's safety following deaths and hepatotoxicity due to intentional and 'therapeutic' overdoses, severe drug interactions, nutritional factors and associated diseases. Paracetamol has been the major cause of drug-related acute liver failure and deaths in the USA and the UK<sup>(13)</sup>. The American Association of Poison Control

Centers (AAPCC) lists paracetamol as the single major cause of death reported to the American poison centers since 1994<sup>(14,15)</sup>. In October 2001, the American Academy of Pediatrics issued a Policy Statement with warnings on the risk factors conducive to paracetamol poisoning, and recommendations for its prevention and early diagnosis<sup>(16)</sup>.

In addition to hepatotoxicity, paracetamol and other non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with analgesic nephropathy. A recent paper has indicated an odds ratio for chronic renal disease of 5.3 for paracetamol and 3.3 for ASA, with increased risk for pre-existing renal disease. Such an association with renal disease was not observed for propoxyphene or metamizole<sup>(17)</sup>. A recent study has linked chronic use and abuse of paracetamol to a major risk of non-genetic and non-environmental asthma, with the risk increasing with cumulative dosage<sup>(18)</sup>. Altered clotting time, especially when associated with the use of warfarin, has also been well documented.

### **In conclusion**

Generally speaking, it might not be suitable to treat yellow fever, dengue, infectious gastroenteritis, and other febrile illnesses that require prolonged treatment, with high doses of paracetamol or NSAIDs due to the risk of hepatotoxicity, nephrotoxicity, severe gastrointestinal irritation and bleeding disorders with chronic use of these drugs. In these instances metamizole might be an alternative choice because of its prolonged action, efficacy, absence of clotting disorders, and low cost. The case presented for metamizole, while open to debate, suggests the need to continuously review evidence for drug safety of all products to reduce the loss of potentially safe, efficacious and cost-effective drugs from the market. It also points to the need for

continuing pharmacovigilance in older, more established drugs.

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