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Reaksi

DRUG SAFETY NEWS

Mission: This publication provides information and recommendations to healthcare professionals to enhance communication of drug safety updates, raise awareness of adverse drug reactions reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

In This Issue:

TO REPORT AN ADVERSE DRUG REACTION

Online

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

Mail

1. Print out the ADR form available from our website.
2. Mail or fax to:
   The Drug Safety Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Control Bureau, Ministry of Health, PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

Telephone

03-7883 5400
(ext. 8460/ 8461/ 8463)

Fax

03-7956 7151

Hydroxyzine: Risk of Effects on Heart Rhythm

Overview

Hydroxyzine, one of the first generation antihistamines, has been known to cause QT interval prolongation and *torsades de pointes*. Apart from its common use in acute management of anxiety and treating generalised pruritus, hydroxyzine also has the potential to block the human Ether-à-go-go-Related Gene (hERG) channels as well as other cardiac channels. This may result in abnormal heart rhythms, and possibly even cardiac arrest in patients with underlying heart disease and cardiac arrhythmia.

Background of Safety Issue

In March 2015, the National Pharmaceutical Control Bureau (NPCB) initiated a review into this safety issue following an alert from the European Medicines Agency (EMA) regarding the risk of effects on heart rhythm with medicines containing hydroxyzine. After reviewing clinical and post-marketing data, EMA restricted the use of hydroxyzine in patients at high risk of arrhythmias, limiting the usage to the lowest therapeutic dose for the shortest duration possible. The maximum recommended dose for adults should not be more than 100 mg/day, and for children weighing below 40 kg, a maximum of 2 mg/kg. EMA also recommended that hydroxyzine should be avoided in patients with cardiovascular disease, as well as in geriatric patients due to reduced elimination of hydroxyzine and greater vulnerability to anticholinergic effects or other adverse reactions.

Local Scenario

In Malaysia, there are currently three (3) registered products containing hydroxyzine, under the brand name Atarax®. All three products share the following indication but at different suggested dosage and frequency:

- In adults, for symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.
- As a sedative used as premedication and following general anaesthesia.
- As symptomatic treatment in atopic pruritus.

The product insert of Atarax® has been updated with the new dosing recommendations and warnings on use in patients who have risk factors for heart rhythm disturbances or who are taking certain other medicines.

ADR Reports

To date, NPCB has received **20 ADR reports** related to hydroxyzine use. A total of 37 adverse events have been reported, **none** of which are related to heart rate or rhythm disorders. The majority of the ADRs reported involved skin reactions, namely pruritus (6), rash (5), dry skin (2) and urticaria (2).

Advice to healthcare providers:

- Hydroxyzine should be used at the **lowest effective dose** for the **shortest possible duration**.
- Use is **contraindicated** in patients with known acquired or congenital QT interval prolongation, or with a known risk for QT interval prolongation such as cardiovascular disease, significant electrolyte imbalance (hypokalemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, or concomitant use of drugs known to prolong the QT interval and/or induce *torsades de pointes*.
- Use is **not recommended** in **elderly** patients.
- Use with caution in patients with bradycardia, or on hypokalaemia-inducing drugs.
- **Please report** any hydroxyzine-related ADR to the NPCB for safety monitoring of this drug, allowing prospective data collection and utilisation in the future.

Reference

European Medicines Agency: New restrictions to minimise the risks of effects on heart rhythm with hydroxyzine-containing medicines – 27 March 2015/ EMA/149624/2015.

Sodium-Glucose Co-Transporter 2 Inhibitors: Possible Risk of Diabetic Ketoacidosis

Overview

The new antidiabetic drug class, sodium-glucose co-transporter 2 (SGLT2) inhibitors (namely canagliflozin, dapagliflozin and empagliflozin), has recently been linked with the risk of causing serious diabetic ketoacidosis (DKA).

Background of Safety Issue

In August 2015, the National Pharmaceutical Control Bureau (NPCB) approved a Direct Healthcare Professional Communication (DHPC) for Forxiga® (dapagliflozin) regarding the risk of DKA during treatment with SGLT2 inhibitors.

There have been reports of serious and sometimes life-threatening cases of DKA in patients treated with SGLT2 inhibitors, the majority requiring hospitalisation. A few of the reports involved off-label use in patients with type 1 diabetes mellitus (T1DM). Healthcare providers are reminded that T1DM is **not** an approved indication for this drug class. The underlying mechanism for SGLT2 inhibitor-associated diabetic ketoacidosis has not been established. The WHO International ADR database (VigiBase®) currently contains more than 350 reports of DKA suspected to be related to SGLT2 inhibitors, reported since year 2014*.

DKA usually occurs in patients with T1DM and is normally accompanied by high blood glucose levels (>14 mmol/L). However, some of the cases in patients treated with SGLT2 inhibitors involved only **mildly raised** glucose levels (<11 mmol/L). This **atypical presentation** may delay diagnosis and treatment.

Local Scenario

There are currently **two (2) products** containing dapagliflozin registered in Malaysia since January 2014 for monotherapy or combination therapy in adults with type 2 diabetes mellitus (T2DM).

Since 2014, NPCB has received **21 ADR reports** with 29 adverse events, suspected to be related to dapagliflozin.

There were no reports of DKA related to dapagliflozin in Malaysia. The most commonly reported adverse events involved urinary system disorders, such as polyuria, pollakiuria, urinary tract infection, and urinary frequency. Other adverse events included skin infection, pruritus of the genital, blisters over the foreskin, and low back pain. All the reports were given a causality of C3 (possibly-related to the drug) as there were concomitant drugs or underlying disease that may have contributed to the adverse events.

NPCB will continue to monitor the benefit-risk balance of these products.

**Disclaimer: The 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 and it does not represent the opinion of the WHO.*

Advice to healthcare providers:

- SGLT2 inhibitors should be used according to the **approved indication** and other prescribing information. Use is **not recommended** in patients with moderate to severe renal impairment.
- Please **counsel** patients on the signs of acidosis and advise them to seek medical attention immediately if they experience symptoms such as tachypnoea, hyperventilation, nausea, vomiting, abdominal pain, anorexia, confusion, and unusual fatigue or sleepiness.
- Patients on SGLT2 inhibitors who present with symptoms of metabolic acidosis should be **tested for ketones**, to ensure quick diagnosis and management.
- **Discontinue** SGLT2 inhibitors if acidosis is confirmed, and take appropriate measures to correct the acidosis and monitor blood glucose levels.
- **Potential triggers** of DKA identified included acute illness (e.g., urinary tract infection, urosepsis, gastroenteritis, influenza, or trauma), reduced caloric or fluid intake, and reduced insulin dose.
- **Please report** any ADR related to SGLT2 inhibitors to the NPCB.