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Ministry of Health, Malaysia

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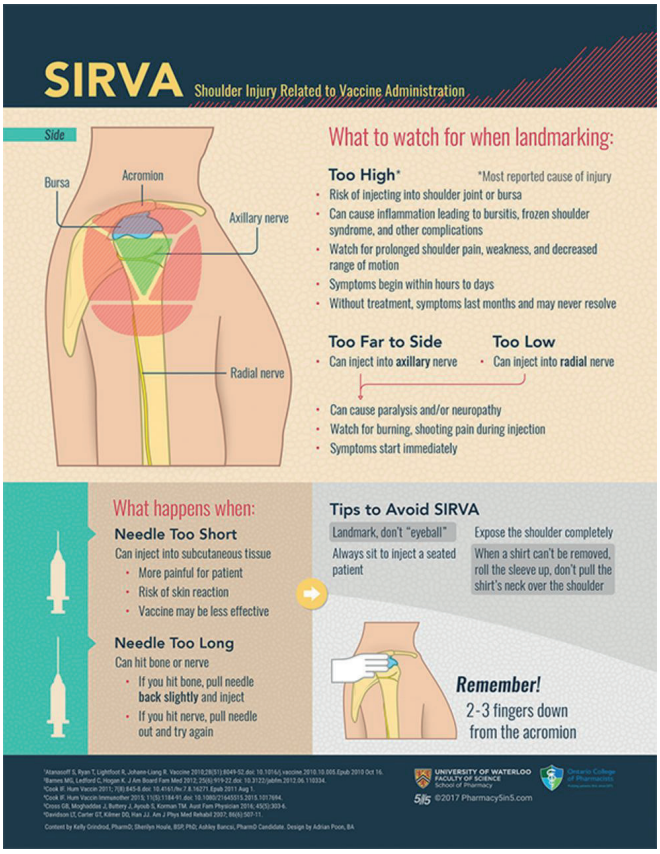
Articles based on Case Reports

Shoulder injury related to vaccine administration (SIRVA): A preventable occurrence

by Norshazareen Abd Manab

Localised reactions at the site of injection due to vaccine administration are among one of the most frequently occurring adverse event following immunisation (AEFI) that are usually transient and mild in nature. The most common localised reactions are injection site pain, oedema and erythema.[1,2] On uncommon occasions, an error in vaccination method can result in severe, persistent shoulder pain with prolonged restriction of movement of the affected limb that may onset within 48 hours post vaccine administration. This AEFI is described as shoulder injury related to vaccine administration (SIRVA).[3,4]

SIRVA occurs when a vaccine intended for intramuscular administration is injected into the shoulder capsule instead of the deltoid muscle, or when the vaccine is administered into the deltoid muscle from a high angle (e.g. vaccinator is at a standing position).[3,4] This triggers an inflammatory response and injury to the shoulder structures which may limit the patient's ability to perform basic daily tasks.[4] As X-ray imaging does not reveal abnormalities, ultrasound or magnetic resonance imaging (MRI) are usually used to detect any presence of intraosseous oedema, bursitis, tendonitis and rotator cuff tears.[2]



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To date, NPRA has not received any report on SIRVA. However, there are four (4) AEFI reports with four (4) adverse events that may be associated to SIRVA, which are decreased mobility of the injected limb (2), vaccination site movement impairment (1) and shoulder pain (1). While most of these patients were reported to recover within a few days without any medical intervention, one (1) patient complained of a painful event which interfered with her day-to-day activities.[5]

As of September 2020, the World Health Organisation (WHO) global ADR database (VigiLyze) identified 123 reports of SIRVA suspected due to incorrect administration of vaccines. The most commonly reported vaccines associated with SIRVA were influenza vaccine (71, 57.7%), pneumococcal vaccine (12, 9.8%), varicella zoster vaccine (9, 7.3%), and diphtheria/pertussis/tetanus combination vaccine (7, 5.7%).[6]*

*DISCLAIMER

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Advice to Healthcare Professionals

1. Recognise the symptoms of SIRVA, which is distinguished as distinctive shoulder pain that is prolonged and limits shoulder movement.
2. SIRVA may be prevented with adequate knowledge of the shoulder anatomical structures and training on correct vaccine administration technique. Several tips on SIRVA prevention include:
   - It is advised that for vaccines that need to be injected intramuscularly on the deltoid muscle, avoid standing while administering the vaccine to a seated patient.
   - Choose the correct needle length and ensure proper needle angle. Good needle selection can prevent injection into the subcutaneous tissue or nerve.
   - Expose the entire arm. Instead of pulling the patient's collar over the shoulder, roll up the shirt's sleeve.
   - Find the correct injection site. Use the triangle method or the fingers method to landmark injection site.
   - Encourage patient to relax the shoulder muscle during vaccination administration.
3. Report any adverse event following immunisation to NPRA at Reporting ADR.

Articles based on Case Reports

Jarisch-Herxheimer reaction: An adverse drug reaction following treatment with benzathine penicillin in syphilis patients

by Ng Jia Mean

Case Report

A 32-year-old male patient with an underlying retroviral disease was diagnosed with syphilis in a district hospital and was given a single dose of intramuscular benzathine penicillin. A day after the injection, he developed itchiness and desquamative maculo-papular rash over his trunk, upper and lower limbs. He was referred to a dermatology clinic at a general hospital for further management, but he only attended the clinic a week later when his condition worsened. He developed fever, generalised body weakness, and immobility due to excessive pain caused by skin peeling. Following the assessment by a dermatologist, he was diagnosed with **Jarisch-Herxheimer reaction (JHR)** and exfoliative dermatitis, secondary to benzathine penicillin. He was given a stat dose of intravenous hydrocortisone, oral chlorpheniramine, topical steroid and emollient. Patient was recovering at the point when the report was made.

Discussion

Benzathine penicillin belongs to the class of beta-lactam antibiotics and it is yielded through hydrolysis of two penicillin G molecules.[1,2] It is active against various gram-positive streptococci as well as spirochetal species. Benzathine penicillin exerts its bactericidal effect by inhibiting biosynthesis of the cell wall peptidoglycan during active bacterial multiplication stage. This inhibition subsequently leads to an osmotically unstable cell wall, causing cell wall lysis and cellular destruction, which results in bacterial cell death.[2]

Currently, there are three (3) registered products containing benzathine penicillin in Malaysia which are indicated for prophylaxis and treatment of infections caused by penicillin-sensitive pathogens such as rheumatic fever, scarlet fever, erysipelas, syphilis and other treponemal infections (for full prescribing information, please refer to product information).[3,4]

JHR is a recognised adverse drug event which could developed in patients with spirochetal infection (including syphilis, leptospirosis, Lyme disease, and relapsing fever) following antibiotic therapy, such as benzathine penicillin.[4,5] Its manifestations include fever, chills, headache, tachycardia, hypotension, hyperventilation, flushing, myalgia and skin rash.[5] In syphilis, lipoproteins of the spirochete *Treponema pallidium* are likely responsible for the inflammatory signs in JHR as the lipoprotein can trigger macrophages to produce tumour necrosis factor.[6,7] JHR can be underreported as its symptoms are either overlooked as signs of the underlying infection or mistaken as a hypersensitivity reaction to the antibiotic treatment.[7,8]

NPRA has received eight (8) adverse drug reaction (ADR) reports with 18 adverse events associated with benzathine penicillin.[9] Some of the common adverse events reported were rash (4), shortness of breath (2) and injection site reaction (2). To date, NPRA has received one (1) report of JHR associated with the use of benzathine penicillin (as discussed above). As of August 2020, a search in the World Health Organisation (WHO) global ADR database revealed a total of 24 reports of JHR suspected to be associated with benzathine penicillin.[10]*

*DISCLAIMER

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Advice to Healthcare Professionals

1. Be vigilant for signs of Jarisch-Herxheimer reactions when monitoring syphilis patients treated with benzathine penicillin as it can easily be overlooked as symptoms of the underlying infection or drug allergy.
2. Antimicrobial therapy in patients who develop JHR may be continued with appropriate vital signs monitoring, fluid administration and symptomatic treatment as stopping the antibiotic inappropriately may worsen the underlying disease.
3. Advise patients on possible symptoms of JHR reaction and seek medical treatment if necessary.
4. Report any ADRs suspected to be related to the use of benzathine penicillin to NPRA.

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Articles based on Case Reports

Rapid correction of hyponatraemia with intravenous saline solution causing osmotic demyelination syndrome

by Yeoh Hee Sheong

Case Report

A 55-year-old female patient was presented to the hospital with vomiting, dizziness and malaise for the past two (2) weeks. She has a medical history of hypertension and was taking daily doses of perindopril, indapamide and amlodipine. Blood investigations were performed during admission and her serum sodium was less than 100 mmol/L and serum potassium was 2.8 mmol/L. She was diagnosed with thiazide-induced hyponatraemia and she was treated with intravenous (IV) normal saline solution with 3 g of potassium infused at 104 ml/hour. After 4 hours, her serum sodium level remained below 100 mmol/L , she was then administered with IV 3% saline solution at a rate of 20 ml/hour for another 4 hours in addition to the IV normal saline with 3 g of potassium. The patient's serum sodium level gradually increased to 115mmol/L over 12 hours. Over the next few weeks, the patient remained lethargic and subsequently developed emotional lability and dysphagia requiring enteral nutrition. A magnetic resonance imaging (MRI) scan of the brain confirmed that the patient was having **osmotic demyelination**. The patient was treated with five (5) cycles of plasma exchange. She was reported to have recovered following treatment, where she slowly regained oral intake without enteral feeding and was ambulating independently. Considering that the patient had underlying hyponatremia and there were multiple concurrent medications that may have contributed to the electrolyte imbalance and osmolarity changes, this case was causally assigned to be possibly-related to the drug.

Discussion

IV saline solution is commonly used for a vast indications: from replenishing fluids and restoring sodium levels in dehydrated patients, to its use as a solvent or diluent for the preparation of parenterally administered drugs. It is one of the drugs of choice in treating patients with hypovolemic hyponatraemia (serum sodium concentrations of less than 135 mmol/L).[1] However, in patients with chronic hyponatraemia where the correction of serum sodium concentration occurs too rapidly, there is a risk of developing osmotic demyelination syndrome (ODS).[2]

Osmotic demyelination syndrome (ODS), or osmotic myelinolysis, is a non-inflammatory disorder involving the breakdown of the myelin sheath that insulates nerve cells at the central pontline and/or extra pontline.[3] The risk is especially high in patients who have developed chronic hyponatraemia where the brain has adapted to the hyponatraemia environment, and sudden increase in serum sodium concentration causes demyelination of the neurons.[2] Early symptoms of ODS include lethargy, dysarthria, and affective changes, which later on may lead to symptoms of spastic quadriparesis and pseudobulbar palsy.[3,4] Apart from the rapid increase of serum sodium, other risk factors of ODS include patient's underlying conditions such as history of excessive alcohol use, hepatic disease, use of thiazide diuretics and antidepressants.[2]

Although limiting the rate of sodium correction could reduce the risk of developing ODS, a rapid correction of serum sodium concentration is warranted in patient with severely symptomatic hyponatraemia as this condition may leads to permanent brain damage or death if left untreated.[5]

There are currently 44 registered IV saline solution in Malaysia, containing sodium chloride as single active or combination with other active ingredient (dextrose or potassium chloride). To date, NPRA has received a total of 36 adverse drug reaction (ADR) reports with 54 adverse events suspected to be related to IV saline containing products. The most commonly reported adverse events were pruritus (7), hot flush (4), and chest tightness (4). There are currently two (2) reports with osmotic demyelination suspected to be associated with IV saline in Malaysia.[6] Globally, 24 reports of ODS associated with IV saline use were identified in the World Health Organisation (WHO) international ADR database.[7]*

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Advice to Healthcare Professionals

1. To prevent ODS, it is recommended to gradually correct the serum sodium in patients with chronic and asymptomatic hyponatraemia especially if patient presents with other risk factors.
2. Monitor patient's serum sodium concentration and restrict increasing sodium concentration less than 10mmol/L in the first 24 hours and and less than 18 mmol/L in the first 48 hours.
3. Monitor for any initial symptoms of ODS in hyponatraemic patients who are treated with IV saline and if necessary, further investigations like MRI should be prompted.
4. Keep in mind that if hypokalaemia is present, correction of the hypokalaemia will contribute to an increase in serum sodium concentration.
5. Report any adverse events suspected to be associated with the use of IV saline to NPRA.

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Articles based on Case Reports

Sulfamethoxazole-trimethoprim-induced drug reaction with eosinophilia and systemic symptoms (DRESS)

by Farah Faridah binti Jamaludin

Case Report 1

A 57-year-old female patient was admitted to Hospital A for 3 weeks in 2019 for the treatment of melioidosis which was complicated with lobar pneumonia. Patient was then transferred to Hospital B for continuation of care. There, she was treated with sulfamethoxazole-trimetoprim (SMZ-TMP) for 5 days and later discharged home with eradication therapy of sulfamethoxazole-trimetoprim (SMZ-TMP) planned for 5 months. During her follow-up at Hospital A on 19/10/2019, it was found that the patient's liver function test was deranged. SMZ-TMP was subse quently withdrawn from her treatment plan and switched to tablet amoxicillin/clavulanate. On 20/11/2019, the patient developed rashes and vomiting. Patient went to Hospital B and later referred to Hospital C on 26/11/2019. There, she was seen by a dermatologist and was reported to have multiple maculopapular eruptions on the trunk and upper limbs, candidiasis on oral cavity and macerated lesion on inguinal region. The diagnosis was concluded to be **drug reaction with eosinophilia and systemic symptoms (DRESS) secondary to SMZ-TMP**. In the ward, counselling was done and an allergic card was issued to the patient. Tablet prednisolone 10mg TDS and topical agents was also prescribed. The dermatologist ordered not to re-challenge with SMZ-TMP. It was report ed that the patient's rashes and itchiness were resolving. As of 01/12/2019, patient still had erythema and improving facial swelling, but there was no new lesion noted and no more mucosal lesion. Prednisolone was planned to continue until the patient's next dermatology outpatient appointment on 08/12/2019.

Case Report 2

A 46-year-old male patient was started on SMZ-TMP tablet indicated for meliodosis. Two (2) weeks later, patient developed rashes which subsequently worsened to erythroderma over his whole body. Patient also had lip swelling and ectropion. The patient was reviewed by a dermatologist and his condition was diagnosed as **DRESS** with erythroderma. The onset of the reaction was 14 days and the extent of the reaction was reported to be severe. The suspected drug was stopped and the patient was reported to have recovered at the time of the report.

Discussion

SMZ-TMP is a combination drug product of two antimicrobial agents sulfamethoxazole and trimethoprim, which is effective against a wide variety of gram-positive and gram-negative bacteria such as *Escherichia coli*, Klebsiella, Enterobacter, *Proteus mirabilis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, Acinetobacter, Salmonella, Shigella, and *P. carinii*.[1,2] Sulfamethoxazole and trimethoprim act synergistically by inhibiting bacterial cell synthesis of essential nucleic acids.[1] The sulfamethoxazole blocks the production of dihydrofolic acid from para-aminobenzoic acid (PABA), whereas trimethoprim inhibits dihydrofolate reductase, therefore preventing the production of tetrahydrofolic acid from dihydrofolic acid.[1,2]

In Malaysia, there are currently 15 registered products of SMZ-TMP.

Drug reaction with eosinophilia and systemic symptoms (DRESS), which is also commonly known as drug induced hypersensitivity syndrome, is a rare but a potentially life-threatening adverse drug reaction.[3,4] DRESS has a prolonged latency (2 to 6 weeks) and presents with fever, skin eruption and internal organ involvement.[4] The severity of this syndrome depends on the extent of its systemic involvement, which may result in multiple organ failure. The diagnosis of DRESS can be challenging due to its diverse array of clinical features and inconsistent levels of eosinophil.[3] DRESS has a tendency to relapse regardless of discontinuation of the suspected drug.[4]

Up to October 2020, NPRA has received 1,264 ADR reports with the total number 2,358 events associated with the use of SMZ-TMP.[5] The majority of the reports involves skin and subcutaneous tissue disorders (1,418 adverse events) such as maculo-papular rash (330), rash (318), pruritus (302), urticaria (78), Stevens-Johnson syndrome (64), erythema multiforme (9) and blisters (8). To date, NPRA has received 37 ADR reports of DRESS associated with SMZ-TMP [two (2) of which are as discussed above]. The onset of all DRESS reported were between seven (7) days to four (4) months, affecting patients from the age of 19 to 80 years old. Majority of the patients were reported to recover after drug withdrawal and treatments.

As of November 2020, there were 120,406 ADR reports linked to the use of SMZ-TMP found in the WHO global ADR database (VigiLyze®).[6] About 61.7% (74,271 reports) were skin and subcutaneous tissue disorders such as rash, pruritus, maculo-papular rash, urticaria and Stevens-Johnson syndrome. There were 999 reports of DRESS associated with SMZ-TMP use, which were co-reported with pyrexia (81), rash (53), eosinophilia (48), and maculo-papular rash (48).*

*DISCLAIMER

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Advice to Healthcare Professionals

1. Be alert on the risk of DRESS following the administration of SMZ-TMP for early detection and withdrawal of the suspected agent is critical to reduce morbidity and mortality.
2. Following the administration of SMZ-TMP, DRESS should be highly suspected with the presence of skin rash, liver involvement, fever, hypereosinophilia, and lymphadenopathy.
3. Treatment for DRESS is largely supportive and symptomatic consisting of emollients and topical steroids to reduce cutaneous symptoms and antipyretics to reduce fever. Systemic corticosteroid therapy and other immunosuppresants may be reserved for more severe cases taking into account the frequent relapses of DRESS associated with quick corticosteroid tapering.
4. Empirical antibiotic therapy should be avoided in the treatment of DRESS, since it may lead to the exacerbation of patient's infection due to its cross-reactivity between drugs.
5. Report any ADRs suspected to be related to the use of SMZ-TMP to the NPRA.

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. Report ADR as healthcare professional.
3. 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.

fv@npra.gov.my

*To join the **NPRA Safety Information Mailing List**, please send an email with your details to **fv@npra.gov.my***

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