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HSA Health Sciences Authority

ADVERSE DRUG REACTION NEWS

## Contents



# VALPROATE-CONTAINING MEDICINES AND RISK OF TERATOGENICITY – AN UPDATE

### Key Points

- HSA would like to remind healthcare professionals of the teratogenic potential of valproate-containing medicines
- Valproate is a known teratogen that has been associated with congenital malformations and developmental disorders in children born to women taking the medicine during pregnancy
- Healthcare professionals are advised to counsel women of childbearing potential on the importance of using effective and reliable contraception while taking valproate and discuss the benefits versus the risks of valproate exposure during pregnancy with their patients

Valproate (Epilim®, sanofi-aventis Singapore) is an anti-epileptic drug that is available in both oral and intravenous formulations. It has been registered locally since November 1990 for the treatment of various types of epilepsy (e.g., generalised, partial epilepsy) and the oral formulation of Epilim® is also approved for the treatment of mania when other therapies are inadequate or inappropriate. Valproate is also registered under two other generic brands, namely Sodium Valproate Wockhardt Solution for Injection or Infusion (United Italian Trading Corporation Pte Ltd) and Valparin XR tablet (Zyfas Medical).

## Valproate-associated teratogenicity

Valproate is a known teratogen that has been associated with congenital malformations and developmental disorders in children born to women taking the medicine during pregnancy. Clinical studies have suggested an increased incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy as compared to the general population,[1] and up to 30% to 40% of *in utero* exposed children experienced neurodevelopmental disorders such as delayed locomotor skills, lower intellectual capacities, poor language abilities and impaired memory.[2-4]

## International regulatory actions

In March 2017, the European Medicines Agency (EMA) conducted a safety review to evaluate the effectiveness of the existing risk mitigation measures that had been put in place in the European Union to address valproate-associated teratogenicity.[5] The review concluded that new measures should be put in place to manage the risk of teratogenicity with valproate-containing products, including a contraindication for the use of valproate-containing medicines in the treatment of bipolar disorder and migraine (migraine is not an approved indication in Singapore) in pregnancy. For the treatment of epilepsy, valproate should not be used in pregnant women unless in situations where it may not be possible to stop valproate. In such situations, pregnant women may continue valproate treatment under specialist care. All WOCP must be enrolled under a pregnancy prevention programme before they can be prescribed valproate.[6]

In June 2013, the US Food and Drug Administration (US FDA) issued a safety communication informing that valproate-containing products are contraindicated in pregnancy for the prevention of migraine. With regard to valproate use in pregnant women with epilepsy or bipolar disorder, it may be used in a WOCP or pregnancy only if alternative therapies are ineffective or unacceptable.[7]

## HSA's advisory

HSA has not received any local cases of adverse events associated with the exposure of valproate during pregnancy. Several risk mitigation measures have been put in place locally to manage the teratogenic risks of valproate so as to ensure the continued positive benefit-risk balance of valproate-containing medicines. These measures include the strengthening of the Singapore package inserts for Epilim® by including warnings and precautions regarding

the risk of teratogenicity and that valproate should not be used during pregnancy and in WOCP unless other treatment options are ineffective or intolerable.[8] Two Dear Healthcare Professional Letters have also been issued by the product registrant (sanofi-aventis Singapore) in February 2016 and March 2018 respectively,[9] to remind healthcare professionals of the teratogenic potential of valproate. Physician educational materials and a pocket-sized Patient Alert Card were also developed as educational tools to counsel patients about the potential risks to the unborn child as a result of *in utero* valproate exposure and the need to use effective contraception during treatment.

Healthcare professionals are advised to discuss the benefits versus the risks of valproate with their patients, including the importance for WOCP to use effective and reliable contraception while taking valproate. Healthcare professionals are encouraged to report any suspected congenital abnormalities associated with *in utero* exposure of valproate to the Vigilance and Compliance Branch of HSA.

**References**

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2. *Arch Dis Child. 2011; 96: 643–647*
3. *Epilepsia. 2010; 51: 2058–2065*
4. *Epilepsy Behav. 2008; 13: 229–236*
5. *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Procedure_started/WC500223242.pdf*
6. *http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/02/WC500243555.pdf*
7. *https://www.fda.gov/Drugs/DrugSafety/ucm350684.htm*
8. *Singapore Package Insert for Epilim® Chrono, enteric-coated tablet, syrup Last revised 20 April 2017*
9. *http://www.hsa.gov.sg/DHCPL*

## AE CASE IN FOCUS: TEST YOURSELF

A male patient in his 60s with underlying chronic kidney disease underwent an elective total hip replacement surgery under spinal anesthesia for avascular necrosis of the left hip. The surgery proceeded uneventfully with an estimated blood loss of 600ml. Blood transfusion was not required after the surgery. Eight hours after the surgery, he developed marked hypotension which was refractory to fluid resuscitation and inotropic support.

He was transferred to the surgical intensive care unit and required intubation and high doses of inotropes and vasopressors. Continuous renal replacement therapy was commenced immediately. Subsequent investigations conducted showed no signs of sepsis, myocardial ischaemia or pulmonary embolism in the patient. His bedside echocardiogram measurements revealed normal cardiac function. In addition, the patient had no known drug allergies.

**Question: What could have caused the severe hypotension in this patient?**

Answers can be found on page 6

*HSA would like to thank Dr. Diana Chan, Dr. Chee Huei Leng, Dr. Jacqueline Goh, and medical student, Zhang Ming Ming from Division of Anaesthesiology at Singapore General Hospital for contributing this article.*

## CONSUMER GUIDE ON ALLOPURINOL

HSA would like to inform healthcare professionals about an educational consumer guide on allopurinol published on HSA's website.[1]

Serious cutaneous adverse reactions (SCAR) have been reported with the use of allopurinol. These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Locally, HSA has received an average of 13 cases of allopurinol-induced SCAR over the last three years (2015-2017 inclusive).

As part of our ongoing communication on health product related risks, HSA has issued several drug safety communications on the risks of developing allopurinol-induced SCAR. These include a Dear Healthcare Professional Letter (issued in 2001), and an ADR Bulletin article (issued in 2009 and 2016). The harm caused by SCAR may be reduced if the ADR is detected early. This latest communication piece targets consumer and alerts them to watch out for the early signs and symptoms of SCAR and to seek medical advice if unwell after use.

Healthcare professionals are encouraged to share this consumer guide with their patients and remain vigilant to these potentially life-threatening adverse reactions.

***Acknowledgements***

*We would like to thank Adjunct Associate Professor Bernard Thong (Divisional Chairman, Medicine, Senior Consultant, Tan Tock Seng Hospital), Adjunct Associate Professor Leong Khai Pang (Senior Consultant, Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital), Dr Pang Shiu Ming (Senior Consultant, Department of Dermatology, Singapore General Hospital) and Dr Teng Gim Gee (Senior Consultant, Division of Rheumatology, National University Hospital) for their valuable inputs in the development of this consumer guide.*

**References**

1. *http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Consumer_Information/Consumer_Guides/Medicine/use-of-allopurinol.html*

# AMOXICILLIN; AMOXICILLIN/CLAVULANATE – REPORTS OF DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SYNDROME

## Key Points

- Overseas and local cases of DRESS syndrome have been reported with amoxicillin and amoxicillin/clavulanate
- DRESS syndrome is a rare and potentially fatal hypersensitivity reaction that is associated with signs and symptoms such as rash, fever, lymphadenopathy, abnormal haematological findings and abnormal liver function tests

HSA would like to draw the attention of healthcare professionals to overseas and local cases of DRESS syndrome associated with amoxicillin and amoxicillin/clavulanate. DRESS syndrome is a rare but potentially fatal hypersensitivity reaction with a delayed onset (usually starts within two to six weeks after exposure to the medicine). It is characterised by rash, fever, lymphadenopathy, abnormal haematological findings (e.g., eosinophilia, leukocytosis), abnormal liver function tests and systemic presentations involving visceral organs (e.g., hepatitis, pneumonitis, myocarditis, pericarditis, nephritis and colitis).

## Background

Amoxicillin (Amoxil™, Glaxosmithkline Pte Ltd) is a beta-lactam antibiotic that has been registered since June 1998. It is a broad-spectrum antibiotic, used for the treatment of commonly occurring bacterial infections such as respiratory tract, genito-urinary and skin and soft tissues infections. It is also available in combination with clavulanate (beta-lactamase inhibitor) under the brand name, Augmentin™ (Glaxosmithkline Pte Ltd). Both amoxicillin and amoxicillin/clavulanate are also available under various generic brands.

## European Medicines Agency's (EMA) review

In July 2017, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a safety review on the signal of DRESS syndrome associated with the use of amoxicillin and amoxicillin/clavulanate. The review took into consideration adverse drug reaction (ADR) reports in the EudraVigilance (European ADR database) and published literature, which concluded that there is a risk of DRESS syndrome associated with the use of amoxicillin and amoxicillin/clavulanate. The PRAC subsequently recommended that the package inserts (PIs) of amoxicillin-containing products be updated to include the risk of DRESS syndrome.[1]

## Local situation and HSA's advisory

As of June 2018, HSA has received six serious local reports of DRESS syndrome associated with the use of amoxicillin/clavulanate. These cases involved patients aged between 13 to 64 years old. Among the cases reported, two described visceral involvements, namely hepatitis and myositis. In four cases, there were concomitant drugs such as NSAIDs, antibiotics (e.g., ceftazidime, cotrimoxazole, doxycycline, piperacillin) and allopurinol, which could have possibly contributed to the DRESS syndrome. In the remaining two cases, the information was insufficient for further investigation.

The Singapore PIs of amoxicillin and amoxicillin/clavulanate are in the process of being updated to include the risk of DRESS syndrome.

Healthcare professionals are also encouraged to report suspected ADRs associated with amoxicillin or amoxicillin/clavulanate to the Vigilance and Compliance Branch of HSA.

**References**

1. *http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2017/07/WC500232408.pdf*

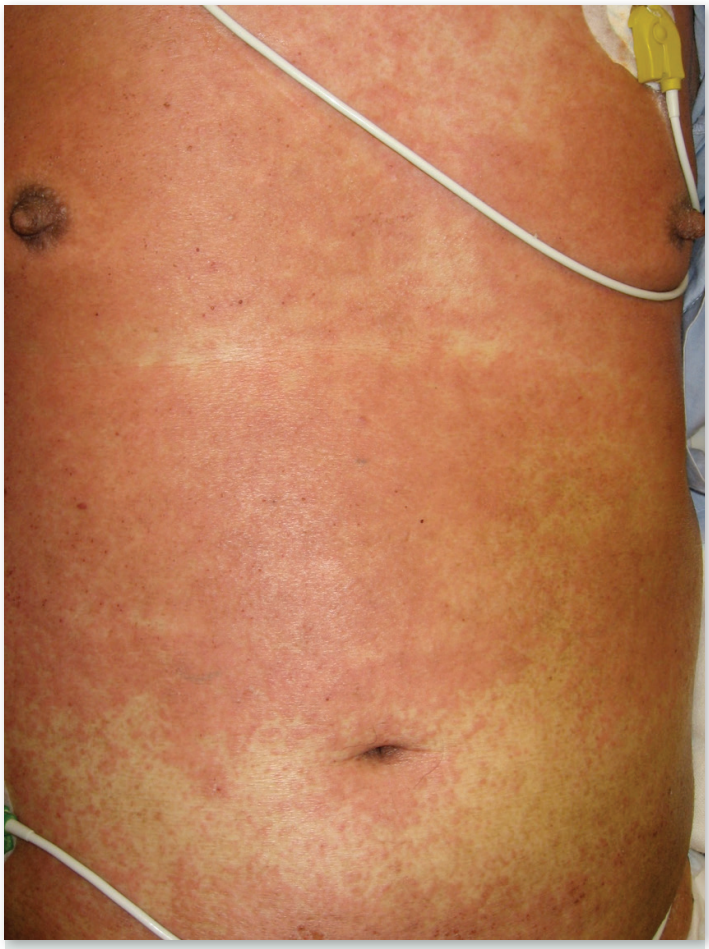

Figure 1. Confluent erythematous patches and plaques in a patient with DRESS

# AE IN FOCUS: VIEKIRA PAK™ AND DRUG-INDUCED INTERSTITIAL LUNG DISEASE (DILD)

Oral direct-acting antivirals (DAA) are first line hepatitis C virus (HCV) therapy which have replaced traditional interferon-based therapies due to its better tolerability profile and higher efficacy in achieving sustained virologic response (SVR). Ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira Pak™, Abbvie Pte Ltd) is a combination of potent DAA and was approved locally in November 2015 for the treatment of adults with genotype 1 chronic hepatitis C infection, including those with compensated cirrhosis. The addition of ribavirin is indicated in non-cirrhotic and cirrhotic patients with genotype 1a infection.

Interstitial lung disease is the most common form of drug-induced lung toxicity. The mechanism of DILD can be broadly classified into two: (1) direct cytotoxic injury by the drug or its metabolites, or (2) indirect immune-mediated response to the drug. Chemotherapeutic agents such as bleomycin, methotrexate and cyclophosphamide are often implicated for DILD. Other usual suspects include amiodarone, nitrofurantoin, sulfasalazine and more recently, monoclonal antibodies.[1] Patients usually present with fever, followed by respiratory symptoms such as dry cough, wheeze and acute shortness of breath. Its onset can vary from days to years.[2] In recent years, there have been a few reports of DILD suspected to be associated with Viekira Pak™.

## Local reports

To date, HSA has received two local reports of DILD suspected to be associated with the use of Viekira Pak™. The first case was of a male patient in his 50s with compensated Child's A cirrhosis who was diagnosed with HCV genotype 1a infection.[3] He had no history of hepatitis B or HIV co-infection and was an ex-smoker of 20 pack-years. His FibroScan® demonstrated a liver stiffness measurement of 13.3 kPa, and his HCV RNA was 6.9 log IU/ml. Treatment with Viekira Pak™ and ribavirin was started. A week later, he was admitted to the intensive care unit (ICU) for sudden onset of dyspnoea, pleuritic chest pain and fever. His arterial blood gas on 15 L of supplemental oxygen showed severe type 1 respiratory failure (pH 7.44, PaO2 64 mmHg, pCO2 30 mmHg and SaO2 93%). He was intubated and given meropenem, azithromycin and oseltamivir empirically. His chest X-ray (Figure 1) showed bilateral air-space consolidations and pleural effusion. Autoimmune serology test results were all negative, except for antinuclear antibody (ANA) of 1:80. His microbiological work-up [i.e. blood, endotracheal aspirates and bronchoalveolar lavage (BAL) for bacterial, fungal, acid-fast bacilli (AFB) cultures and respiratory virus multiplex polymerase chain reaction (PCR)] were all negative. He continued to deteriorate despite treatment with antibiotics. His CT thorax showed confluent air-space opacities of bilateral upper lobes and right middle lobes (Figure 2).

He was diagnosed with DILD and his treatment with Viekira Pak™ was withheld. He was then treated with intravenous hydrocortisone for three days, extubated on day six of admission, and discharged on day 15 with a tapering dose of prednisolone. By day 69, he achieved complete radiological resolution of the chest radiograph (Figure 3). His hepatitis C treatment was switched to Harvoni® (ledipasvir/sofosbuvir) which he tolerated with no adverse events.

The second case involved a man in his 40s with compensated Child's A cirrhosis with HCV genotype 1a infection.[3] He developed a sore throat and a non-productive cough 20 days after initiation of Viekira Pak™ and ribavirin. His initial chest X-rays were unremarkable. At day 40, he was admitted for worsening dyspnoea, with vital signs as follows: temperature 37°C, BP 104/66 mm/Hg, HR 67/min, SpO2 92% on room air. He was started on antibiotics. Subsequently, his blood, sputum and urine samples were tested for bacterial, fungal and AFB and the results were all negative, except for a nasopharyngeal swab for respiratory virus PCR which was positive for rhinovirus. His CT thorax showed bilateral symmetrical ground-glass opacities. He continued to deteriorate with worsening hypoxia, and was intubated and transferred to ICU. His BAL sample was tested for respiratory virus isolate, bacterial culture, *galactomannan*, and *pneumocystis jiroveci* PCR and the results were all negative. His autoimmune screen result was negative, except for ANA 1:160 (speckled pattern). On day 52, his treatment with Viekira Pak™ was stopped, and intravenous hydrocortisone 500 mg was given once daily for three days. His condition improved and he was extubated on day 55. On day 67, he was taken off his oxygen supply, and on day 88, he was discharged after pulmonary rehabilitation. His follow-up review on day 209 showed near complete resolution of dyspnoea and opacities on the chest X-ray.

## Case reports from literature

Two other suspected cases of DILD have been reported in HCV patients in literature. The first case is a 68-year-old Chinese female with Child's A cirrhosis and HCV genotype 1b infection.[2] One week after starting Viekira Pak™, she was admitted to the ICU for respiratory distress and acute kidney injury. Treatment with Viekira Pak™ was withheld on admission into hospital. She was initially diagnosed with community-acquired pneumonia as she improved quickly while on intravenous antibiotics and supported care. No bacterial or viral pathogens were cultured. After her recovery, Viekira Pak™ was restarted, but she was readmitted five days later with more rapidly progressive respiratory failure, requiring intubation and ventilation, inotropic support and haemodialysis. Given the similar presentations on re-challenge with Viekira Pak™, she was diagnosed with DILD and treated with intravenous methylprednisolone for four days with prompt clinical improvement.

In the second case, a 77-year-old Japanese female with HCV genotype 1b infection was initiated on ombitasvir/paritaprevir/ritonavir*.[4] She developed a dry cough four weeks later, but did not require hospital admission. Her chest X-ray and CT chest showed typical features of interstitial pneumonia in the lower lungs, and serum KL-6 levels were elevated. Upon discontinuation of ombitasvir/paritaprevir/ritonavir, the dry cough disappeared gradually and fully resolved without the need for steroid therapy.

## HSA's advisory

As DILD is often a diagnosis of exclusion, recognition of DILD can be especially challenging given its non-specific clinical, radiological and histological findings.[1] This was illustrated in the cases above, where Viekira Pak™ was reintroduced in one of the cases. Although all four patients recovered, three of them required ICU admission, supportive care and steroid treatment in addition to cessation of the drug. Interestingly, all four cases occurred in Asian patients.

Given that possible DILD closely resembles pneumonia in HCV patients, healthcare professionals are advised to be vigilant in managing these patients, as early recognition of DILD can be potentially life-saving. Healthcare professionals are encouraged to report suspected adverse events associated with Viekira Pak™ to the Vigilance and Compliance Branch of HSA.

*In this second case, the suspected drug differed slightly from Viekira Pak™ as it did not contain dasabuvir.

*The contents of this article was adopted with permission from a poster presentation[3] at The International Liver Congress 2018 and edited for the purpose of the bulletin. HSA would like to take this opportunity to thank Dr Eugene Wong Yu Jun, Associate Consultant, Department of Gastroenterology and Hepatology, Changi General Hospital, for his contribution to this article.*

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1. *Respir Res 2012; 13:39*
2. *Case Rep Med 2017*
3. *J Hepatol 2018; 68S1: S275*
4. *Case Rep Gastroenterol 2017: 11:369-376*

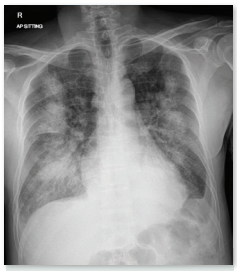

Figure 1. Bilateral air-space consolidations and bilateral pleural effusion seen

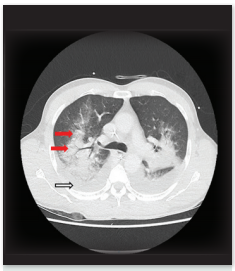

Figure 2. CT of the thorax showed confluent air-space opacities of bilateral upper lobes and right middle lobes with bilateral pleural effusion

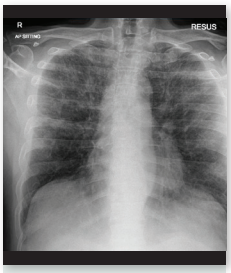

Figure 3. Repeat chest X-ray with complete resolution on day 69

# IODINATED CONTRAST MEDIA AND RISK OF HYPOTHYROIDISM (PARTICULARLY IN INFANTS)

## Key Points

- Rare cases of hypothyroidism following iodinated contrast media (ICM) exposure have been reported overseas, particularly in full term and preterm infants
- Hypothyroidism in infants may have a detrimental effect on infant growth and mental development
- Healthcare professionals are advised to evaluate and monitor thyroid function in infants exposed to ICM, and to continue to monitor any abnormal thyroid function until it has normalised

HSA would like to bring to the attention of healthcare professionals, rare overseas cases of hypothyroidism following ICM exposure, particularly in full term and preterm infants. If left untreated, this might result in severe delays in growth and development, including mental development. As such, thyroid function evaluation and monitoring for infants exposed to ICM is recommended, with initiation of treatment for abnormal thyroid function, if needed.

## Background

ICM products are generally used to enhance visualisation of vascular structures and organs during radiographic procedures such as angiography and computed tomography. As ICM products contain iodine, they may interfere with thyroid hormone production, which may in turn affect proper growth and development (including mental development) in infants and proper metabolic activity in children and adults.

Hypothyroidism following ICM administration might be attributed to the Wolff-Chaikoff effect, an autoregulatory mechanism whereby a large amount of ingested iodine acutely inhibits thyroid hormone synthesis within the follicular cells.[1] In most individuals, the decreased production of thyroid hormones is transient and resumes after adaptation to the Wolff-Chaikoff effect (known as an "escape" phenomenon). However, certain susceptible populations, such as infants (especially those born preterm), the elderly and those with pre-existing thyroid disease, might be at an increased risk of failure to escape from the Wolff-Chaikoff effect, leading to the development of iodine-induced thyroid dysfunction.

There are 21 ICM products registered locally since 1991, comprising nine active ingredients namely, iopamidol, iohexol, ioversol, iopromide, iomeprol, meglumine ioxitalamate, iodixanol, iobitridol, and ethyl esters of iodised fatty acids of poppy-seed oil.

## International regulatory actions

In April 2017, Health Canada (HC) issued a safety alert on the rare potential risk of hypothyroidism with the use of ICM in certain patients, particularly infants.[2] HC had identified 10 international reports of hypothyroidism causally associated with ICM, of which six involved infants less than one year of age. As hypothyroidism in infants might have a detrimental effect on their growth and mental development, HC recommended updating and harmonising the prescribing information for all ICM products to include this safety information.

The US Food and Drug Administration (US FDA) had also issued an alert earlier in November 2015 advising that rare cases of hypothyroidism had been reported in infants following the use of ICM.[3] A search of the US FDA's adverse events database identified 11 cases of hypothyroidism reported with ICM, of which 10 involved infants younger than four months of age. The infants were either premature (n=4) or were born full term with major cardiac abnormalities (n=6). All of them were diagnosed with underactive thyroid within a month of receiving ICM. US FDA's review of the available evidence had concluded that this was a rare occurrence which was usually temporary and would resolve without treatment or any lasting effects.

## Local situation and HSA's advisory

To date, HSA has not received any local adverse drug reaction reports of thyroid dysfunction associated with the use of ICM. The Singapore package inserts for ICM products will be updated on the warnings regarding ICM-induced thyroid function changes.

Healthcare professionals are advised to evaluate and monitor thyroid function in infants exposed to ICM.

**References**

1. *J Clin Endocrinol Metab 2015; 100: 376-383*
2. *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/63086a-eng.php*
3. *https://www.fda.gov/Drugs/DrugSafety/ucm472782.htm*

# ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

## Postoperative hypotension

Postoperative hypotension is a common and potentially serious complication after surgery. There are a variety of underlying causes, including hypovolemia, cardiac failure, or sepsis.[1] In such cases, the patient should be rapidly evaluated and a diligent search for potentially life-threatening causes of hypotension should be done.

Possible causes of hypotension in this patient include:

- Haemorrhage from surgical site
- Perioperative hypovolaemia
- Severe acidosis
- Overdose of opioid analgesia
- Fat embolism or bone cement implantation (usually evident intraoperatively)
- Acute myocardial infarction (usually occurs 48-72 hours postoperatively) and congestive cardiac failure
- Deep vein thrombosis resulting in pulmonary embolism
- Septic shock
- Drug allergy or anaphylaxis
- Adrenal insufficiency (primary or secondary) resulting in patient being unable to mount appropriate stress response perioperatively

In this case, the patient did not experience excessive blood loss during or after surgery and there were no clinical signs of a drug allergy. The investigations conducted also showed no evidence of sepsis, myocardial ischaemia or pulmonary embolism. The patient's bedside echocardiogram measurements showed normal cardiac function. Besides taking blood cultures and starting on broad spectrum antibiotics, the random cortisol level was checked and found to be 360 nmol/L, which was abnormally low. A provisional diagnosis of adrenal insufficiency was made and the patient was given intravenous hydrocortisone.

The patient's condition stabilised rapidly and inotropic support was weaned off over three days, after which he was extubated. His kidney function also recovered quickly and dialysis was no longer needed.

**Further history-taking from the patient's family revealed that he had been taking a variety of supplementary health products for his hip pain and gout, some of which were obtained overseas. The products were tested by HSA's Pharmaceutical Laboratory and one of the products was found to be adulterated with prednisolone, cyproheptadine and piroxicam.**

Synacthen tests were performed which confirmed the diagnosis of adrenal insufficiency due to the long-term steroid ingestion from the adulterated supplementary health product. One of the complications from adrenal insufficiency is hypotension.

The appropriate management of postoperative hypotension should consist of evidence-based clinical reasoning to administer the appropriate treatment to the patient. Other than reviewing the patient's history to identify any conditions that could predispose the patient to bleeding, history-taking of drug allergies and long term medications (including complementary health products) is essential.[1] It is also important to obtain information on recent perioperative events, including the administration of certain medications (e.g., penicillin in a true penicillin-allergic patient, or the stopping of certain drugs that could cause withdrawal effects (e.g., stress dose hydrocortisone in a steroid-dependent patient). This information is crucial to manage and reverse any potential complications experienced by the patient.

## Corticosteroid-related AEs and traditional medicines

Although some traditional Chinese medicinal (TCM) herbs or herbal products are believed to have inherent steroidal properties and have been implicated in causing adrenal insufficiency or Cushing's syndrome in patients with a history of TCM intake, a recent local study concluded that very few herbs used in TCM exhibit clinically relevant steroidal properties.[2] It has been reported that a significant cause of such corticosteroid-related adverse events is the use of adulterated traditional or complementary health products (CHPs) that contain exogenous corticosteroids (e.g., prednisolone, dexamethasone).

## Local reports

Each year, through reports submitted by healthcare professionals, HSA detects about 10 CHPs adulterated with corticosteroids. Of relevance, two reports (including our AE case in focus) of adrenal insufficiency/crisis and hypotension that occurred post-surgery were related to long-term consumption of CHPs which were adulterated with corticosteroids. The patients were in their 60s and 70s respectively and had been taking these products for pain relief. They were admitted to the hospital due to other underlying medical conditions which required surgery and subsequently experienced the AEs after the surgery.

## HSA's advisory

When seeking alternative therapies, chronic pain sufferers comprising mainly elderly patients, may unknowingly purchase or consume adulterated health products. These products are usually obtained from unfamiliar sources or through recommendations by well-meaning friends and are usually labeled as "100% safe" or has "no side effects".

Healthcare professionals are encouraged to ask their patients about the use of CHPs and traditional medicines prior to any surgery or medical intervention. Potentially life-threatening AEs such as adrenal insufficiency may arise from the use of steroid-adulterated CHPs. Knowing their patients' medication and dietary supplement history will help healthcare professionals look out and report AEs that may arise from the use of adulterated CHPs.

**References**

1. *Kim AW, Maxhimer JB. (2008) Hypotension in the Postoperative Patient. In: Myers JA, Millikan KW, Saclarides TJ. (eds) Common Surgical Diseases. Springer, New York, NY*
2. *Singapore Med J 2017; 58: 115-120*

# LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 MAY 2018 TO 31 AUG 2018)

For details of the DHCPL, please log on to MOHAlert via your professional board's website.

## Therapeutic products

| | |
|---|---|
| 30 May 2018 | **TIVICAY/ TRIUMEQ® (dolutegravir)**<br>Important safety update on neural tube defects reported in Tsepamo Study, Botswana |
| 4 Jun 2018 | **NESP® Injection Plastic Syringe (darbepoetin alfa)**<br>Update of package insert to include risk of severe cutaneous adverse reactions |
| 7 Jun 2018 | **Astrodal® capsule 20mg (temozolomide)**<br>Voluntary recall due to an out-of-specification event involving a minor packaging defect |
| 11 Jun 2018 | **Esmya® (ulipristal acetate)**<br>Important safety update on the risk of liver injury and interim measures to be taken when prescribing Esmya |
| 13 Jun 2018 | **Stilnox® (zolpidem)**<br>Important advisory on measures taken to further mitigate the risk of dependence and abuse |
| 29 Jun 2018 | **Astrodal® capsule 20mg (temozolomide)**<br>Follow–up letter regarding temporary change in storage condition of the interim supply |

## 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.

## Medical devices

| | |
|---|---|
| *19 Apr 2018 | **SIGMA® HP PFJ Cemented Trochlear Implants**<br>Voluntary recall for all lots due to elevated revision rates of implants |
| *26 Apr 2018 | **HeartWare® Ventricular Assist Device System**<br>Introduction of an updated HeartWare® Ventricular Assist Device (HVAD) Controller (Controller 2.0) and the removal procedures for previous generation HVAD Controllers which are incompatible with Controller 2.0 |
| 2 May 2018 | **Thoratec® Heartmate III™ LVAS Implant Kit**<br>Important advisory on managing outflow graft twist occlusions in patients |
| 8 May 2018 | **Covidien EEA™ Hemorrhoid and Prolapse Stapler Set with DST Series™ Technology**<br>Voluntary recall of selected lots due to the potential for improper welding of the yellow staple guide to the instrument |
| 9 May 2018 | **Covidien Endo GIA™ Articulating Loading Unit**<br>Voluntary recall of specific lots due to the potential for missing sled component |
| 8 Jun 2018 | **LFIT™ Anatomic CoCr V40™ Femoral Heads**<br>Complaints of femoral head/hip stem dissociation for specific sizes and lots manufactured prior to 4 March 2011 |
| 20 Jun 2018 | **Covidien Endo GIA™ Articulating Loading Unit**<br>Updates on the recall of specific lots with potential for missing sled component. Additional codes and lots were included in the recall |
| 26 Jun 2018 | **ACCOLADE Family of Pacemakers and Cardiac Resynchronization Pacemakers**<br>Potential for early pacemaker replacement due to hydrogen-induced premature battery depletion |
| 26 Jun 2018 | **Thoratec® HeartMate III™ LVAS Implant Kit**<br>Update to previous letter issued on outflow graft twist occlusions. Additional information and recommendations for patient management were included. |
| 27 Jun 2018 | **Fortify™, Fortify Assura™, Quadra Assura™, Quadra Assura MP™, Unify™, Unify Assura™, Unify Quadra™, Promote Quadra™ and Ellipse™ devices**<br>Battery performance alert and cybersecurity firmware updates |
| 28 Jun 2018 | **Medtronic HeartWare™ Ventricular Assist Device™ System**<br>Safety alert regarding the potential for transient power supply interruption |
| 12 Jul 2018 | **EnTrust implantable cardioverter defibrillators**<br>Potential for loss of high voltage and anti-tachycardia pacing therapy upon reaching the elective replacement indicator voltage point |
| 31 Jul 2018 | **Perceval Sutureless Aortic Heart Valve**<br>Important advisory regarding increase cases of valve insufficiency, primarily caused by oversizing leading to "stent folding" |

*DHCPLs not published in May 2018 issue

# LAUNCH OF "ADVERSE EVENT REPORTING MADE EASY FOR HEALTHCARE PROFESSIONALS" EDUCATIONAL VIDEO TO FACILITATE ADVERSE EVENT REPORTING

HSA is pleased to launch our inaugural educational videos (e-video) on adverse event (AE) reporting for healthcare professionals titled **'Adverse event reporting made easy for healthcare professionals'**. Healthcare professionals may now access these videos and the HSA website (Figure 1) and on YouTube (Figure 2). These e-videos bring the busy healthcare professional through the steps in AE reporting and causality assessment in an engaging and easy-to-understand way.

## Addressing the needs of busy healthcare professionals

The learning needs of healthcare professionals were identified through surveys conducted during roadshows with local primary healthcare institutions. The survey results revealed some of the challenges and learning gaps faced by healthcare professionals, namely how to assess causality of the AE and knowing the essential information required in providing a complete AE report. The survey respondents also gave feedback that it is important for healthcare professionals to know how their reports help HSA in detecting significant safety signals arising from the use of health products.

Two versions of the video were created – a shorter one for general viewing and a longer version customised for healthcare professionals working in the public healthcare sector. The customised version incorporates a step-by-step instruction on reporting AEs through the Critical Medical Information System (CMIS), the AE/drug allergy reporting module of the Singapore's National Electronic Health Record (NEHR).

Since the launch in March 2018, HSA has received positive feedback on the e-videos and our healthcare professionals have encouraged the continued use of e-videos as a form of educational tool.

## How to access the e-videos?

The e-video for general viewing is accessible via the **'Report Adverse Events related to Health Products'** webpage on our HSA website at *http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Report_Adverse_Events_related_to_health_products.html*

Both e-videos are also published on 'YouTube'. The 'general viewing' version video is accessible via this URL: **https://youtu.be/4ll-UVEe3QU** and the 'customised viewing' version video is accessible via this URL: **https://www.youtube.com/watch?v=l6izFk0SSuc**

Please provide your feedback on our videos by emailing us at HSA_productsafety@hsa.gov.sg, so that we can continue to create useful and relevant e-videos for healthcare professionals.

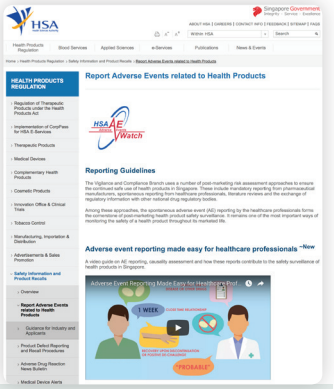


Figure 1. E-video on the 'Report Adverse Events related to Health Products' webpage on HSA's website

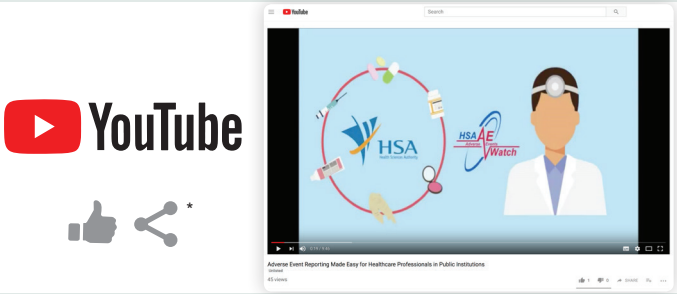


Figure 2: E-video on YouTube

*If you like the video, please give it a 'Thumbs Up' on YouTube and share with your fellow healthcare professionals.

## Useful tips

**Topics covered in the e-video:**

- How to report AEs
- Reporting essential information
- Assessing causality
- Reporting seriousness
- HSA's role in reviewing AE reports

**Useful key words to 'Search' the e-videos on YouTube**

- 'adverse'
- 'adverse event'
- 'reporting'
- 'healthcare professional'
- 'health'



**Please send your enquiries, comments and suggestions to:**

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
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Helios, Singapore 138667

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