

MADRAC *Bulletin*

For healthcare professionals only

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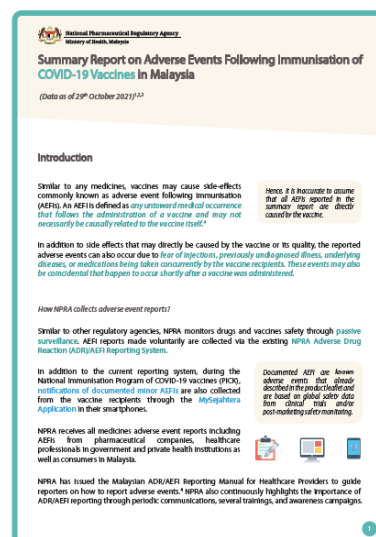
Features

Summary Report on Adverse Events Following Immunisation of COVID-19 Vaccines in Malaysia

The NPRA monitors the safety of COVID-19 vaccines to ensure that they remain safe for use and the benefits of these vaccines continue to outweigh the risks in the Malaysian population. As part of our monitoring efforts, NPRA is publishing key findings of this safety monitoring.

The current summary report is based on data up to 29th October 2021.

[Read the summary report here.](#)



19.5

Minor AEFI responses
per 1,000 doses

0.45

Overall AEFI reports
per 1,000 doses

93.3%

AEFI reports are
non-serious

0.03

Serious AEFI reports
per 1,000 doses

Similar to global scenario⁶, the vast majority of the reported AEFIs in Malaysia are non-serious.³ The most common reactions included injection site pain, headache, fatigue, muscle pain, fever, chills, and acute stress reactions (e.g. anxiety and tremor).

The rate of serious AEFIs reported via the NPRA Reporting System is small at 0.03 per 1,000 doses, most requiring short-term hospitalisation for observation and treatment.³



Based on the current data, the benefit-to-risk-ratio of COVID-19 vaccines registered in Malaysia remains very favourable, indicating that the benefits clearly outweigh the risks.

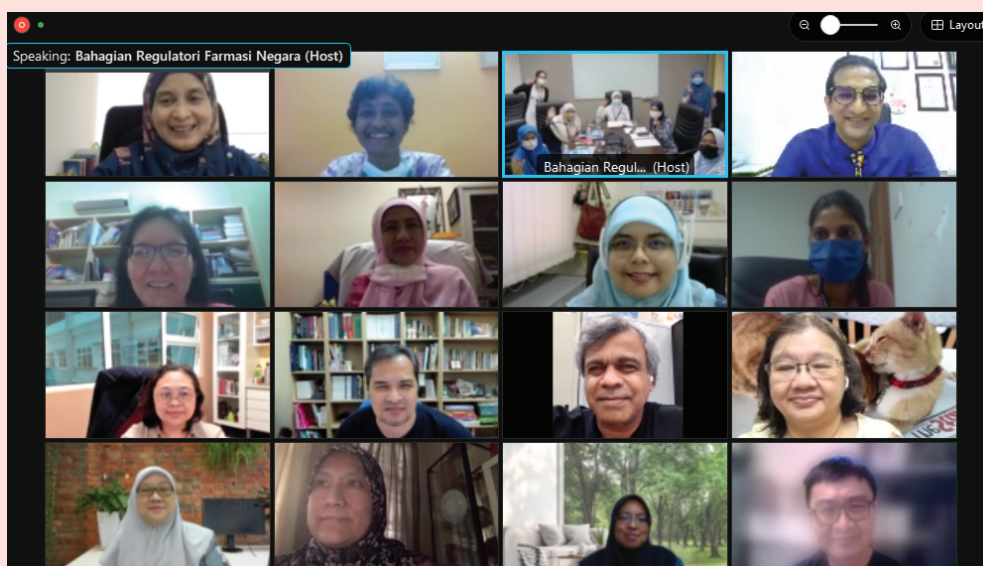
The NPRA encourages all healthcare professionals and patients to report any suspected AEFIs so that potential new risks can be identified, and appropriate safety measures and regulatory actions can be taken to mitigate the risk, if deemed necessary.

Features

Thank you MADRAC 2019-2021

The 180th Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) meeting, which was held virtually on 10th November 2021, marked the final MADRAC meeting for the 2019-2021 session.

NPRA expresses our greatest gratitude to all MADRAC members for their long-standing dedications and contributions in ensuring the safety of medicines and vaccines in Malaysia.



From 2022, new committee members will be appointed to continue and advance the nationwide medicines and vaccines safety monitoring work throughout the 2022-2024 term.

Articles Based on Case Reports

Risperidone: Risk of Hyperprolactinaemia

by Nur Ayuni binti Ahmad

Case Report 1

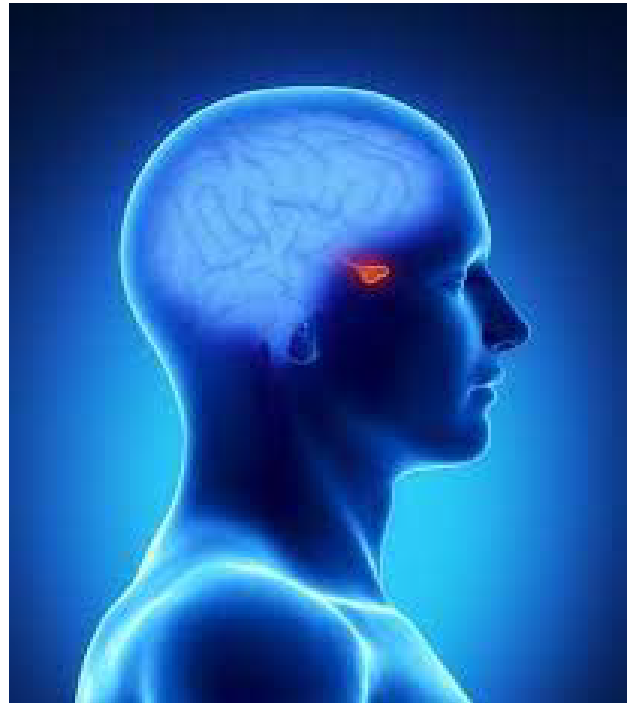
A 19-year-old female patient with an estimated body weight of 45 kg was prescribed tablet risperidone for the management of schizophrenia. After four (4) months on therapy, the patient complained of having irregular menstrual cycles each of which usually lasts for two to three weeks. Blood investigation for prolactin level was done and the finding was 1,240 mIU/L (normal values for non-pregnant female is 40 to 530 mIU/L).¹ Risperidone was withdrawn from her therapy and substituted with tablet aripiprazole. The patient was reported to have recovered from the adverse event.

Case Report 2

A 33-year-old female patient was diagnosed with schizophrenia and was started on tablet risperidone. Over the course of three (3) months, the dose was gradually increased from 2 mg to 4 mg. The patient complained that her period did not come since the second month after therapy initiation. Risperidone was withdrawn and substituted with tablet aripiprazole. The outcome from the adverse event was reported to be unknown.

Discussion

Risperidone, a second generation antipsychotic agent and often referred to as an atypical antipsychotic, is used to treat schizophrenia and manic episodes associated with bipolar disorders.^{2,3,4} It acts by antagonising dopaminergic D2 receptors and serotonergic 5-HT_{2A} receptors in the brain, leading to a reduction in dopaminergic and serotonergic activity of the central mesolimbic pathways and mesocortical pathways, respectively.^{4,5} As dopamine also plays a role in the inhibition of prolactin secretion by the pituitary gland at hypothalamus, the blockade of dopamine receptor by risperidone can cause an increased serum prolactin levels, known as hyperprolactinaemia.^{5,6}



In general, atypical antipsychotics such as clozapine, quetiapine and aripiprazole do not cause increased prolactin levels due to their lower affinity towards D₂ receptors.⁵ However, sustained elevated of prolactin levels are seen in patients on risperidone treatment as it has a high affinity towards dopamine and serotonin receptor of the dopaminergic pathways. Therefore it will antagonise dopamine in tuberoinfundibular system which finally results in high prolactin level.

Although hyperprolactinaemia is known and documented for risperidone, it was postulated that the degree of hyperprolactinaemia is dose-dependent and modulated by genetic differences among individuals.^{2,6} Most patients who have hyperprolactinemia do not show symptoms until a constant increase in serum prolactin levels which implicates the suppression of the hypothalamic-pituitary-gonadal axis. Symptoms of hyperprolactinaemia such as infertility, loss of libido, erectile dysfunction, amenorrhoea, gynaecomastia and galactorrhoea may occur.^{5,6} Long-term adverse effects may also include osteoporosis and possibly an increased risk of breast cancer.⁶

In Malaysia, there are 27 registered products containing risperidone in the form of tablets, syrups and intramuscular injection.⁷ To date, NPRA has received 709 adverse drug reaction (ADR) reports with 1,271 adverse events suspected to be related to risperidone. The most commonly reported adverse events seen with risperidone use are tremor (55), extrapyramidal disorder (45), akathisia (44), musculoskeletal stiffness (41) and dizziness (34). In total there were **12 reports of hyperprolactinaemia** associated with risperidone use, including the two (2) case reports mentioned above. As of March 2021, World Health Organisation (WHO) global ADR database revealed **5,310 reports of hyperprolactinaemia** suspected to be associated with risperidone.^{8*}

***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

- 1 Counsel patients or their caregivers on the symptoms of hyperprolactinaemia such as irregular menses, change in menstrual flow, pain in the breast or vaginal dryness and advise them to consult their doctor for further assessment if these symptoms develop.
- 2 According to The Maudsley Prescribing Guidelines in Psychiatry, it is recommended that prolactin-raising drug is avoided in the following patient groups:
 - a. Patients aged 25 years or less (i.e. before peak bone mass is achieved)
 - b. Patients with osteoporosis
 - c. Patients with a history of hormone-dependent breast cancer
- 3 In patients receiving risperidone, it is suggested that a baseline prolactin level should be measured prior to drug initiation, then at three (3) months, followed by yearly checks to detect risperidone induced hyperprolactinemia.

- 4 In symptomatic hyperprolactinemia, consider dose reduction or changing to an antipsychotic that has a lesser effect on prolactin levels. In cases where patients need to continue on a prolactin-elevating antipsychotic drug, dopamine agonist such as cabergoline and bromocriptine may also be considered.
- 5 Inform female patients that menstruation and fertility will return as their prolactin levels normalise, therefore contraceptive measures may be needed.
- 6 Please report any ADR suspected to be related to risperidone to the NPRA.

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Articles Based on Case Reports

Efavirenz-Induced Gynaecomastia

by Farah Faridah bt Jamaludin

Case Report 1

A 19-year-old seropositive male patient was initiated with efavirenz as part of a highly active antiretroviral therapy (HAART). After one (1) month of therapy, the patient noticed a change in his breast size. He had experienced **breast tissue increase** at the nipple area, but it is neither inflamed nor tender. At the time of reporting, efavirenz was not stopped, and the patient's breast size was continued to be monitored.

Case Report 2

A 28-year-old male patient was started on efavirenz in addition to his current antiretroviral therapy. Two (2) weeks later, the patient noticed that his left nipple was enlarged, hardened, and painful. The reactions were persistent, and one (1) month after the first incidence, he developed right **nipple enlargement**. The patient visited the clinic to inform his doctor and pharmacist of the adverse events. He had claimed that both the pain and size of the left nipple had reduced. The patient was counselled on the adverse event and was given ibuprofen to alleviate the pain when needed.

Discussion

Since the introduction of highly active antiretroviral therapy (HAART), there has been a profound improvement in the prognosis and management of HIV infection.^{1,2} HAART, on the other hand, is associated with a wide variety of adverse events ranging from self-limiting intolerance such as nausea or dizziness to life-threatening adverse events such as hepatic failure and encephalopathy, according to the literature and post-marketing reports.^{1,3,4,5}

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI), and it remains one of the preferred choices in antiretroviral therapy due to its high efficacy and fewer adverse effects.^{1,5} Efavirenz is known to cause adverse effects involving the central and peripheral nervous system,

musculoskeletal and skin, neuropsychiatric disorders and gastrointestinal system.⁶ Gynaecomastia is one of the lesser-known and under-reported adverse effects associated with efavirenz therapy.¹

Gynaecomastia is defined as the benign enlargement of male breast tissue due to the glandular proliferation of the breast tissue.^{1,2} The onset of gynaecomastia may take several months, mostly occurring bilaterally, though it may sometimes be unilateral or asymmetric.^{1,7} Various mechanisms of efavirenz-induced gynaecomastia were suggested, such as increased oestrogen activity, immune response stimulation, and cytochrome P450 inhibition induced by the drug that results in the elevation of oestrogen-androgen ratio.^{2,8} The presence of underlying clinical conditions, comorbidities, or drug therapy could be one of the main factors that make a patient susceptible to histological and clinical breast changes. When human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is regarded as the comorbidity, the patient's suppressed immune system and/or the use of antiretroviral therapy could be contributing factors to the development of gynaecomastia.^{7,9}

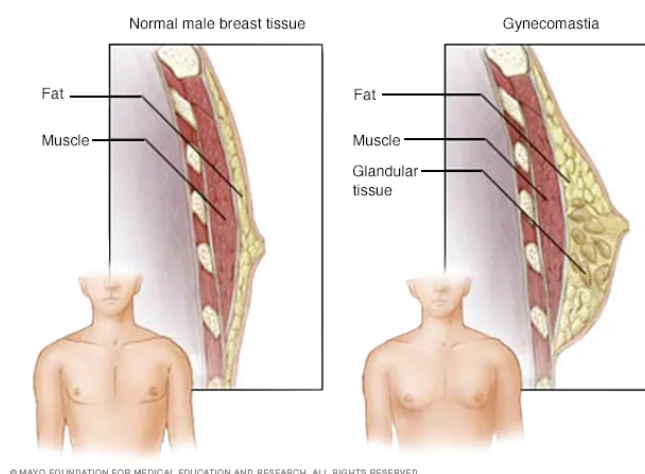


Figure: Enlarged breasts in men (gynecomastia)¹⁰

To date, NPRA has received 848 ADR reports with 1,532 adverse events associated with the use of efavirenz.³ There are 17 adverse events of gynaecomastia linked to efavirenz. Breast swelling (2) and breast lump (1) are two other adverse events related to the reproductive system and breast disorders. At the time of this publication, the World Health Organisation (WHO) global database (Vigilyze®) contains 29,766 adverse events reported with efavirenz use.^{4*} Reports related to reproductive system and breast disorders (1,925) include gynaecomastia (1,572), breast enlargement (147) and breast pain (26).

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Advice to Healthcare Professionals

- 1 Counsel patients taking efavirenz on the risk of gynecomastia and to seek medical attention if symptoms develop.
- 2 Report any adverse drug reactions suspected to be related to the use of efavirenz to the NPRA.

Articles Based on Case Reports

Ceftriaxone: Reminder on the Risk of Encephalopathy

by Jeevenraj Rajagopal

Case Report

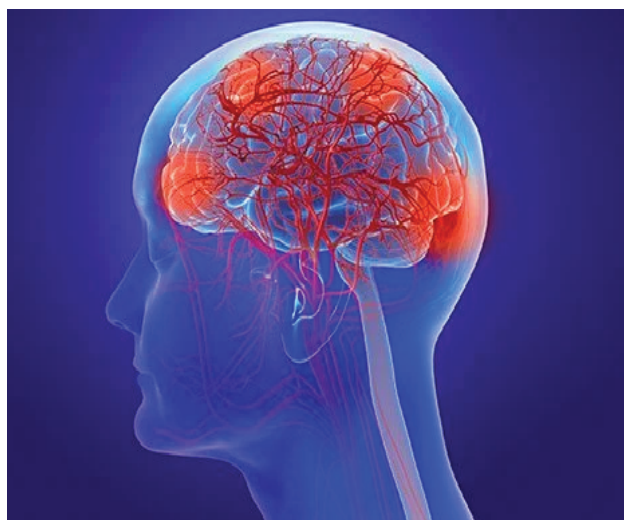
A 61-year-old female patient was admitted due to acute exacerbation of bronchial asthma and acute gastroenteritis. Her past medical history included chronic kidney disease (stage 3), diabetes mellitus, bronchial asthma, gastroesophageal reflux disease (GERD), as well as obesity and symptoms indicative of obstructive sleep apnoea. The patient was initiated with intravenous amoxicillin/clavulanic acid 1.2 grams three times daily for pneumonia, but was later switched to intravenous ceftriaxone 2 grams once a day after patient complained of diarrhoea. After receiving the first dose of intravenous ceftriaxone, the patient experienced loss of consciousness. The suspected drug was withdrawn, and the patient recovered following treatment with intramuscular adrenaline, intravenous magnesium sulphate, and intravenous aminophylline. Given the possibility that other factors such as co-morbid conditions may have also contributed to the adverse event, a causality of possibly drug-related was assigned to the case.

Discussion

Ceftriaxone is a widely used third-generation broad spectrum cephalosporin antibiotic that works against both gram-negative and gram-positive microorganisms.¹⁻² It has a long half-life, efficiently penetrates into systemic tissues, including the central nervous system, and is excreted via hepatic and renal pathways allowing only once daily administration. Ceftriaxone is conveniently prescribed for patients with renal impairment without any dose adjustment.¹⁻⁴ However, according to the literature, ceftriaxone-associated encephalopathy has been increasingly reported in elderly patients with severe renal disease.²⁻⁴ Antibiotics such as other beta lactams, quinolones, metronidazole, and cefepime, a fourth-generation cephalosporin, are known to also be associated with neurotoxicity, including encephalopathy.²⁻³

Encephalopathy is a broad term describing any disease that disrupts the function or structure of the brain. Encephalopathy can present in a very wide spectrum of symptoms that range from mild, such as some memory loss, inability to focus, or subtle personality changes, to severe, such as dementia, seizures, coma, or death, whereby the hallmark of encephalopathy is an altered mental state.⁵⁻⁶

Although the pathophysiological mechanism of ceftriaxone-induced encephalopathy is not totally elucidated, it is thought to be similar to that of beta-lactams and other cephalosporins, mainly owing to the competitive inhibition of γ -aminobutyric acid (GABA) in brain tissues or direct cerebral toxicity through the induction of cytokines. Advanced age, renal insufficiency, central nervous system disorders, and high dose have all been identified as risk factors for cephalosporin-induced encephalopathy.²⁻⁴



Published literature have shown that the onset of neurotoxicity manifestations occur between one (1) to fourteen (14) days after ceftriaxone administration while resolving in one (1) to twelve (12) days after ceftriaxone discontinuation.²⁻⁴ Early diagnosis followed by discontinuation of the offending drug is crucial for preventing serious complications while allowing rapid recovery.²⁻³

To date, NPRA has received a total of **2,840 reports** with **5,122 adverse events** suspected to be associated with ceftriaxone-containing products. Allergic reactions such as pruritus, rash, urticaria, maculo-papular rash, and dyspnoea are the most frequently reported events. There were **no local reports of encephalopathy** suspected to be related to ceftriaxone use. However, there have been **seven (7) cases involving loss of consciousness and eight (8) cases involving convulsions**.⁷ As of early December 2021, the World Health Organisation (WHO) global database of individual case safety reports (ICSRs) has recorded **116 cases of encephalopathy, 1,300 cases of disturbances in consciousness, 561 cases of convulsions, and 40 cases of myoclonus** suspected to be associated with ceftriaxone.⁸

NPRA has previously communicated safety alerts concerning ceftriaxone use, prompting healthcare professionals to be more vigilant on the [risks of disturbed consciousness, convulsions or involuntary movements](#) in January 2019 as well as the [risk of encephalopathy](#) in April 2021. A directive [\[Ruj. Kami: NPRA.600-1/9/13 \(24\)\]](#) requiring all local package inserts of ceftriaxone-containing products to be updated with the risk of encephalopathy has also been issued by the Drug Control Authority (DCA).

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Advice to Healthcare Professionals

- 1 Carefully monitor symptoms of neurotoxicity with the use of ceftriaxone, particularly in elderly patients with severe renal impairment or central nervous system disorders.
- 2 If any of these symptoms are observed, appropriate measures such as discontinuation and/or switch of antibiotic treatment should be considered.
- 3 Report all adverse events suspected to be related to the use of ceftriaxone-containing products to NPRA.

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What's New?

List of Directives Related to Drug Safety Issues

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 and consumer medication leaflets (RiMUP) of all products containing the affected active ingredients are updated with the required safety information. The table below shows the DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredient	Safety Issue	Date	Directive Ref. No.
1	Insulin (including combination products)	Risk of cutaneous amyloidosis	14-Oct-2021	[NPRA.600-1/9/13 (28)]
2	Mycophenolate mofetil (MMF) & mycophenolic acid (MPA)	Risk of de novo purine synthesis inhibitors-associated acute inflammatory syndrome	14-Oct-2021	[NPRA.600-1/9/13 (29)]
3	Bortezomib	Risk of guillain-barré syndrome and demyelinating polyneuropathy	14-Oct-2021	[NPRA.600-1/9/13 (30)]
4	Anastrozole	Risk of depression	14-Oct-2021	[NPRA.600-1/9/13 (31)]
5	Citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine & vortioxetine	Risk of postpartum haemorrhage (PPH)	20-Dec-2021	[NPRA.600-1/9/13 (33)]
6	Decitabine	Risk of differentiation syndrome	20-Dec-2021	[NPRA.600-1/9/13 (34)]

How to report adverse drug reactions?

NPRA encourages all healthcare professionals to report 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. Report ADR **as healthcare professional**.
 - a) Choose **Online Reporting** or
 - b) Download the **ADR manual form** and submit the completed form via email or post:

fv@npra.gov.my



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