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

MADRAC Newsletter

For healthcare professionals only
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Features

Thank you MADRAC 2016-2018

The 166th Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) meeting held on 6th December 2018 marked the final MADRAC meeting for the 2016-2018 session. A small farewell ceremony was arranged to express gratitude to all MADRAC members, who helped ensure the safety of medicines in Malaysia. Beginning 2019, a new commitee will be elected for the 2019-2021 session. While some MADRAC members will continue to serve in the new session, others were celebrated on this day for their dedication and contributions over many years.

Articles based on Case Reports

Amlodipine: Reminder on the Risk of Increase in Urinary Frequency and Nocturia

by Yeoh Hee Sheong

Case Report 1

A 52-year-old woman with hypertension complained of an **increase in urinary frequency** since she was started on amlodipine. This had not only caused her to feel dehydrated, but also affected her sleep at night. Upon withdrawal of amlodipine, her urinary symptom was reported to be resolved. Considering that the patient was also taking other medications (such as hydrochlorothiazide) that might have contributed to the adverse event, this case was classified as possibly-related to the drug.

Case Report 2

A 57-year-old male hypertensive patient on amlodipine therapy complained of experiencing oedema on both legs and **voiding frequency** up to six or seven times at night. When his doctor changed amlodipine to hydrochlorothiazide, his urinary symptoms resolved. This case was classified as possibly-related to the drug.

Discussion

Amlodipine is one of the most widely prescribed calcium channel blockers in East Asia for the treatment of hypertension, with an abundance of evidence-based studies to support its use[1]. It acts by inhibiting calcium influx into myocardial and vascular smooth muscle, resulting in inhibition of cardiac muscle and vascular smooth muscle contraction, leading to decreased peripheral vascular resistance.

Calcium channel blockers such as amlodipine may also affect the contractility of the detrusor muscle (the main muscle of the urinary bladder wall) by altering the amount of intracellular free calcium[2]. The relaxation and contractility of detrusor muscle, in turn, affects the function of bladder filling and micturition[3]. This may lead to an increase in urinary frequency of a patient on amlodipine. The patient may also develop nocturia secondary to peripheral oedema, as the fluid accumulated during the day diffuses into the intravascular compartment as the patient remains in supine position during night time sleep[4].

Amlodipine is approved for the treatment of hypertension and chronic stable angina. There are currently **78 products** containing amlodipine registered in Malaysia as a single agent or in combination with other active ingredients.

Since 2000, NPRA has received **4,854 ADR reports** with **7,825 adverse events** suspected to be related to amlodipine. The most commonly reported adverse events were dizziness (1,331), headache (860), peripheral oedema (731), pruritus (321), and nausea (205)[5].

Adverse events related to renal and urinary disorders that are reported with amlodipine use are minor (28 adverse events, 0.36%), such as **pollakiuria (5)**, **nocturia (3)**, **polyuria (2)** and **increase in urinary frequency (2)**. As these adverse events are often not considered to be associated with amlodipine, the problem arises when the symptoms are persistently present in the patient and the opportunity of a differential diagnosis may be missed.

This was shown in a published case report of a hypertensive patient controlled with a calcium channel blocker who underwent a prostatectomy following symptoms of nocturia and increase in urinary frequency with the assessment result of benign prostatic hypertrophy[6]. The symptoms did not resolve after the procedure but resolved after stopping the drug.

(continued at next page)

Advice to Healthcare Professionals

- Keep in mind the possibility that lower urinary tract symptoms like pollakiuria, increased urinary frequency and nocturia may be caused by a calcium channel blocker such as amlodipine.
- Counsel patients to recognise these symptoms and to inform their doctor if the symptoms are present.
- For patients with prostatic hyperplasia, it is known that the adverse drug reactions of a calcium channel blocker may be similar or masked by the underlying condition of prostatic hyperplasia, hence it is advised that patient's medical history and prescribing history is investigated when he is assessed for prostatectomy[6].
- Given that the incidence of oedema is dose-dependant, reducing the dose and opting for a combination antihypertensive may relieve the symptoms[7].
- All healthcare professionals are encouraged to report any adverse events suspected to be associated with amlodipine use to NPRA.

References

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Articles based on Case Reports

SGLT-2 Inhibitors: Local Reports of Euglycaemic Diabetic Ketoacidosis

by Syifa' Izzati Mohd. Zainul Arifien

Case Report 1

A 41-year-old female patient experienced life-threatening **euglycaemic diabetic ketoacidosis** after one month on empagliflozin therapy. It was reported that patient had the adverse event following her coronary artery bypass graft (CABG) operation, where her arterial blood levels indicated acidosis, blood glucose was more than 12 mmol/L and glucose and ketone were present in the urine (urine glucose 3+, urine ketone 2+). The medication was omitted and treatment for the adverse event included sliding scale insulin and fluid hydration.

Case Report 2

A 63-year-old female patient presented to hospital with shortness of breath, nausea, vomiting, fever and generalised abdominal pain. She was later diagnosed with **euglycaemic diabetic ketoacidosis** secondary to dapagliflozin, which was initiated four days prior to the adverse event. At the time of reporting, the patient was recovering from the event.

Both cases were given a causality of possibly-related to the drug due to the underlying medical conditions and presence of concomitant drugs.

Discussion

Sodium-glucose transport protein-2 (SGLT-2) inhibitors, also known as the gliflozins, are indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus[1] *(for specific indications, please refer to product package insert)*. In Malaysia, there are currently 18 registered products containing SGLT-2 inhibitors that are available either as single ingredient or combination products (canagliflozin, dapagliflozin, dapagliflozin/metformin, dapagliflozin/saxagliptin, empagliflozin, empagliflozin/metformin, empagliflozin/linagliptin, and luseogliflozin).

The use of SGLT2 inhibitors may increase the risk of developing diabetic ketoacidosis (DKA) which is normally accompanied with high blood glucose levels[2]. There have been post-marketing reports of DKA in diabetic patients taking SGLT-2 inhibitors[3]. However, an atypical presentation of DKA may also manifest whereby the glucose levels are within the normal range (euglycaemia) or only slightly elevated. This may delay the diagnosis and management of DKA.

To date, NPRA has received **169 local ADR reports** with **268 adverse events** suspected to be related to SGLT-2 inhibitors[4]. The most commonly reported adverse events are hypoglycaemia (21), diabetic ketoacidosis (10), polyuria (10) and pruritus (7). There are a total of **three (3) reports associated with euglycaemic diabetic ketoacidosis**, two of which are as discussed above. A search in the World Health Organisation (WHO) global ADR database revealed **234 reports of euglycaemic diabetic ketoacidosis** suspected to be associated with the use of SGLT-2 inhibitors[5]*.

*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

- Upon initiation of SGLT-2 inhibitors, patients should be counselled on the possible symptoms of DKA such as nausea, vomiting, decreased appetite, abdominal pain, excessive thirst, difficulty in breathing, confusion, unusual fatigue or sleepiness, frequent urination and fruity-smelling breath. Patients should be instructed to seek **immediate** medical attention when such symptoms occur.
- Whenever DKA is suspected or diagnosed, SGLT-2 inhibitor therapy should be **discontinued** immediately, and appropriate treatment should follow (Please refer to the latest Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus for the management of DKA).
- **Report** any adverse drug reactions suspected to be related to the use of SGLT-2 inhibitors to the NPRA.

References

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5. VigiLyze Uppsala Monitoring Centre, World Health Organisation [Accessed:February 2019].

Articles based on Case Reports

Atezolizumab: Reminder on the Risk of Hyperthyroidism

by Jeevenraj Rajagopal

Case Report 1

A 77-year-old male patient who was on a three-weekly regimen of intravenous atezolizumab 1200 mg developed **asymptomatic hyperthyroidism** on the 12th week of therapy. A blood test was performed, and it showed an elevated free thyroxine (T4) serum level of 24.4 pmol/L (normal range 12-22 pmol/L), which reduced to 22.2 pmol/L and then increased again to 25.0 pmol/L during blood tests repeated throughout atezolizumab therapy. Taking into account that there were concomitant drugs received by the patient during atezolizumab therapy, this case was assigned to be possibly-related to the drug.

Discussion

Atezolizumab is an anti-PD-L1 monoclonal antibody that directly binds to PD-L1 and blocks the interactions between PD-1 and B7.1 receptors found on activated T cells. This suppresses cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production[1,2].

Currently, there is **one (1) product** containing atezolizumab registered with Drug Control Authority (DCA) and its approved indication is the treatment of metastatic non-small cell lung cancer (NSCLC) in patients who have disease progression during or following platinum-containing chemotherapy[2].

NPRA has received **21 ADR reports** with **34 adverse events** suspected to be related to the use of atezolizumab[3]. At present, **three (3) cases of hyperthyroidism** with atezolizumab (including the two case reports above) have been reported to NPRA.

Atezolizumab use has been associated with the risk of hyperthyroidism, and it is documented as a common adverse reaction in the local product packaging insert. The median time to onset was 2.6 months (range: 24 days to 15.7 months) in patients receiving atezolizumab.

A review of the World Health Organisation (WHO) global ADR database (VigiLyze) revealed a total of **22 cases of hyperthyroidism**, **two (2) cases of thyrotoxicosis** and **one (1) case of subclinical hyperthyroidism** suspected to be associated with atezolizumab[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.

Case Report 2

A 62-year-old female patient was receiving intravenous atezolizumab 1200 mg once every three weeks. Six (6) weeks after therapy initiation, she developed **reversible thyrotoxicosis** suspected to be related to atezolizumab. A blood test was performed and revealed an elevated free serum thyroxine (T4) level at 26.2 pmol/L (normal range 12-22 pmol/L). Despite the adverse event, therapy with atezolizumab was continued. Three (3) weeks after the adverse event took place, another blood test was repeated and showed a reduction of serum T4 levels to 15.5 mmol/L. Patient was reported to have recovered from the adverse event. As there were other concomitant medications which may have contributed to the adverse event, this case was assigned to be possibly-related to the drug.

Advice to Healthcare Professionals

- Monitor thyroid function prior to and periodically during treatment with atezolizumab. Consider management for patients with abnormal thyroid function test at baseline. (Please refer to atezolizumab product information for full prescribing details).
- Counsel patients on the symptoms of hyperthyroidism such as tachycardia, palpitations, nervousness, sweating, heat intolerance, muscle fatigue, diarrhoea and weight loss despite increased appetite.
- Advise patients to seek medical attention promptly if symptoms of hyperthyroidism appear.
- Report any adverse events suspected to be associated with the use of atezolizumab to the NPRA.

References

1. Gridelli C, Rossi E, De Chiara G, Ciardiello F, Sgambato A (2016). Thyroid-induced Toxicity of Check-Point Inhibitors Immunotherapy in the Treatment of Advanced Non-Small Cell Lung Cancer. J Endocrinol Diab 3(1): 1 – 10.
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3. The Malaysian Adverse Drug Reaction Database, NPRA [Accessed: January 2019]
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What's New?

List of Directives Related to Drug Safety Issues (September - December 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 September to December 2018, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Atypical antipsychotic agents	Risk of restless legs syndrome, sleep apnoea, urinary retention, hyperglycaemia and diabetes mellitus	23 October 2018	[Ref: (26) dlm.BPFK/PPP/07/25 Jilid 2]
2	Isoniazid	Risk of pancreatitis	23 October 2018	[Ref: (27) dlm.BPFK/PPP/07/25 Jilid 2]
3	Succinylated gelatin (Modified fluid gelatin)	Risk of cross-reaction involving allergen galactose-alpha-1,3-galactose (alpha-gal)	23 October 2018	[Ref: (28) dlm.BPFK/PPP/07/25 Jilid 2]
4	Pemetrexed	Nephrogenic diabetes insipidus and renal tubular necrosis	6 December 2018	[Ref: (29) dlm.BPFK/PPP/07/25 Jilid 2]
5	Filgrastim, pegfilgrastim and lenograstim	Aortitis	6 December 2018	[Ref: (30) dlm.BPFK/PPP/07/25 Jilid 2]
6	Domperidone and clarithromycin	Drug interaction leading to increased risk of QT interval prolongation	6 December 2018	[Ref: (31) dlm.BPFK/PPP/07/25 Jilid 2] [Ref: (32) 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.

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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