

MADRAC *Bulletin*

For healthcare professionals only

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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 health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

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.



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DISCLAIMER

The MADRAC Bulletin is published by the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysia. This publication is meant to provide updates on medication safety issues to health care professionals, and not as a substitute for clinical judgement. While reasonable care has been taken to verify the accuracy of the information at the time of publication, the NPRA shall not be held liable for any loss of whatsoever arising from the use or reliance on this publication. The opinions expressed in all articles are the authors' own and do not necessarily reflect the view of NPRA.

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

Highlights

Research Publication *Strategies to Enhance Risk Communication About Medicines in Malaysia: A Delphi Study Among Multinational Experts*

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Risk communication in Malaysia: Delphi study

Demographics of panel:



27 communicators
(9 countries)



15 recipients
(Malaysian doctors
and pharmacists)

Priority strategies (n = 21)

Domain:	Format	Technology	Collaboration	Integrate into practice	Educational programmes	Evaluate
95%	More concise		Collaboration with: Professional associations		Incorporate in training programmes for newly qualified HCPs	
92%			Clinicians			
87%	Multi-lingual content			Release official directives		
85%		Data repository of safety issues	Government organisations International medicine safety bodies	Incorporate into prescribing systems		Assess reading level and language
82%	Standardised format Communicate uncertainties			Letters from NRA directly to HCPs		
79%		Improve effectiveness of NRA website	Pharma industry Owners of existing websites or apps	Pop-up safety alerts into prescribing systems	Module on medication safety for undergraduate courses	
77%		Use social media	Consumer or patient organisations			

Abstract

Background

Effective risk communication about medicines is crucial to the success of all pharmacovigilance activities but remains a worldwide challenge. Risk communication has been conducted in Malaysia for decades, yet awareness on the communication methods remains low among healthcare professionals. While international guidelines are available, clear guidance on effectively communicating the risks of medicines in specific countries is scarce. This study aimed to establish a consensus on the priority strategies for enhancing risk communication about medicines by regulators.

Methods

We conducted a two-round modified Delphi survey among local and international communication experts, and also recipients of medicines risk communication in Malaysia. We developed a list of 37 strategies based on the findings of our previous studies. In Round 1, participants were asked to rate the priority for each strategy using a 5-point Likert scale and suggest additional strategies via free-text comments. Strategies scoring a mean of ≥ 3.75 were included in Round 2. We defined consensus for the final list of strategies a priori as $> 75\%$ agreement. Data were analysed using descriptive statistics and thematic analysis.

Results

Our final Delphi panel ($n = 39$, 93% response rate) comprised medicines communication experts from nine countries and Malaysian healthcare professionals. Following Round 1, we dropped 14 strategies and added 11 strategies proposed by panellists. In the second round, **21 strategies** achieved consensus. The priority areas identified were to improve the format and content of risk communication, increase the use of technology, and increase collaboration with various stakeholders. Priority ratings for the strategy *"to offer incentives to pharmaceutical companies which maintain effective communication systems"* were significantly higher among recipients compared to communicators [$\chi^2_{(1, N = 39)} = 10.1$; $p = 0.039$] and among local versus international panellists [$\chi^2_{(1, N = 39)} = 14.3$; $p = 0.007$].



Conclusions

Our study identified **21 priority strategies**, which were used to develop a strategic plan for enhancing medicines risk communication. This plan is potentially adaptable to all countries with developing pharmacovigilance systems. The difference in views between communicators and recipients, as well as local and international panellists, highlights the importance of involving multiple stakeholders in research.



SCAN HERE to read more!

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 health care 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 exhaustive but rather represents a selection of clinically relevant items that warrants dissemination.

Azathioprine: Drug-Induced Liver Injury (DILI)

By Farah Faridah binti Jamaludin

Case Report 1ⁱ

A 52-year-old Indian male was newly prescribed with azathioprine 50mg once daily as immunosuppressant therapy on 1st November. He had also been taking carbimazole and atorvastatin. After two weeks, the azathioprine dose was increased to 100mg once daily and later to 150mg once daily. Following this increase in dosage, the patient's liver profile was noted to deteriorate. About two months later, azathioprine was discontinued due to his worsening liver profile.

Figure 1 shows his liver profile readings while on azathioprine therapy. The patient underwent an abdominal ultrasound which showed no abnormality. He was suspected to have **azathioprine-induced liver injury**. His liver enzymes began to decrease after azathioprine was withheld. This adverse event was assessed as being *possibly-related* to azathioprine, due to the presence of concomitant medicines.

Discussion

Azathioprine is a purine analogue which interferes with the cell cycle and inhibits normal function of lymphocytes.² It functions as a steroid-sparing immunosuppressive agent. In Malaysia, there are currently two registered products containing azathioprine in tablet form.

Drug-induced liver injury (DILI) describes the harm that drugs can cause to the liver, including hepatotoxicity, liver failure, or even death in severe cases.³ DILI may be classified as predictable (intrinsic) or unpredictable (idiosyncratic) reactions.⁴ The predictable type is usually dose-related, has a short onset (hours to days), and is due to direct toxicity of the drug or its metabolite. Idiosyncratic DILI is less common (<1 in 10,000 individuals), and may occur days to months after exposure. Idiosyncratic DILI is believed to result from individual differences in susceptibility due to genetic and environmental

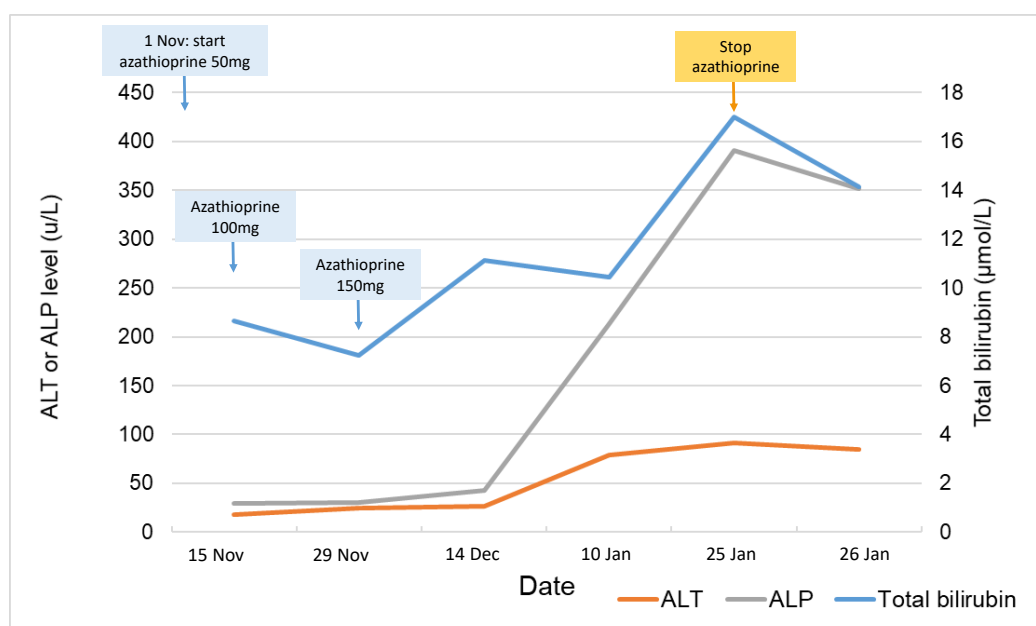


Figure 1: Liver profile of patient during azathioprine therapy

factors.^{3,4} The estimated incidence of DILI varies between regions, ranging from 2.3 to 23.8 cases per 100,000 people per year.⁴⁻⁶ DILI poses concern among clinicians, the pharmaceutical industry and regulatory bodies as it is one of the leading causes for implementing regulatory measures such as issuing warnings, modifying drug use, or withdrawing the drug.³

During the first few months of azathioprine treatment, mild, transient and asymptomatic increases in liver enzyme levels may be seen.^{7,8} These are usually benign, resolving with dose changes or drug cessation. However, azathioprine may also cause idiosyncratic cholestasis or acute liver injury, which manifest as jaundice and fatigue during the early course of therapy, and are linked to increased levels of alanine aminotransferase (ALT) and alkaline phosphatase. Discontinuation of treatment usually leads to improvement of the patient's condition.⁸ The mechanism of azathioprine hepatotoxicity has been postulated to involve depletion of glutathione which leads to mitochondrial damage, eventually leading to cell death.^{9,10}

To date, NPRA has received 206 local adverse drug reaction (ADR) reports with 415 adverse events associated with azathioprine-use.¹ The most frequently reported adverse events were maculopapular rash, pancytopenia, pruritus, vomiting, and fever. There was **one case related to azathioprine-induced liver injury** reported which has been described in this article. Globally, 218 reports of DILI associated with azathioprine-use were identified in the World Health Organisation (WHO) international ADR database.^{11*}

*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 Health Care Professionals

- 1 Be vigilant** on the risk of DILI in patients taking azathioprine.
- 2 Before** prescribing azathioprine, consider factors which may increase the risk of azathioprine-induced liver injury, including concurrent use of other hepatotoxic medications, pre-existing liver disease, and genetic factors.
- 3 Schedule** regular follow-up for patients taking azathioprine to assess treatment response, monitor liver function, and identify adverse effects, including liver injury.
- 4 Educate** patients to identify and promptly report any signs or symptoms of liver injury, such as jaundice, abdominal pain, nausea, vomiting, and fatigue. Advise patients to seek medical advice immediately if jaundice becomes apparent.
- 5 Report** all suspected adverse events related to azathioprine-use to the NPRA.

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Wooden Chest Syndrome: Chest Wall Rigidity with Fentanyl

By Syifa' Izzati Mohd Zainul Arifien

Case Report 1'

An 8-month-old, 9 kg female infant with no prior medical illness was admitted to the Paediatric Intensive Care Unit (PICU) for persistent respiratory distress due to severe bronchopneumonia. Lung examination showed generalised rhonchi with crepitation over the left lower zone, along with subcostal and intercostal recession. In the PICU, she was started on fentanyl infusion for sedation during intubation. The starting dose was 5 µg/kg/hour and was increased to 8 µg/kg/hour on the second day of intubation.

Around one hour after the dose increment, her oxygen saturation and tidal volume dropped to 88% and 3 ml/kg, respectively. Manual ventilation, or 'bagging,' was performed with higher pressure required, reaching up to 35 kPa. **Fentanyl-induced chest wall rigidity** was suspected, prompting cessation of the fentanyl infusion, and naloxone was administered as an antidote. Subsequent examination showed good chest rise, and bagging pressure was reduced to 20 kPa, with no more rhonchi noted. She was extubated the next day and discharged from the hospital a few days later. Due to the presence of concomitant drugs, the adverse event was given a causality *possibly*-related to fentanyl.

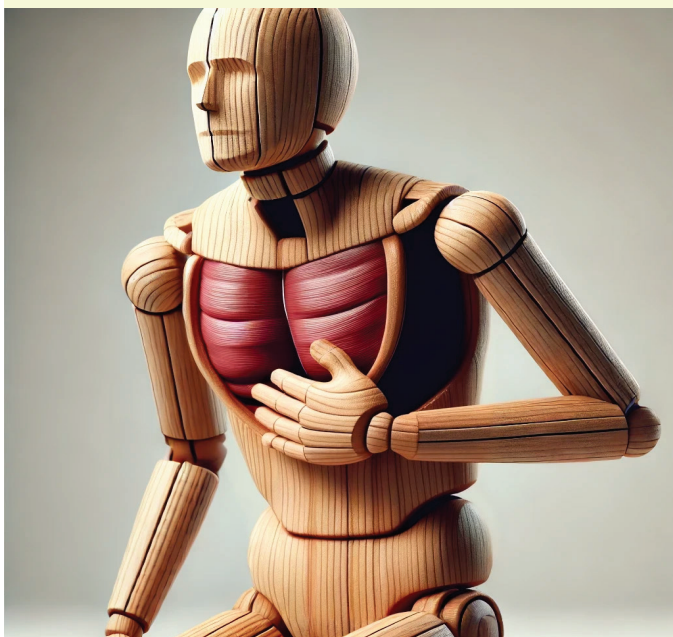
Discussion

Fentanyl is a potent synthetic opioid medication that is used primarily for pain management and as an adjunct in the induction and maintenance of anaesthesia.²⁻⁴ It works by binding to µ-opioid receptors within the central nervous system (CNS), thereby reducing the perception of pain.

The use of fentanyl has been associated with the development of **chest wall rigidity**, also known as **wooden chest syndrome (WCS)**.^{3,4} This syndrome is a rare but serious complication associated with opioid use, characterised by rigidity of the muscles, particularly the skeletal muscles of the chest wall. Other manifestations of WCS include episodes of breath-holding, hypoxia, and hypertension.^{5,6} WCS can lead to respiratory distress and potentially respiratory failure if not promptly treated.

While the exact mechanism behind WCS is not clearly understood, it is believed that the activation of µ-opioid receptors in the CNS via the dopaminergic pathway plays a central role in opioid-induced muscle rigidity.^{5,7} This phenomenon is more commonly observed with fentanyl usage compared to other opioids, possibly due to its high lipid solubility which allows it to readily cross the blood-brain barrier.⁵

Although this effect usually occurs with high doses and rapid administration of fentanyl, reports of WCS following lower doses have been published.^{6,8} Dewhirst et al. discussed the cases of two infants who developed WCS after low-dose fentanyl administration.⁸ They also reviewed nine published case reports which discussed the occurrence of WCS in neonates and infants who received low doses of fentanyl, ranging from 1 to 8 µg/kg (involving both bolus administration and continuous infusion). A case of WCS in an adult receiving a low dose of fentanyl has also been reported.⁶



*AI-generated image

Treatment of WCS typically involves discontinuation of the opioid medication and administering an opioid antagonist, namely naloxone, or neuromuscular blocking agents (NMBAs) such as rocuronium and cisatracurium.⁵ Supportive care, such as manual ventilation, may be necessary to assist the patient's breathing until the effects of the opioid wear off. Several measures have also been suggested to reduce the incidence of WCS, such as premedication with benzodiazepines or $\alpha 2$ -adrenergic agonist, and concurrent use of fentanyl with NMBAs.^{3,8}

In Malaysia, there are currently 16 registered products containing fentanyl, available as sublingual tablets, transdermal patches and parenteral formulations.⁹ To date, the NPRA has received 360 local adverse drug reaction (ADR) reports, with 634 adverse events, suspected to be related to fentanyl.¹ The most commonly reported adverse events involved skin reactions, namely pruritus (79), urticaria (62) and rash (38). There are only **six local reports of fentanyl causing muscle rigidity**, one of which is discussed above.

As of September 2024, the World Health Organisation (WHO) international ADR database has recorded 377 cases of muscle rigidity following the use of fentanyl.^{10*} Based on the extended global search on opioids drug class (ATC code: N02A), fentanyl was the most frequently reported opioid to cause muscle rigidity, followed by tramadol (158), oxycodone (94), and morphine (78). However, information on whether these reports are related to chest wall rigidity, or specifically WCS, was not readily available in the WHO database.

Given the relatively small number of WCS reports received locally, despite muscle rigidity being a known adverse effect of fentanyl or opioids, it is possible that this syndrome may be overlooked or under-reported in Malaysia. Prompt recognition and management are essential to prevent complications and save lives.

***DISCLAIMER**

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Advice for Health Care Professionals

- 1 Be aware** of the rare risk of WCS with the use of intravenous fentanyl.
- 2 Start** fentanyl with the lowest possible dose and adhere to the recommended administration rate.
- 3 Be on the lookout** for manifestation of WCS including tense abdomen, hypoxia, breath-holding spells and stiffening of limbs, even when fentanyl is used in low doses.
- 4 If WCS is suspected, management options include:**
 - (i) withdrawal of fentanyl;
 - (ii) administration of an opioid antagonist such as naloxone;
 - (iii) administration of neuromuscular blocking agents.
- 5 Report** any adverse drug reactions suspected to be related to the use of fentanyl and other opioids to the NPRA.

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What's New

List of Safety Alerts/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/DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Mefenamic Acid	Safety Signal Alert: Generalised Bullous Fixed Drug Eruption (GBFDE)	02-Sep-2024	NPRA.600-1/9/13 (41) Jld.1 [15-Apr-2024]
2	Pseudoephedrine	Risk of Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS)	30-Sep-2024	-
3	Fluconazole	Updates on the Known Risk of Spontaneous Abortion During Pregnancy and Congenital Malformations in Children Exposed to Fluconazole in Utero	01-Oct-2024	-
4	Paracetamol	Fixed Drug Eruption (FDE): Upward Trend of Reports Involving Paediatric Patients	10-Oct-2024	-
5	17-Hydroxyprogesterone Caproate (17-OHPC)	[Updated] Cancellation of Product Registration and Product Recall	14-Oct-2024	-

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:



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