APRIL 2013

MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

ACTIVITIES OF MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (MADRAC) FOR 2012

WELCOMING THE MADRAC COMMITTEE FOR 2013-2015

21 February 2013 witnessed the first meeting of the new MADRAC committee for session 2013-2015. With a number of new faces and additional members joining the group, the atmosphere was enthusiastic and spirited.

The role and functions of MADRAC have evolved since the time it was first established in 1987. Besides dealing with a large increase in the total number of adverse drug reaction (ADR) reports received, the committee also discusses safety issues involving both the public and private healthcare sector. While the public sector is largely limited to using drugs listed in the Ministry of Health Drug Formulary and cost is a major consideration, in the private sector, newer and often more expensive drugs are used more widely. Differences also exist between the public and private healthcare settings in terms of clinical practice. Another challenge faced currently is the low rate of ADR reporting among the private sector (3.1% of the total reports received), which affects signal detection locally.

Previously, MADRAC comprised of 9 appointed committee members from the Ministry of Health (MoH), namely 7 specialists (two consultant physicians, a dermatologist, a psychiatrist, a rheumatologist, a paediatrician, and a nephrologist), a Public Health specialist from the Disease Control Division, and one

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TO REPORT AN ADVERSE DRUG REACTION:

ONLINE:
1. Visit http://www.bpfk.gov.my;
2. Click on ADR Reporting and Product Complaints.
3. Click to report as a healthcare professional via online or hardcopy.
4. Submit the form once completed.

MAIL:
1. Print out the ADR form available on the website and complete it.
2. Mail or fax it to:
   The National Drug Safety Monitoring Centre,
   Centre for Post-Registration of Products,
   National Pharmaceutical Control Bureau,
   Ministry of Health
   PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

Tel : +603-7883 5400
Fax : +603-7956 7151

pharmacist. This number was increased to 14 for the new session, with representatives from professional bodies such as the Malaysian Medical Association (MMA), Malaysian Pharmaceutical Society (MPS), Association of Private Hospitals of Malaysia (APHM), and Federation of Private Medical Practitioner's Association Malaysia (FPMPAM), besides academicians from local universities. A complete list of the MADRAC committee is available on the NPCB website.

The additional membership is in-line with the objectives to increase involvement of the private healthcare sector and obtain input from academicians in handling drug safety issues, together with the current members from the Ministry of Health. This will result in more comprehensive decisions being made, allowing MADRAC to make more balanced safety policy recommendations for regulatory actions.

A SPOTLIGHT ON TRADITIONAL MEDICINES

Traditional medicines (as defined under the Control of Drugs and Cosmetics Regulations 1984) refer to any product used in the practice of indigenous medicine, in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and a homeopathic medicine. All traditional medicines registered with the NPCB contain the alphabet T at the end of the designated registration number, for e.g. MAL19991267T.

In 2012, the NPCB received ADR reports involving 151 traditional products, making up 1.4% of the total reports. These comprised of 39 registered products (26%) and 112 non-registered products (74%). These figures likely represent just the tip of the iceberg as studies show in some Asian and African countries, 80% of the population depend**s** on traditional medicine for primary healthcare, while in many developed countries, 70% to 80% of the population has used some form of alternative or complementary medicine[1].

As of April 2013, there are almost 12,000 registered traditional products in Malaysia. However, in spite of ongoing efforts by the Pharmacy Enforcement Division, non-registered traditional products are still widely available on the market as there is an apparent high demand for them. The Pharmacy Enforcement Division conducts raids, including on retail premises such as sundry shops, traditional and complementary medicine practitioners, night markets, sidewalks and vehicles. Offenders may be prosecuted in court, with fines imposed. Press releases are also published to notify the public of non-registered or adulterated products detected.

"As long as there is demand, the supply continues."

There is a strong need to increase public consciousness on the risk of using unregistered traditional medicines as they are not evaluated for safety and quality

Adulterated Products

The National Pharmaceutical Control Bureau (NPCB) receives ADR reports with samples of products, mainly for traditional medicines, food and cosmetics, sent in by consumers or healthcare professionals who suspect adulteration. These samples are sent for laboratory testing to identify suspected adulterants including steroids, antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), sex hormones, or slimming agents.

In 2012, a total of 681 traditional products (632 registered and 49 non-registered) from Surveilance, Product Complain and Pharmacovigilance were sent to the Centre for Quality Control, NPCB for testing. Five registered traditional products were found to be adulterated, with adulterants including sildenafil, tadalafil, repaglinide, and pseudoephedrine. The registration of these products was cancelled.

Among the non-registered traditional products sent for testing, 12 (63%) were found to be adulterated. The adulterants isolated were dexamethasone, prednisolone, chlorpheniramine, ibuprofen, sibutramine, paracetamol and phenylbutazone. Information on these adulterated non-registered products was conveyed to the Pharmacy Enforcement Division for further action.

Under-reporting

ADRs to traditional medicines, just like for other products, are suspected to be widely under-reported. Under-reporting can result in poor signal detection, therefore potential safety issues with traditional products will be difficult to detect.

Possible factors for under-reporting:

- Lack of control on sale and use. When an adverse reaction occurs, consumers often return to the primary prescriber or seller, and reports are rarely submitted. A survey conducted on 32 patients in Nigeria found that although 3 out of 4 patients (75%) informed health workers when they experienced side effects, only one ADR form was submitted by a health care worker[2].
- Widespread availability, including at coffee shops, night markets, online, and through social networking websites. Approximately 30% of the Malaysian population is thought to use traditional medicines[3].
- Often taken in combination with modern medicines, and are not reported as a suspected drug when an ADR occurs.
- The general perception that "traditional = natural and safe". However, ADRs can occur if the product is of poor quality, adulterated, or it is taken together with certain other drugs[1].
- Lack of understanding on how to report and the importance of reporting ADRs[1].
- Uncertainty of types of reactions to report, for example whether certain ADRs are too trivial or well-known to be reported[4].

Reminder to all healthcare professionals:

Always ask your patients if they are taking any traditional medicines and inform them on the dangers of consuming unregistered medicines. Report to NPCB should you notice an adverse reaction. You do not need to be sure, just suspicious!

Educating a patient a day will keep ADRs at bay.

References:

1. WHO (2008). *Fact sheet: Traditional medicines*. http://www.who.int/mediacentre/factsheets/fs134/en/# [Accessed: 29 April 2013].
2. Nwokike J. (2008). *Monitoring Adverse Drug Reactions in public health programs: the case of the Nigeria TB program*. Submitted to the U.S. Agency for International Development by the TBCAP Project.
3. Aziz Z, Tey NP. (2009). *Herbal medicines: prevalence and predictors of use among Malaysian adults*. Complement Ther Med 17(1):44-50.
4. Aziz Z, Siang TC, Badarudin NS (2007). *Reporting of adverse drug reactions: predictors of under-reporting in Malaysia*. Pharmacoepidemiol Drug Saf. 16(2):223-8.

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REGULATORY MATTERS

TRIMETAZIDINE: NEW RECOMMENDATIONS ON THE RESTRICTION OF USE

In April 2013, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) discussed safety and efficacy issues of trimetazidine, resulting in a proposal to the Drug Control Authority (DCA) to instruct the product registration holders to update their package inserts with the relevant information. This proposal was approved by the DCA in its 263rd meeting on 29 April 2013.

Background

In 2011, the French National Security Agency of Medicines and Health Products (ANSM) raised concerns on the efficacy and safety of trimetazidine, following reports of Parkinson syndrome and other movement disorders.[1-2] As a result, the European Medicines Agency's Committee for Medicinal Products for Human Use (EMA's CHMP) conducted a review and came up with a list of recommendations, including contraindicating the use of trimetazidine in patients with Parkinson's disease or parkinsonian symptoms, and patients with severe renal impairment (creatinine clearance <30ml/min), and removing authorisation for use in the symptomatic treatment of tinnitus, vertigo and visual field disturbances. The use of trimetazidine-containing drugs in prophylaxis of angina pectoris was restricted to second-line, add-on therapy. The European Commission decision on these recommendations was issued on 3 September 2012. [3-4]

In Malaysia

Currently, there are 8 trimetazidine-containing products registered in Malaysia. The drug is listed in the Ministry of Health Drug Formulary under category B (Medical Officers), and indicated as prophylactic treatment for episodes of angina pectoris.[5] It is also listed as one of the recommended pharmacological treatments to improve symptoms and/or reduce ischaemia in patients with stable angina pectoris (SAP) in the Clinical Practice Guidelines for the management of SAP. [6]

In terms of use for the treatment of tinnitus, vertigo and visual field disturbances, the 2012 'Guide to Management of Peripheral Vestibular Disorders in primary care' endorsed by the Malaysian Society of Otorhinolaryngologists - Head and Neck Surgeons (MSO-HNS), does not list trimetazidine as one of the drugs in the management of peripheral vestibular disease. [7]

ADR Reports

Since the year 2000, the National Centre for ADR Monitoring has received 55 reports related to trimetazidine, of which 2 reports involved movement disorders (see Table 1). The other adverse events frequently reported were headache (14 reports), dizziness (8), giddiness (6), generalised weakness, palpitations (4 reports each), drowsiness, nausea, vomiting and rash (3 reports each).[8]

Table 1: Malaysian ADR Reports of Trimetazidine Causing Movement Disorders[8]

No.	Age (years)	Adverse Events	Onset	Extent	Outcome	Causality
1	54	Tremor, giddiness, lethargy	1 day	Moderate	Recovered	C3 (possibly-related)
2	61	Tremor, palpitation	15 minutes	Mild	Recovered	C3 (possibly-related)

Regulatory Actions by DCA

The DCA will issue a directive to instruct all product registration holders to update their package inserts with the following information:

a) Indications

- Trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.
- remove the indication for otology and ophthalmology use

b) Contraindications

- Trimetazidine is contraindicated in patients with Parkinson's Disease or parkinsonian symptoms
- Trimetazidine is contraindicated in patients with severe renal impairment (creatinine clearance <30ml/min)

c) Additional warnings

- Regular monitoring, investigation and appropriate management as trimetazidine can cause or worsen parkinsonian symptoms
- Immediate withdrawal of trimetazidine if movement disorders occur
- Dosage reduction in patients with moderate renal impairment (creatinine clearance 30-60ml/min)

References:

1. *Questions and answers on the review of medicines containing trimetazidine (20mg tablets, 35mg modified-release tablet and 20mg/ml oral solution)*. EMA/412151/2012. [21 June 2012; updated 3 September 2012]
2. *Press release: European Medicines Agency recommends restricting use of trimetazidine-containing medicines*. EMA/CHMP/417861/2012. [22 June 2012; updated 3 September 2012]
3. Servier Malaysia Sdn. Bhd. *EMA recommends restricting use of trimetazidine-containing medicines*. Email. [9 July 2012]
4. EMA. *Trimetazidine*- Article 31 referral- Assessment report. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Trimetazidine_31/WC500133925.pdf [3 September 2012]
5. *Drug Formulary*. Ministry of Health Malaysia. No. 3/2012.
6. *Clinical Practice Guidelines for the Management of Stable Angina Pectoris*. Malaysia. [July 2010]
7. *A Guide to the Management of Peripheral Vestibular Disorders in primary care*. Malaysian Society of Otorhinolarynologists- Head and Neck Surgeons. [2012]
8. The Malaysian National Centre of Adverse Drug Reactions database. [12 April 2013]

<u>Local ADR Case reports:</u>

Case 1: Benzyl benzoate/ Pine Tar – use in an 8-month old

An 8-month old child weighing 8.9kg developed cellulitis and chemical burns after two applications of benzyl benzoate 25% emulsion and pine tar liquid cleanser. The child was prescribed these medications by a general practitioner for the treatment of an alleged insect bite.

The mother applied the pine tar solution on the insect bite wound, then rinsed it off. The benzyl benzoate emulsion was also applied on the insect bite site.

The child was admitted to hospital due to the serious adverse drug reaction, and was treated with intravenous antibiotics and silver sulfadiazine (SSD) dressing. The adverse reaction was reported to have subsided after stopping the suspected drugs. The causality given for this case was C3 (possibly-related).

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Note from the National Drug Safety Monitoring Centre:
Benzyl benzoate 25% emulsion is indicated for the treatment of scabies. The package insert recommends that the product be diluted in 3 parts of water for use in young children. The Ministry of Health Drug Formulary states that benzyl benzoate 12.5% emulsion is indicated for the treatment of scabies and pediculosis in younger children.

The pine tar cleanser is indicated to relieve itching and reduce inflammation associated with dermatitis eczema, chicken pox, prickly heat and psoriasis. The package insert states that it is suitable for use by children, but should not be applied to inflamed or broken skin. Side effects include causing irritation, acne-like symptoms, and photosensitivity.

Healthcare providers should be aware that benzyl benzoate needs to be diluted before use in younger children. Please refer to the product package insert for details. Any persistent or unusual skin condition could be a sign of an ADR. Please report this to us.

Case 2: Medroxyprogesterone – a case of anaphylactic shock

A 29-year-old woman developed anaphylactic shock after a dose of intramuscular medroxyprogesterone acetate.

The woman, who had a history of diabetes mellitus, received medroxyprogesterone 150mg for long-term contraception. Within 3 minutes, she developed itchiness, hypotension, bradycardia, and hypoxaemia. On examination, her BP was 80/60 mmHg, PR 32 beat/min, and oxygen saturation 30% (on high-flow mask 10 litres/min).

She was treated with a dose of IV hydrocortisone 200mg, IM chlorpheniramine 10mg, two doses of IV adrenaline 1mg, and given three pints of normal saline infusion, and subsequently recovered.

This case was assigned a causality of C1 (certain) due to the fast onset time and absence of other possible causes.

Note from the National Drug Safety Monitoring Centre:
In Malaysia, this is the first report of anaphylactic shock related to medroxyprogesterone received by the NPCB.

Anaphylaxis is noted in the product package insert as one of the possible adverse reactions of medroxyprogesterone. The WHO Vigibase™ database of adverse drug reaction reports contains 8 reports of anaphylactic shock associated with the use of medroxyprogesterone*.

Healthcare providers should always be alert for anaphylactic reactions: it can happen anytime, for any drug. Do report this ADR to help increase signal detection locally. You can make a difference!

*[*The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases and it does not represent the opinion of the WHO.]*

OTHER ACTIVITIES BY THE PHARMACOVIGILANCE SECTION

The NPCB Booth at the campaign

Pamphlets available for visitors

- **Increasing Consumer Awareness on NPCB Activities at the Taylor's Health Campaign**

  Date : 19-21 April 2013
  Venue : Tropicana City Mall, Petaling Jaya

The Pharmacovigilance Section of NPCB was involved in manning an information booth at the Taylor's University Health Promotion Campaign, targeting the general public. This campaign was co-organised by the Taylor's University School of Pharmacy and School of Medicine, with several sponsors.

Besides health screening and tests conducted by the organisers, the information booths provided visitors with a chance to deepen their understanding on the various functions of the NPCB, the registration process of medicines, and post-registration activities, as well as enforcement activities carried out by the Pharmacy Enforcement Division.

It was an eye opener for most visitors, learning about the risk of ADRs, how to report ADRs, the importance of reporting, and how ADR reports are processed by the NPCB. Many visitors were not familiar with the NPCB website, therefore were briefed on how to check the registration status of medicinal products and where to obtain ADR reporting forms online.

The three-day campaign recorded over 1600 visitors, and it is hoped that the number of reports received, especially from consumers, will increase steadily. Keep a look-out for more activities by the NPCB on our website, or in coming issues of the MADRAC bulletin.

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- Training for Pharmacists on ADR Report Analysis and Causality Assessment using the WHO Method

Date : 28 February 2013
Venue : NPCB, Petaling Jaya

A training session on analysing ADR reports and Causality Assessment was held involving 16 pharmacists from 6 hospitals in Selangor, Seremban and Melaka. WHO causality assessment involves the structured determination of the likelihood that an adverse event is related to drug exposure, taking into consideration the association in time between drug administration and the ADR, pharmacology, medical plausibility, and the likelihood or exclusion of other causes[1].

The objectives of this intensive training session were to:

- strengthen the skills of hospital pharmacists in analysing ADR reports at hospital level;
- train hospital pharmacists to determine the causality of ADR reports more accurately at hospital level;
- improve the quality of ADR reporting.

This training program was previously conducted twice for other hospitals in Selangor and the Federal Territory, involving 17 pharmacists. As result of the training, an improvement was seen in the quality and completeness of reports received, as well as accuracy of causality set by the reporter.

Ideally, every hospital or health clinic should establish a multidisciplinary team to discuss and determine the causality for each report before it is sent to the NPCB. This could generate local signals and improve drug safety. Obtaining further information about a case would be easier when done at hospital-level compared to later on by NPCB staff, therefore the ADR reports sent in should be more complete. Having an officer in-charge of compiling, analysing and despatching all ADR reports from a particular hospital or clinic, such as the Drug Information Service pharmacist, would also greatly improve the overall quality of ADR reporting nationwide.

Reference:
1. WHO (2000). *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre*. Uppsala Monitoring Centre.

GET YOUR CONSUMER MEDICATION INFORMATION LEAFLET (RIMUP)

- RiMUP is a useful back-up reference for patient to refer and discuss with doctor or pharmacist later when needed.
- Visit http://www.bpfk.gov.my, click on "**Consumers**" and click on "**Patient Information Leaflets (PILs)/ Risalah Maklumat Ubat Pengguna (RiMUP)**"
- Key in the name of your medicine (you may search by the brand name
  Eg. Panadol® or active ingredient eg. Paracetamol)
- Feel free to download and print it for your patients' reference.