National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia

MADRAC Newsletter

For healthcare professionals only

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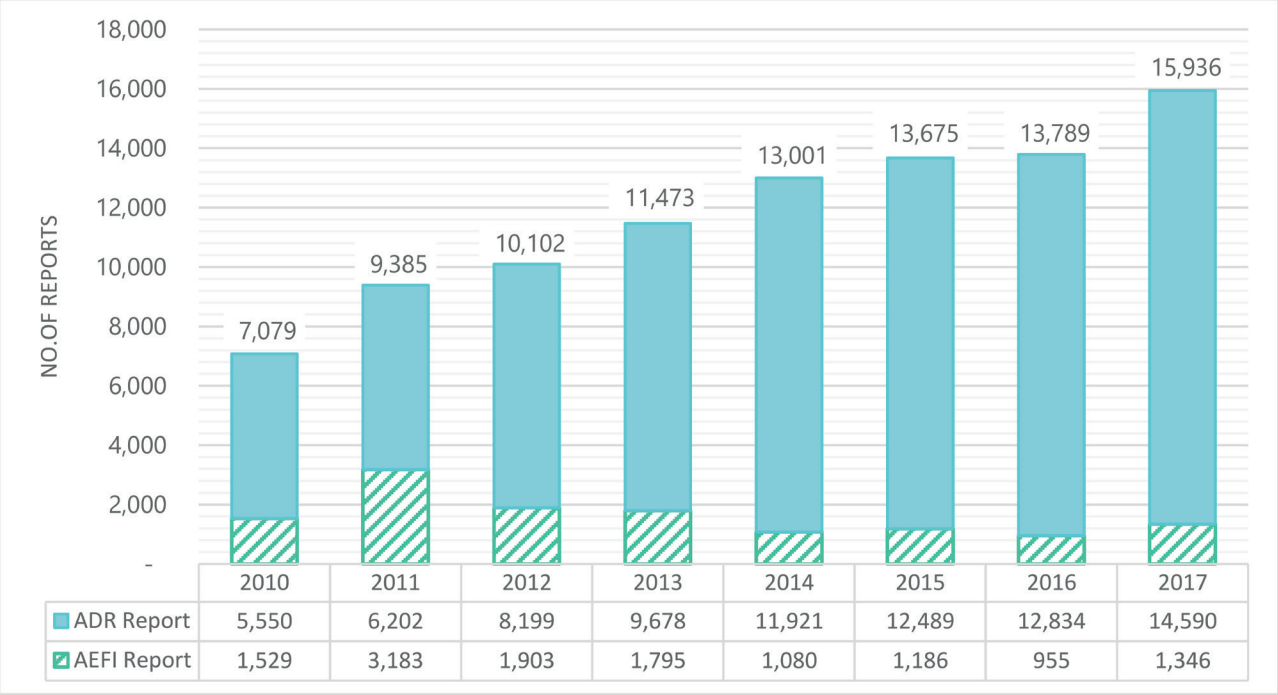
Features

Adverse Event Reports for 2017

In 2017, the Centre for Adverse Drug Reaction Monitoring, NPRA received 15,936 adverse drug reaction (ADR) and adverse events following immunisation (AEFI) reports (refer to Figure 1) involving 16,075 products. The reports are processed and evaluated before they are sent to the World Health Organisation (WHO) Uppsala Monitoring Centre for inclusion into the WHO ADR database.



	2010	2011	2012	2013	2014	2015	2016	2017
ADR Report	5,550	6,202	8,199	9,678	11,921	12,489	12,834	14,590
AEFI Report	1,529	3,183	1,903	1,795	1,080	1,186	955	1,346

Figure 1: Total Adverse Drug Reaction (ADR) and Adverse Events Following Immunisation (AEFI) reports received annually

Articles based on Case Reports

Psychiatric Events Following Administration of Amoxicillin/Clavulanate

by Deborah Quah Ju Shuan

Case Report 1

A 73-year-old male patient with no history of psychiatric illness was started on intravenous amoxicillin/clavulanate for the prophylaxis of community-acquired pneumonia. A day after, he appeared **restless**, claimed he was 'being killed' and **spoke irrelevantly**. A brain CT scan investigation did not reveal any abnormalities apart from a multifocal infarct. The patient was referred to a psychiatric team where he was diagnosed with **amoxicillin/clavulanate-induced psychosis**, and amoxicillin/clavulanate was withdrawn. The next day, the patient appeared normal and had no signs of delirium. The patient was reviewed by a psychiatrist two weeks after hospital discharge and there were no findings of psychosis, disorganised speech or delirium.

Case Report 2

A 39-year-old male patient was initiated with oral azithromycin and intravenous amoxicillin/clavulanate for the treatment of infective acute exacerbation of chronic obstructive pulmonary disease. After a day of drug administration, he developed **auditory hallucination**, was found to be **talking irrelevantly** and was very **irritable**. The patient was diagnosed with **delirium**, with differential diagnosis of azithromycin-induced **psychosis**. Oral azithromycin was withdrawn, and the patient became more irritable and aggressive. On the advice of the psychiatric team, intravenous amoxicillin/clavulanate was then changed to ceftriaxone, and the patient was reported to have recovered from the adverse events.

Discussion

Amoxicillin is a β-lactam antibiotic which exerts its bactericidal activity by interfering with the synthesis of peptidoglycan, an essential building material of the bacterial cell wall. The addition of clavulanic acid, a β-lactamase inhibitor, protects amoxicillin from degradation by binding strongly near or at the active site of the β-lactamase, therefore enhancing and extending the antibacterial effect of amoxicillin.

There are currently **49 products** containing amoxicillin/clavulanate registered with the Drug Control Authority (DCA) in Malaysia. It is indicated for the short-term treatment of infections at the upper respiratory tract, lower respiratory tract, genito-urinary tract, skin and soft tissue, bone and joint, or as a prophylaxis against infections associated with major surgical procedures.

NPRA received a total of **2,239 ADR reports** with **3,999 adverse events** suspected to be related to the use of amoxicillin/clavulanate. Commonly reported adverse events were pruritus (635), maculo-papular rash (406), rash (403), urticaria (388) and diarrhoea (147). To date, there are **four (4) ADR reports** with **seven (7) adverse events** involving amoxicillin/clavulanate with adverse events of **hallucination (2)**, **acute psychosis (1)**, **delusion (1)**, **auditory hallucination (1)**, **irritability (1)** and **psychotic behaviour (1)**. The onset of the adverse events was within one to two days following administration of amoxicillin/clavulanate, and all patients fully recovered with the withdrawal of amoxicillin/clavulanate.

As of July 2018, the WHO global database (VigiLyze®) has 105 reports of hallucination, 36 reports of abnormal behavior, 23 reports of mania, 22 reports of psychotic disorder, 11 reports of delusion and 7 reports of acute psychosis suspected to be related to amoxicillin/clavulanate use, regardless of route of administration*.

*DISCLAIMER
This 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. This information does not represent the opinion of WHO.

There have been literature reports of neuropsychiatric adverse events following use of antibiotics, including amoxicillin/clavulanate, antitubercular agents, macrolides and quinolones. The pathophysiology of these events remains unclear, but may be due to the interaction of antibiotics with different neurotransmitters. In most cases, patients were reported to recover from antibiotic-induced neuropsychiatric ADRs when the suspected drug was withdrawn.

Advice to Healthcare Professionals

- NPRA would like to bring to attention the possible risk of psychiatric adverse events following administration of amoxicillin/clavulanate.
- Please report any ADRs suspected to be related to the use of amoxicillin/clavulanate to the NPRA.

References

1. Amoxicillin/Clavulanate Potassium, Micromedex [Accessed: July 2018].
2. Macknin ML (1987). Behavioral changes after amoxicillin-clavulanate. The Pediatric Infectious Disease Journal. 6(9): 873.
3. Klain V and Timmerman L (2013). Antibiomania, acute manic psychosis following the use of antibiotic. European Psychiatry. 28(S1):1.
4. Lambrichts S, Van Dudenhove L, Sienaert P (2017). Antibiotics and mania: A systematic review. Journal of Affective Disorders 219: 149-156.
5. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: July 2018].
6. Augmentin® Malaysian Product Package Insert [Last revision date: July 2017].

Articles based on Case Reports

Colour Vision Change Following Use of Tranexamic Acid

by Soon Vi Vian

Case Report 1

A 34-year-old woman complained of **colour vision change** (to yellow) 30 minutes after being injected with IV tranexamic acid for menorrhagia. The colour vision change lasted for 30 minutes and thereafter her vision went back to normal. The symptoms reappeared when patient was given IV tranexamic acid for the second time. Otherwise, there was no complaint of blurring of vision, orbital pain, rashes, oedema, shortness of breath, chest pain or palpitations.

Case Report 2

Similarly, another case relates to a 23-year-old woman who developed **colour vision change** and giddiness after she was given oral tranexamic acid for bleeding due to a complete miscarriage. This incident occurred a day after the patient was given several doses of tranexamic acid. The medication was discontinued and symptoms resolved.

Discussion

Tranexamic acid, an antifibrinolytic drug, is a synthetic amino acid which inhibits plasmin and plasminogen activation, thereby promoting hemostasis and thrombosis[1]. This medication comes in two dosage forms, to be used either intravenously or orally.

There are **eight (8) registered products** containing tranexamic acid in Malaysia. The NPRA has received **71 ADR reports** with **143 adverse events** suspected to be related to tranexamic acid use. The most commonly reported adverse events were pruritus, vomiting, dizziness, nausea and rash. To date, NPRA has received **seven (7) ADR reports related to eye disorders**, which are **colour vision change (2)** as discussed above, **blurred vision (3)**, **colour blindness (1)** and **diplopia (1)**.

Based on the global ADR data from the World Health Organisation (WHO), the top three system organ classes (SOCs) for adverse events related to tranexamic acid are gastrointestinal disorders, followed by general disorders and administration site conditions, and skin and subcutaneous tissue disorders. Eye disorders take the eighth position, comprising of 233 individual case safety reports with adverse events such as visual impairment (81 cases) and vision blurred (39 cases)*.

Although the frequency is rare, acquired abnormal colour vision may occur following the use of tranexamic acid[2]. It is suggested that there is a possible link between tranexamic acid and retinal cones, in which there might be a pharmacodynamic effect on the retinal cone pigments involved in colour differentiation.

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Advice to Healthcare Professionals

- Counsel patients that visual abnormalities or vision changes may occur at fairly rare circumstances following tranexamic acid use.
- Advise patients to seek immediate medical attention if they experience any side effects including visual abnormalities.
- Report any adverse events suspected to be associated with the use of tranexamic acid to the NPRA.

References

1. Gravens GT, *et al.* (2006). Antifibrinolytic Therapy Use to Mitigate Blood Loss during Staged Complex Major Spine Surgery: Postoperative Visual Color Changes after Tranexamic Acid Administration. The American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc. Anesthesiology 2006; 105:1274-6.
2. WebMD LLC (2018). Tranexamic acid side effects by likelihood and severity.
3. VigiLyze Uppsala Monitoring Centre, World Health Organisation [Accessed June 2018].
4. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: July 2018].

Articles based on Case Reports

Risk of Hypoglycaemia with Systemic Use of Fluoroquinolones

by Ng Wan Ning

Case Report

A 49-year old female patient with underlying diabetes mellitus and hypertension was reported to develop a **hypoglycaemic episode** with oral ciprofloxacin use. The antibiotic was prescribed to the patient for the treatment of *Pseudomonas aeruginosa* infection. During treatment, the patient had complained of cold sweat, chills and rigor despite consuming a good meal. Upon investigation, patient's hypocount blood glucose level was 2-3.5mmol/L and patient was treated with intravenous dextrose 50% solution. Despite the adverse event, it was reported that ciprofloxacin was continued, with frequent monitoring of blood glucose level and supplementation with intravenous dextrose when patient's blood glucose level dropped below 3.9mmol/L. At the time of reporting, the treatment with ciprofloxacin was still on-going and the outcome of the adverse event was not mentioned. As the patient has a medical history of diabetes and multiple concomitant medications which may have contributed to the adverse event, this case was assigned causality C3 (possibly-related to the drug).

Discussion

Fluoroquinolones are antibiotics that are effective against a broad range of Gram-negative and Gram-positive pathogens through the inhibition of bacterial enzymes DNA gyrase and topoisomerase IV[1].

A recent safety review by the United States Food and Drug Administration (US FDA) has found that systemic use of fluoroquinolones may cause a significant decrease in blood sugar levels[2]. Low blood sugar levels may lead to serious problems, including coma, particularly in elderly patients and diabetic patients who are taking medicines to reduce blood sugar levels. Symptoms of low blood sugar including unusual hunger, dizziness, headache, blurred vision, sweating and irritability may progress and lead to other serious problems such as loss of consciousness and coma.

In Malaysia, there are currently **79 products** containing fluoroquinolones that are registered with the Drug Control Authority (DCA), which comprised of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, and pefloxacin.

To date, NPRA has received **1,093 ADR reports** with **2,066 adverse events** suspected to be related to systemic use of fluoroquinolones. The most commonly reported adverse events were pruritus (298, 14.42%), rash (203, 9.83%), rash maculo-papular (111, 5.37%), urticaria (108, 5.23%), and erythema (58, 2.81%). At the time of this publication, NPRA has received **six (6) reports of hypoglycaemia** involving the use of systemic fluoroquinolones. In all cases, there were no serious events following hypoglycaemia and all the patients were reported to have recovered following the withdrawal of fluoroquinolones.

Fluoroquinolones have been linked to other safety issues, which have been discussed in previous publications by NPRA. For more information on fluoroquinolones safety issues, please click onto the links below:

Fluoroquinolones associated with the risk of retinal detachment and persistence of serious side effects mainly affecting muscles, joints and the nervous system.
[MADRAC Newsletter Volume 25, Issue 01/2018]

Fluoroquinolones: Exacerbation of Myasthenia gravis.
[MADRAC Bulletin August 2011]

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Advice to Healthcare Professionals

- Monitor patients for early symptoms of hypoglycaemia such as sweating, chills, rigor, fatigue, and dizziness, especially in elderly and/or diabetic patients who are on oral hypoglycaemic medication or insulin.
- Counsel patients to watch out for signs and symptoms of hypoglycaemia during treatment with fluoroquinolones and to take precautionary steps to minimise this risk. Advise patients to seek medical attention if they experience any adverse reaction with their medication.
- Report any adverse events suspected to be associated with the use of fluoroquinolones to NPRA.

References

1. L. Mandell and G. Tillotson (2002). Safety of fluoroquinolones: An Update. Can J Infect Dis 2002;13(1):54-61.
2. US FDA (2018). FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes.
3. The Malaysian National ADR Database, NPRA [Accessed: July 2018].

What's New?

List of Directives Related to Drug Safety Issues (May - August 2018)

NPRA reviews and presents drug safety issues at MADRAC meetings to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts of all products containing the affected active ingredients are updated with the required safety information. The following are DCA directives issued between May to August 2018, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Acetazolamide	Severe cutaneous adverse reactions (SCAR)	26 June 2018	[Ref: (16) dlm.BPFK/PPP/07/25 Jilid 2]
2	Prednisone, Prednisolone	Scleroderma renal crisis	26 June 2018	[Ref: (17) dlm.BPFK/PPP/07/25 Jilid 2]
3	Efavirenz	QTc prolongation	26 June 2018	[Ref: (18) dlm.BPFK/PPP/07/25 Jilid 2]
4	Doxycycline	Jarisch-Herxheimer reaction	26 June 2018	[Ref: (19) dlm.BPFK/PPP/07/25 Jilid 2]
5	Azithromycin, Clarithromycin, Erythromycin, Roxithromycin	Severe cutaneous adverse reactions (SCAR)	18 July 2018	[Ref: (22) dlm.BPFK/PPP/07/25 Jilid 2]
6	*Saccharomyces boulardii*	Risk of fungaemia	18 July 2018	[Ref: (23) dlm.BPFK/PPP/07/25 Jilid 2]
7	Iodinated contrast media	Severe cutaneous adverse reactions (SCAR)	18 July 2018	[Ref: (24) dlm.BPFK/PPP/07/25 Jilid 2]

For Healthcare Professionals

How to report adverse drug reactions?

NPRA encourages the reporting of all suspected adverse drug reactions to medicines, including vaccines, over-the-counter medicines, as well as traditional and health supplements.

To report adverse drug reaction:

1. Visit www.npra.gov.my
2. Click on ADR Reporting
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Completed hard copy forms may be submitted via post, email or fax at:

The Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor.

fv@npra.gov.my

+603 7956 7151

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