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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.

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit http://npra.moh.gov.my.
2. Click on 'ADR Reporting'.
3. Click to report as a healthcare professional and print out the ADR form.
4. Scan and submit the completed form via email to fv@npra.gov.my.

Mail

1. Print out and complete the ADR form available from our website.
2. Mail or fax to:
   The National ADR Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health,
   PO Box 319, Jalan Sultan,
   46730 Petaling Jaya,
   Selangor.

Telephone

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

Fax

03-7956 7151

In This Issue:

A bimonthly publication by the
National Pharmaceutical Regulatory Agency (NPRA), Malaysia.

Concomitant Use of Spironolactone and Renin-Angiotensin System Drugs in Heart Failure: Risk of Potentially Fatal Hyperkalaemia

NPRA would like to remind healthcare professionals that the concomitant use of spironolactone with renin-angiotensin system drugs is not routinely recommended due to the risk of severe hyperkalaemia.

About the drugs

Spironolactone is a competitive aldosterone antagonist which increases sodium and water excretion while reducing potassium loss at the distal convoluted renal tubule. This explains how hyperkalaemia can occur, especially in patients with renal impairment.

Renin-angiotensin system drugs include the Angiotensin Converting Enzyme Inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB). Hyperkalaemia is a recognised adverse effect of both drug classes, estimated to occur in between 1 in 100 and 1 in 1000 patients who take an ACEi or ARB[1].

Background of Safety Issue

The United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) reviewed this safety issue following a report of fatal hyperkalaemia. This case involved a patient with heart failure, diabetes and chronic renal failure, who was receiving several medicines including spironolactone. A few days after a low-dose ACEi was added to treat increased blood pressure, the patient was admitted to hospital with severe hyperkalaemia and acute-on-chronic renal failure, and subsequently died.

The MHRA has received 82 spontaneous reports between January 1998 to December 2015, of abnormal blood potassium levels in patients using spironolactone in combination with an ACEi (n=63) or ARB (n=25), including three cases with a fatal outcome.

The number of hyperkalaemia cases reported in the UK for concomitant use of spironolactone and ACEi or ARB has been showing an increase in the past two years, prompting the MHRA to issue a reminder for healthcare professionals regarding the risk of fatal hyperkalaemia in patients taking spironolactone with an ACEi or ARB[1].

Local Scenario

There are currently two (2) products containing spironolactone, 98 products containing ACEi (namely captopril, enalapril, imidapril, lisinopril, perindopril, ramipril) and 128 products containing ARBs (namely candesartan, irbesartan, telmisartan, valsartan, losartan, olmesartan) registered in Malaysia. The ACEi and ARBs are available as either single-ingredient or combination products.

ADR Reports

Between year 2000 to December 2015, the NPRA has received two (2) reports related to hyperkalaemia involving concomitant use of spironolactone and an ACEi or ARB. Both cases were received from Ministry of Health (MOH) facilities.

The first case was concerning a 47-year-old man who was started on both spironolactone and captopril for the treatment of hypertension. Other drugs included frusemide, metoprolol and amlodipine. On an unknown date, the patient's serum potassium level was 6.8 mmol/L (asymptomatic hyperkalaemia). He had not yet recovered at the time of reporting.

The second report involved a 75-year-old female with underlying chronic kidney disease who was on spironolactone, valsartan, and potassium chloride tablets. Other drugs included bisoprolol, omeprazole and frusemide. Two weeks after starting the drugs, her serum potassium level was 6.9 mmol/L and ECG showed sinus rhythm. The physician decided to discontinue spironolactone and potassium chloride. Outcome was unknown at the time of reporting.

Both cases were given causality C3 (possibly-related to drug) because the patients had concomitant medication and underlying illnesses which may have contributed to the adverse event.

Advice for Healthcare Professionals

- Concomitant use of spironolactone with ACEi or ARB is not routinely recommended because of the risk of severe hyperkalaemia, particularly in patients with marked renal impairment.
- If co-administration is considered essential, the lowest effective doses of spironolactone and ACEi or ARB should be used.
- **Monitoring**: Serum potassium levels and renal function should be monitored regularly.
- If hyperkalaemia occurs, interrupt or discontinue spironolactone and ACEi or ARB treatment.
- Please **report** all adverse events suspected to be related to the use of spironolactone, ACEi and ARB to the NPRA.

Noxafil® (posaconazole): Tablet and Oral Suspension Not Interchangeable

Background of Safety Issue

The broad-spectrum triazole antifungal Noxafil® (posaconazole) is available in two oral formulations: a 40mg/ml oral suspension and a 100mg modified-release tablet. These two preparations are **not directly interchangeable** and require **dosage adjustment**, as the tablet has a higher bioavailability than the oral suspension. Direct mg for mg substitution of the two formulations can result in drug levels that are lower or higher than needed to effectively treat certain fungal infections[2].

There have been reports worldwide of patients being provided with the wrong oral dosage form of Noxafil®, which resulted in adverse effects or lack of efficacy[3]. One of the cases reported in the United States resulted in death suspected to be related to invasive *Aspergillus* infection[2]. This patient was given Noxafil® oral suspension in place of the tablets without consideration of the different dosing regimen, resulting in an underdose.

Local Scenario

As mentioned above, there are currently two (2) products containing posaconazole registered in Malaysia. Noxafil® tablet has only recently been registered in April 2016. Both products are indicated for use in the treatment of certain fungal infections, and prophylaxis of invasive fungal infections in adults *[please refer to the product package inserts (PI) for full details]*. Posaconazole oral suspension is listed in the Ministry of Health Drug Formulary (FUKKM) under prescriber category A* (to be initiated by consultants for specific indications only).

The PI of Noxafil® tablet contains the statement that the two formulations must not be used interchangeably, while the PI for the oral suspension is being updated with this information.

ADR Reports

Since the oral suspension was first registered in 2009 until December 2015, the NPRA has received one (1) ADR report related to posaconazole, involving a 45-year-old male patient who was taking the oral suspension. The patient developed generalised maculopapular rashes and periorbital oedema after starting to take posaconazole. The antifungal was discontinued and the patient recovered with treatment. This case was given causality C3 (possibly-related to drug) because the patient had concomitant medication which may have contributed to the adverse events.

Advice for Healthcare Professionals

- Posaconazole tablets and oral suspension are not interchangeable.
- Please specify the dosage form and relevant dose of posaconazole on each prescription.
- Pharmacists must ensure the specified oral dosage form is dispensed to patients.
- **Counselling points**: Please advise patients to seek medical attention if they have[2]:
  - ◊ severe diarrhoea or vomiting.
  - ◊ a change in heart rate or heart rhythm, or any heart disease. Posaconazole should be used with caution in patients with potentially proarrhythmic conditions.
  - ◊ swelling in an arm or leg, or shortness of breath.
  - ◊ liver disease, develop itching, jaundice, they feel more tired than usual or feel like they have the flu.

References:

1. Medicines and Healthcare Products Regulatory Agency (2016). Drug Safety Update: Spironolactone and renin-angiotensin system drugs in heart failure – risk of potentially fatal hyperkalaemia.
2. FDA Drug Safety Communication (2016). FDA cautions about dosing errors when switching between different oral formulations of antifungal Noxafil (posaconazole); label changes approved.
3. European Medicines Agency (2016). EMA warns that Noxafil tablets and oral suspension have different doses and are not interchangeable.