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Articles based on Case Reports

Erythropoiesis-stimulating agents: A reminder on the cardiovascular risk in patients with chronic kidney disease

by Yeoh Hee Sheong

Case Report

A 56-year-old female dialysis patient was started on an erythropoiesis-stimulating agent (ESA) for anaemia associated with chronic kidney disease. Her past medical history included hypertension, diabetes mellitus, hyperlipidaemia, coronary artery disease, heart failure and atrial fibrillation. The patient was a non-smoker and did not have any history of stroke, myocardial infarction, congenital heart disease, valvular heart disease, atherosclerosis or peripheral vascular disease, and venous thromboembolism. Her haemoglobin (Hb) value was monitored throughout the therapy and was between 9.5 g/dL to 10.2 g/dL. Six (6) months after the ESA initiation date, she had a suspected **myocardial infarction** and died due to suspected cardiac arrest. No information was provided regarding autopsy. Considering that the patient had underlying medical illnesses and concurrent medications that may have contributed to the adverse event, this case was causally assigned to be possibly-related to the drug.

Discussion

ESAs mimic the natural function of human protein erythropoietin in the body, such as stimulating the proliferation and differentiation of red blood cell progenitors, as well as preventing apoptosis.[1] With the ability to promote erythropoiesis, ESAs are therefore one of the treatment options for patients with chronic kidney disease (CKD), where anaemia is a common complication.[1,2]

Correction of anaemia generally improves a CKD patient's quality of life and reduces the need for blood transfusion, but it also comes with the risk of adverse reactions, particularly cardiovascular events.[3] Studies have shown that a complete or near-complete anaemia correction is associated with an increased risk of adverse events and mortality as compared to partial anaemia correction. A secondary analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial data has also shown that the dose of ESA administered serves as an important factor in predicting the occurrence of a cardiovascular adverse event, whereby a higher dose of ESA

is associated with greater risk.[1,4] It is therefore essential to individually weigh the potential benefit-risk ratio for each patient before initiating ESA therapy.

In Malaysia, current clinical practice guidelines on the management of CKD recommends an optimal Hb target of 10-12 g/dl for CKD patients with anaemia requiring ESA therapy, but this should be adjusted based on the patient's symptoms and co-morbidities.[5] The Renal Association clinical practice guideline in United Kingdom recommends an upper limit Hb target of 10-12 g/dl to reduce this risk of adverse events[6], while the United States Food and Drug Administration (US FDA) advises that the dose of ESA should be individualised and the lowest possible dose should be given to reduce the need for blood transfusion.[7]

There are currently **36 registered ESA products** in Malaysia, with five (5) types of ESA, namely epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta and epoetin zeta. To date, NPRA has received a total of 280 adverse drug reaction (ADR) reports with 414 adverse events suspected to be related to ESAs. The most commonly reported adverse events were decreased Hb (141), followed by pure red cell aplasia (61), and anaemia (18). Reported adverse events related to cardiac disorders include **myocardial infarction**, **cardiac disorder** and **cardiac arrest**.[8]

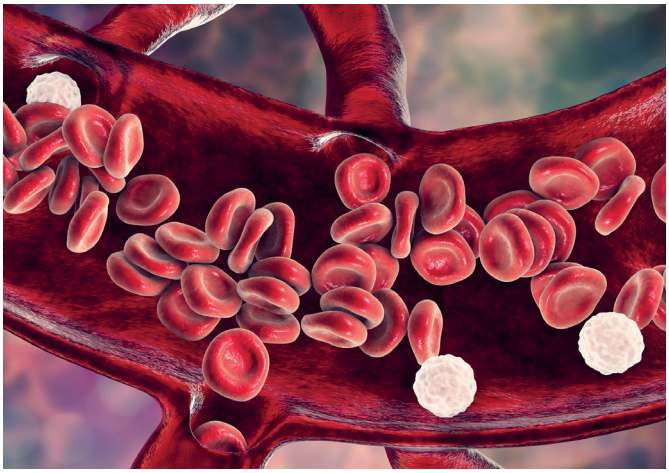
A search of adverse events suspected to be linked to ESA use in the World Health Organisation (WHO) international ADR database has shown a total of 2,098 reports associated with cardiac disorders, with the most common cardiac adverse events being myocardial infarction (486), cardiac failure (280) and cardiac disorder (195).[9]*

NPRA has previously communicated information on this risk and prompted healthcare professionals to be more vigilant on the cardiovascular and cerebrovascular risk in patients with CKD-induced anaemia who were treated with ESAs.[10] For more information on this, please refer to the MADRAC Bulletin December 2011 issue.

*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.

Abbreviations:

CKD:	Chronic kidney disease
ESA:	Erythropoiesis-stimulating agent
Hb:	Haemoglobin
NPRA:	National Pharmaceutical Regulatory Agency
US FDA:	United States Food and Drug Administration



Advice to Healthcare Professionals

- ESAs should only be initiated following the consultation with a nephrologist.[7]
- It is recommended that the dose of ESA should be individualised and the lowest possible dose given to reduce the need for blood transfusion.[6]
- Monitor Hb levels throughout ESA therapy. A moderate Hb target of 10-12 g/dl is advisable and should be adjusted according to the patient's symptoms and co-morbidities.[5,7]
- Blood pressure monitoring should also be conducted as elevated blood pressure is expected in some patients during ESA therapy.[5]
- Please report any adverse events suspected to be associated with the use of ESAs to NPRA.

References

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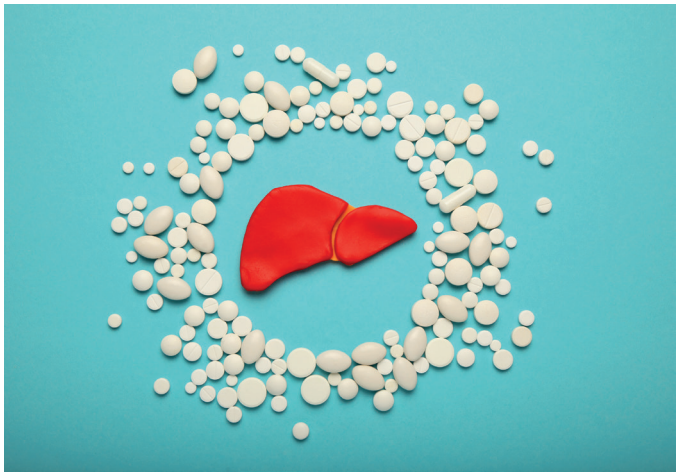
Articles based on Case Reports

Amiodarone: Risk of acute hepatitis

by Siti Fatimah Yaakub



Case Report 1

A 67-year-old male patient was given intravenous amiodarone infusion loading dose of 300 mg over 1 hour and followed by a maintenance dose of 900 mg over 24 hours. The next day, blood investigation results showed a prominent increase in alanine aminotransferase (ALT) and aspartate aminotrasnferase (AST) levels, reaching 2957 u/L and 3966 u/L respectively. Patient was diagnosed with **acute hepatitis**. The suspected drug was withdrawn and patient was treated with intravenous N-acetylcysteine. The levels of ALT and AST decreased gradually to baseline after two weeks. This case was assigned a causality of possibly-related to the drug, due to other contributing factors such as multiple medical illnesses and other medications that may also have led to the adverse event.

Case Report 2

A 34-year-old male patient with decompensated congestive cardiac failure and atrial fibrillation was electively admitted for aortic and mitral valve replacement. He was started on intravenous amiodarone infusion with a loading dose of 300 mg over 1 hour, followed by a maintenance dose of 900 mg over 24 hours. Investigation of the patient's liver profile during the amiodarone therapy showed a drastic **increase of ALT levels**; from 27 u/L (normal level< 32 u/L) to 1153 u/L on the following day. The drug was immediately withdrawn and for the next nine (9) days the ALT levels gradually decreased to 32 u/L. As the patient had other underlying medical conditions and concomitant medications that may have contributed to the adverse event, the case was assigned a causality of possibly-related to the drug.

Discussion

Amiodarone is a class III antiarrhythmic agent commonly used in the management of ventricular arrhythmias and atrial fibrillation.[1] It acts primarily by blocking potassium channels in cardiac myocytes, resulting in an increased action potential duration and a prolonged effective refractory period.[2]

Acute hepatitis is a rare but potentially fatal adverse event of intravenous amiodarone.[3] It can be characterised by sudden hepatic test abnormalities that occur within 24 hours after intravenous amiodarone administration, an increase of aminotransferase levels of more than 50 times the upper limit of normal, and rapid improvement after amiodarone withdrawal.

The pathophysiology of this adverse event remains unclear. There are several different mechanisms that have been proposed, such as immunological-mediated or free radical-potentiated mechanisms. In the case report by Fonseca *et. al* (2015), it was suggested that the mechanism of intravenous amiodarone-induced acute hepatitis may also be attributed to the excipient polysorbate 80 that is present in intravenous amiodarone formulations but absent in oral amiodarone formulations.[3] Several reports reviewed in the study has shown that introduction of oral amiodarone in patients with decompensated heart failure has resulted in no additional liver injury. Nevertheless, the overall evidence is not conclusive and further research is needed to substantiate this suggestion.

In Malaysia, there are currently **seven (7) products** containing amiodarone registered with the Drug Control Authority (DCA). To date, NPRA has received 319 ADR reports with 584 adverse events suspected to be related to the use of amiodarone. The most commonly reported adverse events are **increased ALT levels (114)**, **increased hepatic enzymes levels (61)** and **increased AST levels (54)**. There are a total of **18 ADR reports** of amiodarone in association with **acute hepatitis**, **hepatitis** and **drug-induced hepatitis**.[4]

A search in the World Health Organisation (WHO) global ADR database, VigiLyze, revealed a total of 42,102 reports associated with amiodarone use, with adverse events including acute hepatitis (131), hepatitis (508), increased ALT levels (520), increased hepatic enzymes (433) and increased AST levels (406).[5*]

Advice to Healthcare Professionals

- Keep in mind the possibility of acute hepatitis following treatment with amiodarone.
- Close monitoring of hepatic function during amiodarone therapy is necessary to identify any potential hepatotoxicity and prevent a fatal outcome.
- Report any adverse events suspected to be associated with the use of amiodarone to 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. Lyle A. Siddoway (2003). Amiodarone: Guidelines for Use and Monitoring. Am Fam Physician; 1;68(11):2189-2197.
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Articles based on Case Reports

Levothyroxine: Reminder on the risk of restlessness or irritability

by Ng Jia Mean

Case Report 1

A 40-year-old female patient experienced **agitation** and shortness of breath half an hour after taking a new brand of levothyroxine. She claimed that the symptoms lasted for the whole day and they did not occur when she switched back to her previous medication. The patient performed a rechallenge by taking again the new brand of levothyroxine, and the same symptoms reappeared.

Case Report 2

A 44-year-old female patient complained that she gets **irritated** easily and has bad temper after taking levothyroxine. The symptoms started four (4) days after drug initiation. Her medical history and other concurrent medications were not reported. She also claimed that the symptoms resolved when the medication was withdrawn.

Discussion

Levothyroxine, which is a synthetic form of thyroid hormone, is indicated for the treatment of hypothyroidism, goitre, suppression of thyroid cancer and in other conditions.[1,2]

Adverse reactions are rare in levothyroxine therapy when given at the recommended dose.[4] Symptoms such as cardiac arrhythmias, tachycardia, palpitations, diarrhoea, restlessness, insomnia, and tremor may serve as a sign of therapeutic overdose and this may warrant a repeat thyroid function test.[1] Re-adjustment of the treatment dose (either

reduction of dose or withdrawal for several days) should be carried out if needed.

Currently, there are **six (6) registered products** containing levothyroxine in Malaysia. NPRA has received 184 adverse drug reaction (ADR) reports with 451 events suspected with the use of levothyroxine.[3] Commonly reported adverse events were pruritus (32), dizziness (29), rash (21), and headache (19). To date, there are **three (3) ADR reports related to restlessness or irritability**, including the two (2) described here.

As of January 2020, the WHO ADR database (VigiBase) contained 5,953 reports on irritability and 846 reports on restlessness that were suspected to be associated with levothyroxine use.[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

- Advise patients to seek medical attention if they experience difficulty in controlling their temper during the course of levothyroxine treatment.
- Recognise irritability or restlessness as a clinical symptom typical of hyperthyroidism and monitor patients for treatment overdose accordingly.
- Report any adverse events suspected to be associated with the use of levothyroxine to NPRA.

References

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Articles based on Case Reports

Immunisation anxiety-related reactions

by Norshazareen Abd. Manab

Case Report

A 6–year old boy was reported to develop **dizziness** and **sweating**, then **fainted** following immunisation with a booster dose of Diphtheria/Tetanus (DT) and Measles/ Rubella (MR) vaccines which he received at school. Upon physical examination when he fainted, the patient appeared **pale** and had a **low heart rate**. He was put in supine position and regained consciousness after a few minutes. The patient was brought to hospital for observation, and the event was diagnosed as a **vasovagal attack**. He was discharged on the same day.

Discussion

Immunisation anxiety-related reactions* are adverse events following immunisation (AEFI) arising from anxiety about the immunisation.[1,2] They may happen due to fear while waiting for vaccination or pain as a result of receiving the injection. The reaction is not related to the components of the vaccine.

Most of the signs and symptoms of immunisation anxiety-related reaction are brief and resolve spontaneously. They may occur just before, during, or immediately after immunisation. The severity of an immunisation anxiety-related reaction may range from mild light-headedness to vasovagal syncope (fainting) and in some cases, non-epileptic seizures.

*Editor's Note: In December 2017, the World Health Organisation (WHO) Global Advisory Committee on Vaccine Safety (GACVS) proposed the term 'immunisation stress-related responses', which was considered more appropriate as it covers a broader spectrum of responses that may be experienced in relation to immunisation without implying that these responses are causally related.[3]

NPRA has received **14 AEFI reports** that are categorised as **immunisation anxiety-related reactions**. These reports involved patients between the ages of 6 to 19 years old.[4] The adverse events reported were **dizziness, syncope or fainting, non-epileptic seizure, sweating, vomiting, pallor, nausea and hyperventilation**. All the patients were reported to have recovered from the events.

Fainting or anaphylaxis?

It is important to note that fainting may be falsely diagnosed as anaphylaxis. Vaccinators should be trained to distinguish between these events as it is essential to ensure the identification of life-threatening situations and prompt management of an anaphylactic event.

(please see next page)

Differences between a fainting attack and anaphylaxis		
Clinical Features	**Fainting**	**Anaphylaxis**
Timing	Before, during or a few minutes after injection.	A short time, up to a few hours.
Skin	Generalised pallor, cold clammy skin.	Itching, generalised erythema, urticaria, swelling of lips and face, tingling around lips.
Respiratory system	Normal breathing or shallow breathing.	Tachypnoea, difficulty in breathing, wheezing, stridor, hoarseness, cyanosis, recession of intercostal spaces.
Cardiovascular system	Bradycardia, weak pulse, carotid pulse felt, hypotension may occur – reversed by supine position.	Tachycardia, weak pulse, carotid pulse may be weak, hypotension – not reversed by supine position.
Gastrointestinal system	Vomiting	Vomiting, diarrhoea, abdominal cramps.
Central nervous system	Feeling faint, light-headedness relieved by supine position.	Anxiety and distress, loss of consciousness not relieved by supine position.

Advice to Healthcare Professionals

- Reactions may be aggravated in recipients with needle phobia.
- If a reaction occurs, stay calm and rule out other potential reactions (e.g anaphylaxis). Immunisation anxiety-related reactions usually resolve spontaneously.
- Immunisation anxiety-related reactions may be minimised by:
  (i) Providing a relaxed environment in the waiting area for anticipating individuals (when vaccinating in groups);
  (ii) Conducting vaccine preparation away from the vaccinee's view to reduce exposure to the sight of the needle;
  (iii) Providing simple explanation of the vaccination and confident delivery of the vaccine;
  (iv) Including a conducting teacher to accompany pupils during school-based immunisation programmes;
  (v) Providing short waiting times, comfortable room temperatures, and privacy during the procedure.
- Please report any adverse events following immunisation to NPRA.

References

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What's New?

List of Directives Related to Drug Safety Issues (September - December 2019)

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 2019, which may be downloaded from the NPRA website.

	Active ingredient	Safety Issue	Date	Directive Reference number
1	Retinoids	Updated measures for pregnancy prevention during retinoids use	27 September 2019	[Ref: (16) dlm.BPFK/PPP/07/25 Jilid 3]
2	Loperamide	Unmasking Brugada syndrome with excessive doses of loperamide	4 December 2019	[Ref: (18) dlm.BPFK/PPP/07/25 Jilid 3]
3	Carbimazole, Methimazole	(i) Risk of acute pancreatitis; (ii) Risk of congenital malformations when used in pregnancy	4 December 2019	[Ref: (19) 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, email or fax to:

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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