NPRA MALAYSIA
National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia

MADRAC Bulletin

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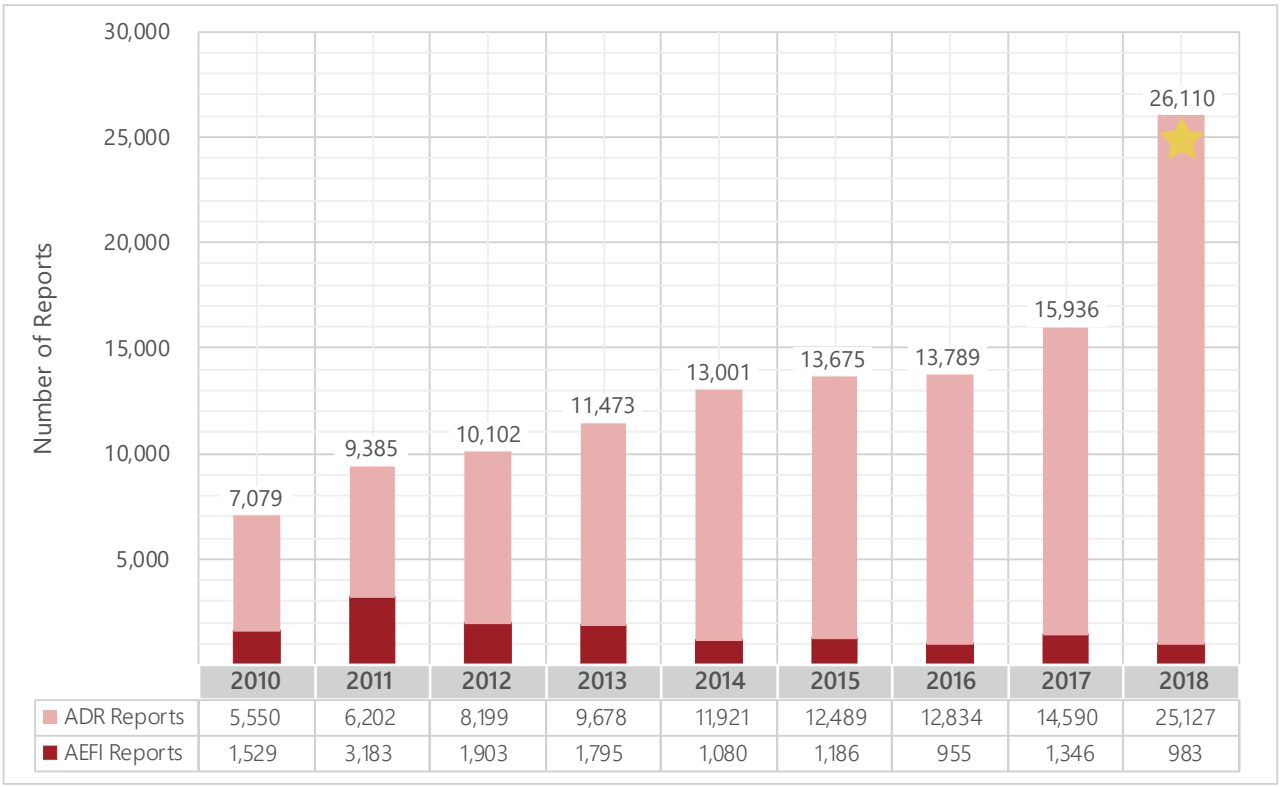
Features

Adverse Event Reports for 2018

In 2018, the Centre for Adverse Drug Reaction Monitoring, NPRA received 26,110 adverse drug reaction (ADR) and adverse events following immunisation (AEFI) reports (refer to Figure 1). 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. There was a sharp increase in the total number of reports received in 2018 due to technological improvements, allowing direct transmission of reports from Ministry of Health hospitals and clinics to the NPRA database.



	2010	2011	2012	2013	2014	2015	2016	2017	2018
ADR Reports	5,550	6,202	8,199	9,678	11,921	12,489	12,834	14,590	25,127
AEFI Reports	1,529	3,183	1,903	1,795	1,080	1,186	955	1,346	983

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

DISCLAIMER:
Figure 1 shows the total reports received by NPRA before the full evaluation was carried out. These adverse events are not necessarily causally related to the product/vaccine.

Articles based on Case Reports

Ophthalmic preparations containing dexamethasone: Risk of Worsening Corneal Ulceration

by Wo Wee Kee

Case Report 1

A 48-year-old female patient complained of pain and redness of the right eye. She was diagnosed with corneal ulcer and was prescribed with a dexamethasone-containing eye drop, lubricant eyedrop, antibiotic and analgesic drugs. After three weeks of full compliance to her treatment, the patient returned with worsening eye redness, pain and reduced vision. The patient was diagnosed with **corneal ulceration** and the dexamethasone-containing eye drop was stopped. Following treatment, the patient was reported to be recovering from the suspected adverse event. This case was assigned a possible drug-reaction causal relationship.

Case Report 2

A 64-year old female patient had been using a dexamethasone-containing eye drop twice daily for the span of a year for the symptomatic relief of recurrent eye redness. She developed **corneal perforation**/corneal melting secondary to prolonged exposure to topical eye drops. The extent of the reaction was serious. The patient was admitted to hospital and surgery was performed. At the time of reporting, the patient was said to be recovering. This case was also assigned a possible drug-reaction causal relationship.

Discussion

Dexamethasone eye preparations are indicated for ocular inflammation of the anterior segment of the eye, recurrent marginal corneal ulceration of toxic or allergic etiology, and thermal or chemical burns to the eyes. Dexamethasone eye preparations are also available in combination with one or two antibiotics, such as neomycin and polymyxin B. These combination preparations are indicated where superficial bacterial ocular infection or a risk of bacterial ocular infection exists alongside ocular inflammation. Currently, there are **14 ophthalmic products** containing dexamethasone as eye drops or eye ointments. Among the 14 products, one (1) product has dexamethasone as a single active ingredient, while the rest are in combination with one or more antibiotics.

A corneal ulcer is a loss of corneal tissue often associated with inflammation and most of the time is infectious, with bacterial, viral or fungal etiologies[1]. Empirical treatment with antibiotic eye drops is generally started at presentation, which is then tailored according to culture and sensitivity results[2]. In this context, a corticosteroid eye drop may be given to suppress inflammation, which may reduce subsequent corneal scarring and visual loss that occurs as a result of the host inflammatory and immune responses to the bacterial infection.

However, the addition of corticosteroid eye drops is controversial in the treatment of corneal ulceration/keratitis because of their potential disadvantages including recurrence of infection, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, delayed corneal healing and increased intraocular pressure[1,2].

According to the bacterial keratitis practice guideline by the American Academy of Ophthalmology, a conservative approach would be to avoid prescribing corticosteroid eye drops for presumed bacterial ulcers until the organism has been identified, the epithelial defect is healing, and/or the ulcer is consolidating. Identifying the organism is **imperative** because if the ulcer is associated with Nocardia bacteria or fungus, the outcomes of corticosteroid therapy are likely to be poor[3]. Prolonged usage of corticosteroid eye drops may also lead to various complications.

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The NPRA has received a total of **26 ADR reports with 35 adverse events** suspected to be related to ophthalmic products containing dexamethasone[4]. A total of **five (5) reports of corneal ulceration/worsening of corneal ulceration** and **one (1) report of corneal perforation** associated with the use of dexamethasone-containing eye preparations (drops and ointment) have been received by the NPRA (including the two cases discussed above).

As of March 2019, the World Health Organisation (WHO) global ADR database revealed a total of **17 reports for ulcerative keratitis** (preferred term for corneal ulceration) suspected to be caused by dexamethasone (16) and dexamethasone/neomycin combination product (1), regardless of the route of administration. There are **two (2) reports for corneal perforation** suspected to be related to the usage of dexamethasone (1) and dexamethasone/neomycin combination product (1)[5]*.

Advice to Healthcare Professionals

- Eye drops containing corticosteroid should be prescribed cautiously in the case of infectious corneal ulceration/ulcerative keratitis especially if the type of organism has not been identified.
- Patient should be counselled not to use corticosteroid eye drops longer than the duration prescribed as prolonged use may have deleterious effects.
- Please report any adverse events suspected to be related to the use of dexamethasone containing products to the NPRA.

*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.

References

1. Borke J, Tai AX. (2018). Corneal Ulcer and Ulcerative Keratitis in Emergency Medicine. Medscape.
2. Palioura S, Henry CR, Amescua G, Alfonso EC. (2016). Role of Steroids in the Treatment of Bacterial Keratitis. Clin Ophthalmol. 10: 179–186.
3. American Academy of Ophthalmology. (2018). Bacterial Keratitis Preferred Practice Pattern.
4. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: Feb 2019]
5. VigiLyze Uppsala Monitoring Centre, World Health Organisation [Accessed: March 2019].

Articles based on Case Reports

Heparin-induced Thrombocytopenia

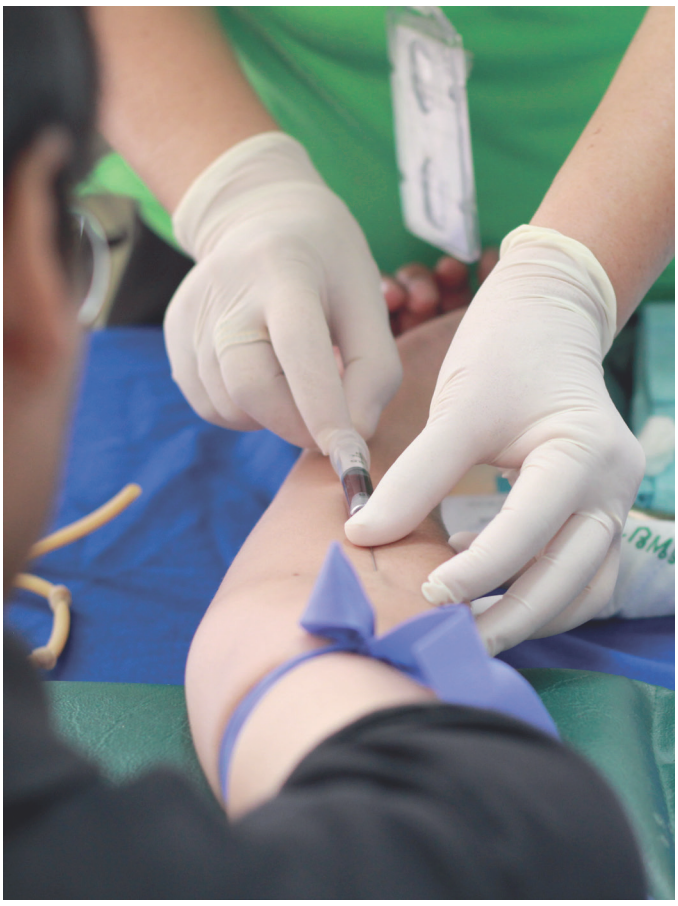
by Nurul Aimi Mohd. Reduzan

Case Report 1

A 56-year-old female patient was started on subcutaneous heparin 5,000 IU twice daily dosage for the prophylaxis of deep vein thrombosis (DVT). After 7 days, she developed sudden onset of dyspnoea with hypotensive episode. An urgent CT pulmonary angiogram was performed and showed extensive pulmonary artery thromboembolism. Heparin was stopped and patient was thrombolysed with IV Streptokinase. This case was assigned a possible drug-reaction causal relationship

Case Report 2

A 65-year-old female patient received subcutaneous enoxaparin 60 mg daily for DVT prophylaxis. After 11 days, she was reported to have breathing difficulties and decreased oxygen saturation. It was later found that the patient was having pulmonary embolism. Enoxaparin was discontinued and appropriate treatment followed, but the outcome of the patient at the time of reporting was not mentioned. This case was assigned a possible drug-reaction causal relationship



Discussion

Heparin is an injectable anticoagulant agent that is used to manage and treat blood clots that may occur in the heart, legs and lungs. It is also used to prevent blood clotting during blood transfusion, hemodialysis, blood sample collection, or after surgery.

In Malaysia, there are two (2) types of heparin registered which are unfractionated heparin and low molecular weight heparin such as enoxaparin and tinzaparin.

Heparin-induced thrombocytopenia (HIT) is one of the complications of heparin therapy[1] that often goes unrecognised. There are two types of HIT: Type I HIT is a non-immune disorder that usually occurs within the first two days after heparin initiation, is not associated with increased risk of thrombosis, and the platelet count normalizes with continued heparin therapy. Type II HIT is an immune-mediated disorder that has life- and limb-threatening thrombotic complications and usually develops after 4-10 days post-exposure to heparin. In this article, the term HIT will be used to refer to Type II HIT.

The main manifestation of HIT is thrombocytopenia, which occurs in about 95% of patients in temporal association with heparin therapy[2]. Unlike other forms of thrombocytopenia, HIT is generally marked by venous thromboembolism such as deep venous thrombosis and pulmonary embolism, and less frequently, arterial thrombosis such as myocardial infarction. For this reason, the disorder is sometimes termed heparin-induced thrombocytopenia and thrombosis (HITT).

Since 2001, NPRA has received **430 ADR reports with 769 adverse events** suspected to be related to heparin usage (heparin, tinzaparin and enoxaparin)[3]. The most commonly reported adverse events are pruritus (63), dyspnoea (36) and thrombocytopenia (35). At present, NPRA has received a total of **ten (10) ADR reports of thrombotic events** associated with heparin, which are **pulmonary embolism (7)**, **cerebral venous thrombosis (1)**, **coronary artery thrombosis (1)** and **pulmonary artery thrombosis (1)**.

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A review of the World Health Organisation (WHO) global ADR database showed a total of **2,399 adverse reaction reports related to pulmonary embolism** and **1,497 reports related to thrombosis** that were associated with heparin use[4]*.

*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.

Advice to Healthcare Professionals

- As there is a risk of heparin-induced thrombocytopenia, platelet counts should be measured in patients receiving heparin treatment for longer than 5 days and the treatment should be stopped immediately in those who develop thrombocytopenia.
- Keep in mind that heparin-induced thrombocytopenia with thrombosis can occur up to several weeks after discontinuation of heparin therapy.
- Inform patients to seek immediate medical attention if they experience pain in the chest, groin or legs, have difficulty in breathing, suddenly develop a painful headache, or experience a loss of coordination or any visual disturbances.
- Please **report** any adverse drug reactions suspected to be related to heparin to NPRA.

References

1. Sancar Eke (2018). Heparin-Induced Thrombocytopenia. Medscape: Drugs & Diseases. Updated: April 24, 2018 [Accessed: April 2019]
2. Gowthami M. Arepally (2016). Clinical Platelet Disorders: Heparin-induced thrombocytopenia. Blood, 25 May 2017, Volume 129: Number 21, p2864–2872.
3. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: March 2018]
4. VigiLyze Uppsala Monitoring Centre, World Health Organisation [Accessed: February 2019].

What's New?

List of Directives Related to Drug Safety Issues (January - April 2019)

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 January to April 2019, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Beta-lactam antibiotics	Severe Cutaneous Adverse Reactions (SCARs)	18 January 2019	[Ref: (2) dlm.BPFK/PPP/07/25 Jilid 3]
2	Lamotrigine	Risk of hemophagocytic lymphohistiocytosis (HLH)	18 January 2019	[Ref: (3) dlm.BPFK/PPP/07/25 Jilid 3]
3	Noradrenaline	Stress cardiomyopathy	27 March 2019	[Ref: (5) dlm.BPFK/PPP/07/25 Jilid 3]
4	Oral retinoids	Neuropsychiatric disorders	27 March 2019	[Ref: (6) dlm.BPFK/PPP/07/25 Jilid 3]
5	Montelukast	Risk of obsessive-compulsive symptoms	18 April 2019	[Ref: (8) dlm.BPFK/PPP/07/25 Jilid 3]
6	Fluoroquinolones (Oral and injection products only)	Risk of aortic aneurysm and aortic dissection	18 April 2019	[Ref: (9) dlm.BPFK/PPP/07/25 Jilid 3]

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

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*To join the **NPRA Safety Information Mailing List**, please send an email with your details to **fv@npra.gov.my***

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http://www.npra.gov.my