We are pleased to report that the first meeting of the newly established Advisory Committee on Safety of Medicinal Products was held in October. This meeting was very productive and a number of recommendations as published in this issue were made. A statement was made by this Committee recommending the need to incorporate pharmacovigilance in the WHO strategy to provide antiretrovirals to three million people by 2005. The feature article emphasizes the urgency in evolving a safety strategy for herbal issues as these remain largely un-addressed.

Representatives from WHO attended the International Conference on Harmonization (ICH) expert working group meetings in November, in Osaka, as observers. The document Pharmacovigilance Planning, which describes the link between pre- and post-marketing surveillance will now be circulated to Member States for comments. The 26th Annual Meeting of the National Centres participating in the International Drug Monitoring Programme will be held in December, in India. The meeting will focus on ADR reporting and how it can be improved. A detailed report of this meeting will appear in one of the later issues.
REGULATORY MATTERS

ASTEMIZEOL -- Withdrawn due to ventricular arrhythmias .......................................................... 1
BICALUTAMIDE -- Withdrawn due to accelerated deaths ................................................................ 1
DACLIZUMAB -- Warning about hypersensitivity reactions, increased mortality in cardiac transplant study .................................................................................................................. 1
DANAZOL -- Use restricted to second line therapy in endometriosis.................................................. 1
LEVACETYLMETHADOL -- Product to be withdrawn due to adverse cardiac events; safer alternatives to be adopted .......................................................................................................................... 2
MOROCTOCOG ALFA -- Reports of lack of effect in prophylaxis patients ........................................... 2
NEFAZODONE -- Sale discontinued due to adverse hepatic events ...................................................... 2
NIMESULIDE -- Product under ‘special pharmacovigilance’ .................................................................. 2
OSELTAMIVIR -- Adverse reactions section to include acute renal failure, thrombocytopenia, leukopenia ........................................................................................................................................... 3
PHENYLPROPANOLAMINE -- New warnings on cardiovascular risks to be added ............................ 3
SOMATROPIN -- Refused approval for use in AIDS-related wasting syndrome ..................................... 3
TERFENADINE -- Withdrawn due to ventricular arrhythmias ............................................................... 3
VALSARTAN -- Reports of interstitial pneumonia .................................................................................. 3

SAFETY OF MEDICINES

ROFECOXIB/CELECOXIB: -- GI adverse effects ................................................................................. 4
HRT -- CPMP to re-evaluate risk-benefit ................................................................................................. 4
LEVETIRACETAM & LOPINAVIR/RITONAVIR -- Potential for dispensing errors .................................... 4
MEFLOQUINE HYDROCHLORIDE -- Issuance of medication guide for travellers ................................... 4
REPAGLINIDE & GEMFIBROZIL -- Risk of hypoglycaemia with concomitant use ............................... 4
SALMETEROL -- New safety information for use in asthma ................................................................. 5
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) -- Adverse effects in neonates ............... 5
VENLAFAXINE -- Unfavourable risk/benefit ratio for use in children and adolescents .......................... 5

DRUGS OF INTEREST

HMG-CoA Reductase Inhibitors and Ocular Haemorrhage .................................................................. 7

FEATURE

Safety Issues Involving Herbal Medicines: Kava as a Case Study .......................................................... 8

MISCELLANY

Recommendations from 1st Meeting of the Advisory Committee on Safety of Medicinal Products, 20-22 October 2003, Geneva ........................................................................................................................................... 10
ANTIMICROBIALS

Cefuroxime
Withdrawn in Argentina

Argentina. As of 19 August 2003, the Food, Drug and Medical Devices agency in Argentina, ANMAT, has withdrawn all medicinal products containing ceftizoxime since these products have the potential to cause life-threatening ventricular arrhythmias. (See also WHO Pharmaceuticals Newsletter No 4, 1993; 7 & 8, 1999; 3, 2003).

Reference:

REGULATORY MATTERS

ASTEMIZOLE
Withdrawn due to ventricular arrhythmias

Argentina. As of 19 August 2003, the Food, Drug and Medical Devices agency in Argentina, ANMAT, has withdrawn all medicinal products containing astemizole since these products have the potential to cause life-threatening ventricular arrhythmias. (See also WHO Pharmaceuticals Newsletter No 4, 1993; 7 & 8, 1999; 3, 2003).

Reference:

BICALUTAMIDE
Withdrawn due to accelerated deaths

Canada, UK. Following discussions with Health Canada, AstraZeneca has issued a ‘Dear Health Care Professional’ letter recommending that, due to a trend towards accelerated deaths, clinicians discontinue use of bicalutamide (Casodex) 150mg in patients with localised prostate cancer otherwise managed by watchful waiting (i.e., therapy initiated only if signs or symptoms of disease progression occur). Approval was granted in November 2002 for bicalutamide 150mg as immediate therapy in some patients with localised prostate cancer for whom surgery or radiation was inappropriate. Health Canada has now withdrawn this approval after reviewing data from a planned second analysis of the Early Prostate Cancer trial programme that show a trend towards accelerated deaths in patients with localised prostate cancer who received bicalutamide 150mg, compared with those who received placebo (196 [25.2%] deaths vs 174 [20.5%] deaths; hazard ratio 1.23; 95% CI 1–1.5). Based on this data, along with the absence of factors suggesting a high risk of disease progression in patients with localised prostate cancer otherwise managed by watchful waiting, AstraZeneca has recommended that bicalutamide 150mg be discontinued in such patients. Patients taking bicalutamide 50 mg/day for metastatic prostate cancer are not affected by this new information (1). The Committee on Safety of Medicines in the UK has advised that for patients with localised prostate cancer, the balanced risk benefit of bicalutamide is unfavourable and the product is no longer licensed for the treatment of this condition. Other approved uses are not affected. Patients receiving bicalutamide for localised prostate cancer should be reviewed at the earliest opportunity and treatment discontinued (2).

References:

DACLIZUMAB
Warning about hypersensitivity reactions, increased mortality in cardiac transplant study

USA. The US prescribing information for daclizumab (Zenapax) has been updated to include two new warning statements regarding increased mortality seen in a cardiac transplant study and hypersensitivity reactions. Roche Pharmaceuticals has issued a ‘Dear Healthcare Professional’ letter informing prescribers of the updates. The addition of information to the ‘Warnings’ section of the product label regarding increased mortality reflects the findings of a randomised, double-blind, placebo-controlled trial of daclizumab (Zenapax) for the prevention of allograft rejection, in which 434 cardiac transplant recipients received concomitant cyclosporin, mycophenolate mofetil and corticosteroids. In the study, increased mortality was seen at 6 and 12 months in patients receiving daclizumab (Zenapax) compared with those receiving placebo (7% vs 5% and 10% vs 6%, respectively). Some of the increased mortality appeared to be related to a higher incidence of severe infection. Other sections of the product (Zenapax) labelling affected by the addition of this information have also been updated. Current information relating to the risk of hypersensitivity reactions has also been added to the ‘Warnings’ section, which states that severe, acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure and following re-exposure to the product. Permanent discontinuation of daclizumab is advised in the event of a severe hypersensitivity reaction.

Reports in WHO-file: Allergic reaction 3, anaphylactoid reaction 2

Reference:

DANAZOL
Use restricted to second-line therapy in endometriosis

UK. The use of danazol (Danol) has been restricted to second-line therapy in endometriosis and benign fibrocystic breast disease, as a result of safety and risk-benefit assessments suggesting that it may increase the baseline risk of ovarian cancer in patients being treated for endometriosis. The following indications have been removed from the Danol Summary of Product Characteristics (SPC): gynaecomastia, pre-operative thinning of the endometrium prior to surgery, dysfunctional uterine bleeding...

WHO Pharmaceuticals Newsletter No. 5, 2003 • 1
presenting as menorrhagia to control excessive blood loss and to control dysmenorrhoea, control of benign, multiple or recurrent breast cysts in conjunction with aspiration.

Reference:

LEVACETYL-METHADOL

Product to be withdrawn due to adverse cardiac events; safer alternatives to be adopted

USA. Roxane Laboratories is to discontinue the sale and distribution of levacetylmethadol (Orlaam) Oral Solution 10 mg/mL in the US due to increasing reports of severe adverse cardiac events. Since the product (Orlaam) was introduced in 1995 for the management of opioid dependence, Roxane has received 15 reports of QT interval prolongation, eight of torsade de pointes and six of cardiac arrest, as well as reports of arrhythmias, syncope and angina. These reports led to the removal of levacetylmethadol (Orlaam) from the European market in March 2001 and extensive changes to the US package insert in April 2001. With less toxic treatment alternatives available, the company now believes that the risks of levacetylmethadol (Orlaam) use no longer outweigh its benefits. The product will be discontinued after the current inventory is depleted, which is estimated to occur in early 2004.

Reference:

MOROCTOCOG ALFA

Reports of lack of effect in prophylaxis patients

Canada. Wyeth Canada is informing physicians of changes to the Precautions and Adverse Reactions sections of the product monograph for morocotocog alfa (Refacto, Recombinant Antihaemophilic Factor). Morocotocog alfa (Refacto, Antihaemophilic Factor Recombinant) has been licensed in Canada since 2002 and is indicated for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A. Reports of lack of effect, mainly in prophylaxis patients, have been received during the clinical trials and in the post-marketing setting with this product (Refacto, Antihaemophilic Factor) in Canada. The lack of effect and/or low factor VIII recovery has been reported in patients with inhibitors and also in patients who had no evidence of inhibitors. The lack of effect has been described as bleeding into target joints, bleeding into new joints, other bleeding or a subjective feeling by the patient of new onset bleeding. The product insert now reflects these observations and advises that, in view of these reports of less than expected therapeutic effect, it is important to individually titrate and monitor each patient’s dose of morocotocog alfa (ReFacto), particularly when initiating treatment, to ensure an adequate therapeutic response.

Reference:

NEFAZODONE

Sale discontinued due to adverse hepatic events

Canada. On 27 November 2003 Bristol-Myers Squibb Canada will discontinue the sale of nefazodone (Serzone-SHT2), indicated for the symptomatic relief of depressive illness. This decision follows several reports of hepatotoxicity associated with nefazodone use. Since its introduction in 1994, nefazodone has been temporally associated with hepatic adverse events such as jaundice, hepatitis and hepatocellular necrosis in patients receiving therapeutic doses. As of December 2002 there were 51 Canadian reports of hepatotoxicity ranging from no symptoms to transplantation, suspected to be associated with nefazodone use. Cases of liver injury have occurred as early as a few weeks after initiation of therapy or after continuous use for up to three years. Physicians are advised to arrange alternate therapies before 27 November 2003 for their patients currently on nefazodone and to consult the product monographs for both nefazodone and the chosen alternate antidepressant before making the switch.

Reference:

NIMESULIDE

Product under ‘special pharmacovigilance’

Argentina. The food, drug and medical devices agency in Argentina, ANMAT, has directed that nimesulide should be brought under the category of products under ‘special pharmacovigilance’. This category includes those drugs that are put under high alert and scrutiny for adverse reactions. Manufacturers are obliged to report all adverse effects associated with nimesulide use. (For other related information on nimesulide, see WHO Pharmaceuticals Newsletter No. 2, 3 & 4, 2002; 3 & 4, 2003).

Reference:
Disposicion de ANMAT no 4087/03, 6 Aug 2003.
OSELTAMIVIR
Adverse reactions section to include acute renal failure, thrombocytoppenia, leucopenia Japan. The Pharmaceuticals and Food Safety Bureau’s Safety Division has advised that acute renal failure, leucopenia and thrombocytoppenia should be added as clinically significant adverse reactions to the product insert of oseltamivir (Tamiflu) indicated in the treatment of influenza. These additions are based on reports associating oseltamivir (Tamiflu) use with acute renal failure and acute hepatitis. It is recommended that patients be carefully observed upon onset of acute renal failure and appropriate measures taken immediately if any abnormalities occur. In case of leucopenia and thrombocytoppenia, the drug should be discontinued.


PHENYLPROPANOLAMINE
New warnings on cardiovascular risks to be added Japan. The Ministry of Health, Labour and Welfare (MHLW) has asked manufacturers of products containing phenylpropanolamine (PPA) to include new warnings on cardiovascular risks. The move follows several reports of cerebral haemorrhage and other problems associated with the use of PPA containing products. Around 170 products, mostly OTC cough and cold preparations containing PPA, are available in Japan. Although a US study published in 2000 suggested a link between PPA and haemorrhagic stroke, the Japanese government did not impose use restrictions at the time since the US study observations were based on a much higher dose (150 mg) used in appetite suppressants and diet aids compared with the more conservative maximum daily dose of 100 mg in the OTC preparations in Japan; appetite suppressants are not approved in Japan. The PPA products in Japan already carry warnings about the potential risk in people with a history of high blood pressure or other cardiovascular problems. Despite these, there have been several adverse drug reaction reports necessitating the current move by MHLW to include stricter warnings on possible side effects, including cerebral haemorrhage. The MHLW has not restricted sales but is encouraging manufacturers to develop non-PPA products. (Also see WHO Pharmaceuticals Newsletter No. 4, 1996).


SOMATROPIN
Refused approval for use in AIDS-related wasting syndrome Europe. The Committee for Proprietary Medicinal Products (CPMP) in Europe has once again refused to approve the use of Serono’s somatropin (Serostim) in treating AIDS-related wasting syndrome (cachexia). The company’s application was similarly turned down earlier in the year. The CPMP said it was unable to identify a target population for somatropin (Serostim) treatment because of the heterogeneity of the study group in terms of body composition and antiviral options. A lack of long-term efficacy data, concerns over the safety profile following repeated administration in AIDS patients and doubts about the clinical relevance of the primary endpoints are also cited as reasons for the refusal. The US FDA has accorded full approval for using somatropin (Serostim) in cachexia.


TERFENADINE
Withdrawn due to ventricular arrhythmias Argentina. As of 19 August 2003, the Food, Drug and Medical Devices agency in Argentina, ANMAT, has withdrawn the marketing authorization for all products containing terfenadine. This measure follows associations of life-threatening ventricular arrhythmias with terfenadine. (Also see WHO Pharmaceuticals Newsletter No. 3&4, 5&6, 1998; 5&6, 9&12, 1999 for previous withdrawals).


VALSARTAN
Reports of interstitial pneumonia Japan. The Pharmaceuticals and Food Safety Bureau’s Safety Division has advised that interstitial pneumonia should be added to the list of adverse reactions associated with the use of the antihypertensive valsartan (Diovan). The product insert will now warn that interstitial pneumonia-associated symptoms such as fever, cough, dyspnoea and abnormalities in chest X-rays may occur with the use of valsartan (Diovan). If such symptoms are observed following treatment with valsartan, the drug should be discontinued and appropriate measures such as adrenocorticosteroid hormone administration should be initiated.

SAFETY OF MEDICINES

ROFECOXIB/CELECOXIB

GI adverse effects

Australia. A significant number of cases of GI adverse effects associated with rofecoxib and celecoxib have been reported to the Adverse Drug Reactions Advisory Committee (ADRAC), many involving elderly patients with known risk factors. However, 16 reports of celecoxib-associated peptic ulcer and 16 of celecoxib- and 5 of rofecoxib- associated GI haemorrhage occurred in patients aged less than 60 years with no stated risk factors. The Committee points out that 'the serious events reported to ADRAC suggest that selective COX-2 inhibitors should be treated with similar caution to other NSAIDs'.

Reference:

HRT

CPMP to re-evaluate risk-benefit

France. The French Regulatory Agency AFFSSAPS, in collaboration with the European Medicines Evaluation Agency, will re-evaluate the risk-benefit profile of hormone replacement therapy (HRT) in order to see how the results of the Million Women study might be incorporated into the body of knowledge for HRT. As reported earlier (WHO Pharmaceuticals Newsletter No. 4, 2003), the Million Women study has confirmed the breast cancer risks associated with HRT products. The current re-evaluation will help decide whether any changes need to be made to the labelling of HRT products, particularly the indications or, whether new usage guidelines need to be prepared.

Reference:

LEVETIRACETAM & LOPINAVIR/RITONAVIR

Potential for dispensing errors

USA. UCB Pharma, in collaboration with the US FDA is warning healthcare professionals about the potential for dispensing errors with levetiracetam (Kepra) and lopinavir/ritonavir (Kalera) products on account of their similar sounding trade names. Levetiracetam (Kepra) is an antiepileptic, while lopinavir/ritonavir is an antiretroviral. Physicians are requested to spell the drug names correctly and to write clearly as can be easily read and understood by the person filling the prescription. And, where appropriate, the intended use should also be indicated; patients should be advised to carefully counter-check all medications they receive at the pharmacy and to immediately contact the pharmacist for any observed discrepancies.

Reference:

MEFLOQUINE HYDROCHLORIDE

Issuance of medication guide for travellers

USA. Roche Laboratories has produced a medication guide (MedGuide) for mefloquine hydrochloride (Lariam) anti-malarial tablets. This guide was developed in collaboration with the US FDA to help travellers understand the risks of malaria, the risks and benefits associated with taking mefloquine hydrochloride (Lariam) to prevent malaria and the rare but potentially serious psychiatric adverse events associated with use of the drug. The guide uses consumer language to summarize information in the professional package insert, including the approved indication and major adverse events. Healthcare professionals are advised to provide this guide to anyone who is given mefloquine hydrochloride (Lariam) for the prophylaxis of malaria. The guide is intended only for travellers who are taking mefloquine hydrochloride (Lariam) to prevent malaria and may not apply to patients who are sick with malaria and who are taking the product to treat malaria.

Reference:

REPAGLINIDE & GEMFIBROZIL

Risk of hypoglycaemia with concomitant use

Canada. Novo Nordisk Canada Inc. has informed healthcare professionals that the concomitant use of repaglinide and gemfibrozil is now contraindicated, following the publication of a study in healthy volunteers demonstrating a markedly enhanced blood glucose-lowering response to repaglinide (GlucoNorm) with concomitant gemfibrozil. The Company says that these findings indicate a potential risk of severe and prolonged hypoglycaemia and it has therefore contraindicated the concomitant use of these agents. In addition, Novo Nordisk’s international safety database contains five reports of serious hypoglycaemia in patients receiving concomitant repaglinide and gemfibrozil.

Reference:

WHO Pharmaceuticals Newsletter No. 5, 2003 • 4
SALMETEROL
New safety information for use in asthma

Canada. Following discussions with Health Canada, GlaxoSmithKline (GSK) has highlighted safety information from the SMART study in a ‘Dear Healthcare Professional’ letter and in a Public Advisory2. In the US, the Salmeterol Multicenter Asthma Research Trial (SMART) was halted due to an increase in asthma-related deaths in patients receiving salmeterol (Serevent) compared with those receiving placebo. GSK announced that in Canada, salmeterol (Serevent) is not approved as monotherapy for asthma, should not be used alone for the maintenance treatment of asthma and is not a substitute for inhaled or oral corticosteroids. Salmeterol (Serevent) is a long-acting beta2-agonist and a ‘controller’ medication for preventing asthma symptoms like wheezing, shortness of breath and coughing. It is to be used as an add-on therapy in those patients already managed with appropriate maintenance doses of inhaled corticosteroids. Patients should not stop taking salmeterol (Serevent) or salmeterol/fluticasone propionate preparation (Advair) without consulting a physician as symptoms may recur after discontinuation. In the US, the labelling for salmeterol (Serevent) has been updated accordingly (see WHO Pharmaceuticals Newsletter No. 4, 2003).

References:

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
Adverse effects in neonates

Australia. It is warned that taking SSRI antidepressants during or after pregnancy can result in adverse effects such as hypotonia and agitation in newborn babies. The Adverse Drug Reactions Advisory Committee (ADRAC) has received 26 reports in which neonates developed symptoms attributed to withdrawal effects of maternal ingestion of SSRIs (paroxetine, sertraline, fluoxetine, citalopram) during the third trimester of pregnancy. Onset of symptoms occurred within 0−4 days of life and in most cases resolved in 2−3 days. ADRAC has also received 13 reports of neonatal adverse effects probably arising from breast milk SSRi-transfer. In Australia paroxetine, sertraline and fluoxetine are listed as ‘C’ drugs, that is, drugs that have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. Citalopram is given a B3 classification in being a drug that has been taken only by a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformations or other direct or indirect harmful effects.

References:

VENLAFAXINE
Unfavourable risk/benefit ratio for use in children and adolescents

UK, USA, Canada, Sweden. The Expert Working Group of the Committee on Safety of Medicines (CSM) has advised that venlafaxine should not be used in children under the age of 18 years for the treatment of depressive illness since the balance of risks and benefits of this drug venlafaxine is unfavourable in this population. New results from clinical trials do not demonstrate the efficacy of venlafaxine in depressive illness in children between the age of 6−17 years; the data show an increase in the harmful outcomes including hostility, suicidal ideation and self-harm in the venlafaxine (Effexor, Effexor XL) group compared with the placebo group. The efficacy and safety of venlafaxine for other indications in this age group have not yet been established. However, venlafaxine should not be stopped abruptly but the dose gradually reduced over two weeks to minimise the risk of withdrawal reactions.

Wyeth Pharmaceuticals has issued a ‘Dear Healthcare Professional’ letter, both in the US and in Canada for the above safety and prescribing information.

The Swedish Medical Products Agency notes that the risk benefit ratio of venlafaxine in adolescents is being evaluated on the EU level and that the agency will hold a workshop in 2004 to come up with recommendations for the treatment of depression; the agency requests those prescribing venlafaxine to be alert to suicidal thoughts in children and points out that venlafaxine is not approved for use in this age group.
References:
HMG-CoA Reductase Inhibitors and Ocular Haemorrhage

F.W. Fraunfelder M.D. Casey Eye Institute, Portland, Oregon, U.S.A.

HMG-CoA reductase inhibitors, also referred to as “statins”, act by blocking the rate-limiting step in cholesterol biosynthesis and are therefore effective in the lowering of blood plasma cholesterol levels. Statins include lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin; the last drug has been removed from the world market due to rhabdomyolysis. Clinical trials have documented the efficacy and safety of statins in preventing coronary heart disease, cerebrovascular accidents and death from hypercholesterolemia related disease(1).

The major systemic adverse effects reported for statins are hepatotoxicity and myopathy. Initial concern over cataracts did not become a proven effect over time(1). The Physicians Desk Reference in the USA mentions eye haemorrhage as a possible side effect for some of the statins(2).

The WHO Centre for International Drug Monitoring and the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Portland, Oregon) received 95 spontaneous reports of ocular haemorrhage from 1988 to present. The WHO-UMC database recently generated positive information component values (IC) for the statins and ocular haemorrhage lending more significance to this possible drug adverse reaction combination(3). Included in the case reports are 23 retinal haemorrhages, 9 conjunctival haemorrhages, 7 vitreous haemorrhages, 1 hyphema, and 55 ocular haemorrhages otherwise unspecified. There were 53 males and 42 females with an average age of 62 years. Average duration of therapy was 288 days on standard dosages of medication. There were 11 positive dechallenge cases and 2 positive rechallenge cases.

Comment

Statins have been prescribed since at least 1987 (FDA approval of lovastatin) and the adverse effect profile has been addressed many times over the last 15 years. The spontaneous reports of ocular haemorrhage probably represent coincidence for the following reasons:

1. Patients, in whom ocular haemorrhages are reported, are at risk for this ocular event due to the friability of blood vessels in this age group (average age of 62 years).
2. Haemorrhages in small blood vessels elsewhere in the body are not associated with the use of statins; there is no reason why blood vessels in the eye would be affected while the vasculature elsewhere is not.

Nevertheless, the possibility that this effect is real cannot be ruled out. For instance, there is evidence that statins reduce platelet aggregation and decrease thrombi formation and it is possible that this occurrence alone could lead to ocular haemorrhages(4). In addition, small blood vessels are mainly apparent in the eye and haemorrhages in other small vessels, for example the kidney, would not be readily evident because physicians cannot examine the external appearance in clinic.

If clinicians suspect an adverse ocular reaction to statins or any other medication, the national registry of drug-induced ocular side effects is a good site to report data (www.eyedrugregistry.com). The association between statins and ocular haemorrhage is most likely categorized as “possible” but not “certain” or “probable”(5).

References:
Safety Issues Involving Herbal Medicines: Kava as a Case Study

Background

Traditional herbal preparations account for 30-50% of the total medicinal consumption in China. In Ghana, Mali, Nigeria and Zambia herbal medicines constitute the first-line of treatment for 60% of children with high fever resulting from malaria. Recent years record a growing interest in the usage of herbal medicines also in the rest of the world. The increasing demand for medicinal plants and the products derived from them has led to concerns over their safety and efficacy. In general, use of herbal medicines has not evolved around scientific evidence. The evaluation of herbal medicines to ensure their safety and efficacy presents important challenges. Recent reports of fatalities and adverse reactions with products such as Ma Huang (Ephedra) and kava-kava (Piper methysticum), with the resultant regulatory decisions to ban the products in many parts of the world, suggest that there is an urgent need to assist countries in creating a stronger evidence-based on the safety, efficacy and quality of herbal medicines.

Kava–kava

Kava or Awa (Piper methysticum) is a plant growing in the South Pacific Islands. Eight species of kava are identified by the local cultivators on the basis of the plant’s growth habitat such as mountainous versus lowland derived, shade grown versus full sun - derived etc. In the Pacific Island countries kava has been widely consumed as a traditional ceremonial beverage and for its mood-altering and stress relieving properties. Traditional preparations use aqueous emulsion of the crushed fresh or dried roots or lower stems of the kava shrub. The last ten years saw an expanding global market for herbal preparations containing kava extracts in the western countries. For the most part, western use of kava largely evolved in Germany. Kava extracts were sold in many German herb shops in the 1890s and, thirty years later, the first pharmaceutical preparation, a kava tincture was made available as a mild sedative and to lower blood pressure. Standardized kava root tablets, capsules, tinctures and dried root were later introduced in the American and European markets. In the UK, three licensed medicines and a large number of unlicensed herbal remedies containing kava were available until before the ban on kava products. These products were marketed for the treatment of anxiety, insomnia, premenstrual syndrome and stress and sold over the counter as complementary medicines or as dietary supplements and nutraceuticals.

The pharmacological properties of kava have been attributed to a group of components collectively known as kava pyrones or kava lactones.

Hepatotoxicity with kava

Since 1999, several cases of severe hepatic toxicity in people using kava-containing herbal products were reported in Europe and in the United States. By late 2002 there were 10 reports of patients requiring liver transplants (8 in Europe and 2 in the US; one died post-transplant) following hepatic failure associated with the use of kava-containing products. This led to various worldwide regulatory measures against kava-containing products, ranging from a total ban of such products to consumer advisories warning about the adverse effects with kava(1). Understandably, the bans, restrictions, alerts and market recalls have had a tremendous economic impact on the South Pacific kava industry. The Centre for the Development of Entreprise (CDE), based in Brussels, commissioned Phytopharm Consulting, Germany, to prepare a detailed report of the scientific and technical evidence that led to the kava restrictions. The CDE is an institution established by the Group of ACP (Asian, Caribbean and Pacific) states and the European Union within the framework of the Cotonou Agreement. In its summary analysis, Phytopharm Consulting has stated that, of the 76 hepatotoxicity reports that were studied, only 4 were possibly linked to kava-intake(2).

The WHO Global Database for Adverse Drug Reactions has altogether 23 case reports of liver injury in suspected connection with the use of kava (Piper methysticum) containing products, coming from Canada, Germany, Switzerland, UK and the US; majority of these reports are from Germany. In addition, the database contains 26 reports of a variety of hypersensitivity reactions.

The mechanism of kava-toxicity remains to be elucidated. Histological examinations show portal inflammation with lymphocytes and eosinophils(3,4). An idiosyncratic immune response to a reactive metabolite has been suggested as a possible cause(4). Genetic differences in liver metabolism of kava lactones may also need to be examined(4).

The adverse reaction reports with kava need to be examined against the following considerations:

1. Very few kava-related adverse reaction reports are available from the Pacific Island Countries where traditional preparations of kava have been used for over two thousand years. This could be due to under-reporting or due to the lack of systematic studies investigating the adverse effects of traditional kava preparations.

[1] WHO Global Database for Adverse Drug Reactions
[2] Phytopharm Consulting, Germany
[4] WHO Global Database for Adverse Drug Reactions

WHO Pharmaceuticals Newsletter No. 5, 2003 ● 8
2. Traditional kava preparations used water-based beverages made from the roots and underground stump called rootstock. The more ‘modern’ capsules and tablets contain a concentrated extract of kava lactones and other compounds from kava roots and peelings dissolved by non-aqueous solvents like ethanol and acetone. The observed hepatic reactions with these latter preparations may have depended on the concentration of the kava lactones or on the plant parts used; extraction with non-aqueous solvents could have eluted less polar kava alkaloids such as pipermethystine that are known to have toxic effects on liver cells.

3. Liver function abnormalities have been reported in heavy kava drinkers. The abnormalities in liver function returned to normal within 1-2 months of stopping kava use; and the serum alanine aminotransferase (ALT) levels were always within normal limits. This is inconsistent with changes documented in the cases of hepatotoxicity with other herbal products (Germander, Black cohosh, etc) where aminotransferase levels are seen to be especially high.

4. In many of the reported cases the patients were using other medications as well. Furthermore, in several cases, detailed information on the patient’s history, alcohol habits and other particulars were missing.

To summarize, the situation with kava is far from clear. There is much uncertainty about causation and extent of the problem. However, kava as a case study emphasizes the value in understanding the principles of traditional practices. An in-depth re-analysis of existing data and studies designed to compare traditional versus standardized preparations of kava could go a long way in understanding the special safety issues while dealing with herbal preparations. Towards this we need to:

- collect unbiased information on natural kava products and their safety
- re-evaluate all available data on kava products
- compare and investigate safety effects due to extraction procedures across preparations.

The above steps could help establish clear safety guidelines for kava in particular and herbal preparations in general.

References:
1. Pharmaceuticals: Restrictions in Use and Availability, April 2003, WHO.
Recommendations from the first Meeting of the Advisory Committee on Safety of Medicinal Products, 20-22 October 2003, WHO, Geneva

Setting Priorities

The Committee raised the following issues as key points in promoting drug safety activities through the WHO International Drug Monitoring Programme.

1. Advocacy: There is a real need to convince the public and politicians of the importance and impact of adverse drug reaction (ADR) reporting. An advocacy document should be drafted to outline a common vision for excellence in pharmacovigilance and the positive cost/benefit value of ADR monitoring, with a link to rational drug use around the world.

2. Development of risk management plans: A well-designed risk management strategy should be in place, complementing the methods of risk assessment. A workshop should be organized to develop and implement such a strategy.

3. Alternative approaches to drug safety-monitoring: Methods such as cohort (prescription event) monitoring should be encouraged, in addition to the current spontaneous ADR reporting system, to account for local situations and practices and thus providing a more complete and comprehensive picture.

4. Traditional Systems of Medicine: There needs to be additional focus in special areas such as traditional Chinese medicine.

Pharmacovigilance in Public Health

1. Public health programmes could serve as important gateways to introduce and implement pharmacovigilance in countries currently lacking safety monitoring programmes.

2. The draft document on ‘Pharmacovigilance in Public Health: emerging needs’ was discussed and the Committee proposed that the document should clearly identify policy makers and public health programme managers as target audiences. The introductory section should stress the vision of the document by including the following:

   - Medicines in public health programmes should be used safely and effectively to achieve the best possible health outcomes
   - All public health programmes should include a medicine risk management strategy, defined prior to the implementation of a project
   - All public health programmes should promote pharmacovigilance in the countries in which they operate.

3. Progress in pharmacovigilance for antimalarials:

   - Following the initial launch of the programme to monitor artemisinin combination therapy (ACT) in the five countries of Burundi, DRC, Mozambique, Tanzania and Zambia, the initiative will be rolled out to include other countries in Africa

   - The Committee acknowledged the rapid progress made with this initiative, recognizing the significance of what has been achieved to date. The committee recommended that this important activity should be endorsed by WHO, extended and used as a model for other disease-driven projects such as HIV and TB.

4. Pharmacovigilance in lymphatic filariasis:

   - Experience from national programmes on filariasis will be reviewed by a subgroup of the committee and later discussed at the next meeting of the Advisory Committee.

5. Pharmacovigilance in parasitic disease programmes:

   - Further data on praziquantel use in pregnancy should be reviewed
   - The initial surveillance of triclabendazole in fascioliasis (foot-borne trematode) should be followed by an ongoing monitoring.

6. Pharmacovigilance in herbal medicines:

   - The Committee’s approval of the proposed WHO Guidelines on Safety Monitoring and Pharmacovigilance of Herbal Medicines is solicited
   - Committee members will provide written comments to WHO by mid-December prior to further revision and wider consultation in early 2004.

Pharmacovigilance for antiretrovirals

1. The Committee unanimously recommended that the issue of patient safety as an aspect of the 3 by 5 initiative is of paramount importance.

2. The Committee prepared a document detailing the challenges, specific safety concerns and proposals to address these issues and enhance the success of the programme.
MISCELLANY

Current safety issues

1. Chlorproguanil/dapsone: use in African countries
A statement was drafted and will be published at a later date.

2. Isotretinoin: teratogenicity
The committee agreed that a review of isotretinoin should be undertaken but limited to its inappropriate or illicit use, with a request for information circulated via vigimed; it may be necessary to consult with external agencies (e.g. police departments, enforcement groups etc) at the national level.

3. Thalidomide: current status of registration
The current status of review of thalidomide at the EU level, availability of any evaluation reports and the proposal for monitoring thalidomide within the 'Steps' programme will be investigated. The outcome will determine future needs to commission an expert review of available evidence-base for concerns associated with thalidomide use, including the Cochrane database.

4. Kava-kava: traditional use
- The Committee endorsed the recommendation to obtain data/assessments from countries from whom kava-use associated adverse reaction reports are available, including comprehensive literature reviews.
- The WHO Collaborating Centre for International Drug Monitoring would help compile the available data on kava-products and their safety as well as re-evaluate all data thereafter.
- The investigation, comparison of extraction and analysis procedures across the various kava preparations could be undertaken possibly as a PhD project in a suitable location.