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Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
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FEATURES

MACROLIDES: OVERVIEW OF LOCAL ADR DATA AND UPDATES ON THE RISK OF QT INTERVAL PROLONGATION

by Norshazareen Abd. Manab

Introduction

Macrolides are a class of antibiotics mainly active against Gram-positive bacteria, with limited efficacy against some Gram-negative organisms. Macrolides inhibit protein synthesis by attaching to the ribosome 50S subunit of susceptible bacteria[1]. Among the drugs in this class are erythromycin, clarithromycin, roxithromycin, telithromycin, and spiramycin. This article will focus on the three commonly-used macrolides in Malaysia: erythromycin, clarithromycin and azithromycin.

Long QT syndrome is a disorder of the electrical activity of the heart. It is characterised by prolongation of QT interval on the electrocardiogram (ECG). A QT interval is corrected (QTc) for heart rate, commonly using Bazett's formula, with an interval greater than 0.44 seconds usually considered prolonged[2-3]. A prolonged QTc predisposes to the development of polymorphic ventricular tachycardia or torsades de pointes, which may lead to ventricular fibrillation and sudden cardiac death.

Prolongation of the QTc is either due to congenital long QT syndrome, or acquired later in life. It may be induced by drugs, or disease and metabolic conditions such as severe bradycardia or hypokalaemia. Drugs that were initially known to cause QTc prolongation are class I and III antiarrhythmic drugs. Amongst other drug classes with this effect include antiinfectives, antidepressants and antipsychotics[2-3].

CONTENT

To report an adverse drug reaction:

1. Visit http://www.bpfk.gov.my
2. Click on the red box: 'Reporting Medicinal Problems'.
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Alternatively, please contact:

The Drug Safety Monitoring Centre,
National Pharmaceutical Control Bureau,
Ministry of Health
PO Box 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

Tel : +603 78835400
Fax : +603 79567151

Macrolides are thought to be the antiinfective agents associated with the greatest risk of QTc prolongation and torsades de pointes[4]. This risk is already documented in the package inserts (PIs) of erythromycin, clarithromycin, roxithromycin and telithromycin, while the PIs of azithromycin have been updated in 2014 following a safety review of this drug.

Background on the Safety Issue

In March 2013, the U.S. Food and Drug Administration (FDA) issued a safety announcement warning the public on the risk of azithromycin causing **abnormal changes to electrical activity** of the heart that may lead to potentially fatal **irregular heart rhythm**[5]. This was based on review of a study published in the New England Journal of Medicine (NEJM) by Ray, Murray, Hall *et al.* in 2012, as well as results of a clinical QT study conducted by the product registration holder of the innovator products, Zithromax® and Zmax®. As a result, the U.S. FDA updated the product labels with information regarding the risk of QT prolongation and torsades de pointes. This safety issue has been featured in a previous NPCB publication (*Reaksi Drug Safety News - May 2013*) which is available on the website (www.bpfk.gov.my).

Local scenario

Currently there are 129 products containing macrolides registered in Malaysia, namely clarithromycin (43 products), erythromycin (42), azithromycin (35), roxithromycin (6), spiramycin (2) and telithromycin (1).

Adverse Drug Reaction Reports

Since year 2000, the NPCB Drug Safety Monitoring Centre has received a total of 1,097 adverse drug reaction (ADR) reports related to macrolides. The highest number of ADR reports was received for erythromycin (725 reports), followed by azithromycin (248), clarithromycin (101), roxithromycin (6) and spiramycin (1). There have been no Malaysian ADR reports involving telithromycin[6].

The top three system organ classes (SOCs) of adverse events reported were the same for all the commonly-used macrolides, as shown in Table 1 below. The main adverse events reported for erythromycin, azithromycin, and clarithromycin were rash, itching/ urticaria, diarrhoea, nausea, vomiting, and oedema.

Table 1: Top Three System Organ Class of Suspected Adverse Drug Reactions Reported for Macrolides

System Organ Class (SOC)	Number of adverse events (%)		
	Erythromycin	Azithromycin	Clarithromycin
Skin & appendages disorders	662 (51.8)	129 (30.5)	72 (35.6)
Gastrointestinal disorders	209 (16.4)	76 (17.8)	43 (20.7)
Body as a whole – general disorders	140 (11.0)	52 (12.2)	26 (13.7)

More patients on erythromycin (51.8%) reported skin adverse events, generally composed of mild reactions such as rash and itching. There were 36 reports of serious skin reactions related to **erythromycin** [Stevens Johnson Syndrome - SJS (20 reports), erythema multiforme (8), AGEP* (5), toxic epidermal necrolysis – TEN (2) and DRESS* (1)], five (5) reports of SJS for **clarithromycin**, and four (4) serious skin reactions related to **azithromycin** (erythema multiforme, SJS and AGEP*).

AGEP: acute generalised exanthematous pustulosis
DRESS: drug reaction with eosinophilia and systemic symptoms

Reports related to heart rate and rhythm disorders

A total of 15 reports (16 adverse events - AEs) related to heart rate and rhythm disorders were associated with azithromycin, 14 reports (16 AEs) for erythromycin, four reports (4 AEs) for clarithromycin, and one report (1 AE) for roxithromycin. The most frequently reported adverse events were palpitation, tachycardia, tachyarrhythmia and bradycardia.

Erythromycin, clarithromycin and azithromycin each had one report on **QT prolongation**, with one report of **torsades de pointes** associated with erythromycin[6].

Time to onset of the adverse reactions mentioned above ranged from a few minutes to 3 days for azithromycin, 30 minutes to 2 days for erythromycin, and 1-3 days for clarithromycin.

There were similar numbers of reports associated with both **dosage forms** of azithromycin (oral and intravenous - IV). Among the reports for erythromycin, nine adverse events (namely palpitation, tachycardia and bradycardia) were related to the oral dosage form, five events (including QT prolongation, torsades de pointes, and tachyarrhythmia) were associated with the IV product, and in the remaining two cases the type of dosage form was not reported. Both clarithromycin and roxithromycin are only available in oral dosage form in Malaysia.

Local package insert updates[7-8]

The local PIs for Zithromax® and Zmax® (azithromycin) have been updated with information on the risk of developing QT interval prolongation and arrhythmias during treatment with azithromycin and other macrolides, under the sections 'Special Warnings and Precautions for Use' as well as 'Undesirable Effects'. As mentioned above, this risk is already documented in the PIs of the other commonly-used macrolides.

Conclusion

Based on local data, there have been ADR reports of QT prolongation and abnormal heart rhythm related to azithromycin use. NPCB will continue to monitor the safety of macrolides, to ensure any signals are detected and managed as soon as possible.

Advice for Healthcare Professionals

- Always **consider the risk** of torsades de pointes and fatal arrhythmia when choosing between macrolides and other antibacterial drugs, especially for patients who are at higher risk of cardiovascular events.
- The potential risk of QT prolongation should be **weighed against the side effects** of alternative drugs, which may also cause QT prolongation or other significant adverse events.
- Patients should be advised to **seek immediate medical attention** if they experience an irregular heartbeat, shortness of breath, dizziness or fainting while taking a macrolide.
- Any adverse event suspected to be associated with the use of macrolides, even those which are common or well-known, should be **reported** to the Drug Safety Monitoring Centre, NPCB.

References:

1. Kucers A & Bennett N (1979). *The Use of Antibiotics, 3rd*. Wm Heinemann Medical Books Ltd, London, UK.
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5. United States Food and Drug Administration (2013). Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms. http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm.
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7. Zithromax® Package Insert, Malaysia [version: June 2014].
8. Zmax® Package Insert, Malaysia [version: June 2014].

THE ASSOCIATION OF HUMAN LEUKOCYTE ANTIGENS AND DRUG HYPERSENSITIVITY SYNDROME
by Norleen Mohamed Ali

Adverse drug reactions (ADRs) cause significant morbidity and mortality, as well as increase healthcare-related financial burden. ADRs may be classified as either 'type A' reactions, which are predictable based on the drug pharmacology, or the less common 'type B' reactions, which are often allergic reactions, not dependent on dosage, unpredictable based on pharmacology and more related to genetic factors of the host[1].

The most common ADRs reported in Malaysia are cutaneous adverse reactions[2]. These reactions range from mild, to severe and life-threatening, such as drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

It is essential to be able to recognise severe reactions, promptly withdraw the culprit drug and initiate proper treatment in order to minimise morbidity and prevent death[3].

Human Leukocyte Antigens and Drug Hypersensitivity Syndrome

Growing evidence supports that variations of human leukocyte antigen (HLA) genotype are a major factor predisposing individuals to develop hypersensitivity immune-mediated reactions[4]. HLA is located at the major histocompatibility complex (MHC) region on human chromosome 6. It plays a central role in immune response by presenting antigens to the T-cell receptor (TCR). In the presence of a proper co-stimulatory molecule, the HLA antigen–TCR complex will form a synapse, which produces a response with immunological memory[4].

The HLA genes are highly polymorphic, with the *HLA-B* locus being the most variable[5]. There have been more than 800 variants already reported for this locus, and a single change of amino acid in the *HLA–B* molecule is sufficient to develop alloreactivity *in vivo*[6].

Cases of severe drug hypersensitivity have been reported in identical twins. In one case, a pair of twins was treated with carbamazepine for epilepsy, and both developed the same hypersensitivity syndrome[7]. Another study by Gennis *et al.* (1991) using the *in vitro* lymphocyte cytotoxicity test, showed that cells from affected patient and four siblings who have never been exposed to carbamazepine showed higher death rate *in vitro* compared to controls, suggesting an inherited predisposition[8].

Several studies have demonstrated the association between HLA polymorphism and drug hypersensitivity. For example *HLA-A29*, *HLA-B29* and *HLA-DR7* have been associated with sulphonamide-related SJS, while *HLA-A2* and *HLA-B12* were linked to oxicam-related SJS/TEN[3]. *HLA-B*58:01* has been associated with severe cutaneous adverse reactions suspected to be due to allopurinol. Other HLA associations with drug hypersensitivity based on population are listed in **Table 2**.

Translating HLA testing into routine clinical care would allow prediction of individuals predisposed to severe cutaneous drug reactions due to genetic factors[9]. With advances in technology and more sophisticated tools available to analyse genes, more HLA associations with drug hypersensitivity are likely to emerge.

Increasing knowledge with regards to HLA associations, drug–HLA interactions (altered peptide model), and the immune pathogenesis of drug hypersensitivity syndrome will pave the way for the development of pre-clinical pharmacogenomic screening strategies that would lead to safer, more cost-effective drug design and development.

Table 2: List of HLA polymorphisms and populations associated with drug hypersensitivity

Syndrome and drug	Alleles	Populations
SJS/TEN		
Allopurinol	*B*58:01* or *B*58* haplotype	Han Chinese, Thai, European, Italian, Korean
Carbamazepine	*B*15:02*	Han Chinese, Thai, Malaysian, Indian
	*B*15:11*	Korean, Japanese
	*B*15:18*, *B*59:01* and *C*07:04*	Japanese
	*A*31:01*	Japanese, northern European, Korean
Oxcarbazepine	*B*15:02* and *B*15:18*	Han Chinese, Taiwanese
Lamotrigine	*B*15:02*	Han Chinese
	*B*38*	European

Syndrome and drug	Alleles	Populations
SJS/TEN		
Phenytoin	*B*15:02*, *B*13:01*, *Cw*08:01* and *DRB1*16:02*	Han Chinese
Sulfamethoxazole	*B*38*	European
Methazolamide	*B*59:01*, *Cw*01:02* and *B*59:01–Cw*01:02* and *A*24:02* haplotype	Korean and Japanese
Sulphonamides	*A*29*, *B*12* and *DR7*	European
Oxicam	*B*73*	European
	*A*2* and *B*12*	European
HSS/DIHS/DRESS		
Abacavir	*B*57:01*	European, African
Allopurinol	*B*58:01* or *B*58* haplotype	Han Chinese, Korean, Japanese, Thai, European
Nevirapine	*DRB1*01:01* and *DRB1*01:02*	Australian, European, South African
	*Cw*8* or *CW*8–B*14* haplotype	Italian, Japanese
	*Cw*4* and *DRB1*15*	Han Chinese
	*B*35:05*	Asian
	*B*35:01* and *B*15/DRB1*15*	Australian
Carbamazepine	*HLA A*01:01*, *Cw*07:01*, *B*08:01*, *DRB1*03:01*, *DQA1*05:01*, *DQB1*02:01*)	Caucasians
	*A*31:01*	Northern European, Japanese, Korean
Delayed rash (nonsystemic)		
Efavirenz	*DRB1*01*	French
Nevirapine	*DRB1*01*	French
	*Cw*04*	African, Asian, European, Thai
	*B*35:05*;	Thai
Aminopenicillins	*A*2* and *DR*52*	Italian

Key:

SJS: Stevens-Johnson syndrome; TEN: Toxic Epidermal Necrolysis; HSS: Hypersensitivity Syndrome; DIHS: Drug-induced hypersensitivity syndrome; DRESS: Drug reaction with eosinophilia and systemic symptoms (Source: Pavlos et al., 2012).

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REGULATORY MATTERS

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATIONS (DHPCs) REVIEWED AND APPROVED BY NPCB IN 2014

Direct Healthcare Professional Communications (DHPCs) are issued by product registration holders with approval from NPCB, to increase awareness on particularly important safety issues or changes in prescribing information involving a product. The following table lists all the DHPCs approved by NPCB in 2014.

NO.	DATE	PRODUCT NAME (ACTIVE INGREDIENT)	DRUG SAFETY ISSUE
1	21 Feb	Benlysta® (belimumab)	*Two post-marketing reports of Progressive Multifocal Leukoencephalopathy (PML) in patients with Systemic Lupus Erythematosus (SLE) treated with Benlysta®*
2	26 Mac	Nizoral® (ketoconazole)	*Discontinuation of use of oral ketoconazole tablets*
3	31 Mac	Vectibix® (panitumumab)	*Additional mutations of RAS*
4	4 Apr	Tykerb® (lapatinib)	*Comparative data have shown that lapatinib based regimens are less effective than Herceptin® (trastuzumab) based regimens in certain settings*
5	11 Apr	Concerta® (methylphenidate)	*New warning on priapism*
6	14 Apr	Zofran® (ondansetron)	*Dose-dependent QT interval prolongation updated information on posology for intravenous use*
7	17 Apr	Erbitux® (cetuximab)	*Additional mutations of RAS*
8	18 Apr	Ultracet® (tramadol + paracetamol)	*Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*
9	25 Apr	Frisium® (clobazam)	*Update to include serious skin reactions in package insert for Malaysia*
10	21 May	Dilatrend® (carvedilol)	*Warnings and precautions for severe cutaneous skin reactions with Dilatrend®*
11	9 Jun	Risperdal®, Risperdal Consta® (risperidone) Invega®, Invega sustenna® (paliperidone)	*Risk of Intraoperative Floppy Iris Syndrome (IFIS) in patients undergoing cataract surgery*
12	7 Jul	Vectibix® (panitumumab)	*Rare cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported in patients treated with Vectibix®*
13	7 Jul	Mencevax ACWY® (meningococcal polysaccharide vaccine)	*New antibody persistence data suggest that individuals at high risk of exposure to serogroups A, W-135 and Y should be considered for earlier revaccination*
14	8 Jul	Ritalin® & Ritalin LA® (methylphenidate)	*Risk of priapism in patients taking methylphenidate*
15	6 Aug	Gran® (filgrastim) & Peglasta® (pegfilgrastim)	*Risk of capillary leak syndrome in patients with cancer (filgrastim & pegfilgrastim) and in healthy donors (filgrastim only)*
16	13 Aug	Protaxos® (strontium ranelate)	*New restricted indication and contraindications for the use of Protaxos®*
17	18 Aug	Neupogen® (filgrastim) & Neulastim® (pegfilgrastim)	*Risk of capillary leak syndrome in patients with cancer (filgrastim & pegfilgrastim) and in healthy donors (filgrastim only)*
18	7 Oct	Revatio® (sildenafil citrate)	*Safety information regarding Revatio® tablets for the treatment of pulmonary arterial hypertension (PAH)*
20	17 Oct	Topamax® (topiramate)	*Updated warnings and precautions on visual field defects*
21	17 Dec	Reminyl® (galantamine hydrobromide)	*New Warning: Serious skin reactions (Stevens-Johnson Syndrome [SJS] and acute generalised exanthematous pustulosis [AGEP])*

TOPIRAMATE: ASSOCIATION WITH VISUAL FIELD DEFECTS

Topiramate is a sulfamate-substituted monosaccharide with antiepileptic activity registered in Malaysia since year 2000 for the treatment of epilepsy and prophylaxis of migraine (*please refer to the package inserts for full prescribing information*).

Visual field defects have been reported in patients taking topiramate, independent of elevated intraocular pressure. This safety issue was detected following a review by Janssen, a division of Johnson & Johnson Sdn. Bhd., the product registration holder of the innovator product, Topamax®. Janssen performed a cumulative search of the company's safety database which revealed an increased incidence of visual field defects associated with topiramate use.

In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In the small proportion of postmarketing cases where an outcome was reported, the majority were reversible.

Visual field defects is a recognised ADR listed in the 'Adverse Effects' section of the innovator PIs. However following the review, a DCA directive was issued on 24 December 2014 for the 'Special Warnings and Precautions for Use' sections in package inserts of all topiramate products to be updated with additional safety information to increase awareness on this serious risk.

Local scenario

Currently, there are 18 products containing topiramate registered with the DCA. These include tablets of strength 25, 50, 100 or 200 mg, and 15-25 mg sprinkle capsules which may be swallowed whole or sprinkled on a teaspoonful of soft food to be swallowed immediately.

Since year 2000, the NPCB Drug Safety Monitoring Centre has received **19 ADR reports** related to topiramate, with 31 adverse events. The most commonly reported adverse events were decreased weight (5 events), coughing, and speech disorder (2 each).

Two (2) of the reports involved patients suffering vision disorders, as detailed below:

Case 1:
32-year-old female who suffered decreased vision one month after starting topiramate 50mg twice daily for epilepsy. Topiramate was stopped, but the patient had not yet recovered at the time of reporting. Concomitant drugs were phenytoin 100mg at night and sodium valproate 400mg twice daily, which were continued post-ADR. This case was assigned causality C2 (probably-related to the drug) by MADRAC.

Case 2:
Female patient in her mid-twenties with underlying bipolar disorder and mood disorder. Concomitant treatment reported were olanzapine and fluvoxamine. Suffered blurred vision and acute angle-closure glaucoma to the point of loss of vision, nine (9) days after topiramate 50mg daily was started for an unspecified indication. Treatment with topiramate was stopped immediately. During follow-up two months later, the patient was reported to have recovered her vision. This case was given MADRAC causality C3 (possibly-related).

Advice for Healthcare Professionals

- If visual problems occur at any time during topiramate treatment, consideration should be given to stopping the drug.
- Patients (and caregivers) should be informed of the risk of visual field defects and counselled to seek immediate medical attention if they experience blurred vision, visual disturbances or periorbital pain while using topiramate.
- Please report all adverse events suspected to be associated with topiramate to the NPCB.

ARTRODAR® (DIACEREIN): RISK OF SEVERE DIARRHOEA AND HEPATOTOXICITY

Diacerein is an anthraquinone used to treat osteoarthritis. It is thought to inhibit the production of interleukin-1 beta, thus reducing the inflammation and destruction of cartilage associated with degenerative joint diseases. In general, it is considered supplementary therapy to analgesics and anti-inflammatory drugs. Diacerein has been associated with the **risk of severe diarrhoea**, especially in patients aged 65 years and above. **Potentially serious cases of hepatotoxicity** have also been reported, leading to a full review of the safety profile by the European Medicines Agency (EMA). Following this review, several risk minimisation measures (as detailed below) were put in place to ensure a favourable benefit/risk balance.

Local scenario

Artrodar® is currently the only product containing diacerein registered in Malaysia. The **approved indication** is symptomatic treatment of functional signs of osteoarthritis. It is not listed in the Ministry of Health Drug Formulary (FUKKM), but is mainly sold to private hospitals, clinics and retail pharmacies.

Since the product was registered in 2004, the NPCB has received **three (3) ADR reports** related to diacerein. **None** of these involved the adverse events **diarrhoea and hepatotoxicity**. The reported reactions were bruising, leg oedema, and increased blood pressure.

Following NPCB review of this safety issue, several sections of the Artrodar® package insert were updated to reduce the risk of serious adverse events. The product registration holder is also issuing a Direct Healthcare Professional Communication (DHPC) regarding these safety changes.

Advice for Healthcare Professionals

- Diacerein is **contraindicated** in patients with current and/or a history of liver disease.
- Use of diacerein is **not recommended** in patients aged 65 years and above.
- Treatment with diacerein should be **initiated by specialists** experienced in the management of osteoarthritis.
- The recommended **starting dose** is 50mg daily for the first 2-4 weeks, then 50mg twice daily with meals.
- **Monitoring** of liver function is recommended prior to starting treatment and throughout treatment duration.
- Treatment should be **stopped immediately** in case of diarrhoea, increased liver enzymes, or signs and symptoms liver damage.
- All adverse events suspected to be associated with diacerein should be reported to the Drug Safety Monitoring Centre.

GUIDE FOR ADR REPORTERS

COSMETICS MAY CAUSE ADVERSE REACTIONS TOO

Please report.

All cosmetics must be notified with the NPCB before they can be manufactured and marketed in Malaysia. Over the past three years, the NPCB has received between 13-45 reports annually on adverse events following use of notified cosmetics, with reactions ranging from itching to acute pancreatitis.
Stay tuned to upcoming issues of the MADRAC Bulletin for more information on this topic.

How to report

Using the blue ADR form (for healthcare professionals) or Consumer Complaints Form available on 'www.bpfk.gov.my ⟶ Consumers ⟶ Reporting'.

What to report

Any suspected adverse reaction may be reported.

Please provide as much detail as possible on the product(s) and reaction(s), attaching the NPCB Cutaneous ADR Classification form if applicable.

Product samples may be sent in for testing if adulteration is suspected.

For further information, please contact:
The NPCB Cosmetics Section
Tel: 03-78835400 (ext. 5537)
Fax: 03-79556772