EDITORIAL

The delay in this issue of the Pharmaceuticals Newsletter has been due to staffing changes in Headquarters. This edition encompasses two issues: numbers 2 and 3. Routine regulatory and safety information provided by the WHO Collaborating Centre for International Drug Monitoring is included. We are also providing an article on the project on pharmacovigilance in the Newly Independent States of Eastern Europe which we hope you will find of interest. It shows how much has been done in these countries in a relatively short time. Three follow-up articles based on the information from the Uppsala ADR database are also included in this issue.

WHO has held two meetings which may be of interest to our readers. The first was a consultation to review the use of ICH guidelines. It considered issues relating to recent developments in the activities of global harmonization of regulatory requirements for pharmaceuticals, especially those linked to the activities of the International Conference on Harmonization. Recommendations were made that WHO should be encouraged to find ways to work more closely with ICH to engage and seek input from other countries. The other meeting was a consultation on safety monitoring. This consultation covered a wide range of issues relating to pharmacovigilance. A major recommendation from this was that safety of medicines should become one of WHO’s priorities in the next biennium.

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ARISTOLOCHIA
Alert against products containing aristolochic acid

Canada, USA. In June 2001, the FDA issued a nation-wide alert recalling 13 'Treasure of the East' herbal products containing aristolochic acid (1). Aristolochic acid, found in certain plants and botanicals is a potent carcinogen and can cause serious kidney damage. A complete list of the recalled products may be found on the FDA website, under FDA recalled products may be found (http://www.fda.gov). Earlier to this alert, the FDA had issued several warnings:

1. On 4 April 2001 a 'Dear Health Professional' letter was sent drawing attention to serious renal disease associated with the use of aristolochic acid-containing dietary supplements or 'traditional medicines' (2). Health professionals were urged to review patients who had experienced unexplained renal disease, especially those with urothelial tract tumours and interstitial nephritis with end-stage renal failure, to determine if such products had been used.

2. On 9 April 2001 a letter to industry associations was sent, which details the reported cases of renal disease associated with aristolochic acid (3).

3. On 11 April 2001 the FDA cautioned consumers to immediately discontinue use of any dietary supplements or 'traditional medicine' that contain aristolochic acid, including products with 'Aristolochia', 'Bragantia' or 'Asarum' listed as their ingredients (4).

In a related action, Health Canada has warned consumers not to use the paediatric product Tao Chih Pien (5). This Chinese product, which is sold in the form of tablets, is said to be a diuretic and a laxative. It is not labelled to contain aristolochic acid. However the Chinese labelling says that it contains Mu Tong, a traditional term used to describe numerous herbs, including aristolochia. Subsequent product analysis has found that Tao Chih Pien does indeed contain aristolochic acid. Health Canada has now advised individuals in possession of this product not to consume it and to return it to the place of purchase. It has also issued a Customs Alert for the product to prevent the importation and sale of Tao Chih Pien.

Reports in WHO-file: Renal function abnormal 1

Reference:

AMIODARONE
Important monograph additions

Canada, USA. Wyeth-Ayerst Pharmaceuticals (USA) notified healthcare professionals of two safety-related changes to the amiodarone prescribing information, describing potentially fatal or developmental side effects associated with the use of this product in neonatal and infant pediatric patients. These safety related changes are:

1. The dosage and administration section warns of possible leaching of di-(2-ethylhexyl) phthalate (DEHP), the concern being that exposure to DEHP may adversely affect male reproductive development.

2. The precautions now describe 'a gasping syndrome' in neonates, which may be fatal, following administration of intravenous solution containing the preservative benzyl alcohol.

Sabex Inc. in Canada has made similar additions in the 'Dosage and Administration' section of the Product Monograph/Package Insert as well as the 'Precautions, Use in Pediatrics' section for amiodarone hydro-chloride injection, warning about the DEHP leaching and the gasping syndrome associated with benzyl alcohol in the product.

Reference:

BOTULINUM TOXIN
Warning against unauthorised use

Ireland. The Irish Medicines Board (IMB) is advising potential customers that the medicinal product Botox, which has the active ingredient Clostridium botulinum toxin type A (a highly potent neurotoxin) is a prescription-only product and that only registered medical doctors or dentists should administer this medicine in accordance with the conditions of the licence. The reason for this is that investigations by the IMB have revealed that a number of beauty salons, cosmetic clinics and private individuals use the product for correcting wrinkles. Botox can produce a number of serious side effects such as ptosis, facial weakness, visual disturbance and corneal ulceration. Other equally serious but less frequent adverse effects include cardiac effects such as abnormal cardiac rhythms and heart attacks.

Reference:
CANNABIS
Medical use legalized

Canada. The Canadian federal health department for controlled substances has passed new regulations on the medical use of cannabis. These regulations, which came into effect at the end of July, will allow cannabis to be used by seriously or terminally ill people, making Canada the first country to take such a step. The federal department has emphasized that the government was not encouraging the use of cannabis but only making it available under certain conditions when conventional treatments fail and the benefits outweigh the risks of cannabis use.

Under the new regulations, a doctor must sign the application form and set the dose. The patient can then apply for permission to use cannabis. Earlier, before the new regulations came into force, anyone wishing to use cannabis for medical purposes had to apply for a special exemption from prosecution under the law, which required detailed submissions from doctors.

Reference:

CERIVASTATIN
Voluntary withdrawal by Bayer

Worldwide. Bayer Pharmaceutical Division voluntarily withdrew Baycol (cerivastatin) from the world market following reports of rhabdomyolysis, a severe muscle adverse reaction that can sometimes have fatal consequences(1-4).

Baycol (cerivastatin) belongs to a group of cholesterol lowering drugs referred to as ‘statins’. While all statins could potentially cause this dangerous muscle reaction, rhabdomyolysis appears more frequent with cerivastatin, especially when used in high doses, in the elderly or, when taken along with gemfibrozil, another cholesterol lowering drug (5). Bayer withdrew all dosages of Baycol/Lipobay throughout the world except in Japan where gemfibrozil is not available. However, subsequent regulations ensured the removal of the drug from Japan as well.

Lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), luvastatin (Lescol) and atorvastatin (Lipitor) are five other statins that may be used as alternatives to cerivastatin.

Reference:

CLARITHROMYCIN
Change of labelling

Japan. The Ministry of Health, Labour and Welfare (MHLW) in Japan has called for hepatic dysfunction, jaundice and rhabdomyolysis to be included in the ‘Clinically significant adverse reactions’ section of the clarithromycin-containing products ‘Clarith’ and ‘Klaricid’ for paediatric use. Previously, various liver disorders were included in the ‘Other adverse reactions’ section, while rhabdomyolysis was included in the ‘Drug interactions’ section as an interaction with HMG-CoA reductase inhibitors. This labelling change has been made in response to 23 reported cases of hepatic dysfunction and 6 of rhabdomyolysis, associated with clarithromycin use, since 1996.

Reference:
MHLW Pharmaceuticals and Medical Devices Safety Information. ADR updates from Japan. Media Release, Mar 2001.

EPHEDRA
Serious reactions with other stimulants

Canada. Health Canada has warned its consumers not to use products containing the herb Ephedra, either alone or in combination with caffeine and other stimulants. Typically, the preparations to watch out for are those products listing ma huang, Chinese Ephedra, ma huang extract, Ephedra, Ephedra Sinica, Ephedra extract, Ephedra herb powder, Sida Cordifolia or Epitonia in their contents. The source of caffeine or other stimulants in these preparations may include green tea, guarana, yerba mate, cola nut and yohimbine. Ephedra is the botanical source of the drug. Ephedrine and preparations containing either Ephedra or Ephedrine are used in Canada, either as weight loss products or as energy substitutes. When consumed alone or in combination with other stimulants such as caffeine, they can cause serious and sometimes fatal adverse reactions in the body.

Reference:

GAMMA HYDROXY BUTYRATE
Fantasy drugs to be classified

New Zealand. The Expert Advisory Committee on Drugs (EACD) in New Zealand has advised the New Zealand Medicines and Medical Devices Safety Authority to schedule...
Gamma hydroxy butyrate, 1,4 butanediol and other ‘party drugs’ under the Misuse of Drugs Act 1975. This is because these drugs are dangerous in that there is often only a very narrow margin between the dose producing the desired effect and the potentially toxic or even fatal dose. The committee is now in the process of finalising the most appropriate schedule in the Act for these drugs.

Reference:

ITRACONAZOLE
Labelling changes

USA. On 9 May 2001 the US FDA announced the following labelling changes for itraconazole (‘Sporanox’) products, including capsules, injection and oral solution:

a) Treatment should be discontinued in patients receiving itraconazole for fungal nail infections who exhibit signs and symptoms of congestive heart failure (CHF).

b) For patients with more serious fungal infections who experience signs and symptoms of CHF while receiving itraconazole, the continued use of the agent should be reassessed by the physician.

This was in response to 94 reports of CHF in patients receiving treatment with itraconazole. Of the 58 patients in whom the agency believes that itraconazole was contributory, 28 were hospitalised and 13 died. A causal relationship between death and itraconazole was not established due to the presence of confounding factors. All patients received itraconazole for fungal nail infections. In addition, by March 2001, the FDA had received 24 reports of cases of liver failure possibly associated with itraconazole use. The FDA has, therefore, reiterated the warnings of liver effects as well.

Reference:

LEVOCETYL-METHADOL
Suspension of marketing authorisation

Europe. The Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA), during its meeting of 26-28 March 2001, recommended the suspension of the marketing authorisation of levocetylmethadol (Orlaam)\(^1\). The committee’s decision is based on reports of the pro-arrhythmic potential of levocetylmethadol with its ability to consistently and significantly increase the QTc interval in electrophysiological and clinical studies\(^2\). A reassessment of the risk-benefit balance of levocetylmethadol does not identify any special advantage over existing alternatives, nor does it identify a therapeutic niche where the benefits would outweigh the occurrence of severe, serious and unpredictable cardiotoxicity associated with its use.

In view of their decision, the EMEA has advised physicians to review patients currently on levocetylmethadol and to switch them to an existing alternative such as methadone. Decisions to detoxify patients on levocetylmethadol will have to be considered on an individual basis, depending on whether a gradual reduction (5 to 10% a week) or an abrupt withdrawal is indicated. Patients currently being treated with levocetylmethadol should be advised not to stop levocetylmethadol suddenly; they should contact their physicians without delay.

Reference:

LEVCAR-NITINE
Revised labelling

USA. A ‘Dear Health Care Professional’ letter has been issued by Sigma Tau Pharmaceuticals, the manufacturer of levocarnitine (‘Carnitor’), to emphasise that only i.v. preparations of this drug are approved for use in patients with end-stage renal disease (ESRD).

The company has received several reports that oral levocarnitine is being administered to patients with ESRD and has thought it necessary to make appropriate labelling changes in the ‘Precautions’ section. The changes outline the following points.

- Patients with severe renal impairment or ESRD should not be administered long-term, high-dosage levocarnitine due to the accumulation of major metabolites, specifically trimethyl-amine-N-oxide, which cannot undergo efficient renal clearance in such patients.
- The formation of these metabolites does not occur to the same extent when levocarnitine is administered intravenously.
- Increased trimethylamine concentrations have been associated with possible neurophysiological effects and a ‘fishy’ body odour.

Sigma Tau Pharmaceuticals lists nausea, vomiting, body odour, gastritis and seizures as adverse events reported with levocarnitine.
**REGULATORY MATTERS**

**METHADONE**

**New regulations to promote safer use**

**Germany.** The federal government of Germany has introduced new regulations aimed at improving the safety of methadone use. The new regulations follow a dramatic increase in the methadone-misuse related deaths in Germany in recent times. Physicians prescribing methadone will now have to register centrally with the Federal Drug Agency in Berlin and register all their medical prescriptions. The prescriptions will be coded for protecting personal data. These measures are expected to help identify multiple prescriptions immediately and trace them to the doctors issuing them. The new regulations, which enjoy the support of the German Medical Association, will become effective from July 2002.

**Reference:**


**MICONAZOLE**

**Possible interaction with warfarin prompts labelling changes**

**Canada.** Miconazole, an antifungal agent, can be bought as an over the counter, non-prescription, vaginal cream or suppository. Reports with the U.S. FDA and the Canadian Adverse Drug Reaction database record that women using vaginal miconazole while on a concomitant anticoagulant therapy such as warfarin have prolonged partial thromboplastin and prothrombin time. This has led Health Canada to ask manufacturers of vaginal miconazole products to add a new warning to the product monograph and to the product label. The warning will now state that those who are taking prescription anticoagulants such as warfarin should consult their physician or pharmacist before using vaginal miconazole, due to the risk of bleeding or bruising.

**Reports in WHO-file: Miconazole and warfarin reported as interacting drugs**

**Reference:**


**OXYCODONE**

**Labelling changes to address inappropriate prescribing**

**USA.** The labelling for oxycodone (‘OxyContin’) has been strengthened by the drug’s manufacturer, Purdue Pharma, in consultation with the US FDA.

Purdue Pharma has issued a ‘Dear Healthcare Professional’ letter outlining the changes to the labelling. Among these changes is the inclusion of a ‘black box warning’ that details the following points:

- Oxycodone is a schedule II controlled substance*, with abuse properties similar to those of morphine.
- The abuse potential of oxycodone should be considered when the agent is being prescribed.
- ‘OxyContin’ tablets are controlled-release formulations indicated for use when continuous analgesia is required for severe pain, and are not intended for use ‘as required’.
- Oxycodone tablets should not be broken, crushed or chewed; such use leads to a rapid release of a potentially fatal dose of the agent.
- Oxycodone 80 and 160 mg tablets are for use only in patients with opioid tolerance.

Many of these points are reiterated in the revised ‘Warnings’ and ‘Indications and Usage’ sections of the labelling.

These labelling changes have been made because a number of reports of abuse and diversion with oxycodone have been received during recent months, says the FDA. The agency states that the changes are designed to ‘change prescription practices as well as increase the physicians’ focus on the potential for abuse, misuse and diversion’, and reduce the likelihood that oxycodone is prescribed inappropriately. Furthermore, the agency emphasises that it is the severity of pain, not the disease causing the pain, that is the important factor to be considered when prescribing oxycodone.

The FDA encourages other drug companies to voluntarily re-evaluate, and revise where necessary, the warnings and precautions of their opioid products to address the risks associated with abuse, misuse and diversion, and encourage good prescribing practices.

*Schedule II provides for the maximum amount of control under the US Controlled Substances Act.

**Reference:**


**PHENYLPROPANOLAMINE (PPA)**

**Product withdrawal from the market**

**Canada.** Subsequent to the advisory issued by Health Canada, warning consumers against using PPA containing products until further notice, the organization undertook a complete safety assessment of...
PPA. It has concluded that the occurrence of haemorrhagic strokes with PPA, however rare, poses a serious threat to consumers and that all products containing PPA should be removed from the market. The Drug Identification Numbers (DINs), which provide manufacturers with the authority to market drug products in Canada, have been cancelled for all PPA-containing products. Manufacturers have been directed to remove all existing prescription as well as non-prescription PPA-products from the retail market. Several manufacturers are reformulating their cough, cold, sinus and allergy medications by either removing PPA or replacing it with a safer and effective nasal decongestant. Consumers in possession of PPA containing products are advised to direct their questions on the safe disposal of those products to a pharmacist or to call the toll-free customer service number indicated on the product label.

Readers may refer to the information provided in the WHO Pharmaceuticals Newsletter No.4, 2000 for a full overview of various national actions on PPA.

Reference:

PROPOFOL
Not to be used for sedation in paediatric patients

USA. AstraZeneca has issued a ‘Dear Healthcare Professional’ letter emphasising that propofol (‘Diprivan’) is not indicated for sedation in paediatric patients(1).

The letter was issued after the US FDA reviewed data from a randomised, controlled clinical trial, in which the safety and efficacy of propofol, compared with standard sedative agents such as lorazepam, chloral hydrate, fentanyl, ketamine, morphine and phenobarbital, was investigated in 327 paediatric patients in an intensive-care setting.

In this study, 109 and 113 such patients received propofol 1% and 2%, respectively, while the remaining patients received standard sedative agents. The patients received an infusion of propofol 5.5 mg/kg/h, titrated as required to maintain sedation. During 28 days of follow-up, more deaths occurred in the patients who received propofol (see table).

Deaths in paediatric intensive-care patients over a 28-day period following administration of propofol or standard treatments for sedation*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of deaths</th>
<th>Number of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol 1%</td>
<td>109 (11)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Propofol 2%</td>
<td>113 (11)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Standard sedative agents*</td>
<td>105 (4)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

* such as lorazepam, chloral hydrate, fentanyl, ketamine, morphine and phenobarbital

The FDA determined that important safety concerns exist for propofol as a sedative in paediatric patients in intensive care. The agency believes that careful review of the deaths in the study did not establish a correlation with underlying disease status, nor was a definitive pattern of cause of death revealed.

AstraZeneca has announced that it will initiate a clinical study that will evaluate differences in adverse reactions and deaths among paediatric patients receiving propofol and standard sedative agents in an intensive-care setting. The company also encourages the reporting of any adverse event information associated with propofol.

It is interesting to note that the WHO issued a drug alert for propofol in April 1992 (Alert No. 26) through the Pharmaceutical Information Exchange Service System. The alert, warning against the use of propofol for intensive care sedation in children, was issued in the wake of 2 reports of death in children received by the Norwegian Medicines Control Authority(2).

Reference:

RITUXIMAB
Revised warnings section

Canada. Hoffman La Roche Ltd., the manufacturer of Ritu-ximab (Rituxan®) has issued a ‘Dear Healthcare Professional’ letter for their recent revision of the Warnings section of the Product Monograph. The revised monograph will now include information regarding the severe mucocutaneous skin reactions with the drug. The reactions are variably described as Stevens-Jonson Syndrome, toxic epidermal necrolysis, paraneoplastic pemphigus, lichenoid dermatitis or vesiculobullous dermatitis, with an onset time of a few days to several months following Rituximab exposure. No definitive predisposing factors have been identified. Patients experiencing any of the above mentioned reactions are advised to interrupt treatment and seek medical evaluation immediately.

Reference:

SEIROGAN
OTC remedy and hepatic dysfunction

Japan. Three cases of hepatic dysfunction during treatment with the over-the-counter product ‘Seirogan’, which contains glycyrrhiza, creosote, gambir, phellodendron bark and citrus unshiu peel, have been reported; the product is indicated for the treatment of diarrhea, vomiting, food...
poisoning, etc. The MHLW has responded by calling for hepatic dysfunction to be added to the product label’s ‘Precautions’ section; the paragraph ‘The patient should consult a physician in the following cases’, is to include hepatic dysfunction as a serious adverse event that may occur rarely.

Reference:
MHLW Pharmaceuticals and Medical Devices Safety Information. ADR updates from Japan. Media Release, Mar 2001.

**TERBINAFINE TABLETS**

**Revised monograph for usage information**

Canada, USA. Novartis Pharmaceuticals (1, 2) has issued a ‘Dear Healthcare Professional’ letter informing them of the revisions in the warnings, precautions and adverse reactions sections of the product monograph for terbinafine (Lamisil®). The revisions are aimed at providing more detailed information regarding the use of terbinafine tablets in patients with liver disease and are in response to reports of rare cases of hepatic failure, some leading to death or liver transplant subsequent to therapy. Contraindications now include pre-existing liver disease in patients with liver disease and are in response to reports of rare cases of hepatic failure, some leading to death or liver transplant subsequent to therapy. Contraindications now include pre-existing liver disease in patients and chronic or active liver disease. The drug-interactions section draws attention to the fact that terbinafine is a potent inhibitor of the CYP 2D6 enzyme (2). Physicians are therefore required to exercise great caution while prescribing terbinafine in patients receiving concomitant therapy with drugs metabolised by this enzyme system, especially those with a narrow therapeutic window.

Reference:


**THIORIDAZINE QT prolongation risk prompts prescribing update**

**New Zealand.** The prescribing information for thioridazine (‘Melleril’, ‘Aldazine’) has been updated in New Zealand following recommendations made by the Medicines Adverse Reactions Committee in that country. In suggesting the changes, the committee considered a Medsafe-commissioned expert report and international regulatory action, and it concluded that it would be prudent to take steps to reduce the risk of QT interval prolongation in thioridazine recipients.

Thioridazine is now contraindicated in the presence of the following risk factors for arrhythmia:

- use of drugs that inhibit the metabolism of thioridazine (e.g. cimetidine, pindolol, propranolol and most antidepressants)
- use of medicines known to be associated with QT interval prolongation (e.g. cisapride, most anti-arrhythmics and some antipsychotics)
- existing QT interval prolongation (QTc = 500 ms) or factors which predispose the patient to QT interval prolongation.

Treatment with thioridazine should only be initiated by a specialist as third-line therapy, and with observation of the following precautions for new patients.

Risk factors for arrhythmia should be assessed.

- QTc interval should be <500ms and any abnormal potassium level should be corrected.

Reference:
Medsafe. Available from URL: http://www.medsafe.govt.nz

Reports in WHO-file: QT prolonged 34
ACICLOVIR & VALACICLOVIR

Reports of Neurotoxicity

Sweden. Aciclovir is an antiviral agent useful in the treatment of Herpes, Varicella-Zoster and other infections. According to the Swedish Medical Products Agency (MPA), as on November 2000, 54 of the 96 Adverse Drug Reaction (ADR) reports on aciclovir included CNS associations such as confusion, hallucinations, psychosis, agitation, seizures, impaired coordination, etc. Similar reactions were seen in 20 out of the 27 reports filed on valaciclovir, the prodrug for aciclovir.

Many of the affected patients had renal insufficiency and most were aged over 60 years. Approximately half the patients with renal insufficiency who experienced CNS effects received higher than recommended dosages of the drugs; the product information states that the dosage should be adjusted to a patient’s degree of renal insufficiency. Concomitant psychoactive medications could have also been a risk factor, says the MPA. Such adverse CNS reactions with aciclovir or valaciclovir can be treated with haemodialysis, which results in symptomatic improvement.

Reports in WHO-file: Confusion 330, delirium 30, hallucination 202, psychosis 37


ALLOPURINOL

Adverse reactions include fatal aplastic anaemia

Sweden. As of November 2000, 311 reports have been filed for allopurinol, an anti-gout drug, detailing 423 adverse drug reactions (ADRs), in the Swedish ADR database. Common ADRs in the reports were skin reactions (n = 220), blood dyscrasias (69), general symptoms and findings (40), liver and bile disorders (35) and gastrointestinal effects (19).

Among the blood dyscrasias, 6 cases of fatal aplastic anaemia were reported, involving 4 women and 2 men who received allopurinol 100–300 mg/day; 5 patients were over 70 years, while one of the men was 55 years of age. Four patients received allopurinol for 3–5 months before developing symptoms of aplastic anaemia, while the remaining 2 patients had received treatment for several years and had been hospitalised weeks or months before aplastic anaemia developed. All the patients were also receiving medications for other concurrent diseases. Signs and symptoms leading to the diagnoses of aplastic anaemia included thrombocytopenia, which was severe and dominant in several patients, haematoma, fainting, chest pain, anaemia, purpura, fatigue and epistaxis. All the patients died within 2 days to 4 months of diagnosis.

Allopurinol dosage adjustments according to renal function are important in patients with kidney damage. Concomitant psychoactive medications could have also been a risk factor, says the MPA. Such adverse CNS reactions with aciclovir or valaciclovir can be treated with haemodialysis, which results in symptomatic improvement.

References:

• Reports in WHO-file: Anaemia aplastic 69

BUPROPION

Early prediction of ADRs following widespread use

Australia, Singapore, UK. Bupropion, an antidepressant, has been in the news lately, following its widespread introduction in late 2000 as an aid to quit smoking. Since November 2000 the Adverse Drug Reactions Advisory Committee (ADRAC) in Australia has received 780 reports of suspected adverse drug reactions with bupropion (amfebutamone)(1). Most of these were hypersensitivity reactions, or neurological or psychiatric effects. Hypersensitivity reactions included urticaria (167 reports), other
rashes (86) and pruritic reactions (46), facial or angioneurotic oedema (62) and serum sickness-like reactions (33). Neurological and psychiatric reactions consisted of dizziness/ataxia (78 reports), insomnia (78), headache (68), agitation (58), tremor (57), seizures/twitching (48), depression (45) and paraesthesia/hypoaesthesia (40). ADRAC points out that bupropion is contraindicated in patients with epilepsy, and should be used with caution in those with a predisposition to seizures, those taking substances known to lower the seizure threshold and those with a history of psychiatric conditions, particularly if they are also taking other medications.

Other ADRs reported with bupropion include nausea (87 reports), chest pain (54), shortness of breath (38), increased sweating (33) and vomiting (30). There were 9 reports with fatal outcome in patients aged 30-61 years. However, ADRAC points out that the deaths may have been coincidental and that so far bupropion has not emerged as a cause of unexpected deaths.

The Singaporean Pharmacovigilance Unit has received 3 reports of seizures with bupropion (amfebutamone) in recipients who had not consumed alcohol and had no history of seizure disorders. The men, aged 37-41 years, were hospitalized with seizures 5-10 days after starting treatment with bupropion 150mg twice daily. They all subsequently recovered and did not experience any more seizures. The risk of seizures in patients with factors that may predispose them to this condition is emphasised by the Singaporean Pharmacovigilance Unit. Other adverse events reported in association with bupropion in Singapore include insomnia, facial oedema, chest pain and vomiting. Reports in the WHO-file from Singapore include 929 cases of convulsions, 5 reports of aggravated convulsions and 410 cases of grandmal convulsions.

A total of 6570 reports of suspected adverse drug reactions associated with the use of bupropion have been received via the Yellow Card Scheme in the UK up to 24 September 2001, says the Medicines Control Agency (MCA). However, it is emphasised that these suspected reactions may have been associated with other factors, such as nicotine withdrawal or concomitant medicines or disease. There have been 160 reports of seizures associated with the use of bupropion in the UK. However, in approximately half of the reports the patients had a history of, or risk factors for, seizures says the MCA. Reports in WHO-file record 115 bupropion related deaths in the UK with 24 sudden deaths.

In view of the adverse reaction reports, GlaxoSmithKline (manufacturer of Zyban and Wellbutrin SR) has sent out a 'Dear Health Professional' letter, reiterating the contraindications, drug interactions, risk of seizures and precautions thereof with bupropion. Professor A Breckenridge, Chairman, Committee on Safety of Medicines, U.K., has advised prescribers to start with the lower (150 mg) dose of Zyban (bupropion/amfebutamone) for the first six days, increasing to 150 mg twice daily only on the 7th day, in contrast to the previous practice of increasing the dose on the 4th day. Further, in patients with a known risk for seizures, he advises using the lower dose (of 150 mg daily) throughout the treatment period, provided there is compelling clinical justification for the use of Zyban in these patients.


CETIRIZINE

Serious liver disorders underlying non-specific symptoms

Sweden. Serious liver disorders occurred in a 9-year-old girl who was receiving cetirizine (‘Zyrlex’) for allergic rhino-conjunctivitis with pruritus. During the 6-12 months after starting cetirizine, the girl developed abdominal pain and episodes of nausea and vomiting. She was admitted to a children’s clinic 18 months after starting cetirizine. Her AST and ALT levels were elevated at 7.24 pkat/L and 14.4 pkat/L, respectively, and her lactate dehydrogenase level was elevated at 11 pkat/L. Treatment with cetirizine was discontinued. Within 1 week, the girl’s elevated liver enzyme levels had decreased by about 50%, and they continued to improve over the next 6 weeks. At follow-up, she had completely recovered.

The reported case emphasises the importance of following up non-specific symptoms in patients, which can sometimes hide a serious adverse drug reaction.

Reports in WHO-file: SGOT increased 12, SGPT increased 13, hepatic failure 1, hepatic necrosis 1


ETHINYL-ESTRADIOL/DESOGESTREL

Fatal pulmonary embolism in patient with risk factors for thrombosis

Sweden. A 16-year-old girl with known risk factors for thrombosis
SAFETY OF MEDICINES

died from a pulmonary embolism after receiving the oral contraceptive ethinylestradiol/desogestrel (‘Mercilon’). The girl, a smoker, had venous deformities and a hereditary disposition for thrombosis. She suddenly went into respiratory and circulatory arrest 5 months after receiving a prescription for ethinylestradiol/desogestrel. She underwent resuscitation, but she died upon arrival at hospital. The Swedish Medical Products Agency wants to call the attention of all prescribers of oral contraceptives to check the risk factors before prescribing oral contraceptive pills.

Reference:
Medical Products Agency: 45, Apr 2001

GEMFIBROZIL

Pancreatitis: serious case report

Sweden. Treatment with gemfibrozil (‘Lopid’) was associated with pancreatitis on more than 1 occasion in a 47-year-old woman with hypercholesterolaemia and hypertension, and a history of cholecystectomy. The woman, who was also receiving furosemide and atenolol, developed abdominal pain, liver reactions and an increased amylase level during treatment with gemfibrozil twice daily (dose and duration of treatment not stated). An abdominal CT scan showed an enlarged pancreas with some indistinct contours. The woman was hospitalized on 3 different occasions with abdominal complaints. Each time pancreatitis was evident for the subsequent 5 weeks. During each episode, gemfibrozil was withdrawn and her abdominal pain resolved. Fibrates, like statins, can cause pancreatitis in rare cases. The Swedish Medical Products Agency urges medical professionals to be vigilant and report suspected cases.

Reference:
Medical Products Agency: 44, Apr 2001

LEFLUNOMIDE

Concomitant therapy with methotrexate can precipitate adverse reactions

Australia. The immunomodulator leflunomide has been associated with 191 suspected ADRs since its launch in early 2000, and in many of these cases, the patient was also receiving methotrexate, despite leflunomide’s registration being based on monotherapy (see table). ADRAC says prescribers need to be aware that concomitant methotrexate use may predispose patients to ADRs with leflunomide.

Reference:

Incidence of adverse drug reactions (ADRs) in Australia for leflunomide since its launch

<table>
<thead>
<tr>
<th>ADR</th>
<th>Total</th>
<th>Number of reports with concomitant methotrexate</th>
<th>With a fatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin disorders</td>
<td>64</td>
<td>13</td>
<td></td>
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<tr>
<td>- serious skin disorders*</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td>Liver dysfunction</td>
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<td>15</td>
<td>2</td>
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<td>Haematological disorders</td>
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<td>11</td>
<td>6</td>
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<tr>
<td>- pancytopenia</td>
<td>11</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>- leucopenia/neutropenia</td>
<td>6</td>
<td>2</td>
<td>1**</td>
</tr>
<tr>
<td>- anaemia</td>
<td>4</td>
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<td>- thrombosis</td>
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<td>Respiratory disorders</td>
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<tr>
<td>- adult respiratory distress syndrome</td>
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<td></td>
<td></td>
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<tr>
<td>Nausea/vomiting</td>
<td>31</td>
<td>11</td>
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<tr>
<td>Diarrhoea/abdominal pain</td>
<td>63</td>
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<td>Alopecia</td>
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<tr>
<td>Facial or angioneurotic oedema</td>
<td>10</td>
<td>2</td>
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<tr>
<td>Bodyweight loss</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Blank cells indicate data not provided
* including bullous eruption, skin ulceration, Steven's Johnson syndrome, vasculitis, erythema multiforme and skin necrosis
** with neutropenia
NEFAZODONE
Risk of severe liver injury
Canada. Nefazodone is an antidepressant sold in Canada under the trade names of Serzone, Lin-Nefazodone and Apo-Nefazodone. A worldwide post marketing surveillance of nefazodone has revealed reports of jaundice, hepatitis, and liver failure with occasional hospitalisations, liver transplantations or death. Health Canada has therefore issued an advisory to consumers encouraging patients to contact their physicians regarding the signs and symptoms of possible liver dysfunction and to discuss the need for laboratory tests for liver function monitoring. While patients must contact the physician before discontinuing the drug, they should stop the medication and see their physician immediately if they develop signs of jaundice or pass brown-coloured urine. The symptoms of liver injury from nefazodone include nausea, vomiting, unusual tiredness, weakness, stomach or abdominal pain and/or loss of appetite and patients experiencing any of the above effects should contact their doctor right away.

Reference:

NSAIDs
Risk of lower GI tract damage
New Zealand. Nonsteroidal antiinflammatory drugs (NSAIDs) may cause damage to the distal small intestine and large intestine, in addition to their known effects on the stomach and duodenum, according to the Centre for Adverse Reactions Monitoring (CARM), New Zealand. While minor damage to the lower GI tract is common, more serious adverse effects are thought to occur rarely, with haemorrhage and perforation estimated to occur in 1 in 5000 NSAID users per year.

Two cases of intestinal ulcers associated with NSAID use have recently been reported to the CARM. In the first report, a 39-year-old woman, who had been taking slow-release ketoprofen for many years, experienced repeated episodes of intestinal obstruction and iron deficiency anaemia over a 5-year period. She was found to have intestinal mucosal ulceration and diarrhoea strictures. In the second report, a 73-year-old woman, who had taken slow-release diclofenac for several months, experienced massive GI haemorrhage and was found to have colonic and ileal ulceration. She recovered following drug withdrawal and blood transfusion.

In addition to haemorrhage and ulceration, NSAIDs may cause GI obstruction due to diarrhoea stricture formation. These strictures are characteristic of NSAID-induced intestinal damage. Reports of diarrhoea strictures in the large intestine have been published, mostly associated with slow-release or enteric-coated NSAID preparations. Blood loss, anaemia and obstruction (due to diarrhoea stricture formation) may suggest small intestine damage. In addition, postprandial colicky pain with a history of iron deficiency and hypoalbuminaemia suggests diarrhoea strictures in the small intestine. Chronic diarrhoea, iron deficiency anaemia and bodyweight loss are all suggestive of ulcers and diarrhoea strictures in the large intestine. NSAIDs may also complicate existing bowel disease such as Crohn's disease or ulcerative colitis, and distinction between relapse and NSAID-induced exacerbation may be difficult.

When NSAID-induced GI complications are suspected, immediate investigation and referral to a specialist is recommended. In addition, all NSAID use should be discontinued while investigations are carried out.

Reference:

OMEPRAZOLE
Iron deficiency anaemia: first case report
Sweden. Long-term treatment with omeprazole ("Losec") was associated with iron malabsorption resulting in anaemia in a 44-year-old man. He had been receiving omeprazole for several years (dosage and therapeutic indication not stated).

During a period of hospitalisation for severe alcoholic hepatitis, the man's haemoglobin level was consistently < 100 g/L, and upon admission his transferrin saturation was 50%. At a follow-up visit 1 month after discharge, his transferrin saturation was 6% and he had a haemoglobin level of 90 g/L and a pathologically low mean cell haemoglobin level. He was treated with ferrous sulfate, but his haemoglobin had not increased 2 weeks later. An iron absorption test showed a very weak rise in his serum iron levels. Treatment with omeprazole was withheld. A repeat iron absorption test 2 days later revealed similarly reduced iron absorption, but another test 3 weeks after omeprazole was stopped showed improved iron absorption. At that time, the man's transferrin saturation had increased to 11%, and it had normalised 2 months after stopping omeprazole; his haemoglobin level was 122 g/L. The marked improvement of the patient's iron status and ability to absorb iron following withdrawal of treatment suggests a considerable inhibition of iron absorption during treatment.

Reference:

Reports in WHO-file: Ketoprofen:
Intestinal obstruction 4; diclofenac:
Colitis ulcerative 32

Reference:

Reports in WHO-file: Anaemia
hypochromic 43
SAFETY OF MEDICINES

**PROPOFOL**

**Warnings against heart failure with high dosages**

**Norway.** The Norwegian Medical Products Agency has announced the following recommendations in response to reports of heart failure with high dosages of propofol.

- Careful monitoring is necessary when adults receive propofol infusions for more than 48h.
- Propofol 4 mg/kg/h (the recommended maximum dosage) should not be exceeded during long-term sedation.
- Signs of heart failure, metabolic acidosis or increased serum creatine kinase levels in patients receiving long-term sedation must be investigated immediately. If other causes cannot be determined, propofol infusion must be discontinued and a different anaesthetic should be used.

The announcement described 2 related incidents of adverse reactions associated with high propofol dosages:

1. A condition characterized by arrhythmias, heart failure, metabolic acidosis and rhabdomyolysis observed in children sedated with relatively high dosages of propofol for >48h.
2. Seven adults treated in an intensive care unit in The Netherlands for head injuries who died after developing similar symptoms. The affected patients had received higher dosages of propofol when compared to similar patients who did not develop the condition (6.5 mg/kg/h vs 4.8 mg/kg/h, respectively). The report notes that high vasopressor dosages may have been a contributory factor.

**References:**


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**RANITIDINE**

**Serious haemolytic anaemia in an elderly patient**

**Sweden.** Treatment with ranitidine (‘Zantac’) was associated with the development of haemolytic anaemia in a 68-year-old man with recurrent gastritis. The man had been treated with ranitidine 300 mg/day for approximately 2 years when he was hospitalised with fatigue. His haemoglobin level was low at 73 g/L, 26% of his RBCs were reticulocytes, and a Coombs’ direct test was positive, suggestive of haemolytic anaemia. Treatment with ranitidine was stopped and the man was treated with cortisone. Four months later, his haemoglobin level and reticulocyte count had normalised.

**References:**


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**ROSIGLITAZONE**

**Hepatic and cardiovascular ADRs reported**

**Canada.** Between March 2000 and 23 Feb 2001, there were 166 rosiglitazone (‘Avandia’)–associated adverse drug reactions (ADRs) reported to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP). Of these, 38 were classified as serious; there were 20 reports of cardiovascular disorders, 10 of liver and biliary disorders, and 8 of haematological disorders. The serious reports included the following 3 fatal cases.

- A 51-year-old man with hepatitis B antigens had normal baseline liver enzyme levels that became elevated 6 weeks after starting rosiglitazone. Rosiglitazone

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**PRAMIPEXOLE & ROPINIROLE**

**Sleep attacks**

**Canada.** Recent adverse drug reaction reports associated with pramipexole (‘Mirapex’; Boehringer Ingelheim) and ropinirole (‘Requip’; SmithKline Beecham) have included a higher proportion of sleep disorder cases according to the Canadian Adverse Drug Reaction Newsletter.

Sleep-related disorders constituted 26/57 and 16/17 of the reports of adverse reactions associated with ropinirole and pramipexole, respectively, made to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) as of 10 October 2000. 19 of those associated with ropinirole, and all 16 of those associated with pramipexole, were of sudden onset of sleep, or variants thereof. In some of these cases, the patient was driving when the event occurred. The episodes typically only last for a few seconds and are often not preceded by warning symptoms such as unusual fatigue.

Warnings not to drive or engage in other activities in which impaired alertness may impose increased risk to the patient or others have been previously issued by the manufacturers of both drugs. The Canadian Medical Association has published guidelines to assist physicians in evaluating a patient’s ability to drive.

**References:**

- **Medical Products Agency:** 44, Apr 2001.

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**References:**

- **Canadian Adverse Drug Reaction Newsletter 11:** 1-2, Apr 2001.
was stopped, but he died 1 week later due to liver failure.  

- A 56-year-old woman developed shortness of breath 4 months after starting rosiglitazone. She was hospitalized where an examination showed sinus tachycardia with premature ventricular contractions. She died 3 weeks later of a probable pulmonary embolism.  

- A 75-year old man was hospitalized with weakness during treatment with rosiglitazone (duration of therapy not stated). He experienced a myocardial infarction and subsequently died.

In all 10 reported cases of rosiglitazone-associated liver ADRs, increases in liver enzyme levels of <2 to >3 times the upper normal limits were seen during a treatment period of a few weeks to 6 months. At least 3 patients had a history of known liver disorders. Among the 20 reports of cardiovascular disorders during treatment with rosiglitazone, there were 8 reports of congestive heart failure; in 5 cases, this occurred within 3-6 days of starting rosiglitazone. Reports of oedema in the absence of heart failure have also been received. Reported cases of haematological disorders include anaemia, iron-deficient anaemia, low haemoglobin level, neutropenia, leucopenia, pancytopenia, decreased platelet production, thrombocytopenia and prolonged prothrombin time.

To minimise the risk of hepatic and CV ADRs with rosiglitazone, physicians should comply with all recommendations associated with the drug and exercise caution when prescribing rosiglitazone to patients with fluid retention, mildly elevated liver enzyme levels or underlying cardiac conditions. Furthermore, patients receiving the agent should be advised to be vigilant for signs of congestive heart failure and liver disorders.

Reports in WHO-file: Liver and biliary system disorders 510

**SILDENAFIL**

Not to be prescribed with nitrates

**New Zealand.** Medsafe has emphasised the importance of asking patients about sildenafil (‘Viagra’) use before administering any formulation of nitrates; patients prescribed nitrates should be reminded not to take sildenafil. Also, patients being prescribed sildenafil should be asked about regular or intermittent nitrate use, including recreational use.

Medsafe says that patients taking sildenafil who develop acute angina pectoris should be given analgesics for pain and/or other angina treatments, e.g. aspirin, morphine, oxygen, β-blockers and heparin. In cases of serious or complicated angina or chest pain in sildenafil recipients, advice from a cardiologist should be sought and the patient should be hospitalized immediately. While it has been indicated that it is safe to administer nitrates 24 hours after sildenafil has been taken, factors which impair sildenafil clearance, such as age >65 years, hepatic or renal impairment, or concomitant use of CYP3A4 inhibitors, will extend the time for which nitrates should be withheld. If there is doubt about whether it is safe to administer nitrates, advice from a cardiologist or emergency physician should be sought.

Coadministration of sildenafil and nitrates has the potential to cause an additive vasodilatory effect resulting in severe, possibly life-threatening, hypotension. If a decision to administer nitrates to patients who have received sildenafil is made, or if inadvertent co-administration of these agents has occurred, the patient must be closely monitored with readily available facilities for fluid and vasopressor support, and emergency resuscitation.

**Reference:**
Canadian Adverse Drug Reaction Newsletter 11: 2-3, Jul 2001

**TRASTUZUMAB**

Avoid anthracyclines for 22 weeks following therapy

**Europe.** The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement advising that anthracycline therapy should be avoided for 22 weeks following the discontinuation of trastuzumab (‘Herceptin’). Concomitant use of trastuzumab and anthracyclines is associated with an increased risk of cardiotoxicity. Data from an ongoing clinical study indicate that the half-life of trastuzumab is approximately 25 days, not 5–6 days as previously believed. As such, trastuzumab may remain in a patient’s circulation for ~18 weeks (range 15–22) after the drug is discontinued, and therefore an increased risk of cardiotoxicity with concomitant anthracyclines may exist.

The EMEA advises that where a necessity for anthracycline therapy exists after stopping trastuzumab, careful monitoring of the patient’s cardiac function should be performed. Physicians are advised to continue to prescribe trastuzumab in accordance with the current approved prescribing information to ensure that patients receive adequate treatment with the drug.

**Reference:**

**Available from URL:**
http://www.eudra.org
Mesenteric ischaemia during the use of sumatriptan and other triptans

The use of selective 5HT1-receptor agonists or ‘triptans’ is frequently associated with diarrhoea and gastric symptoms. Constipation, dysphagia and gastroesophageal reflux are infrequent. Gastrointestinal bleeding, hematemesis, melaena, peptic ulcer and gastrointestinal pain have occurred rarely (i.e. as events, not as established adverse effects). These drugs are not known to cause colitis or intestinal ischaemia.

There are now a total of 24 reports of colitis as suspected adverse effects of sumatriptan in the UMC database and two additional reports in association with respectively naratriptan and rizatriptan. Interestingly in 11 of these reports the term Colitis ischaemic is explicitly used. Four of the reports are probably duplicate reports. Furthermore, there are 8 reports of Intestinal ischaemia and 9 of Intestinal necrosis, with or without simultaneous (ischaemic) colitis. Of these 43 reports 41 came from the USA, one from New Zealand and one from Germany.

Since Colitis ischaemic is not a WHO Adverse Reaction Terminology (WHOART) preferred term but an included term, it is difficult to calculate the statistical parameters. A number of reports of clinical ischaemic colitis may have been coded with the preferred term Colitis (in connection with any drug) and most reports of colitis in the database are not ischaemic colitis.

In most if not all case reports the connection between the drug and mesenteric ischaemia is uncertain. It is noteworthy that there are 12 case reports with a ‘positive dechallenge’ (two probable duplicate reports excluded) and that there are 5 reports with a ‘positive rechallenge’. This may be suggestive of a genuine relationship, but these observations need to be studied in more detail. There is a remarkably wide variation in the interval between the start of the drug and the start of the reaction and in many reports the outcome is not documented. There is a predominance of 30+ female patients, which is likely to reflect the epidemiology of migraine. In most of the reports the route of administration is recorded, but unfortunately the dose is not.

In none of the reports there were other drugs simultaneously reported as suspected. It is noteworthy that six patients have also been taking oestrogens, another possible cause of mesenteric ischaemia. On the other hand, the use of hormones could be expected from the age and sex of these patients.

Ischaemic colitis develops secondary to a process that decreases the mesenteric blood supply. A number of case reports with a short interval of only 1-12 days and the reports with a positive dechallenge or a positive rechallenge may be suggestive of a direct action on the arterial blood supply, e.g. arteriospasm (as in the case of ergotamine). Several reports with a long latency period (> 1 year), on the other hand, might be secondary to an indirect process, e.g. fibrosis or vasculitis; in one case report the term arteritis is included.

The number of cases of a ‘Large intestinal ulcer’ is difficult to assess, since the corresponding preferred term is ‘Gastric ulcer’. There are 54 reports of other adverse reactions, i.e. GI haemorrhage, Haemorrhage rectum, GI mucosal necrosis general, Diarrhoea bloody, Rectal bleeding, Blood in stool, Small intestine obstruction, Melaena, Large intestinal ulcer or Gastric ulcer, that may also be of additional interest. In as many as 27 of these cases these latter terms were reported together with colitis, intestinal ischaemia and intestinal necrosis. Of these 54 reactions 11 were reported in countries other than the USA. The reports of rectal bleeding and proctitis are remarkable since in ischaemic colitis the rectum is usually not involved.

Triptans such as sumatriptan are selective agonists for a vascular 5-hydroxytryptamine 1 receptor subtype (probably a member of the 5-HT 1D family), have only a weak affinity for 5-HT 1A , 5-HT 5A , and 5-HT 7 receptors and have no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT 2 , 5-HT 3 , or 5-HT 4 receptor subtypes or at alpha 1-, alpha 2-, or beta-adrenergic, dopamine 1, dopamine 2, muscarinic, or benzodiazepine receptors. 5-HT1 agonists can cause coronary artery spasm and cardiac ischaemia. Perhaps occasionally also mesenteric arterial constriction may occur and lead to ischaemic colitis. In other cases, a vasculitis or a fibrotic process might underlie mesenteric ischaemia.

The data reported in the USA and occasionally in other countries suggest that sumatriptan and other 5HT1-receptor agonists can occasionally cause intestinal ischaemia, leading to ischaemic colitis and intestinal haemorrhage or necrosis. Further study is needed to find out if the connection is true or not and more information...
would be needed with regard to the pathology, the mechanism and the frequency of this rarely reported but serious adverse event.

**Clopidogrel, agranulocytosis and other blood dyscrasias**

Clopidogrel (Plavix) is used for the prevention of thrombotic events such as myocardial infarction or stroke in patients with atherosclerosis. In the UMC Associations Database of the last quarter of 2000, there were significant connections found between clopidogrel and agranulocytosis and granulocytopenia. Because of the chemical relationship with ticlopidine, itself a notorious cause of agranulocytosis and thrombocytopenia, it is of interest to know whether or not clopidogrel can cause agranulocytosis and how frequent it would be. Although in the Physicians Desk Reference and the EMEA Summary of Product Characteristics (March 2001) the words agranulocytosis and granulocytopenia are not used, the following information is given: 'Severe neutropenia (<0.45 x 10⁹/l) was observed in 4 patients (0.04%) that received clopidogrel and 2 patients (0.02%) that received ASA. Two of the 9599 patients who received clopidogrel and none of the 9586 patients who received ASA had neutrophil counts of zero. One case of aplastic anaemia occurred on clopidogrel treatment’. No recommendations are given regarding the monitoring of leukocyte and platelet counts and the warning signs of agranulocytosis and thrombocytopenia. Since bleeding disorders are relatively common during the use of clopidogrel the recognition of underlying thrombocytopenia may be delayed.

Reports in the UMC database suggest that, in addition to granulocytopenia and agranulocytosis, clopidogrel also causes other serious haematological reactions (e.g. thrombocytopenia and thrombotic thrombocytopenic purpura). The statistical parameters show that clopidogrel is substantially more frequently reported in combination with haematological events than expected from the background of the database. To enable a thorough evaluation of the balance of benefit and risk of clopidogrel, prescribers need precise information on the frequency of agranulocytosis and other haematological reactions. Patients using clopidogrel should be closely monitored.

**Reference**

1. Physicians Desk Reference

**Signal follow-up: Itraconazole use during pregnancy**

By April 2000 the UMC had received 43 case reports from 5 countries regarding the use of itraconazole by pregnant women. 25 of these pregnancies ended in embryonic or foetal death. The remaining 19 reports described a variety of congenital malformation or neonatal disorders. In the 38 reports in which the route of administration was specified the drug was taken orally. The data suggested that:

1. inspite of the approved recommendations and warnings itraconazole is being taken by pregnant women for minor indications,
2. reported human experience seems to lend support to the experimental evidence that itraconazole is teratogenic,
3. there is a predominance of abortion, and
4. more firm warnings may be needed in the product information.

Although not apparent from the UMC reports, a further question of interest was if itraconazole might decrease the reliability of oral contraceptives and so lead to unintended exposure in pregnancy.

Given below is a summary of the follow-up information provided in the responses from national centres and by the Janssen Research Foundation:

**Germany**

BfArM in Germany received a total of 15 cases of abortion or foetal death, reported in suspected association with itraconazole (February 2000). In addition there were 6 reports of a variety of different congenital anomalies and, interestingly, a further 10 reports describing macrosomia, in several cases together with hypoxia and acidosis. Macrosomia is a well-known manifestation of diabetes mellitus, but is not a recognised adverse drug reaction. In only 1 of the 10 macrosomia reports the mother was recorded to have also been using an antidiabetic drug (insulin). (Since macrosomia is not a WHOART term, these cases are coded as ‘neonatal adverse effect’.) The possible connection between maternal itraconazole and neonatal macrosomia is currently under investigation. Most case reports regarding pregnant women documented the route of administration; itraconazole was administered parenterally in only four.

**United Kingdom**

Up till February 2000 the Medicines Control Agency (MCA) had received 5 case reports describing a variety of congenital anomalies reported in suspected connection with the maternal use of itraconazole. Abortion or intrauterine death was reported in a further 8 patients. There was one ectopic pregnancy. In 9 of these cases the indication was reported: 6 patients had vaginal candidiasis, one ‘candida nos’, one dermatomycosis and one onychomycosis. The MCA has
received two reports of unintended pregnancy occurring during the use of itraconazole; both patients had simultaneously been taking an oral contraceptive. There were a further 9 reports of menstrual disorders, including 4 patients who had simultaneously been using oral contraception. MedDRA has macrosomia as a preferred term, but this condition does not appear to have been reported in association with itraconazole in the UK.

**USA**

World-wide, the FDA Office of Postmarketing Drug Risk Assessment (OPDRA) has collected data regarding 55 cases of adverse pregnancy or foetal events after maternal exposure to itraconazole during pregnancy (April 2000). In all reports the indication for use was either vulvovaginitis, onychomycosis or an unspecified mycosis. All but one patient took the drug orally. There were 15 abortions or intrauterine death and one ectopic pregnancy. 30 reports referred to a variety of malformations or neonatal disorders, including 8 cases of skeletal malformations, 4 of heart abnormalities and another 4 of chromosomal abnormalities. 16 of these 55 reports were from the United States, including 7 cases of abortion. In the USA no cases of macrosomia have been reported.

In total there were four cases of unintended pregnancy – three in the USA and one in Belgium (in addition to the two reports in the UK, see above); three more patients had simultaneously been taking birth control pills.

Janssen Research Foundation Pregnancy Database (JPDA) and literature contains information regarding 263 women who used itraconazole and have approached Janssen Pharmaceutica while being pregnant. These women are prospectively followed-up with regard to the outcome of pregnancy. In a recent study of the JPDA the results were presented regarding 229 of these pregnancies (156 live births\(\textsuperscript{1}\)). The findings were compared with the pregnancy outcomes in women who had, for one or another reason, contacted the teratogen information service of the Canadian Motherisk Programme and had not taken itraconazole at any moment during pregnancy (199 187 live births). In the itraconazole group there were major malformations in 3.2% of the children as compared to 4.8% in the control group. The relative risk for the itraconazole group was 0.67 (95% CI 0.23-1.95). The rate of pregnancy loss (including therapeutic abortion) was higher in the itraconazole group (RR = 1.75, 95% CI 1.47-2.09) and also the birth weight was lower as compared with the control group. A question of some interest may be if the malformations in the Motherisk Programme comparison group are a representative background or may have been influenced by selection bias.

Prescription Event Monitoring data at the Southampton Drug Surveillance Unit showed that the proportion of live infants with a congenital malformation born to mothers who were exposed to a number of newly marketed drugs were similar to that estimated by the Office for National Statistics\(\textsuperscript{2}\). In this series there were 53 women exposed to itraconazole and 94 exposed to fluconazole.

**UMC point of view**

It is inherent in the spontaneous reporting system that only adverse pregnancy outcomes are reported and that healthy babies remain unrecorded. In other words, adverse experiences are selectively accumulating in the UMC database. In all case reports of abortion or malformation the connection with itraconazole is uncertain or doubtful. The various reported adverse events may not differ from the random background occurrence. With 10 such case reports, there is a possibly interesting association between itraconazole and neonatal macrosomia. This finding is confirmed to Germany, however, and currently under investigation. Apart from macrosomia and a predominance of intrauterine death, there is in international pharmacovigilance not a particular pattern visible of congenital malformations occurring after intrauterine exposure to itraconazole.

The reports show that itraconazole is often taken by pregnant women for non-serious indications, disregarding the approved recommendations for use. Most reports refer to oral use and few to vaginal application.

In the data collected in the pregnancy database of the Janssen Research Foundation and at the Southampton Drug Surveillance Unit the frequency of malformations after exposure to itraconazole was not increased. In a recent study using the UK General Practice Research Database, on the other hand, the relative risk of having a baby with a congenital disorder for women having used 'an oral azole antifungal drug' (apparently itraconazole) was 2.1 as compared with non-exposed women\(\textsuperscript{3}\). Because of the small number of cases there was a 95% confidence interval as wide as 0.7 - 6.8. Although the first two quoted studies are reassuring, for the time being itraconazole remains to be a potentially teratogenic agent. More studies are needed to decide whether or not itraconazole is safe in pregnant women.

Although there is a suspicion that itraconazole may interact with oral contraceptives and may delay withdrawal bleeding in the pill-free period the evidence is suggestive of oestrogen potentiation and not inhibition\(\textsuperscript{4,5}\), making a decrease of effectiveness less likely. Only few cases have been reported, in the literature\(\textsuperscript{6,7}\) as well as in international pharmacovigilance, of unintended pregnancy during...
the combined use of itraconazole and oral contraceptives.

Reference:

Events
1. The 24th Annual Meeting of Representatives of National Centres Participating in the WHO Drug Monitoring Programme was held in Dunedin, New Zealand from 19-23 November, 2001.
2. The Tenth International Conference of Drug Regulatory Authorities (ICDRA), which was originally scheduled for 5-8 November, 2001, has been postponed to the year 2002. The new schedule will be announced at a later date. The meeting will be preceded by the WHO organized one-day satellite workshop (the pre ICDRA workshop) on ‘The Impact of Regulation on the Safe Use of Drugs’.
A growing menace

Russia, USA. The Russian health ministry announced that 56 drugs and medicines were counterfeited in Russia in the year 2000. The ministry reports that up to 3.6% of all drugs in Russia are fakes. Most of the fake drugs in Russia are ‘high volume, low cost’ antibacterials. The Association of International Pharmaceutical Manufacturers has called on the Russian government to form a special commission to combat the illegal trade.

The number of parcels of counterfeit and other prescription drugs seized by the US Customs Service increased sharply from 2145 in 1998 to 9725 in 1999. More recently, in the year 2001, three counterfeit prescription drugs were identified in the American Pharmacies. The drugs included filgrastim (Neupogen), an anticancer drug sold by Amgen and two versions of the human growth hormone somatropin, Serostim, made by Serono and Nutropin, which is sold by Genentech. All three companies informed the US FDA which launched an investigation in May 2001.

Reference:
WHO project on implementation and development of national and regional systems of pharmacovigilance in the Newly Independent States of Eastern Europe

Prof Vladimir K. Lepakhin, Senior Clinical Adviser, Essential Drugs and Medicines Policy, WHO

Since the last decade the Newly Independent States (NIS) of Eastern Europe (former republics of the Soviet Union) have been encountering the very complicated processes related to the transitional period. Widespread economic and social changes have substantially affected health care in general, and the pharmaceutical sector in particular, in these countries.

From the very beginning WHO has been providing help in different areas of health care to NIS which has a total population of 285 million. The special project for NIS, Pharmaceutical Sector Reforms, was started in 1994 by the Action Programme on Essential Drugs (now Essential Drugs and Medicines Policy (EDM) based in WHO Headquarters and the Regional Office for Europe (EURO) with the purpose of creating sustainable capacity, mechanisms and systems in NIS that ensure that good quality drugs are accessible for the entire population and are prescribed and used rationally.

In 2000, in response to requests of eight NIS countries the WHO Headquarters (Essential Drugs and Medicines Policy/Quality Assurance and Safety: Medicines, (QSM)) started a new 3-year project “Implementation and Development of National and Regional Systems of Pharmacovigilance in NIS”. The objective of the Project is to reduce drug-related morbidity and mortality by establishing contemporary systems of drug monitoring, which should improve risk-benefit assessment of medicines and provide reliable information resulting in more rational use of drugs.

The following eight countries became participants of the Project:

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<td>Armenia</td>
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Preliminary investigations and evaluation of the current status in 2000 of the issue of drug safety monitoring revealed that the situation with regard to adverse drug reactions study and evaluation varies dramatically between these countries, depending on their particular stages of development and national capacities. Some of them, (Armenia, Russia and Ukraine) had a basic structure in place; others had no mechanisms for ADR monitoring.

A meeting of responsible representatives of Drug Authorities of all eight countries was convened in Moscow in April 2000 and the targets, indicators, outcomes and work plan for the project were elaborated. The working group for implementation and monitoring was established.

The following targets were agreed upon:

- inclusion of a special item on drug safety control into national legislation and/or regulations;
- establishing and strengthening of National and Regional (if relevant) ADR monitoring centres;
- human capacity development/education and training of specialists on pharmacovigilance;
- putting into practice systems of drug safety information for healthcare providers;
- establishing NIS network on pharmacovigilance;
- involving Member States in the WHO International Drug Monitoring Programme.

Educational and training materials were prepared and two training seminars (using "train the trainers" principle) were conducted for representatives of nine countries (the Deputy-Minister of Azerbaijan, Ministry of Health, joined the last seminar). All participants received relevant documentation for their practical activities.

WHO Guidelines for setting up and running a Pharmacovigilance Centre were adopted for NIS, translated into Russian and provided to the responsible officers in Drug Authorities of all countries.

Taking into account the local peculiarities and concrete realities in different countries, specific recommendations for setting up and the development of national systems of pharmacovigilance were given to each Member State of the Project. For example, it was recommended to the Russian Federation and Ukraine-states with large populations and big territories to establish the "regional system" of pharmacovigilance with the Federal Centre and a number of Regional Centres on Drug Monitoring.

The implementation of pharmacovigilance systems is a very complicated and difficult process and it can take years before the systems begin to work properly.

The preliminary results of the Project are the following:

- Four countries have included special items on pharmacovigilance in their legislation
and another four have prepared proposals for relevant amendments to their drug laws;

• All eight countries delegated functions of drug safety monitoring to their Drug Regulatory Authorities;

• Armenia, Moldova, Russia and Ukraine established and developed their National Centres for ADR monitoring;

• Regional ADR Centres were organized in the Russian Federation (29) and in the Ukraine (15);

• Armenia, Moldova and Russia started to publish special Bulletins on Drug Safety;

• The most difficult part, which may require years, is creating a reporting culture among practitioners. 7 countries have managed to start reporting of ADR.

• The most successful parts of the Project are informational and educational activities. All eight countries took steps for implementing education on drug safety into the curricula of under- and postgraduate education of medical students and doctors. More than 50 seminars, workshops and symposia on drug safety and rational use of drugs were organized using WHO educational materials. More than 2,000 doctors and pharmacists participated in these meetings and received relevant information.

In conclusion, one may say that for a relatively short period of time, much has been achieved, yet there is still a huge amount of work to be done for the real implementation of pharmacovigilance in the medical practice in NIS countries and the overall progress of the project will depend on continuing support from WHO.

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<tr>
<th>Countries</th>
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