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) Upssala 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.

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.
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.
The NPRA has received a total of 26 ADR reports with 35 adverse events suspected to be related to ophthalmic products containing dexamethasone. 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).

*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

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.
**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 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. 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). 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).

*(please see next page)*
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.

*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**

## 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.

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

### 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:
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

### NPRA Safety Information Mailing List

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

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**DISCLAIMER**

This publication is aimed at health professionals. The information is meant to provide updates on medication safety issues, and not as a substitute for clinical judgement. While reasonable care has been taken to verify the accuracy of the information at the time of publication, the NPRA shall not be held liable for any loss whatsoever arising from the use of or reliance on this publication.