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45

MADRAC Bulletin

For healthcare professionals only

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In this issue

The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among healthcare professionals.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

Articles Based on Case Reports

Features

What's New

We would like to thank the Director General of Health, Malaysia for his permission to publish the signal/case report articles.

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).[1] The case reports presented in this section are intended to serve as a reminder of potential adverse events that healthcare providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not comprehensive but rather represents a selection of clinically relevant items that warrants dissemination.

Watch Out for PRIS!

A Local Case Report on Propofol-Related Infusion Syndrome

By Syifa' Izzati Mohd Zainul Arifien

Case Report 1[1]

A 38-year-old male with underlying bronchial asthma and retroviral disease (RVD) was sedated in the intensive care unit (ICU) with propofol ranging from 100 to 240 mg per hour. He was initially hospitalised for acute exacerbation of asthma due to community acquired pneumonia. Six (6) days after initiation of propofol, he developed a set of events: acute kidney injury, hyperkalaemia, rhabdomyolysis and worsening of metabolic acidosis, which led to the discontinuation of propofol due to **suspicion of propofol-related infusion syndrome (PRIS)**. He was started on continuous venovenous haemodiafiltration and eventually recovered from the syndrome. Unfortunately, the patient passed away a month later due to septic shock with multi-organ failure. The adverse event, PRIS, was given a causality of *possibly*-related to the drug.

Discussion

Propofol is an intravenous anaesthetic agent typically used for induction and maintenance of general anaesthesia and for sedation of ventilated adult patients in the ICU.[2-3] There are currently nine (9) registered products containing propofol in Malaysia.[4]

The use of propofol in critical care settings has been associated with the development of **PRIS**.[3] This syndrome is characterised by a combination of events including metabolic acidosis, rhabdomyolysis, hyperkalaemia, hyperlipidaemia, and multi-organ (namely cardiac, renal, and hepatic) dysfunction or even failure.[3,5]

While the exact mechanism behind PRIS is not clearly understood yet, it is believed to be linked with how propofol affects energy metabolism.[5-7] Under normal conditions, glucose is the major energy source in the body. However, there is a transition in energy source from glucose to free fatty acids (FFA) in certain circumstances, such as fasting, stress, and critical illness. It is thought that propofol may inhibit the function of an outer membrane mitochondrial enzyme that transforms FFA to fatty acyl carnitine which can be transported into the mitochondria.[5-6] This leads to impairment of FFA utilisation. Another theory is that propofol can directly inhibit the mitochondrial respiratory chain, which leads to impaired metabolic activities.[5-6] The disruption of these biochemical and metabolic processes ultimately leads to manifestations of PRIS such as metabolic acidosis and hyperlipidaemia. Therefore, proper caution should be taken when using propofol in patients with underlying mitochondrial disease and disorders of fat metabolism[3,5]

The risk of developing PRIS is greater, especially in critically ill patients receiving propofol at higher doses and for a prolonged duration of usage (usually more than 48 hours).[3] The recommended propofol infusion rate should not exceed 4 mg/kg/hour when used in ventilated patients for sedation.[3,5-8] This recommendation is substantiated by the findings of a literature review published in 2019 which analysed case reports of PRIS. The analyses revealed that, in adults, the cumulative dose of propofol was significantly associated with (i) the number of PRIS clinical features reported, and (ii) the number of organ systems involved.[7] Other risk factors for PRIS development include concomitant use of propofol with catecholamines (e.g., dopamine, noradrenaline) and glucocorticoids, young age, traumatic head injury, and sepsis.[3,5-7]

Although PRIS is a rare occurrence, it can be fatal if not recognised and treated accordingly.[5] Whenever PRIS is suspected, propofol should be immediately discontinued and replaced with other anaesthetic agents.[5-7] There is no specific treatment available for PRIS, only supportive care and management of each manifestation of the syndrome. Renal replacement therapy (e.g., haemodialysis and haemofiltration) should be considered when there is presence of metabolic acidosis, rhabdomyolysis, and hyperkalaemia.[5-7]

To date, the NPRA has received **127 local adverse drug reaction (ADR) reports** with **187 adverse events** suspected to be related to propofol.[1] The most commonly reported adverse events involved skin reactions, namely rash (27), urticaria (18) and pruritus (8). There is only **one (1) locally reported case of PRIS,** which we discussed above. As of October 2023, the World Health Organisation (WHO) international ADR database has recorded **654 cases of propofol infusion syndrome.**[9*]

Looking at the relatively small number of ADR reports related to PRIS received locally, there is a possibility that this syndrome may be overlooked or under-reported. PRIS can be difficult to diagnose as these events (e.g., renal dysfunction, electrolyte imbalance, acidosis and rhabdomyolysis) also commonly occur in ICU patients as manifestations of the underlying critical conditions.[10] Thus, it is important for healthcare professionals to be aware of other possible causes of this cluster of events, including the use of medications like propofol, to prevent further complications to the patients.

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

Advice for Healthcare Professionals

1. Limit the dosage of propofol (not more than 4mg/kg/hour) and duration of use (not to exceed 48 hours).
2. Be on the lookout for early manifestation of PRIS especially when propofol is used at higher dosage and with longer duration of use. Carefully monitor for signs and symptoms of metabolic and organ system impairments.
3. Immediately discontinue propofol and replace it with other anaesthetic agents whenever PRIS is suspected.
4. Be aware of the risk factors for PRIS, such as concomitant use of vasopressors, so that proper caution and monitoring can be exercised during propofol administration.
5. Report any adverse drug reactions suspected to be related to the use of propofol to the NPRA.

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When the Liver Shouts S.O.S.

A Case Report on Oxaliplatin-Induced Sinusoidal Obstruction Syndrome (SOS)

By Yeoh Hee Sheong

Case Report 1 [1]

A 36-year-old woman was diagnosed with adenocarcinoma of the transverse colon with liver metastases. She completed five cycles of the FOLFOX chemotherapy regimen (folinic acid, 5-fluorouracil, and oxaliplatin). Three (3) months after chemotherapy was started, she underwent surgery for liver resection and splenectomy, during which her liver was noted to have a distinct mottled appearance with diffuse sinusoidal congestion. These findings led to a diagnosis of **sinusoidal obstruction syndrome (SOS) secondary to oxaliplatin**, and right portal vein ligation was performed. At the time of reporting, the patient was still under monitoring and her outcome was unknown. The drug-event causal relationship assigned for this case was "*possible*", considering potential confounding factors, including comorbidities and concomitant drugs.

Discussion

Oxaliplatin is a platinum-based anticancer medication used for the treatment of metastatic colorectal cancer and adjuvant therapy for stage III colon cancer. It exerts its cytotoxic effect by forming both inter- and intra-strand cross-links with DNA, causing the disruption of DNA synthesis which leads to cytotoxic and antitumor effects.[2] There are currently 11 registered products containing oxaliplatin in Malaysia.[3]

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease, is the occlusion of small hepatic blood vessels due to the damage of sinusoidal endothelium.[4] The occluded blood vessel could cause portal hypertension which may progress to liver injury and cirrhosis.[5] The main causes of SOS are treatment with systemic chemotherapy, myeloablative treatment before haematopoietic stem cell transplant, and the use of herbal remedies containing pyrrolizidine alkaloids.[4,6]

Oxaliplatin-induced SOS is a rare adverse event which remains poorly understood. It has been reported to mimic liver metastasis of colon cancer.[7-8] Risk factors for oxaliplatin-induced SOS include pre-existing liver disease and cumulative dose of oxaliplatin.[5-9] The proposed pathogenesis involves oxidative stress, inflammatory damage, liver fibrosis, as well as platelet aggregation and adhesion.[5-10]

SOS initially presents as abdominal pain and distention, weight gain, jaundice and portal hypertension which normally last a few months.[5] It could then progress to liver nodule regenerative hyperplasia, splenomegaly and thrombocytopenia if left untreated.[2,5,6] It has been shown that SOS could decrease tumour response towards chemotherapy, reduce liver function reserve and increase the rate of liver failure in patients who have undergone liver resection.[5] Management of SOS includes discontinuing chemotherapy and symptomatic support. Defibrotide and reduced glutathione were shown to be beneficial treatments for SOS.[4-5] Several studies have found that the monoclonal antibody, bevacizumab, has a protective effect against SOS.[5,9,11]

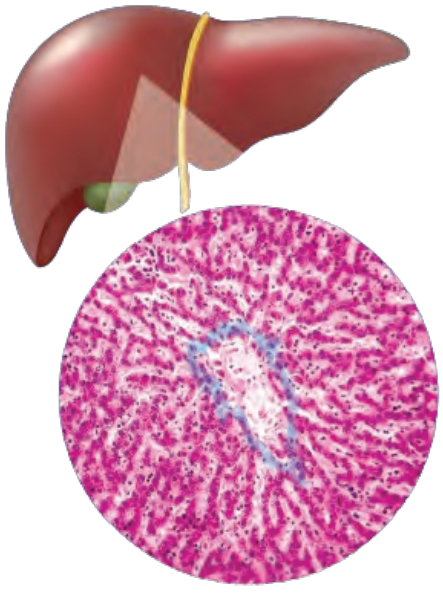

Image Source: Chan SS. Exploring the Critical Role of Radiologists in Diagnosis and Monitoring of VOD/SOS: An Illustrative Case Discussion. Physicians Education Resource [Internet]. 2021 [cited 2023 Oct 23]. Available fro: https://www.diagnosticimaging.com/view/exploring-the-role-of-radiologists-in-diagnosis-and-monitoring-of-vod-sos-an-illustrative-case-discussionm

To date, NPRA has received a total of **662 adverse drug reaction (ADR) reports** with **1,586 adverse events** suspected to be related to oxaliplatin.[1] The most commonly reported adverse events were pruritus (258), followed by erythema (89), and rash (68). There is currently **one (1) report of SOS** suspected to be related to oxaliplatin received in Malaysia,[1] while the World Health Organisation (WHO) international ADR database contains **113 reports** of this reaction.[12*]

*DISCLAIMER

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Advice for Healthcare Professionals

1. Be aware of the risk of SOS in patients with pre-existing liver disease who have undergone multiple cycles of oxaliplatin treatment.
2. Consider further investigation for SOS when a patient treated with oxaliplatin presents with splenomegaly, thrombocytopenia, and raised liver enzymes.
3. Early detection and management by discontinuing chemotherapy and active symptomatic support could prevent further deterioration of liver function.
4. Please report any adverse events suspected to be associated with the use of oxaliplatin to NPRA.

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Features

Training

Pharmacovigilance: Our Shared Responsibility

A Seminar for Doctors, Pharmacists and Nurses

Doctors, pharmacists and nurses play a key role in medicines safety. While pharmacovigilance has been conducted in Malaysia since 1987, many healthcare professionals are not aware of the activities involved in keeping medicines safe. Thus, NPRA conducts regular training seminars in efforts to educate and increase awareness.

On 24 October 2023, we hosted a half-day seminar entitled "**Overview of Registration and Post-Marketing Activities of Registered Products in Malaysia**". More than 200 public-sector healthcare professionals from across Malaysia participated in this virtual event.

Besides providing information on pharmacovigilance activities in Malaysia, this seminar aimed to enlighten participants on the fast-track product registration process and product quality monitoring. Thus, participants were able to obtain a more comprehensive understanding of how the various aspects of regulatory pharmacy help ensure the quality, safety and efficacy of registered products in Malaysia.

During the sessions on pharmacovigilance, participants were reminded on the importance of reporting adverse drug reactions (ADR) or adverse events following immunisations (AEFI), and how to prepare high-quality reports. They were then exposed to "signal detection", which is one of the newer pharmacovigilance activities by NPRA to detect new safety signals related to medicines. We wrapped up this seminar with a talk on the review of safety issues and implementation of risk minimisation measures. It was encouraging to note that many participants found the seminar informative and useful for their routine work.

NPRA will continue to host further training sessions on pharmacovigilance and other regulatory activities. Is there **any specific topic** you would like us to cover? Do let us know via email: fv@npra.gov.my.

Features

Publication

Thrombocytopenia and Venous Thromboembolic Events after BNT162b2, CoronaVac, ChAdOx1 Vaccines and SARS-CoV-2 Infection: A Self-Controlled Case Series Study

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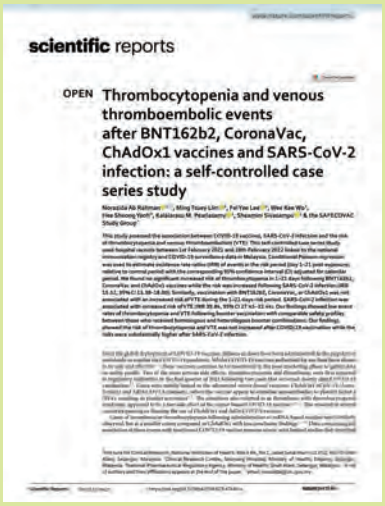
scientific reports

OPEN Thrombocytopenia and venous thromboembolic events after BNT162b2, CoronaVac, ChAdOx1 vaccines and SARS-CoV-2 infection: a self-controlled case series study

Abstract:

This study assessed the association between COVID-19 vaccines, SARS-CoV-2 infection and the risk of thrombocytopenia and venous thromboembolism (VTE). This self-controlled case series study used hospital records between 1st February 2021 and 28th February 2022 linked to the national immunisation registry and COVID-19 surveillance data in Malaysia. Conditional Poisson regression was used to estimate incidence rate ratios (IRR) of events in the risk period (day 1–21 post-exposure) relative to control period with the corresponding 95% confidence interval (CI) adjusted for calendar period. We found no significant increased risk of thrombocytopenia in 1–21 days following BNT162b2, CoronaVac and ChAdOx1 vaccines while the risk was increased following SARS-CoV-2 infection (IRR 15.52, 95% CI 13.38–18.00). Similarly, vaccination with BNT162b2, CoronaVac, or ChAdOx1 was not associated with an increased risk of VTE during the 1–21 days risk period. SARS-CoV-2 infection was associated with increased risk of VTE (IRR 39.84, 95% CI 27.45–32.44). Our findings showed low event rates of thrombocytopenia and VTE following booster vaccination with comparable safety profiles between those who received homologous and heterologous booster combinations. Our findings showed the risk of thrombocytopenia and VTE was not increased after COVID-19 vaccination while the risks were substantially higher after SARS-CoV-2 infection.

For more information, read the full article published in Scientific Reports.

Ab Rahman, N., Lim, M.T., Lee, F.Y. et al. Thrombocytopenia and venous thromboembolic events after BNT162b2, CoronaVac, ChAdOx1 vaccines and SARS-CoV-2 infection: a self-controlled case series study. Sci Rep 13, 20471 (2023). Available from: https://doi.org/10.1038/s41598-023-47486-x

SCAN HERE

What's New

List of Safety Alerts and Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) 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 information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts and DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
		Title	Date	
1	Isotretinoin	Risk of Psychiatric Disorders and Sexual Dysfunction	13-Oct-2023	-
2	Topiramate	[Updated] Neurodevelopmental Disorders in Children Exposed to Topiramate during Pregnancy	29-Nov-2023	NPRA.600-1/9/13 (29) Jld.1 [12 Oct 2023]
3	Loperamide	[Updated] Risk of Acute Pancreatitis	29-Nov-2023	NPRA.600-1/9/13 (28) Jld.1 [12 Oct 2023]
4	Ibrutinib (IMBRUVICA®)	Package Insert Updates to Dose Modifications for Adverse Reactions and to Special Warnings and Precautions for Use	30-Nov-2023	-

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

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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NPRA Safety Information Mailing List

To join the mailing list, complete the **subscription form** available on the NPRA website, or send an email with your details to **fv@npra.gov.my**