MALAYSIAN ADVERSE DRUG REACTIONS NEWSLETTER

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

September 2007

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CONTENTS

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2000 – 2006)

In 2006, MADRAC received the highest number of adverse drug reactions (ADRs) from traditional medicines as a group. A total of 68 reports were received related to traditional medicines. Diclofenac Sodium, Carbamazepine, Nifedipine and Allopurinol followed as the drugs with the next most reported cases of ADRs. These four drugs are commonly known to cause ADRs and have been listed among the top ten since 2000. Most of the ADRs reported relate to skin reactions.

The following table shows the number of ADRs reported for the years 2000 to 2006. However, it must be noted that these figures are obtained from random reporting and are not absolute and it should not be interpreted to imply that these drugs are associated with more ADRs than others in the same class.

NO.	2000	2001	2002	2003	2004	2005	2006
1	CO-TRIMOXAZOLE (47)	CLOXACILLIN (34)	CO TRIMOXAZOLE (36)	ALLOPURINOL (33)	ALLOPURINOL (37)	CAPTOPRIL (52)	TRADITIONAL MEDICINES (68)
2	DICLOFENAC (33)	CARBAMAZEPINE (33)	CARBAMAZEPINE (32)	CLOXACILLIN (30)	PARACETAMOL (29)	ALLOPURINOL (51)	DICLOFENAC SODIUM (65)
3	AMOXYCILLIN (23)	CO-TRIMOXAZOLE (23)	CLOXACILLIN (31)	MEFENAMIC ACID (25)	CARBAMAZEPINE (29)	CLOXACILLIN (50)	CARBAMAZEPINE (62)
4	CARBAMAZEPINE (23)	ENALAPRIL (23)	AMOXYCILLIN (28)	DICLOFENAC (24)	NIFEDIPINE (28)	DICLOFENAC SODIUM (44)	NIFEDIPINE (58)
5	CLOXACILLIN (15)	DICLOFENAC (20)	ALLOPURINOL (22)	CHLOROTHIAZIDE (22)	CO-TRIMOXAZOLE (28)	NIFEDIPINE (44)	ALLOPURINOL (57)
6	ALLOPURINOL (15)	PERINDOPRIL (19)	TRADITIONAL MEDICINES (22)	CARBAMAZEPINE (19)	ERYTHROMYCIN (23)	METFORMIN (39)	PERINDOPRIL (57)
7	IBUPROFEN (14)	ALLOPURINOL (17)	ALENDRONATE SODIUM (19)	TRADITIONAL MEDICINES (18)	AMOXYCILLIN (23)	PARACETAMOL (38)	CO-TRIMOXAZOLE (55)
8	NIFEDIPINE (13)	AMOXYCILLIN (17)	DICLOFENAC (19)	AMOXYCILLIN (18)	MEFENAMIC ACID (21)	CO-TRIMOXAZOLE (37)	ASPIRIN (41)
9	ASPIRIN (12)	GENTAMICIN (13)	ISOSORBIDE DINITRATE (18)	PENICILLIN G SODIUM (15)	ASPIRIN (19)	ATENOLOL (37)	ERYTHROMYCIN (40)
10	PHENYTOIN (12)		LOVASTATIN (13)	VANCOMYCIN (15)	CLOXACILLIN (18)	CEFUROXIME (36)	PHENYTOIN (39)

ISSUES OF CURRENT INTEREST

METOCLOPRAMIDE – TIGHTENED USE IN PAEDIATRICS

Following an increase in the number of registered cases of extrapyramidal symptoms in children receiving metoclopramide, the Netherlands Medicines Evaluation Board (MEB) has taken the decision to restrict the use of metoclopramide in children. MEB suggested that metoclopramide should be used only in the treatment of severe nausea and vomiting of known origin, and only if treatment with other products is ineffective or is not possible.

The MEB stated that there are better alternatives to metoclopramide. For example, Domperidone is the better alternative to treat post – operative nausea and migraine in children because the risk of extrapyramidal effects is lower. Similarly, 5-HT3 receptor antagonists, for example, Ondansetron, are the 1st choice of drugs to treat nausea due to strongly emetogenic chemotherapy because of better efficacy and fewer adverse events.

In Malaysia, MADRAC has received 24 reports of metoclopramide causing extrapyrimidal effects in children. The ADRs include spasm (2), oculogyric crisis (21), dystonia (1), convulsion (2), jaw stiffness (1), jerky movement (1) and neck stiffness (1). Healthcare professionals are encouraged to report any suspected adverse reactions related to metoclopramide to MADRAC.

References :

1. WHO Reaction Weekly Issue No. 1133
2. MADRAC's Database

ANTIPSYCHOTICS – REPORTS OF NEUROLEPTIC MALIGNANT SYNDROME

The atypical antipsychotics, clozapine and olanzapine were previously reported to cause neuroleptic malignant syndrome (NMS) in Australia (1997 – 1999). It now appears that all of the atypical antipsychotics available in Australia can cause NMS. In the Australian database there are 16 reports NMS with quetiapine (this being 5.2% of all reports received for this medicine), 45 for risperidone (5.7%), 15 for amisulpiride (6.7%) and 15 for aripiprazole (10.3%). Although with the Australia data it appears NMS occurs most with aripiprazole, this trend is not seen in the WHO global database.

Clinical features of NMS include autonomic instability, confusion, disorientation or other cognitive function changes, fever, muscle rigidity and profuse sweating. Increased creatinine kinase (CK) is often noted. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) advises that NMS can be life – threatening and rapid recognition and treatment are important.

In Malaysia, MADRAC has received 4 cases of NMS with olanzapine, and 2 cases for risperidone and clozapine respectively. For aripiparazole, only reports on muscle rigidity were received.

References :

1. WHO Pharmaceutical Newsletter, No.2, 2007
2. MADRAC's Database

OSELTAMIVIR – MONITOR FOR SIGNS OF UNUSUAL BEHAVIOUR

Oseltamivir is an antiviral agent for the treatment and prevention of influenza in adults and children >1 year old. According to Health Canada, abnormal behaviour, hallucinations and self harm were observed in patients who were receiving this drug. 84 reports of adverse events were reported in Canadian patients, of which 10 patients had a fatal outcome. A causal relationship of adverse events to Oseltamivir has not been confirmed in these cases.

Health Sciences Authority (HSA) Singapore also reviewed the data from their post marketing reports. There were 103 cases of neuropsychiatric adverse events suspected to be associated with Oseltamivir. These events included delirium with prominent behavioral disturbances and suicidal events including self injury and suicidal ideation.

The majority of the cases were reported from Japan (92%) and Oseltamivir was predominantly used for the treatmentof influenza among paediatric patients aged 1.5 to 17 years old. Most of the adverse events occurred during the 1st day of Oseltamivir use.

The connection between Oseltamivir and the reported adverse events has not been proven because high fever or other influenza complications can affect mental state, leading to abnormal behaviour.

Currently, in Malaysia, MADRAC has not received any adverse drug reaction reports regarding Oseltamivir. Close monitoring for this emerging safety concern has to be performed. Healthcare professionals are encouraged to report all serious adverse reactions, especially neuropsychiatric events, suspected to be associated with Oseltamivir.

Due to adverse events reported during the post marketing clinical use of Oseltamivir, Roche Malaysia has updated the Package Insert of Tamiflu and also produced a "Dear Healthcare Professional Letter" to inform the newly stated precautions of Tamiflu. The following statements will be included in the Package Insert under a new "Neuropsychiatric Events" subheading:

- There has been post-marketing reports of delirium and self injury associated with the use of Tamiflu in patients with influenza virus infections, these reports were mostly from Japan and mainly occurred in paediatric patients. The relative contribution of Tamiflu to these events is unknown.
- Patients with influenza virus infections should be monitored closely for signs of abnormal behaviour during the treatment period.

References:

1. Health Canada Media Release 29 Nov 2006 available at http://www.hc-sc.gc.ca
2. Reactions Weekly 9th December 2006 No. 1131
3. HSA Adverse Drug Reaction News, December 2006 Vol. 8, No.3
4. Reactions Weekly 18th November 2006 No. 1128

ROSIGLITAZONE AND ROSIGLITAZONE – CONTAINING PRODUCTS UPDATE

A paper, "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes" that was published in the New England Journal of Medicine (NEJM) has raised a significant amount of concern with regard to the use of rosiglitazone and rosiglitazone – containing products.

The paper which is based on the meta-analysis of 42 clinical studies published in the New England Journal of Medicine on May 21, 2007, reported that there was a statistically significant increased risk of myocardial infarction and a statistically non-significant increase in the risk of cardiovascular death associated with the use of rosiglitazone in comparison to the use of a placebo or other anti – diabetic therapy. However, further investigations are needed to confirm the studies' outcome as some of the studies included patients who were not treated in line with the indication approved for the use of rosiglitazone.

Drug Control Authority (DCA), Ministry of Health Malaysia has made a statement to advise patients who have underlying heart disease or are at risk of heart attack to talk to their doctor about this new information in order for their doctors to evaluate the available treatment options for their Type 2 Diabetes. DCA also advised patients not to stop their medications before consulting their doctors. A Dear Healthcare Professional letter has been circulated to the relevant healthcare providers to update them about this safety issue.

Following so, Glaxo SmithKline (GSK), Malaysia has updated the prescribing information for their rosiglitazone and rosiglitazone – containing products (rosiglitazone – metformin and rosiglitazone – glimepiride). The update is related to congestive heart failure patients with Type 2 Diabetes Mellitus who are using these products as treatment.

GSK has updated their prescribing information to include:-

Congestive heart failure

Initiation of rosiglitazone and rosiglitazone – containing products are contraindicated in patients with NYHA Class III and IV heart failure. In addition, use of rosiglitazone containing products is not recommended in patients with symptomatic heart failure.

Patients should be monitored for signs and symptoms of adverse reactions relating to fluid retention, including heart failure after initiation of rosiglitazone and rosiglitazone – containing products or when there is a dose increase. If symptoms of heart failure develop, these symptoms should be managed according to current standards of care and discontinuation or dose reduction of rosiglitazone must be considered.

References:

1. Dear Health Provider Letter, "Update Regarding Rosiglitazone and Rosiglitazone – Containing Products", 13 August 2007.
2. DCA Statement of the NEJM Article on Cardiac Safety of Rosiglitazone (Avandia®, Avandamet®).
3. Press Release, "GSK Responds to NEJM Article on Avandia", http://www.gsk.com.
4. Press Release, "EMEA Statement on Recent Publication on Cardiac Safety of Rosiglitazone (Avandia, Avandamet, Avaglim)", 23 May 2007.
5. "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes", The New England Journal of Medicine 2007;356, http://www.nejm.org.

CURRENT REGULATORY ISSUES

GADOLINIUM BASED CONTRAST AGENTS AND NEPHROGENIC SYSTEMIC FIBROSIS

The U.S. Food and Drug Administration (FDA) has instructed manufacturers to include a new boxed warning on the product labelling of all gadolinium-based contrast agents which are used to enhance the quality of magnetic resonance imaging (MRI). The warning will state that patients with severe kidney insufficiency who receive these agents are at risk for developing a debilitating and potentially fatal disease known as nephrogenic systemic fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD). U.S. FDA first notified healthcare professionals and public about this safety issue in June 2006 particularly on Omniscan®. Information on the risks was updated in December which involved another five (5) gadolinium-based products.

Based on this recent safety issue, the DCA at its 195th meeting has agreed with MADRAC's proposal that all gadolinium-based contrast agents should carry the following warnings in their product inserts:

a) Boxed Warning

- Exposure to gadolinium – based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:
  - o acute or chronic severe renal insufficiency (glomerular filtration rate <30mL/min/1.73m^2),
    or
  - o acute renal insuficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering a GBCA, do not exceed the dose recommended in product labelling. Allow sufficient time for elimination of the GBCA prior to any readministration.

b) New Additional Warning

1. Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.
2. For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if haemodialysis prevents NSF.
3. Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA.

4. The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

5. Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs.

Reference :

1. USFDA News 2007 (Available at http://www.fda.gov)
2. WHO Pharmaceuticals Newsletter No. 3 2007

SEDATIVE-HYPNOTIC DRUG PRODUCTS – ANAPHYLAXIS REACTIONS AND COMPLEX SLEEP - RELATED BEHAVIOURS

The DCA at its 193rd meeting has agreed with MADRAC's proposal that products which contain *Zolpidem, Flurazepam Triazolam and Midazolam* should include warnings about the following potential adverse events in their package inserts:

- Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling), which can occur as early as the first time the product is taken.

- Complex sleep-related behaviours which may include sleep-driving, making phone-calls, preparing and eating food (while asleep).

This is based on the U.S FDA request to strengthen the labeling of thirteen (13) sleep disorder products registered in the U.S. after reviewing the available post-marketing adverse events for these products. Out of these, only 3 active ingredients are registered in Malaysia and MADRAC at its 97th meeting proposed to include the warnings to midazolam since it has been used as a sedative-hyptonic in Malaysia.

However, after reviewing all sedative-hypnotics registered in Malaysia, a number of benzodiazepines and benzodiazepine like products which are not marketed in the USA have been identified as available in Malaysia and indicated for insomnia. Some benzodiazepines and benzodiazepine like products indicated as anxiolitic have also been used to treat anxiety related with insomnia in Malaysia. The WHO global database also records reported cases of these potential adverse events related to benzodiazepines and benzodiazepine like products.

The DCA at its 195th meeting has agreed with MADRAC's proposal to include another 7 benzodiazepines and benzodiazepine like products to carry the same warnings. The additional 7 ingredients are:

- Nitrazepam
- Alprazolam
- Zopiclone
- Diazepam
- Bromazepam
- Clobazam
- Lorazepam

Reference :

1. USFDA Medwatch (Available at http://www.fda.gov)
2. WHO database

RESTRICTED USE FOR SYSTEMIC PIROXICAM

The European Medicines Agency (EMEA) has recommended restrictions on the use of systemic piroxicam containing products due to the risk of gastrointestinal side effects and serious skin reactions. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that systemic piroxicam should no longer be used for treatment of short term painful and inflammatory conditions. It still can be used to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. However it should not be the 1st choice of non-steroidal anti-inflammatory drug (NSAID) treatment.

In addition, the CHMP also recommended that piroxicam must be initiated by a prescriber experienced in the treatment of rheumatic diseases. The treatment should be used in the lowest dose (not more than 20mg/day) and for the shortest duration possible and should be reviewed after 14 days.

In Malaysia, the DCA has registered 17 systemic products containing piroxicam (16 oral, 1 injectable). To address this safety issue, the DCA at its 197th meeting agreed that the indication of all systemic piroxicam should be restricted to:

"FOR THE SYMPTOMATIC RELIEF OF PAIN AND INFLAMMATION IN PATIENTS WITH OSTEOARTHRITIS, RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS.

HOWEVER IT SHOULD NOT BE THE FIRST CHOICE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) TREATMENT IN THESE CONDITIONS."

The following warnings, precautions and contraindications must be included in the package insert of all systemic piroxicam products:-

Warnings and Precautions:

- **TREATMENT SHOULD ALWAYS BE INITIATED BY A PHYSICIAN EXPERIENCED IN THE TREATMENT OF RHEUMATIC DISEASES.**
- **USE THE LOWEST DOSE (NO MORE THAN 20MG PER DAY) AND FOR THE SHORTEST DURATION POSSIBLE. TREATMENT SHOULD BE REVIEWED AFTER 14 DAYS.**
- **ALWAYS CONSIDER PRESCRIBING A GASTROPROTECTIVE AGENT**

Contraindications:

- **PIROXICAM SHOULD NOT BE PRESCRIBED TO PATIENTS WHO ARE MORE LIKELY TO DEVELOP SIDE EFFECTS, SUCH AS THOSE WITH A HISTORY OF GASTRO-INTESTINAL DISORDERS ASSOCIATED WITH BLEEDING, OR THOSE WHO HAVE HAD SKIN REACTIONS TO OTHER MEDICINES.**
- **PIROXICAM SHOULD NOT BE PRESCRIBED IN ASSOCIATION WITH ANY OTHER NSAID OR AN ANTICOAGULANT.**

Reference :
1. European Medicines Agency (EMEA). Press Release 25th June 2007 (Available at http://www.emea.europa.eu).

LOCAL CASE REPORT

Sticopus horrens (GAMAT EXTRACT) – RENAL FAILURE/NEPHROTIC SYNDROME

Gamat extracts have been registered as traditional medicines in Malaysia and are widely used to heal cuts and wound inflammation, and as a health supplement for general health. During the period April-August 2007, MADRAC received twelve (12) ADR reports associated with the use of gamat extract or Sticopus horrens. The following three cases are among the eight (8) reports received which related renal failure/ nephrotic syndrome as adverse reactions associated with the use gamat extract.

A 59 year old female patient with hypertension and diabetes mellitus experienced hyperkalaemia and chronic renal failure after 3 days on oral gamat extract for her cuts and wounds inflammation. Her laboratory investigation showed a raised level of creatinine kinase. The patient was on insulin injection, prazosin tablet, perindopril and nifedipine for her diabetes mellitus and hypertension. She was also a few other supplements such as vitamin b complex, folic acid, ferrous fumarate and spirulina. She was warded due to this problem and had not yet recovered by the time of reporting.

A 50 year old lady developed acute renal failure after 7 days on gamat extract orally. She had been taking gamat extract as a health supplement and for general health. She was not reported to have other concomitant drugs. A peritoneal dialysis was carried out to overcome the problem.

Another case reported was a 19 year old female patient who was taking gamat extract as a supplement. She was noted to have nephrotic syndrome after oral administration of gamat extract but no onset time was stated by the reporter. No other concomitant drugs were taken at the same time. The extract was stopped immediately and the patient has recovered.

Out of these 12 reports only 2 products were not registered with the DCA. A contributory role of gamat extract in these cases cannot be excluded. Upon analysis of samples sent by reporters and collected from the market, it was shown that the products passed the limit tests for microbial contamination and heavy metals and tested negative for adulterants including steroids and NSAIDs. However, MADRAC will continue to monitor these reactions and the products since the number of reports is increasing.

References:
1. MADRAC's Database

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