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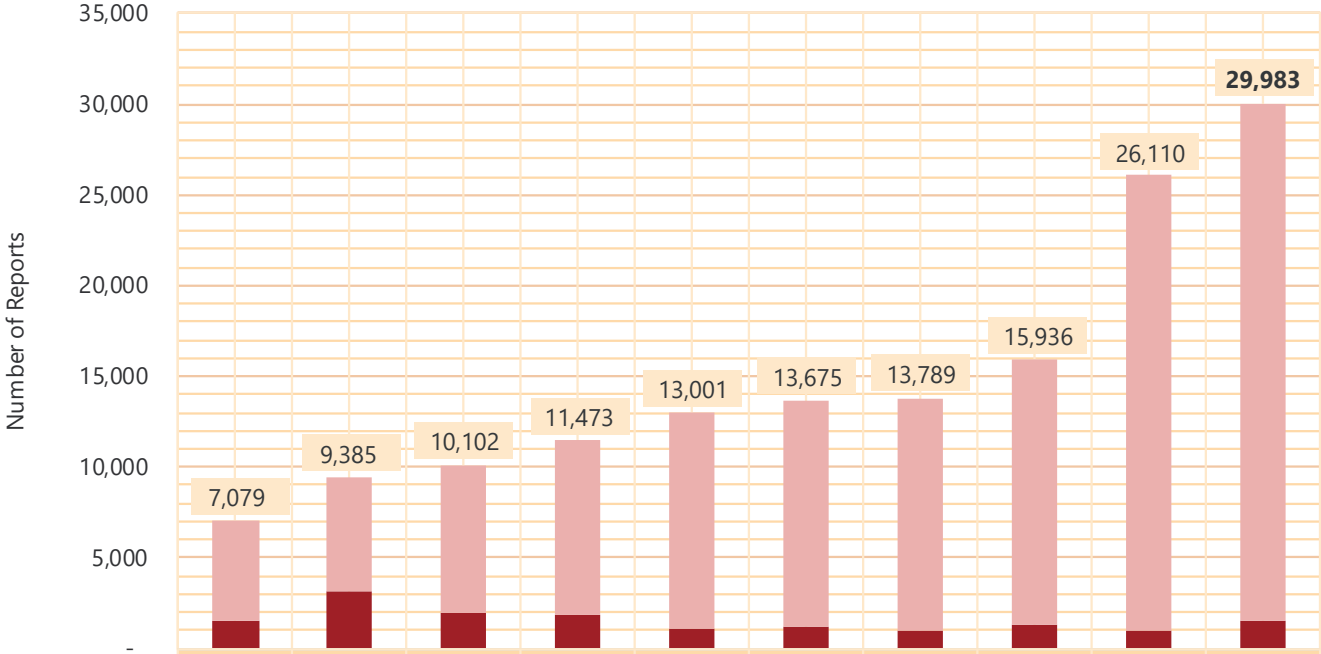
Features

Adverse Event Reports for 2019

In 2019, the Centre for Adverse Drug Reaction Monitoring, NPRA received 29,983 adverse drug reaction (ADR) and adverse events following immunisation (AEFI) reports (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 starting 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	**2019**
ADR Reports	5,550	6,202	8,199	9,678	11,921	12,489	12,834	14,590	25,127	28,505
AEFI Reports	1,529	3,183	1,903	1,795	1,080	1,186	955	1,346	983	1,478

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

Aminophylline overdose: Risk of urinary retention

by Wo Wee Kee

Case Report

A 75-year-old male patient with an estimated body weight of 60 kg was given an intravenous aminophylline 250 mg slow bolus as a loading dose at night, followed by a 50 mg/hour infusion (0.9 mg/kg) over 23 hours for the treatment of acute exacerbation of chronic obstructive pulmonary disease (COPD). The next morning, he was unable to urinate. He also complained of lower abdominal pain for the whole night with no urination. Patient did not have underlying benign prostatic hyperplasia and claimed that he had never encountered urinary retention prior to this. The infusion was stopped and a catheter for continuous bladder drainage was inserted, draining one litre of urine. After removing the catheter, patient was able to urinate as usual. No therapeutic drug monitoring for aminophylline was carried out for this patient.

Discussion

Aminophylline, a drug which falls under the methylxanthine group, is a combination of theophylline andethylenediamine in a 2:1 ratio.[1] It has the same mechanism of action as theophylline as it releases free theophylline upon administration. Theophylline exerts bronchodilatory effect in the lungs and suppresses airway responses to stimuli, as well as increases the force of diaphragm contraction in chronic obstructive pulmonary disease (COPD) or asthmatic patients experiencing bronchospasms.[1,2] It is thought that theophylline inhibits phosphodiesterase (PDE) III and IV which leads to an increase in tissue cyclic adenine monophosphate (cAMP) and cyclic 3',5' guanosine monophosphate concentrations. This results in smooth muscle relaxation in the bronchi, bronchioles and pulmonary blood vessels, therefore achieving bronchodilation.[3,4] However, this increased production of cAMP may also contribute to detrusor muscle relaxation of the urinary bladder leading to urinary retention, especially in elderly male patients with prostatism tendency.[5,6]

As elderly patients may have reduced theophylline clearance, this population should be given a lower aminophylline dosage as compared to normal adult dosing to avoid theophylline toxicity.[2] The recommended dosage for intravenous aminophylline for elderly patients above 60 years old is 5.7 mg/kg over 30 minutes as loading dose followed by a maintenance dose of 0.38 mg/kg/hour.[1]

Urinary retention is said to be one of the most documented adverse effects when the peak theophylline serum concentration is more than 30 µg/ml (normal range: 10- 20 µg/ml).[7]

In Malaysia, there are two (2) registered products containing aminophylline, both of which are in the form of injection. NPRA has received 46 adverse drug reaction (ADR) reports with 76 adverse events associated with aminophylline use.[8] From this total, there are **two (2) reports** linked to **urinary retention** (4.3%). On the other hand, theophylline has one (1) report each for urinary retention and difficulty in urination. As of February 2020, the World Health Organisation (WHO) global ADR database contains 25 and 30 reports of urinary retention suspected to be caused by aminophylline and theophylline respectively.[9]*

Advice to Healthcare Professionals

- The dosage for aminophylline should be reduced in the elderly population.
- Patients on aminophylline therapy, particularly elderly male patients with risk of prostatism should be monitored for signs and symptoms of urinary retention or difficulty in urinating.
- Aminophylline overdose may cause urinary retention. Difficulty in urination is a documented adverse event and is reported to occur even in normal peak serum concentrations of aminophylline.[7]
- Please report any ADR suspected to be related to aminophylline 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. Micromedex Drug Monograph: Aminophylline. [Accessed: February 2020]
2. Aminophylline Malaysian product package insert. [Last revision: February 2017]
3. Gondal AZ and Zulfiqar H (2020). Aminophylline. StatPearls [Internet]. StatPearls Publishing LLC. Retrieved from https://www.ncbi.nlm.nih.gov/
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Articles based on Case Reports

Levothyroxine: Risk of myocardial infarction

by Syifa' Izzati Mohd. Zainul Arifien

Case Report

An 80-year-old female patient was newly diagnosed with subclinical hypothyroidism and was started on levothyroxine 50 µg tablet daily. The next day, she developed **non-ST segment elevation myocardial infarction (NSTEMI)** suspected to be precipitated by levothyroxine. After the drug was withdrawn, the reaction subsided and patient gradually recovered. Her relevant medical conditions included congestive heart failure, atrial fibrillation, hypertension, and dyslipidaemia. Due to the presence of underlying medical conditions and concomitant drugs, the adverse event was given a causality of possibly-related to the levothyroxine.

Discussion

Levothyroxine is the first-line drug indicated as a substitution therapy in hypothyroidism, generally to suppress thyroid-stimulating hormone (TSH) secretion.[1,2] There are currently six (6) registered products containing levothyroxine in Malaysia.[3]

To date, NPRA has received 223 local adverse drug reaction (ADR) reports with 571 adverse events suspected to be related to levothyroxine.[4] The most commonly reported adverse events are pruritus (48), dizziness (34), rash (30), headache (22) and bloating (16). There is **one (1) report** associated with **NSTEMI**, as discussed above. As of March 2020, a search in the World Health Organisation (WHO) global ADR database revealed five (5) reports of NSTEMI and 27 reports of acute myocardial infarction suspected to be associated with levothyroxine.[5*]

Thyroid hormones have a major role in regulating cardiac function, and this may work both ways. The use of levothyroxine to treat subclinical hypothyroidism is thought to improve cardiac function in acute myocardial infarction patients.[6] However, the risk of developing myocardial infarction following levothyroxine use is also documented in the product information.[7] This risk is especially high in the elderly population and in those with underlying cardiovascular disease, due to an increase in heart rate, cardiac wall thickness and cardiac contractility that may lead to angina or arrhythmias related to therapeutic overdosage. As myocardial infarction is a relatively common occurring event in these populations, there is a possibility that this adverse event may be overlooked and often misdiagnosed. Looking at the relatively small number of ADR reports received locally and globally, there is also a chance that this adverse event may be under-reported.

Advice to Healthcare Professionals

- Exercise extra caution when initiating levothyroxine in elderly patients and in patients with underlying cardiovascular disease. In these populations, the **lowest possible dose** should be initiated (e.g. 12.5 µg daily) and increased slowly every 6 – 8 weeks with adjunct monitoring of thyroid hormones.[1,6]
- Report any adverse drug reactions suspected to be related to the use of levothyroxine 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. Levothyroxine Malaysian Package Insert [Last revision date: October 2018].
2. MIMS Clinical Tables (2019). Management of Hypothyroidism.
3. Quest 3+ System (2020). National Pharmaceutical Regulatory Agency (NPRA).
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7. Levothyroxine, Micromedex [Accessed: March 2020].

Articles based on Case Reports

Rare case of hypotonic-hyporesponsive episode following pentavalent vaccine immunisation

by Norshazareen Abd Manab

Case Report

A 2-month-old male infant was reported to develop a **hypotonic-hyporesponsive episode (HHE)** after 5 hours following his first dose of pentavalent vaccine. He was at the babysitter's house when he had inconsolable crying for 15-20 minutes. One hour later, the child became quiet and was not responding to call. During the event, the child was weak, flaccid with bilateral uprolling of eyeballs and cyanosis – the child remained unresponsive for 20 minutes.

The child was immediately brought to a clinic. He regained consciousness and was responsive at the clinic. He was then referred to hospital for further management.

Physical examinations were unremarkable, blood investigations were within normal range and cranial ultrasound was grossly normal. Observed in the hospital ward, the child was active, and was discharged well.

Discussion

HHE is a rare adverse event with reported rates of 14-62 events per 100,000 doses (acellular DTP vaccine).[1] It is defined by **a sudden onset of muscle limpness, reduced responsiveness and pallor or cyanosis**. HHE has been more often associated with whole-cell pertussis vaccines than acellular, and it is also documented to occur after immunisation with diphtheria, tetanus, *Haemophilus influenzae* type B and hepatitis B vaccines.[2] Most reported cases of HHE occur **within 24 hours post immunisation** and affect **children aged below 2 years old**. The cause of HHE is unknown but recovery occurs spontaneously and **no long-term sequelae has been documented**.

The pentavalent vaccine provides protection to a child from five (5) life-threatening diseases - diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenza* type B. Currently there are **two (2) products** containing pentavalent vaccine registered with Drug Control Authority (DCA). The pentavalent vaccine was first introduced into the Malaysian National Immunisation Programme (NIP) in 2008. The programme schedules it to be given to children at age 2 months, 3 months, 5 months and 18 months.

Vaccines are safe. Any vaccines that are licensed are thoroughly tested across multiple phases of trials before it is approved for use, and are regularly reassessed once it is on the market.

NPRA constantly monitors information from several sources for any sign that a vaccine is suspected to cause an adverse event. Most vaccine reactions are usually minor and momentary, such as a sore arm or mild fever. In the rare event where a serious side effect is reported, it is immediately investigated.

While the risk of any serious injury or death caused by vaccines cannot be fully eliminated, the benefits of vaccination greatly outweigh the risks[5], and many millions more lives were protected from illness.

In 2018, NPRA has received 184 AEFI reports with 415 adverse events suspected to be related to pentavalent vaccine[3] (Note: In 2018 alone, more than one million doses of pentavalent vaccine were administered in Malaysia).[4] Most of the AEFI reported were minor, such as injection site swelling, injection site erythema, pyrexia, rash, injection site pruritus and injection site pain. Since the start of pentavalent vaccine use, NPRA has received **three (3) reports on HHE** involving the use of pentavalent vaccine (one is as described above).

Advice to Healthcare Professionals

- Occurrence of HHE is not a contraindication for the next doses of pentavalent vaccine.
- Report any adverse events suspected to be associated with use of pentavalent vaccine to NPRA.

References

1. WHO Information Sheet (2014). Observed Rate of vaccine reactions Diphtheria, Pertussis, Tetanus Vaccine.
2. Buettcher M., Heininger U., Braun M. *et al.* (2007). Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data collection, analysis and presentation. Vaccine 25:5875-81
3. The Malaysian Adverse Drug Reaction data base, NPRA [Accessed Oct 2018].
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What's New?

List of Directives Related to Drug Safety Issues (January - April 2020)

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 2020, which is available on the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Sulphasalazine	Interference with dihydronicotinamide-adenine dinucleotide/dihydronicotinamide-adenine dinucleotide phosphate (NADH/ NADPH) reaction assays	8 January 2020	[Ref: (20) dlm.BPFK/PPP/07/25 Jilid 3]
2	Sodium valproate	(i) Risk of congenital malformation in neonates and neurodevelopmental problems in children exposed to sodium valproate during pregnancy; (ii) Additional educational material for healthcare professionals and patients/caretakers	8 January 2020	[Ref: (21) 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 reactions:
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 hardcopy forms may be submitted via post or email to:

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

fv@npra.gov.my

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

We would like to thank the Director General of Health Malaysia for his permission to publish the case report articles.