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ADVERSE REACTION NEWSLETTER 1997:2

**NATIONAL DRUG MONITORING CENTRES -
DRUG SAFETY ISSUES**

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NATIONALLY CIRCULATED INFORMATION

Australia

ADRAC Bulletin Vol 16, No 2, May 1997.

Kombucha tea

Kombucha tea has become increasingly popular in recent years because it has been claimed to have a large number of beneficial effects including the prevention of cancer, relief of arthritis, treatment of insomnia, stimulation of the immune system and even the regrowth of hair. The tea is brewed from the kombucha mushroom which is actually a symbiotic yeast and bacteria aggregate surrounded by a permeable membrane. The "mushroom", which grows like a round flag gray fungus about the size of a dinner plate, is fermented in sugared tea to obtain the kombucha tea. The mushrooms are sold or distributed by naturopaths and other alternative practitioners and are often passed on from person to person. The tea has been described to contain a mixture of many substances including alcohol, glucuronic acid, acetic acid, heparin and lactic acid.

In the last year, ADRAC has received two reports of hepatotoxicity in association with kombucha tea. There have also been reports of both hepatotoxicity and lactic acidosis in the United States.

Reports in WHO files: No relevant cases found

Clozapine induced neuroleptic malignant syndrome

Clozapine (Clozaril) is an antipsychotic drug used in the treatment of schizophrenia resistant to other therapies. From 1993 to April 1997, ADRAC has received a total of 436 reports in association with clozapine. The drug is systematically monitored because of the risk of agranulocytosis, and therefore the proportion of adverse events detected is probably higher than with other drugs. The product information indicates that the incidence of extra pyramidal reactions with clozapine is less than with other antipsychotics. However, in common with other antipsychotic drugs,

the use of clozapine has been associated with neuroleptic malignant syndrome (NMS). Common clinical features of NMS are: fever, rigidity, autonomic instability and altered consciousness.

ADRAC has received 11 reports describing NMS in males aged 14 to 52 years with clozapine being the only suspected drug cause in all but one case.

The product information for clozapine states that neuroleptic malignant syndrome is estimated to occur with an incidence of less than 0.1%, but reports to ADRAC would suggest that the incidence is considerably higher.

Reports in WHO files: Neuroleptic malignant syndrome 178 from 12 countries.

The Achilles heel of fluoroquinolones

The occurrence of tendinitis is one of the more unusual adverse reactions known to be associated with the fluoroquinolone antibiotics. This is a serious effect since it may progress to tendon rupture with many weeks of disability as a result.

More than 200 cases have been reported in the literature with the majority from France. Most members of the class including ciprofloxacin, enoxacin, ofloxacin, and norfloxacin have been implicated. The Achilles tendon is most often involved.

In Australia, there have been 25 reports of tendinitis in association with fluoroquinolones (22 reports have been with ciprofloxacin and the other three with norfloxacin).

A number of risk factors have been identified with regard of this adverse reaction. These include old age, renal dysfunction, and concomitant corticosteroid therapy.

To reduce the risk of tendon rupture, the antibiotic should be withdrawn immediately.

Reports in WHO files:

	Ciprofloxacin	Enoxacin	Ofloxacin	Norfloxacin
Tendinitis	127	8	141	68
Tendon disorder	74	3	66	14
Tenosynovitis	11	-	4	1

Canada

Canadian Adverse Drug Reaction Newsletter, Vol 7, No2, April 1997

Adverse drug reaction reporting - 1996

In 1996, more than 4000 spontaneous case reports were submitted to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP). These reports were received from:

- Drug manufactures (40%)
- Regional ADR centres (25%)
- Hospitals (17.5%)
- Pharmacists and physicians in the community (12.5%)
- Professional associations, Nursing homes, Health Protection Branch regional inspectors, Coroners, Nurses, Dentist and others (5%).

Potential abuse of butorphanol nasal spray

The CADRMP has received 48 reports of ADRs associated with the administration of butorphanol tartrate nasal spray since November 1994. The CADRMP reviewed 15 reports that indicated suspected drug-seeking behaviour, drug abuse or addiction.

Although butorphanol nasal spray may have a lower abuse potential than morphine, reports suggestive of possible abuse are mentioned in the precautions section of the current product monograph. The section also states that special care should be exercised in administering butorphanol to emotionally unstable patients and to patients with a history of drug misuse. This information contributes to the determination of the relative potential for abuse of any drug. Furthermore, drug abuse or dependence is considered a serious ADR because it can be life threatening or may result in persistent or significant disability.

Butorphanol nasal spray is a controlled drug under Schedule G of the Food and Drug Act and was approved for marketing in Canada in July 1994. It is indicated for the relief of moderate to severe acute pain. Butorphanol acts as an agonist at kappa-opioid receptors and a mixed agonist-antagonist at mu-opioid receptors in the central nervous system to alter the perception of pain.

The analgesic potency of butorphanol is about 4 to 8 times that of morphine, 30 to 40 times that of

meperidine and 16 to 24 times that of pentazocine.

Reports in WHO files: Drug dependence USA 492; YUG 1.

Amino glycoside ear drops and ototoxicity

Ototoxic effects are well-documented, clinically important side effects of parenteral Amino glycoside use. However, not as well documented are ototoxic effects from topical Amino glycoside use. Although Amino glycoside ear drops are generally considered safe when used in the presence of an intact tympanic membrane, controversy exists in the literature as to their safety in the presence of a membrane defect.

The CADRMP has received 7 reports in which the use of Garasone ear drops (gentamicin sulfate and betamethasone sodium phosphate) in the presence of tympanic-membrane perforation resulted in ototoxicity.

Although the CADRMP has not received reports of similar ADRs for other Amino glycoside otic preparations, all aminoglycosides are capable of affecting both cochlear and vestibular function. Some preferential toxicity is evident. Of the aminoglycosides commonly found in ear drops (gentamicin, neomycin and framycetin) neomycin and framycetin primarily affect auditory function, and gentamicin primarily affects vestibular function. In the absence of hearing loss, the vestibular toxicity of gentamicin is often missed or is assumed to be inadvertently due to labyrinthitis. Despite the widespread use of Amino glycoside ear drops, ototoxicity in the presence of tympanic-membrane defects appears to occur in a small percentage of patients. However, its incidence and prevalence may be higher than reported because of the difficulty in distinguishing between the natural course of the disease and the drug's toxicity.

France

Minutes from the French Pharmacovigilance Commission meeting, December 12th, 1996, February 6th, March 6th, 1997.

Lysedem - hepatic reactions

The National Pharmacovigilance advisory board has reevaluated the safety of the synthetic coumarine

Lysedem.

33 validated hepatic adverse effects have been reported to the French pharmacovigilance system or to the company Knoll.

Cytolytic hepatitis are reported in 85% of cases and jaundice is observed in 13 cases. Mean time of onset is over 2 months in 2/3 of cases and daily dosage is generally in accordance with the marketing authorization. Some of these effects are serious, leading to an hospitalisation in 42% of cases. Three hepatic failures occurred, 2 of them were fatal and the last required hepatic transplantation.

As a consequence, considering that the efficacy of the drug is moderate and that physical methods represent the first line treatment of lymphoedema after radio/surgery treatment of breast cancer, the French Marketing Authorization Commission has decided to suspend the marketing authorisation of Lysedem

Benzbromarone - hepatic reactions

A national pharmacovigilance survey has provided evidence of rare, sometimes serious cases of hepatic toxicity during treatment with benzbromarone, the active ingredient in the proprietary medicinal products Desuric and Desatura (benzbromarone).

This cytolytic hepatic effect mainly occurs during the first months of treatment. It may exceptionally take the form of fulminant hepatitis.

Measures have been taken by the French Agency, considering the potential seriousness (unpredictable damage):

- a dear doctor letter has been sent to the health professional with information concerning the risk of hepatotoxicity and warnings about the association with hepatotoxic drugs.

- current SPC sections to be amended

Reports in WHO files: Benzbromarone; hepatitis 4; hepatitis cholestatic 2.

Atrium

The results of the national inquiry on the adverse effects of Atrium (phenobarbital, febarbamate, difebarbamate),

marketed by Riom laboratories - CERM, has been examined by the French pharmacovigilance committee. 148 cases of liver damage were reported to the national system or to the company, between 1 January 1986 to 30 June 1996.

In agreement with the French Pharmacovigilance Committee (6/02/97), the French Advisory Board (14/03/97) has considered that:

- 1- There is insufficient evidence on the efficacy of Atrium 100 mg in the treatment of minor anxiety.

Considering the potential risk of liver damage the benefit/risk ratio appears unfavourable and the product is therefore withdrawn from the market.

- 2- Concerning the treatment of alcoholic withdrawal syndrome with the 300 mg dosage, Atrium 300 mg is especially prescribed for the prevention of physical symptoms of withdrawal, as convulsions, which can occur rapidly and requires short-term treatment.

The major alternatives to the use of Atrium in the treatment of alcoholic withdrawal symptoms are benzodiazepines and meprobamate, associated with a drug dependency risk and misuse.

Atrium 300 mg therapeutic indication should be limited to treating the alcoholic withdrawal syndrome with a maximal treatment duration of 4 weeks.

Reports in WHO files: Hepatic function abnormal 4; hepatocellular damage 1; liver fatty 1.

Droperidol - cardiac rhythm disorders

The French national commission of pharmacovigilance has examined the results of the national inquiry on sudden death and cardiac rhythm disorders linked to the use of Droleptan (droperidol).

Droleptan has been marketed in 10 ml vials of 5 mg/ml (or 50 mg by vials) since 1967 in France, by Janssen-Cilag company and the risk of sudden deaths and cardiac rhythm disorders have already been mentioned in the SPC (since 1993).

26 cases of sudden death have been reported since its

introduction on the market.

The estimated frequency of sudden death is 1 case for 55 000 vials sold.

Given the misuse of this drug, and the results of studies showing that 5 mg is efficient for agitation, it was proposed to:

- a- decrease the dosage to 5 mg
- b- modify the SPC:
 - 1- with a clear mention of the risk factors of QT interval increase and cardiac rhythm disorders.
 - 2- by reinforcing the warning in alcoholic patients.

Reports in WHO files: Death(FRA 2; UNK 2; USA 17) Arrhythmia 6; Cardiac arrest 20; Cardiac failure 3.

Buprenorphine - hepatic reactions

The French national commission has examined the results of the pharmacovigilance inquiry on the adverse effects of Subutex (buprenorphine).

Subutex is used as a substitute treatment in pharmacodependence with opiates.

Given the data presented, the National Commission decided that undesirable hepatic effects and the observation of deaths from respiratory failure, mainly during misuse and when used in association with benzodiazepines, justified a modification of the marketing authorisation.

Reports in WHO files: Buprenorphine, death 51; Hepatic enzymes increased 2; Hepatic function abnormal 4; Hepatocellular damage 2.

Germany

Deutsches Ärzteblatt 94, No.17, 25 April 1997 (70) A-1154

Risks of carbamazepine in out-patient alcohol withdrawal

In recent times, carbamazepine drugs have justifiably been used to an increasing extent for alcoholics willing to undergo withdrawal treatment on an out-patient basis, although the manufactures expressly point out the need for monitoring in hospital when the

carbamazepine is used to prevent convulsions in cases of alcohol withdrawal syndrome.

Reports in WHO files: Withdrawal syndrome 58.

Mistletoe extract and organ or enzyme preparations

The Drug Commission of the German Medical Profession has received 43 spontaneous reports of adverse drug reactions in the period from 1976 to 1989, and a further 36 since 1990 for preparations containing mistletoe extract, most frequently prescribed for tumour patients. The corresponding figures for organ and enzyme preparations, insofar as use in the treatment of cancer is included among the indications claimed for them, add up to 16 reports between 1976 and 1989, and another 15 since 1990.

Some of the reports on preparations containing mistletoe extract and organ or enzymes preparations relate to possible side-effects of a moderate nature. In some reports, the causal relationship with the suspected preparation is unclear, owing to inadequate documentation, advanced stages of disease, complex diseases or extensive concomitant medication. The side-effects reported also include severe allergic reactions including anaphylactic shock.

Reports in WHO files: Anaphylactic shock 5.

Deutsches Ärzteblatt 94, No. 13, 28 March 1997 (69) A-857

Three suspected cases of post-vaccinal Guillain-Barré syndrome

The Drug Commission of the German Medical Profession has received 3 suspected cases of acute febrile polyneuritis in the form of the Guillain-Barré syndrome (GBS) following influenza vaccination, within two months. These possible adverse drug reactions occurred within 10 days of vaccination in each case.

The Guillain-Barré syndrome is the most common acquired demyelinating neuropathy. The initial symptoms are a feeling of heaviness, frequently distal-symmetrical and primarily commencing in the lower

limbs, followed by debility and, ultimately, flaccid paralysis with an absence of proprioceptive muscular reflexes. In addition to motor disorders, the first signs of Guillain-Barré syndrome can also be paraesthesia and perception disorders. The risks of the disease, which can rapidly become life threatening at an unpredictable speed, are respiratory failure as a result of paralysis of the respiratory muscles, cardiovascular disorders and subsequent sequelae to immobilisation, such as thrombosis or embolism.

The diagnosis of "Guillain-Barré syndrome" is confirmed by the clinical findings, examination of the cerebrospinal fluid and specific electroneurography.

Ireland

Irish Medical Board Drug Safety Newsletter, No 4, 19th May 1997

Paracetamol

While paracetamol is acknowledged as an effective and safe medicine when used properly, the consequences of overdose are potentially very serious with the risk of irreversible liver damage.

A revised conditions (such as: warnings; packaging; pharmacy sales etc.) which will apply to the sale of paracetamol has been approved by the Minister for Health.

Terfenadine

Terfenadine is an antihistamine agent that has been authorised in Ireland for over 15 years, and has been available as an over-the-counter medicine since 1987. It has a good safety record when used as recommended but in certain circumstances it may cause arrhythmias. This association with cardiovascular events, especially when used in combination with other specific drugs is well known.

The National Drug Advisory Board has considered it necessary to recommend that terfenadine should only be used under medical supervision and therefore has decided to change its status to a prescription only medicine.

Precautions and warnings:

- 1- Terfenadine should not be used by patients with cardiac or hepatic disease.
- 2- The recommended dosage must not be exceeded (i.e. 120 mg/day for adults).
- 3- Terfenadine should not be taken with grapefruit juice.
- 4- The following drugs have been reported to cause interactions: Ketoconazole, Itraconazole and related imidazole anti-fungal agents, Erythromycin, Clarithromycin and related macrolide antibiotics.

Reports in WHO files: Arrhythmia 126.

Philippines

Signals in Adverse Drug Reactions Monitoring, Vol 2, No 05, May 1997

All is set for the 2nd national ADR training course

The second National Adverse Drug Reaction Training Course was held May 14-15, 1997 at the Palm Plaza Hotel, Ermita, Manila.

The second day of the training course, with 16 CME units, was aimed at training community medical practitioners to become effective Adverse Drug Reaction collaborators and work with the Adverse Drug Reaction Monitoring Programme in the promotion of safe drugs and drug use.

Don't say we didn't warn you

Terfenadine and astemizole are used as antihistamines. Recent findings have indicated that although incidence is low, serious cardiac arrhythmias and death can develop following the use of these medications.

In the Philippines, terfenadine is a prescription drug while astemizole can be bought over-the-counter.

Some precautions to be considered:

- 1- Pre-existing cardiac and hepatic disease.
- 2- Concomitant use of antifungal or antimicrobial as there might be drug interactions.
- 3- Avoid grapefruit juice

South Africa

Lamotrigine follow-up

Lamotrigine remains indicated as add-on treatment for partial epilepsy not satisfactorily controlled with other antiepileptic medicines.

Monotherapy in children under 12 years of age is not recommended.

The Medicines Control Council has described the risk of skin reactions more clearly in the summary of product characteristics and the particularly high risk in children is now stated as a boxed warning. The importance of adhering to dosing guidelines, particularly with regards to the combined use with valproate and the need for careful dose escalation is emphasised.

Reports in WHO files: Flushing 13; Skin exfoliation 6; Skin ulceration 3.

USA

FDA MedWatch News 1997-06-11

Cidofovir - serious renal impairment

Cidofovir is indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Gilead Sciences has issued a warning letter to health care professionals because it has become aware of several reports of severe renal impairment associated with the use of cidofovir injection (VISTIDE).

Two cases of acute renal failure resulting in dialysis and/or contributing to death associated with the administration of only one or two doses of Vistide have recently been reported.

Reports in WHO files: Renal failure acute 6; Renal function abnormal 6.

FDA MedWatch News 1997-06-16

Diabetes and hyperglycaemia in patients receiving protease inhibitors

As of May 12, 1997, there have been 83 cases reported to FDA of diabetes mellitus or hyperglycaemia in HIV-infected patients who were receiving anti-retroviral

protease inhibitor therapy; 27 of the 83 cases were reported to require hospitalization. Fourteen patients were known to be diabetics; for these patients, there was a loss of glucose control. The average time of onset was approximately 76 days after initiating protease inhibitor therapy, but occurred as early as four days after starting therapy. Five cases of diabetic ketoacidosis occurred, including patients who were not reported to be diabetic; however, the baseline status of these patients is not well characterized.

Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for the treatment of these events. On an average, 50 percent of patients discontinued their protease inhibitor therapy as a result of this acute adverse event. Hyperglycaemia persisted in some patients after protease inhibitor therapy was withdrawn, including patients not known to be diabetic at baseline; however a causal relationship between protease inhibitor therapy and these events has not been established.

Many of these reports occurred in patients with confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Diabetes and hyperglycaemia have been reported to varying degrees for Crixivan® (indinavir), Invirase® (saquinavir), Norvir® (ritonavir) and Viracept® (nelfinavir).

FDA believes that there exists no conclusive evidence establishing a definite causal relationship between protease inhibitor therapy and the incidence of diabetes and hyperglycaemia.