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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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AE Case in Focus 1: Test Yourself

What could have caused this patient's presentation?

Pg 6

This is a case of a male patient in his 60s, who presented to the Emergency Department (ED) with symptoms of acute onset facial and upper limb numbness, dizziness, nausea and vomiting, as well as, chest discomfort after consuming a herbal decoction which was based on a recipe that was found on social media. He was a chronic smoker with a past medical history of gout for which he was not on any regular prescription medication. At the ED, he was conscious and alert but was also diaphoretic, with a heart rate of 110 bpm, blood pressure of 62/34 mmHg and SpO2 was 98% on room air. His other examinations were unremarkable. His electrocardiogram (ECG) reading showed sinus tachycardia with frequent premature ventricle complexes. His biochemistry investigations and toxicology screens were also unremarkable.

AE Case in Focus 2: Test Yourself

What could have caused the rash in this patient?

Pg 8

This is a case of a patient in his 50s who received his first dose of COVID-19 Moderna vaccine in mid-April 2021 on his left deltoid. One week later, he developed an erythematous plaque over his left arm which was associated with tenderness. There was no associated fever or other systemic symptoms. He was seen by a primary care physician and treated with co-amoxiclav. His medical history was significant for asthma and temporal giant cell arteritis and he had known drug allergies to diclofenac, montelukast and sulphonamides which had resulted in urticarial reactions.

Dear Healthcare Professional Letters on safety concerns

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

HSA_productsafety@hsa.gov.sg

https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 October 2021.

SERTRALINE AND RISK OF MICROSCOPIC COLITIS

Key Points

- Isolated cases of microscopic colitis associated with the use of sertraline have been reported overseas and in published literature
- While microscopic colitis can result in severe prolonged diarrhoea and substantial weight loss, published case reports revealed that the condition resolved progressively following swift cessation of sertraline
- Healthcare professionals are advised to consider the possibility of microscopic colitis in patients on sertraline who present with prolonged or severe diarrhoea

HSA would like to update healthcare professionals on the potential risk of microscopic colitis associated with the use of sertraline.

Sertraline is a selective serotonin reuptake inhibitor that has been registered in Singapore since 1992 for the treatment of depression, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social phobia and pre-menstrual dysphoric disorder. Diarrhoea is a common adverse drug reaction (ADR) associated with the use of sertraline.

About microscopic colitis

Microscopic colitis is a rare inflammatory disorder of the colon. It presents with chronic, non-bloody diarrhoea, abdominal pain, weight loss and fatigue. It can be divided into two subtypes, namely lymphocytic colitis or collagenous colitis, which are clinically indistinguishable but have different histopathologic features. Both subtypes are typically characterised by a marked and diffuse excess of lymphocytes interspersed among the surface colonocytes and within the lamina propria. In collagenous colitis, a subepithelial collagen band can be seen in the colon on biopsy in addition to increased intraepithelial lymphocytes.

The exact mechanism of microscopic colitis is poorly understood; an inflammatory mechanism triggered by environmental factors such as an infection, toxin or drugs has been suggested.

Published literature

(i) Case-control study[1]

In 2013, a Spanish prospective case-control study which investigated the epidemiological risks factors in microscopic colitis found sertraline to be associated with an increased risk for lymphocytic colitis. The study included 120 patients with collagenous colitis, 70 with lymphocytic colitis and 128 controls from teaching and community hospitals across Spain from March 2007 to May 2010. Drug exposure before the onset of diarrhoea (for cases) or at study recruitment (for controls) was recorded for medicines taken ≥ 3 days per week for ≥ 2 weeks. Of the patients recruited, seven lymphocytic colitis cases and none of the controls took sertraline, contributing to a statistically significant association between sertraline intake and lymphocytic colitis [odds ratio 17.5 (2.0-149.2)]. These findings were similar to those from an earlier case-control study and were in line with the documented association of sertraline with high likelihood of triggering microscopic colitis.

(ii) Case reports[2-4]

Three case reports of microscopic colitis related to the use of sertraline described patients who presented with prolonged non-bloody diarrhoea lasting from over 20 days to three months, resulting in substantial weight loss of up to 20 kg in one report from the literature. In all three cases, microscopic colitis associated with sertraline was diagnosed based on temporal association with sertraline initiation and biopsies from the colon and/or rectum that revealed an increase in intraepithelial lymphocytes, which is characteristic of the condition. All the patients recovered upon discontinuation of sertraline.

International situation

In January 2020, the European Medicines Agency (EMA) identified the signal of microscopic colitis from the European spontaneous adverse event reporting database. Following a review of the available evidence in the database and in literature, the EMA requested for the product labels of sertraline-containing products to be updated to state 'microscopic colitis' as an undesirable adverse effect with unknown frequency.[5] Similar regulatory actions were also taken by the Australian Therapeutic Goods Administration (TGA).[6]

Local situation

To date, HSA has received five ADR reports of diarrhoea associated with the use of sertraline, none of which involved microscopic colitis.

Based on post-marketing experience, the association of microscopic colitis with sertraline use has been reported overseas and in published literature. HSA is working with the product registrants of sertraline-containing products to update the local package insert to include microscopic colitis as an adverse event that has been observed in the post-market setting.

HSA's advisory

While microscopic colitis related to the use of sertraline can result in severe prolonged diarrhoea and substantial weight loss, published case reports revealed that the condition resolved progressively following swift cessation of sertraline. Healthcare professionals are advised to consider the possibility of this adverse event in patients on sertraline who present with prolonged or severe diarrhoea.

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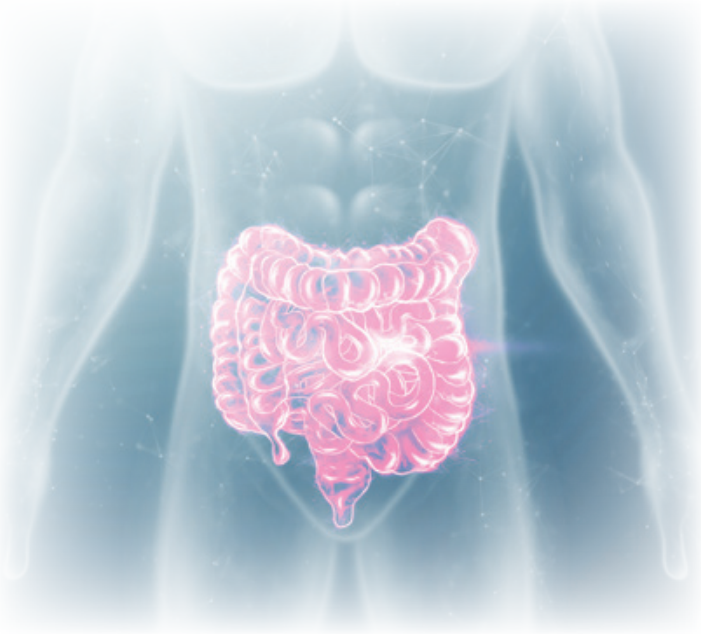

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

OVERVIEW OF SERIOUS ADVERSE EVENTS REPORTED WITH TARGETED THERAPIES IN BREAST CANCER

Key Points

- Targeted therapies in breast cancer are associated with serious adverse events (AEs) that may be unpredictable in terms of onset, severity and type
- Some of the more significant AEs observed with these therapies include haematological toxicities, hyperglycaemia with ketoacidosis, pneumonitis and other immune-related AEs
- Healthcare professionals are advised to look out for the various serious AEs associated with targeted cancer therapies and their potential for drug interactions that may increase the risk of serious AEs from these agents

Targeted therapies are increasingly used in the treatment of cancers. These novel agents act by, directly or indirectly, attacking a specific genetic biomarker found in a given cancer, leading to the killing or inhibition of tumour growth. Several targeted therapy agents have been approved in breast cancer and may be divided into the following five classes:

1. Human epidermal growth factor receptor 2 (HER2) inhibitors
2. Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors
3. Phosphoinositide 3-kinase (PI3K) Inhibitors
4. Polyadenosine diphosphate ribose polymerase (PARP) inhibitors
5. Programmed death ligand 1 (PD-L1) inhibitors

CDK 4/6, PI3K and PARP inhibitors are orally administered agents while HER2 receptor inhibitors and PD-L1 inhibitors are intravenously administered antibody-based agents. The drug classes, brands and locally approved indications of the targeted cancer therapies used in breast cancer are listed in Table 1.

This review article aims to provide an analysis on the serious adverse events (AEs) reported locally with the use of targeted breast cancer therapies as of 30 June 2021. AEs from targeted therapies manifest in a wide range of organ systems and may be less predictable in terms of onset, severity and type, relative to that of traditional cytotoxic chemotherapy, which has a more predictable adverse effect profile.[1]

Table 2 provides the number of serious AE reports received as of 30 June 2021, for each targeted therapy class as well as the potential for drug interactions with the oral agents (PARP, CDK 4/6 and PI3K inhibitors). Drug interactions can increase the risk of serious AEs when administered with interacting agents as all oral targeted therapies used in breast cancer are substrates of the CYP3A4 metabolic pathway.

Serious adverse events

(i) Pneumonitis

Drug-induced pneumonitis is a serious immune-related AE that can arise following the use of several classes of targeted therapies in breast cancer. Early detection and immediate discontinuation of the offending agent can result in reversible lung injury (with or without treatment). However, continued exposure may lead to a permanent disease condition (e.g. pulmonary fibrosis) and death.[2] The onset and progression of pneumonitis are often insidious and symptoms can be non-specific, with latency spanning between months to years following drug exposure.[2]

Locally, six reports of pneumonitis associated with targeted therapy agents from three different drug classes have been reported to date (Table 2). Two reports of pneumonitis associated with pertuzumab (Perjeta®, Roche Singapore Pte Ltd) had occurred approximately after five months of exposure, while two other reports involving atezolizumab (Tecentriq®, Roche Singapore Pte Ltd) occurred after approximately two months. One report involving olaparib (Lynparza®, Astrazeneca Singapore Pte Ltd) had a latency of over a year. Another report involving trastuzumab emtansine (Kadcyla®, Roche Singapore Pte Ltd) did not report a latency period. However, published literature has suggested that pneumonitis associated with the use of trastuzumab emtansine can occur anytime between two and 53 months post-exposure to the drug.[3,4]

Internationally, there have been reports of pneumonitis following the use of CDK 4/6 inhibitors [palbociclib (Ibrance®, Pfizer Pte Ltd), ribociclib (Kisqali®, Novartis (Singapore) Pte Ltd) and abemaciclib (Verzenio®, DKSH Singapore Pte Ltd)]. In 2019, the US Food and Drug Administration (FDA) had released a Drug Safety Communication to warn on the risk of pneumonitis with CDK 4/6 inhibitors.[5] A recent analysis of reports in the FDA's Adverse Event Reporting System (FAERS) also suggested a higher-than-expected number of reports of pneumonitis in association with CDK 4/6 inhibitors.[6] In June 2021, the UK Medicines and Healthcare products Regulations Agency (MHRA) had similarly issued a drug safety update following 27 reports of pneumonitis with CDK 4/6 inhibitors as of January 2021. To date, HSA has not received any reports of pneumonitis associated with CDK 4/6 inhibitors.

Pneumonitis has also been reported in clinical trials of PI3K inhibitor, alpelisib (Piqray®, Novartis Singapore Pte Ltd) and is listed in the locally approved package insert with an incidence of 1.8%.[7] However, as of 30 June 2021, there have not been any local reports of pneumonitis associated with the PI3K inhibitor, alpelisib, reported to HSA.

While early detection is ideal, drug-induced pneumonitis remains a diagnosis of exclusion. Causality assessments can be challenging in cancer patients owing to a variety of possible alternative causes including radiation exposure from concurrent radiotherapy in breast cancer. However, emerging evidence describing the unique radiographic features of pneumonitis from specific targeted therapy agents are beginning to elucidate useful indicative features that may aid causality assessments.[8-10]

(ii) Haematological toxicities

As with cytotoxic chemotherapy, targeted therapies for breast cancer are also commonly associated with different types of haematological toxicities, including anaemia, neutropenia and thrombocytopenia. Other rare AEs include venous thromboembolism risks with selected CDK 4/6 inhibitors (e.g. abemaciclib) and myelodysplastic syndrome with PARP inhibitors. Haematological AEs are among the most frequently reported AEs with CDK 4/6 and PARP inhibitors (Table 2).

As of 30 June 2021, there have been four reports of anaemia following PARP inhibitor use occurring between three weeks and six months after therapy initiation, of which all the patients required red blood cell

Table 1. Recently approved targeted therapy agents used in breast cancer

Class	Drug (Brand Name)	Target	Approved
Antibody-drug conjugate	Ado-trastuzumab emtansine (Kadcyla®)	Human epidermal growth factor 2 (HER2)	January 2014
Monoclonal antibody	Pertuzumab (Perjeta®)		February 2014
Immune checkpoint inhibitor	Atezolizumab (Tecentriq®)	Programmed death ligand 1 (PD-L1)	February 2018
Small molecule inhibitor	Olaparib (Lynparza®) Talazoparib (Talzenna®)	Polyadenosine diphosphate ribose polymerase (PARP)	April 2019 May 2020
Small molecule inhibitor	Palbociclib (Ibrance®) Ribociclib (Kisqali®) Abemaciclib (Verzenio®)	Cyclin-dependent kinase 4/6 (CDK 4/6)	July 2016 January 2018 August 2019
Small molecule inhibitor	Alpelisib (Piqray®)	Phosphoinositide 3-kinase (PI3K)	March 2020

Table 2. Local reports of serious adverse events and the risk of drug interactions with targeted therapy agents approved in breast cancer.

Drug (Brand Name)	Serious adverse events (number of reports received)	Drug interaction potential
Ado-trastuzumab emtansine (Kadcyla®)	Thrombocytopenia (5), Pericarditis (1), Pneumonitis (1), Transaminitis (1)	-
Pertuzumab (Perjeta®)	Heart failure (5), Pneumonitis (2), Granulocytopenia (1)	-
Atezolizumab (Tecentriq®)	Colitis (2), Pneumonitis (2), Hepatitis (2), Encephalitis (2), Guillian-Barre Syndrome (1), Myasthenia Gravis-like Syndrome (1), Hypophysitis (1), Uveitis (1), Thyroiditis (1)	-
Olaparib (Lynparza®) Talazoparib (Talzenna®)	Anaemia (4), Thrombocytopenia (4), Myelodysplastic syndrome (1), Pneumonitis (1)	CYP3A4 substrate
Palbociclib (Ibrance®) Ribociclib (Kisqali®) Abemaciclib (Verzenio®)	Neutropenia (25), QT interval prolongation (5), Thrombocytopenia (4), Renal impairment (2), Hepatotoxicity (2), Thromboembolism (1)	CYP3A4 substrate
Alpelisib (Piqray)	Renal impairment (3), Hyperglycemia (2), Diabetic ketoacidosis (1), Stevens-Johnson Syndrome (1), Thrombocytopenia (1)	CYP3A4 substrate

transfusion. There was one case of severe neutropenia (Grade 3) with co-reported Grade 4 thrombocytopenia which was reported to have occurred three weeks after PARP inhibitor initiation.

Conversely, more cases of neutropenia (25) than anaemia (1) were reported with CDK 4/6 inhibitors. Based on the reports received, the time-to-onset for neutropenia ranged between one week and six months following CDK 4/6 inhibitor initiation. There has been no deaths from neutropenia reported to HSA.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are infrequent AEs that can occur with PARP inhibitors at an estimated incidence of 1.8%.[11] A numerically higher number of MDS and AML were observed in several randomised controlled trials (RCTs) of PARP inhibitors. A combined meta-analysis and retrospective analysis of the World Health Organization's pharmacovigilance database suggests a significantly increased risk of MDS and AML following PARP inhibitor exposure [Peto odds ratio: 2·63 (95% CI 1·13–6·14), p=0·026].[12] The latency for MDS may range between one and 67 months while for AML, it can occur between eight and 30 months following PARP inhibitor therapy. [12]

As of 30 June 2021, HSA has received one report of MDS in a female in her 50s who was treated with olaparib for two months. Severe anaemia was also reported, which is often present in MDS (sometimes accompanied with neutropenia and thrombocytopenia). As MDS consists of a heterogeneous spectrum of blood disorders, the risk of progression to AML and outcomes is equally wide ranging with the presence or absence of various other prognostic factors influencing overall survival.[13]

Close monitoring of blood counts and further evaluation in patients with prolonged haematological abnormalities may be necessary to detect such potential delayed toxicities that may arise in patients on PARP inhibitors.

(iii) Glucose-related disorders

Hyperglycaemia can occur in up to 65% of patients on the PIK inhibitor, alpelisib and can be a potentially therapy limiting AE. Grade 3 hyperglycaemia [fasting blood glucose (FPG) levels > 14 mmol/L] and Grade 4 (FPG > 28 mmol/L) may occur at incidences of 33% and 4%, respectively and may precipitate risks of ketoacidosis which can be life-threatening. RCT evidence suggests that the median time to first occurrence of hyperglycaemia is approximately 15 days (range: 5 to 517 days).

HSA has received one report of ketoacidosis in a female in her 50s with a history of Type 2 Diabetes, following seven months of alpelisib therapy. The first sign of hyperglycaemia appeared 28 days after drug initiation. She required significant medical intervention before her blood glucose levels returned to acceptable baseline, where oral antihyperglycemic agents were deemed sufficient.

A variety of oral agents and insulin may be used in the treatment of alpelisib-related hyperglycaemia. This may include Sodium-Glucose Co-transporter 2 (SGLT2) inhibitors which are increasingly prescribed for managing hyperglycaemia, but independently is also associated with the risk of euglycaemic ketoacidosis. While it remains unclear if the concomitant use of a PI3K inhibitor and a SGLT2 inhibitor increases the risk of DKA, there has been one published report of ketoacidosis following concomitant use of both agents.[14]

Drug interactions as precipitants of serious AEs

All three classes of oral targeted therapies used in breast cancer carry significant risks of drug-drug interactions as they are substrates of the cytochrome P450 3A4 metabolic pathway (Table 2). This is noteworthy given that all three class agents are administered daily (typically as tolerated or till disease progression) or given on a three-weeks on, one-week off dosing regimen. Continual exposure of these oral agents may increase the risk of interactions with commonly prescribed 3A4 inhibitors and inducers which can potentiate the risk of AEs from targeted therapies and/or the interacting drug. For instance, the concomitant use of antimicrobial agents [e.g. clarithromycin (CYP 3A inhibitor)] or antifungal agents [e.g. azoles (CYP 3A inhibitor)] with CDK 4/6 inhibitors may increase the risk of QT prolongation.[15] The high incidence of All-Grade neutropenia (75 to 80%) in patients on CDK 4/6 inhibitors may put patients at risk of infections and potentially interacting antimicrobial/antifungal agents may be prescribed for use.[16,17] Where appropriate, close monitoring with/without dose adjustments or avoidance and use of alternative agents may be necessary.[1]

Conclusion

Healthcare professionals are advised to look out for the various serious AEs associated with targeted cancer therapies and their potential for drug interactions that may increase the risk of serious AEs from the use of these agents. Healthcare professionals are also encouraged to report suspected targeted therapy-induced adverse events to the Vigilance and Compliance Branch of HSA.

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AE CASE IN FOCUS 1: TEST YOURSELF

A male patient in his 60s, presented to the Emergency Department (ED) with symptoms of acute onset facial and upper limb numbness, dizziness, nausea and vomiting, as well as chest discomfort after consuming a herbal decoction. He was a chronic smoker with a past medical history of gout for which he was not on any regular prescription medication.

Upon arrival at the ED, he was conscious and alert but was also found to be diaphoretic, with a heart rate of 110 bpm, blood pressure of 62/34 mmHg and SpO2 was 98% on room air. His other examinations were unremarkable. His electrocardiogram (ECG) reading showed sinus tachycardia with frequent premature ventricular complexes (Figure 1). A total of 2L of fluid boluses were immediately administered and vasopressor support with noradrenaline of up to 0.15 mcg/kg/min was initiated. He was also given intravenous amiodarone 150 mg bolus followed by an infusion at 1 mg/min over 6 hours, and 0.5 mg/min over the next 18 hours.

His biochemistry investigations and toxicology screens were unremarkable. Upon further history-taking, he revealed that the herbal decoction which he had consumed was based on a recipe that he found on social media. It consisted of *Radix Aconiti Lateralis Praeparata* (lateral root of *Aconitum Carmichaeli* (also known as Fuzi or 附子), *Panax Ginseng*, *Rhizoma Atractylodis Macrocephalae* (also known as Baizhu or 白术), *Radix Paeoniae* Alba (also known as Baishao or 白芍) and *Poria cocos mushroom* (also known as Poria Fuling or 茯苓).

He was transferred to the Medical High Dependency Unit where he remained haemodynamically stable and was gradually weaned off from his vasopressor support over the next 24 hours. An ECG test was repeated on day 2 of admission which showed normal sinus rhythm. A transthoracic echocardiogram showed normal left ventricular systolic function with no significant valvular pathology. He recovered fully and was discharged on day 3.

Question: What could have caused this patient's presentation?

HSA would like to thank Dr. Rita Lai Wei Lien, Senior Resident and A/Prof Tai Yeng Huoa Dessmon, Senior Consultant, Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital for contributing this article.

ANSWER TO AE CASE IN FOCUS 1: TEST YOURSELF

Aconitum

Aconitum, also known as aconite, monkshood and wolfsbane, is a genus of at least 350 species of herbaceous plants. Aconitine, an alkaloid and other types of alkaloids are found in all parts of the *Aconitum* plant and are most abundant in the roots. Traditionally, it has been used in the Indian Aryuvedic treatment and in the Traditional Chinese Medicine for the treatment of rheumatism, arthritis and pain. Specifically, in Traditional Chinese Medicine, root tuber of *Aconitum Carmichaelii* (also known as *Radix Aconiti Cocta* , Zhichuanwu or 制川乌) and root tuber of *Aconitum Kusnezoffii* (also known as *Radix Aconiti* Kusnezoffii Cocta, Zhicaowu 制草乌), and lateral root tuber of *A. carmichaeli* (also known as Fuzi or 附子) are often used. However, raw aconite roots are highly toxic cardiotoxins and neurotoxins. In fact, they have been used in the past as arrow poisons. The estimated lethal dose of pure aconitine has been reported to be as low as 2mg and 1g of the wild plant.[1]

Hence, aconite roots are only used after processing (by prolonged soaking or boiling) which leads to the hydrolysis of aconitine alkaloids and reduction of alkaloid content of up to 90%.[2]

Aconitum toxicity usually results either from the accidental ingestion of wild plants, inadequate processing (commonly due to a shorter than required duration of boiling) or erroneous prescription.[3,4] Inappropriate usage of *Aconitum* plants appears to be a common feature among previously reported cases of *Aconitum* toxicity. A locally published case report describes an accidental over-dosage of aconite caused by the incorrect transcription of an internet herbal recipe.[5] In the case above, it may be possible that the patient had not boiled the herbal decoction for a sufficient amount of time.

Mechanism and features of *Aconitum* toxicity

Aconitine binds with high affinity to the open state of voltage-sensitive sodium channels in the excitable membranes (myocardium, nerve, muscle), resulting in persistent activation, continuing sodium influx and sustained depolarisation.[6] Patients with aconite poisoning classically present with a combination of neurological, cardiovascular and gastrointestinal features. Short latency (as short as 10 minutes) between the ingestion of aconite and onset of symptoms has been described in literature.[3,7] Likewise our patient developed symptoms of paraesthesia, chest discomfort, nausea and vomiting within 30 minutes of consumption of the herbal decoction.

Some of the cardiovascular features include hypotension, heart palpitations, chest pain, bradycardia, sinus tachycardia and ventricular arrhythmias. Aconitine can induce ventricular arrhythmia including ventricular ectopics, ventricular tachycardia, *torsades de pointes and* ventricular fibrillation. This is caused by myocardium automaticity triggered by the delayed afterdepolarisation and early afterdepolarisation.[1]

Neurotoxicity of aconitine is precipitated by its action on voltage-sensitive sodium channels in axons which block the release of acetylcholine. Neurological features include sensory (paraesthesia and numbness of the face, perioral area and the four limbs), motor (muscle weakness) or both.[1]

There is no specific antidote to aconite poisoning and supportive care is the mainstay of treatment. Mortality from aconite toxicity has been described to be 5.6%.[8] Ventricular arrhythmias secondary to aconite toxicity are often refractory to cardioversion and anti-arrhythmic drugs. Anti-arrhythmics of choice described in previous case reports for the treatment of aconite induced ventricular arrhythmias include flecainide and amiodarone.[1,9]

Conclusion

Adverse events may occur with herbal-based traditional remedies, such as the *Radix Aconiti Lateralis Praeparata* or other aconite-containing herbs. Healthcare professionals are encouraged to ask patients if they are taking any traditional herbal remedy, be vigilant for suspected adverse events associated with its use and report the suspected adverse events to the Vigilance and Compliance Branch of HSA. Your support towards the national adverse event monitoring programme is invaluable in safeguarding public health.

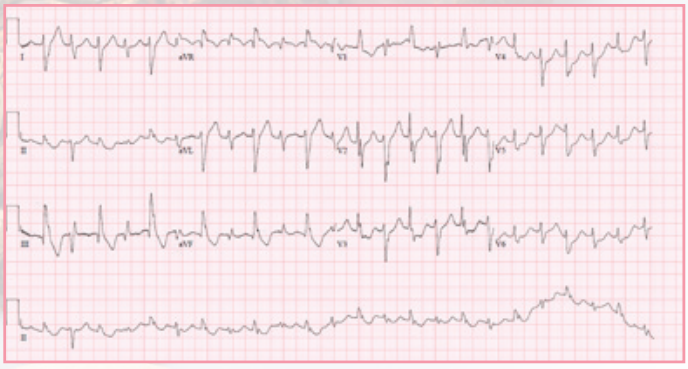

Figure 1. Electrocardiogram (ECG) performed upon patient's presentation showing multiple monomorphic premature ventricular complexes.

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ANAPHYLAXIS POST-COVID 19 mRNA VACCINES

Key Points

- Two mRNA vaccines, Pfizer-BioNTech and Moderna vaccines, are currently authorised locally for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals
- As of 31 July 2021, HSA has received 58 adverse event (AE) reports from healthcare professionals on anaphylaxis which were adjudicated by its expert panel based on the Brighton Collaboration Case Definition criteria
- Anaphylaxis is a known but rare AE associated with vaccines in general. They should be distinguished from other events such as clinical manifestations that occur coincidental to vaccination (e.g. anxiety) and vasovagal responses
- The overall local incidence of anaphylaxis with the mRNA vaccines is estimated to be similar to the incidence rate reported overseas. Measures to mitigate the risk of anaphylaxis are in place
- Healthcare professionals are encouraged to report suspected serious AEs associated with COVID-19 vaccines to HSA for better computation of AE frequencies

The Pfizer-BioNTech (Pfizer) and Moderna vaccines were authorised by the Health Sciences Authority (HSA) under the Pandemic Special Access Route (PSAR)[1] on 14 December 2020 and 3 February 2021 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals. With the use of the two mRNA vaccines internationally, rare reports of anaphylaxis, a severe life-threatening allergic reaction, started to be reported. Locally, HSA has received 58 adverse event (AE) reports from healthcare professionals on anaphylaxis which were adjudicated by its expert panel on hypersensitivity reactions based on the Brighton Collaboration Case Definition criteria.[2] We would like to provide a brief update on these cases and the measures that have been put in place by HSA to mitigate the risk of anaphylaxis in individuals given the mRNA vaccines.

Anaphylaxis and its association with vaccines

Anaphylaxis is a rare and potentially life threatening generalised or systemic allergic or hypersensitivity reaction that can occur post-vaccination in certain susceptible individuals. It is a known AE associated with vaccines in general and reported to occur rarely in about 1 in 100,000 – 1 in 1 million doses administered. These severe allergic reactions should be distinguished from other events such as clinical manifestations that occur coincidental to vaccination (e.g. anxiety) and vasovagal responses.[3]

The interim authorisation of the mRNA vaccines under PSAR by HSA is based on ongoing clinical data provided by the company to support the continued positive benefit-risk balance of the vaccine for use in the COVID-19 pandemic. While there were no imbalances of serious AEs detected in clinical trials between the vaccine and placebo arms of the mRNA vaccines, certain serious AEs, such as those of rare occurrence, may emerge when the vaccines are used in real world setting.

Adverse event reports of anaphylaxis with mRNA vaccines

The Pfizer vaccine has been in use since 30 December 2020 when Singapore started its national COVID-19 vaccination programme and the Moderna vaccine has been deployed for use on 12 March 2021. HSA has also granted approval for the use of the Pfizer vaccine in the 12 to 15 years age group on 18 May 2021, which was rolled out to students aged 12 years and above on 3 June 2021.

HSA has been closely monitoring the incidence of anaphylaxis associated with the mRNA vaccines. As the diagnosis of anaphylaxis can be subjective, HSA has convened an Expert Panel on Hypersensitivity reactions to adjudicate the reports. The Brighton Collaboration Case Definition criteria for anaphylaxis was applied in the adjudication of the cases as per international practice.[2]

As of 31 July 2021, 58 local AE reports were adjudicated to be anaphylaxis. The overall incidence of anaphylaxis with the mRNA vaccines is estimated to be 0.86 per 100,000 administered doses, which is similar to the incidence rate reported overseas. Forty-seven (81%) of these cases were reported with Pfizer vaccine and 11 with Moderna vaccine. Twenty-nine cases were assigned level 1 Brighton level of diagnostic certainty*, 28 as level 2 and the remaining one as level 3. Forty (69%) cases occurred with dose 1 and 18 cases occurred with dose 2 vaccination. Forty-eight of these 58 (83%) cases involved females. The median age of the 58 patients was 42 years (range: 16 to 76 years). Forty-one (71%) patients had a known history of atopy, allergies, or allergic reactions to drugs and/or foods. For most cases (66%), the interval from vaccination to onset of symptoms were within 30 minutes. Majority of the patients were treated with epinephrine as part of the management. Twenty-seven patients were hospitalised for observation and 30 were treated in the emergency department. All of the 58 patients have since recovered. Overview of the cases are presented in Table 1.

Table 1. Overview of the local cases of anaphylaxis post-vaccination with the mRNA vaccines from 30 December 2020 to 31 July 2021

Characteristics	No. (%) of cases
	Pfizer-BioNTech and Moderna (n=58)
Female	48 (83%)
Age in years, median (range)	42 (16-76)
History of atopy or allergies	41 (71%)
Symptom onset, min ≤20min, ≤30min, >30min	22 (38%) 38 (66%) 20 (34%)
Vaccine dose - First dose - Second dose	40 (69%) 18 (31%)
Anaphylaxis incidence rate (cases per 100,000 doses administered)	0.86

MOH and HSA's actions and advisory

Several measures have been introduced to mitigate the risks of anaphylaxis with mRNA vaccines. They include:

- Pre-vaccination screening prior to vaccination. Individuals with a history of allergic reaction or anaphylaxis to mRNA COVID-19 vaccine or any of its components are not recommended to receive the vaccines.
- Observing individuals closely for 30 minutes after vaccination and giving post-vaccination advice to watch out for signs and symptoms of severe allergic reaction, and to seek immediate medical attention should they experience them.
- Ensuring that all vaccination centres are medically equipped and staffed by qualified medical professionals at all times to provide medical treatment in the rare event that they are needed.

Healthcare professionals are required to report all suspected serious AEs associated with COVID-19 vaccines to HSA. The reports will allow better computation of the frequency of AEs in Singapore and potentially in subgroups of individuals, for the monitoring of the safety of these vaccines to ensure that their benefits continue to outweigh their risks.

Healthcare professionals are encouraged to refer to the anaphylaxis guide at *https://www.hsa.gov.sg/adverse-events/healthcare-professionals'-guide-to-adverse-events-reporting* for reporting of anaphylaxis.

**There are 3 levels of diagnostic certainty: Brighton level 1 represents the highest level of diagnostic certainty that a reported case is indeed a case of anaphylaxis; levels 2 and 3 represent successively lower levels of diagnostic certainty.[4]*

References

1. *https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/psar-emergency-therapeutic-product*
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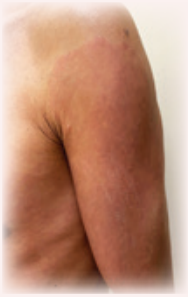
3. *World Allergy Organ J. 2016; 9(1):32*
4. *The Brighton Collaboration: Creating a Global Standard for Case Definitions (and Guidelines) for Adverse Events Following Immunization. In: Henriksen K, et al. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Rockville (MD): Agency for Healthcare Research and Quality (US); 2005. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20507/*

AE CASE IN FOCUS 2: TEST YOURSELF

A patient in his 50s received his first dose of Moderna COVID-19 vaccine in mid-April 2021 in his left deltoid. One week later, he developed an erythematous plaque over his left arm which was associated with tenderness (Figure 1). There was no associated fever or other systemic symptoms. He was seen by a primary care physician and treated with co-amoxiclav. His medical history was significant for asthma and temporal giant cell arteritis and he had known drug allergies to diclofenac, montelukast and sulphonamides which all resulted in urticarial reactions.



Question: What could have caused the rash in this patient?

HSA would like to thank Dr April Toh and Clinical A/Prof Lee Haur Yueh, Head and Senior Consultant, Department of Dermatology, Singapore General Hospital, for contributing this article.

Figure 1. Erythematous well demarcated plaque over left arm

ANSWER TO AE CASE IN FOCUS 2: TEST YOURSELF

Delayed localised hypersensitivity reaction to Moderna COVID-19 vaccine

This patient was reviewed at the outpatient allergy clinic and was diagnosed with delayed localised hypersensitivity reaction to the Moderna vaccine. He was treated with potent topical corticosteroids and the rash resolved within three days. He was advised to proceed with the 2nd dose of vaccination which was completed without any recurrence.

Clinical presentation and management

Delayed localised hypersensitivity reaction to the Moderna COVID-19 vaccine (also known as "COVID-arm") was initially reported in 0.8% of patients in the phase 3 trial of Moderna vaccine against the SARs-Cov-2.[1] However, it is believed to be more common in clinical practice.[2]

These delayed injection site reactions typically occur seven to eight days following the initial vaccination with the Moderna COVID-19 vaccine and has been reported to recur in 50% of the cases after the 2nd dose.[2,3] These recurrent reactions typically occurred earlier than after the 1st dose, at a median of two days after the 2nd dose and the lesions were not more severe and remained self-limiting.

Clinically, they present as pruritic, with variably tender erythematous plaques near the injection site. Although, these plaques may be larger than 10 cm in diameter, they typically resolve after four to five days.[2,3] In a minority of cases (15%), additional sites of involvement such as the elbows, hands and thighs may be concurrently involved (Figure 2).[3] Histopathologic findings include perivascular and interstitial inflammatory infiltrate with lymphocytes and eosinophils with minimal epidermal change. These features are characteristic of dermal hypersensitivity reactions and may be seen in response to medications.[4] As medication-associated delayed hypersensitivity reactions are T-cell mediated, it has been hypothesized that the delayed localised injection site reactions to the Moderna COVID-19 vaccine may be associated with T-cell responses to a vaccine excipient, lipid nanoparticle, or the mRNA component.[2] To date, most of these reactions have been seen with the Moderna COVID-19 vaccine, and is less commonly documented with the Pfizer BioNTech COVID-19 vaccines.[2,5]

With the rolling out of massive vaccination programmes worldwide, healthcare providers need to recognise such emerging adverse reactions. In particular, these lesions need to be differentiated from immediate hypersensitivity reactions such as urticaria, angioedema as well as cellulitis. This would prevent unnecessary allergy labelling or the use of antibiotics. The overall prognosis of such reactions is good, and patients can safely receive subsequent doses of the mRNA vaccines.[2,3,5]

Local reports received by HSA

As of 1 July 2021, HSA has received 125 adverse event reports of delayed injection site reactions following the administration of the two mRNA vaccines, i.e., the Moderna and Pfizer-BioNTech COVID-19 vaccines. Most (87%) of the cases were reported with the Moderna COVID-19 vaccine and were reported mostly in females (85%), in line with what was observed in published literature.[2,5] The median age of the patients was 48 years (range, 21-87 years). Based on the available information, the median time to onset of the injection site reactions was seven days (101 cases, range 0-14 days) and all (100%, 75 cases) occurred following the 1st dose of the vaccine.

The local cases presented with symptoms including erythema, swelling, induration, pain and warmth at the injection site. These tend to be non-serious and were self-resolving. It was reported in 30 of the cases, that the individuals were given medicines such as oral or topical forms of antihistamines, steroids and antibiotics. There were three serious cases reported. These involved hospitalisations and comprised two cases of cellulitis and a case of secondary spread of the delayed reaction to the other parts of the body.

As highlighted in this article, delayed hypersensitivity reactions to mRNA vaccines are commonly associated with the Moderna vaccines and are usually non-serious and short-lived. Notwithstanding this finding with the Moderna COVID-19 vaccine, there were also delayed hypersensitivity reactions reported with Pfizer-BioNTech COVID-19 vaccine. Having these localised reactions do not preclude one from having a repeat vaccination. In unusual cases, other regions of the body are involved. Healthcare professionals are advised to be vigilant of the presentation of these reactions in their clinical practice and to advise their patients accordingly.

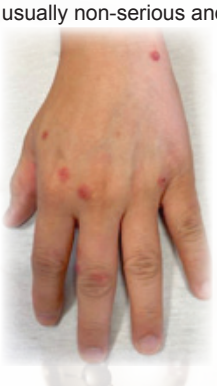


Figure 2. Discrete erythematous papules on the dorsum of the hand in another patient with a delayed hypersensitivity reaction on the arm

References

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3. *N Engl J Med 2021; 384(13):1273-1277*
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5. *J Allergy Clin Immunol Pract 2021; 9(6):2480-2481*

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