



MALAYSIAN ADVERSE DRUG REACTIONS NEWSLETTER

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

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CONTENTS

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2000-2005)

ISSUES OF CURRENT INTEREST

- Gadolinium and Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD)
- Raloxifene (EVISTA) Associated with Increased Risk of Death Due to Stroke.
- Lamotrigine and Risk of Oral Clefts

LOCAL CASE REPORTS

- Suspected Hepatotoxicity Associated with the Use of *Camellia Sinensis*
- Carbimazole and Dysphagia
- Setraline and Cleft Palate

CURRENT REGULATORY ISSUES

- Black Cohosh, Root: Warning Statement on Hepatotoxicity
- Promethazine and The Potential for Fatal Respiratory Depression

REPORTS FROM JOURNAL

- ACE Inhibitors and Congenital Anomalies
- Attention-Deficit Hyperactivity Disorder (ADHD) Drug Labels

ADR MONITORING:

A CO-OPERATIVE PROGRAMME FOR ENHANCING THE SAFER USE OF MEDICINES

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2000-2005)

Captopril reported as a drug with the most number of adverse drug reactions (ADRs) in 2005. A total of 52 reports were received related to this substance. This is followed by Allopurinol, Cloxacillin, Diclofenac Sodium and Nifedipine. These four drugs are quite common to cause ADRs and have been listed among the top ten since 2000. Most of the ADRs reported are related to skin reactions.

However, for the drugs reported with the most ADRs, it must be noted that these figure are not absolute figures and should not interpreted to imply that these drugs are associated with more ADRs than other drugs in the same class.

The following table shows the number of ADRs reported in 2000.

TEN DRUGS WITH THE MOST REPORTED ADRs

NO.	2000	2001	2002	2003	2004	2005
1	CO-TRIMOXAZOLE(47)	CLOXACILLIN(34)	CO-TRIMOXAZOLE(36)	ALLOPURINOL(33)	ALLOPURINOL(37)	CAPTAPRIL(52)
2	DICLOFENAC(33)	CARBAMAZEPINE(33)	CARBAMAZEPINE(32)	CLOXACILLIN(30)	PARACETAMOL (29)	ALLOPURINOL(51)
3	AMOXYCILLIN(23)	CO-TRIMOXAZOLE(23)	CLOXACILLIN(31)	MEFENAMIC ACID(25)	CARBAMAZEPINE(29)	CLOXACILLIN(50)
4	CARBAMAZEPINE(23)	ENALAPRIL(23)	AMOXYCILLIN(28)	DICLOFENAC(24)	NIFEDIPINE(28)	DICLOFENAC SODIUM(44)
5	CLOXACILLIN(15)	DICLOFENAC(20)	ALLOPURINOL(22)	HLOROTHIAZIDE (22)	CO-TRIMOXAZOLE (28)	NIFEDIPINE (44)
6	ALLOPURINOL(15)	PERINDOPRIL(19)	TRADITIONAL MEDICINES(22)	CARBAMAZEPINE(19)	ERYTHROMYCIN(23)	METFORMIN(39)
7	IBUPROFEN(14)	ALLOPURINOL(17)	ALENDRONATE SODIUM(19)	TRADITIONAL MEDICINES(18)	AMOXYCILLIN(23)	PARACETAMOL(38)
8	NIFEDIPINE(13)	AMOXYCILLIN(17)	DICLOFENAC(19)	AMOXYCILLIN(18)	MEFENAMIC ACID(21)	CO-TRIMOXAZOLE(37)
9	ASPIRIN(12)	GENTAMICIN(13)	ISOSORBIDE DINITRATE(18)	PENCILLING SODIUM(15)	ASPIRIN(19)	ATENOLOL(37)
10	PHENYTOIN(12)		LOVASTATIN(13)	VANCOMYCIN(15)	CLOXACILLIN(18)	CEFUROXIME(36)

ISSUES OF CURRENT INTEREST

GADOLINIUM AND NEPHROGENIC SYSTEMIC FIBROSIS OR NEPHROGENIC FIBROSING DERMOPATHY (NSF/NFD)

MADRAC has received 4 reports with regards to the use of gadolinium recently (2005-1; 2006-3). Gadolinium has been registered and marketed in Malaysia since 1992. To date, the DCA has registered 9 products containing gadolinium. It has been used for contrast enhancement in cranial and spinal magnetic resonance imaging (MRI) and for contrast enhancement in whole body MRI.

The adverse reactions associated with the use of gadolinium were rash maculo-papular, dyspnoea, vomiting, giddiness, chest pain and itchiness. From the journal, the gadolinium chelates are considered to be very safe. These agents are thought to be safer than nonionic iodinated contrast agents. Minor adverse reactions have been reported including nausea and hives occur in a low percentage of cases.

FDA MedWatch recently notified all healthcare providers and consumers regarding new reports have identified a possible link between Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD) and exposure to gadolinium especially in patients with kidney failure.

References: 1) Health Canada, MedEffect, July 12, 2006 2) FDA Medwatch June, 2006

RALOXIFENE (EVISTA) ASSOCIATED WITH INCREASED RISK OF DEATH DUE TO STROKE.

The Raloxifene Use for The Heart (RUTH) study was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled, parallel study enrolling 10,101 postmenopausal women (average age = 67 years) with established coronary heart disease, or at increased risk for a major coronary event to one of two therapy groups, raloxifene hydrochloride 60mg/day or placebo. The study involved 26 countries and the subjects were followed for up to seven years.

The two primary objectives were to assess the effect of raloxifene on coronary events and invasive breast cancer, and there were multiple secondary endpoints.

The preliminary results of RUTH study demonstrated an increase

References: Reactions Weekly 3 Jun 2006 No.1104

LAMOTRIGINE AND RISK OF ORAL CLEFTS

The North American Antiepileptic Drug Pregnancy Registry (NAAED) has recently published the finding on major congenital malformations in new born infants of women who had taken lamotrigine monotherapy during the first trimester of pregnancy.

The recent published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1,000.

The UK Epilepsy Pregnancy Registry also recently published a

Twenty five (25) cases reported over a period of four years, originating from two hospitals in Austria and Denmark, of Nephrogenic systemic sclerosis/Nephrogenic fibrosing dermopathy (NSF/NFD) following administration of Omniscan Injection were received. Of these cases, 15 were serious in nature, involving disability with or without hospitalization, and 10 were non-serious with mild symptoms.

Current labeling in Europe and the USA mandate caution in patients with severely impaired kidney function i.e. the group which may develop NSF/NFD. However, NSF/NFD currently is not labeled events.

A direct causal link between gadolinium exposure and NSF/NFD has not been established and the company is working with the reporting hospitals, medical experts, and regulatory authorities, to further investigate this issue.

MADRAC in the recent meeting has decided that the product holders of gadolinium need to take full responsibilities to inform all relevant prescribers on this cautionary issue.

in mortality due to stroke for Raloxifene (Evista) compared to placebo. The incidence of stroke mortality was 1.5 per 1000 women per year for placebo versus 2.2 per 1000 women per year for Evista ($p = 0.0499$). The incidence of stroke, myocardial infarction, hospitalized acute coronary syndrome, cardiovascular mortality, or overall mortality (all causes combined) was comparable for Evista and placebo.

In Malaysia, Eli Lilly (M) Sdn Bhd has submitted changes to the package insert based on the outcome of the RUTH study and a Dear Healthcare Professional Letter has been issued on 20th July, 2006 to inform health professionals about this new safety issue.

report on the outcome of the overall rate of major congenital malformations on pregnant women with epilepsy at the rate of 3.2% in 647 exposures. Based on these findings, GlaxoSmithKline (GSK), the product holder of lamotrigine has issued a Dear Healthcare Professional Letter on 19th June, 2006 to inform prescribers about these new safety issues and the possible risk of oral clefts associated with the use of lamotrigine.

GSK has also submitted an application to update the pregnancy statement of the prescribing information for lamotrigine in order to bring it in line with the new version of the International Prescribing Information.

LOCAL CASE REPORTS

SUSPECTED HEPATOTOXICITY ASSOCIATED WITH THE USE OF CAMELLIA SINENSIS

A 32 year old Chinese lady was admitted to hospital with symptoms of diarrhoea since 4 weeks ago and jaundice since 2 weeks prior to admission. Upon investigation, she was diagnosed as having acute hepatitis. She had an underlying condition of hyperthyroidism which was being managed with Carbimazole and Propranolol.

From the drug history, it was found that she had been taking several types of herbal products that she claimed were for general health since two months ago and one of which contained Camellia Sinensis.

A similar case has been published in Reactions (18 March 2006 No. 1093) of a 37 year-old woman who took a product containing Camellia Sinensis and developed liver injury but without positive rechallenge. In the WHO database, there are 7 reports of hepatitis associated with the use of this herbal ingredient.

In Malaysia, the Drug Control Authority has registered 212 products containing Camellia Sinensis in various dosage forms. Healthcare professional are encouraged to report any suspected adverse reaction to Camellia Sinensis to MADRAC.

CARBIMAZOLE AND DYSPHAGIA

A 20 year old lady developed dysphagia, throat soreness and throat tightness 24 hours after ingestion of carbimazole 10mg daily for her hyperthyroidism. Use of any other concomitant medications was not reported.

The reactions subsided once the drug was discontinued but reappeared after another dose was given to the patient. The reactions were reported to have quite mild and no medication was given to treat the adverse events. MADRAC has received

three (3) other reports of similar events - dysphagia(1), and sore throat (2). These adverse effects are not listed in the product insert for carbimazole and no similar case reports were found in the literature.

Prescribers should always cautious when prescribing this drug and to report such similar adverse effects observed to MADRAC.

SETRALINE AND CLEFT PALATE

A child was born with a cleft lip and palate to a woman who had been prescribed Setraline 50mg daily until week five of her last menstrual period. The use of setraline was restarted during the second trimester of pregnancy but was only given for a period of two days. The patient was also on Lorazepam 1mg at the same time.

A literature search did not reveal any other cases of fetal malformations or oral cleft associated with the use of Setraline or Lorazepam except for one animal study where the use of lorazepam was thought to be associated with cleft palate.

However, in the WHO database, there were nine (9) reports of cleft palate attributed to the use of Setraline and four (4) for Lorazepam.

CURRENT REGULATORY ISSUES

BLACK COHOSH, ROOT: WARNING STATEMENT ON HEPATOTOXICITY

Black cohosh (*Cimicifuga racemosa*), a plant originated from North America has been used therapeutically by the North American Indians to treat various medical conditions. In the EU and UK, *Cimicifuga racemosa* rhizoma (Black Cohosh, root) is widely used by women as an alternative to hormone replacement therapy (HRT) to treat minor peri and post-menopausal symptoms. In Malaysia, there are several products which have been approved by the Drug Control authority with the indication to relieve menopausal symptoms.

However, safety information received from the Medicines and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA) stated that based on adverse drug reactions reports which have been received, there appears to be a risk of hepatotoxicity associated with the use of black cohosh root.

Based on a review of 42 case reports conducted by the Herbal Medicinal Products Committee (HMPC) in Europe, there was a temporal association between the use of *Cimicifuga racemosa* rhizoma (Black Cohosh, root) and the occurrence of hepatic reactions in four cases (2 autoimmune hepatitis, 1 hepatocellular liver injury and 1 fulminant hepatic failure). The mechanism for hepatotoxicity with black cohosh is not known.

“Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately.”

PROMETHAZINE AND THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION

Through the FDA Alert, it has been announced that medications containing promethazine hydrochloride should not be used for children less than two years of age because of the potential for fatal respiratory depression. The US FDA has received reports of serious adverse events, including seven deaths in children under two¹.

“Promethazine hydrochloride (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression”

The Therapeutics Goods Administration, Australia has also reviewed the safety of black cohosh as a result of which the labelling of products containing black cohosh has been strengthened to state that black cohosh may harm the liver.

In Malaysia, the Drug Control Authority (DCA) has approved registration of 114 products containing black cohosh but to date, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) has not received any local reports of hepatotoxicity related to the use of these products.

Although the incidence of hepatic reactions associated with the use of products containing *Cimicifuga racemosa* rhizoma (Black Cohosh, root) worldwide is quite small, in the interest of public safety especially since these products can be purchased and used without medical supervision in Malaysia, MADRAC has proposed that a warning be placed on the product label.

During the 183rd DCA meeting held on 27 July 2006, a decision was taken that all products containing *Cimicifuga racemosa* rhizoma (Black Cohosh, root) with an indication for relieve menopausal symptoms carry the following statement either on the product label or in the product insert:

Although MADRAC itself has not received any reports of fatal respiratory depression linked to the use of promethazine in children less than two years of age, the DCA at its 181 meeting held on 29th May 2006 has agreed with MADRAC's proposal to that the use of products containing promethazine is not indicated in children under the age of two years. All products containing promethazine should now carry the following statement on the label or in the product insert:

Reference: 1) FDA Alert 04/2006

REPORTS FROM JOURNALS

ACE INHIBITORS AND CONGENITAL ANOMALIES

Treatment with ACE-inhibitors during the first trimester of pregnancy has been associated with an increased risk of congenital malformations¹.

The use of ACE-inhibitors for the treatment of hypertension is contraindicated in later pregnancy (2nd and 3rd trimesters) because of an association with a characteristic foetotoxicity syndrome but there has been limited human data on their use in the first trimester.

Based on a study involving 29,507 infants born between 1985 and 2000, researchers identified infants who had been exposed to ACE-inhibitors only during first trimester, other antihypertensive drugs during the first trimester, and no

exposure to such drugs at any time. Infants whose mothers were diabetic were excluded. The primary outcome was the presence of a major congenital outcome unrelated to a chromosome defect or clinical genetic syndrome.

Of the total study population, 209 infants were identified with relevant exposure to ACE-inhibitors and 202 with exposure to other antihypertensive drugs. The results of this study showed the significant increased risk of major congenital malformations in infants whose mothers were exposed to ACE-inhibitors. On this basis, the researchers concluded that use of ACE-inhibitors during the first trimester of pregnancy cannot be considered safe and should be avoided.

Reference: NEJM 2006, 354: 2433-51, 2498-500

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) DRUG LABELS

An article published in the New England Journal of Medicine states the incidence of myocardial infarction, stroke, and sudden death in children and adults who are taking ADHD stimulants. These data have been derived from the FDA's Adverse Event Reporting System (AERS), a database containing reports of adverse events submitted by health care providers.

The drug-related events reviewed by a committee included 25 cases of sudden death in children or adults, some with evidence on autopsy of undiagnosed congenital heart disease, such as hypertrophic obstructive cardiomyopathy. Many additional cases

of major adverse cardiovascular events, including myocardial infarction, stroke, and serious arrhythmias, were reviewed by the committee. However, the documentation of cases was frequently incomplete, and neither the FDA reviewers nor the committee considered the AERS data to be definitive.

Based on that, the committee has recommended that the psychiatric risks be described in the WARNING Sections of ADHD drug labels and that the current language on amphetamine labels about CV risks in patients with structural cardiac abnormalities should be extended to all ADHD drug labels.

Reference: Reactions 1 Apr 2006 No. 1095 N Engl J Med 2006; 354:1445-1448, Apr 6, 2006

ADR MONITORING: A CO-OPERATIVE PROGRAMME FOR ENHANCING THE SAFER USE OF MEDICINES

REPORT ON SUSPECTED ADVERSE DRUG REACTIONS
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING
www.mafraq.gov.my/medfraq

(Please report all suspected drug reactions including those for vaccines and traditional medicines. Do not hesitate to report if some details are not known. Identities of Reporter, Patient and Institution will remain Confidential.)

REPORT No. _____ (for official use only)

A. PATIENT INFORMATION

Initials or R/N only	Age	Sex	Wt(kg)	Ethnic Group	Hospital/Clinic
7682	24	M	55	MALAY	HOSP. ABC

B. ADVERSE REACTION DESCRIPTION

Rash Maculo-papular

Time to onset of reaction (hour/days): 1 day Date of reaction: 23/5/06

Reaction subsided after stopping drug / reducing dose: Yes No Unknown

Reaction reappeared after reintroducing drug: Yes No

Extent of reaction: Mild Moderate Severe

Treatment of adverse reaction: T. O. ph. n. t. ing TDS

Outcome: Recovered Unlikely Fatal-Date of death: _____

Drug Reaction Relation: Certain Probable Possible Unlikely Unclassifiable

Suspected drug(s) and other	Manufacturer No. & Batch No.	Therapy Dates Start	Stop	Indication
Amoxicillin	ABC-Pharma	22/9/06	24/9/06	Bacterial Infection

Mark * for suspected drug(s) and please use trade names where possible*

D. RELEVANT INVESTIGATIONS/ LABORATORY DATA **E. RELEVANT HISTORY** (e.g. hepatic/renal dysfunction, allergies, etc.)

— —

F. REPORTER

Name: Dr. ABC Signature: *[Signature]* Date: 24/9/2006

Address: HOSPITAL ABC Tel. No: 03-12345678

If you would like further information about other reports associated with the suspected drug, please tick here:

Submission of a report does not constitute an admission that medical personnel or the products caused or contributed to the reaction. Thank you for reporting.

REPORTING ADVERSE DRUG REACTION

Contact:
Adverse Drug Reaction Monitoring Centre
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia
P.O. Box 319, Petaling Jaya
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