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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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Fimasartan and local reports of liver injury

- Fimasartan, an angiotensin II receptor blocker (ARB), has been associated with four local cases of serious liver injury, two of which involved patients who had taken other ARBs in the past without any issues.

Advisory

Healthcare professionals are advised to take into consideration the local reports of liver injury when prescribing fimasartan and report any suspected cases to HSA.

Safety update on gentian violet antiseptic

- Current evidence on the carcinogenicity of gentian violet (GV) has mainly been observed with high-dose oral exposure to GV in animal studies (rats and mice).

Advisory

Healthcare professionals are reminded that GV-containing antiseptic is limited to short-term external use only.

Risk of adverse outcomes with light-exposed parenteral nutrition products when used in neonates and children below two years old

- Exposure of parenteral nutrition (PN) products containing amino acids and/or lipids to light, especially in admixtures with vitamins and/or trace elements, may cause the formation of peroxides and photodegradation products.
- Premature neonates are particularly susceptible to oxidative stress arising from PN photodegradation products, which can increase the risk of neonatal complications such as respiratory distress syndrome and bronchopulmonary dysplasia.

Advisory

Healthcare professionals are advised to consider the importance of light protection measures when PN products containing amino acids and/or lipids are used in neonates and children below two years of age, to minimise the risk of adverse outcomes in this vulnerable population.

Analysis of Adverse Events

Analysis of adverse event reports for year 2019

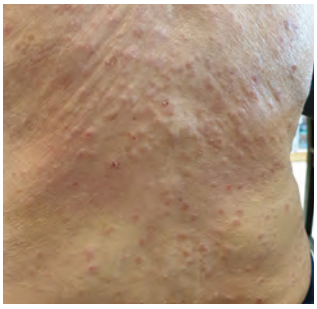
- In 2019, HSA received 37,563 adverse event (AE) reports. NSAIDs and antibiotics were the two highest reported pharmacotherapeutic groups of chemical drugs suspected to cause AEs.
- Two hundred and six of the 366 vaccine AE reports involved children. In children aged 12 years and below, the most commonly reported AE were febrile and afebrile seizures with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1, pneumococcal conjugate or hepatitis B vaccines. In adults, the most commonly reported AEs were allergic reactions and injection site reactions with pneumococcal, tetanus, MMR or seasonal influenza vaccines.
- There were 171 AE reports involving complementary health products and cosmetics. Ninety-nine (57.9%) reports involved hypersensitivity reactions associated with glucosamine-containing products.

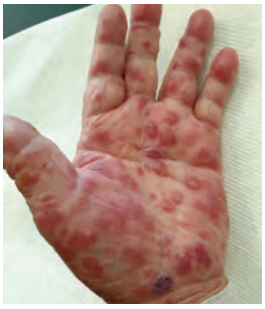
Published by the Health Products Regulation Group, HSA and the HSA Product Vigilance Advisory Committee

AE Case in Focus: Test Yourself

What could have caused the development of bullous pemphigoid-like lesions on the patient's palms and soles and macular pruritic lesions on his body trunk? Pg 6,7,8

This is a case study of an 86-year-old Chinese male patient who presented with maculopapular rash that developed into bullous pemphigoid-like lesions over his palms and soles of his feet and macular pruritic lesions on the body trunk. He has a medical history of cerebrovascular disease with expressive dysphasia, Type 2 diabetes mellitus, chronic obstructive pulmonary disease, osteoarthritis of the knees and hips, dementia, acute kidney injury and recently experienced heart failure. He was prescribed an anticoagulant, rivoraxaban while on many other medications.





Regulatory Update

MOH's National Drug Allergy Reporting Guidelines to reduce medication errors

- The reporting of Adverse Drug Reactions (ADRs) and Drug Allergies (a subset of ADRs) are important for patient care and management. In addition, such reports when reported and captured in the patient medical records, also feed into the national ADR reporting system administered by the Health Sciences Authority (HSA) to enable post-market monitoring of drug safety.
- In general, for post-market monitoring of drugs, HSA requires a minimum data set of an identifiable patient (such as patient's initial, name, gender and/or age), the reporter's details, an adverse event and a suspected product for a valid report. This is because HSA is looking out for safety signals in the first instance. Upon detection of a potential risk, we may require further information for validation of causality. On the other hand, detailed assessment and accurate reporting is required for documenting drug allergies due to implications to patient management and avoidance of medication errors.
- The Ministry of Health (MOH) has published the National Drug Allergy Reporting Guidelines in 2018. The guidelines provide recommendations for a systematic approach to the diagnosis and labelling of drug hypersensitivity reactions and drug allergies, to facilitate patient care and reduce preventable medication errors.
- Healthcare professionals are encouraged to refer to these guidelines for better reporting and documentation of allergies in the patient's medical records and to ensure that critical medical information is captured for patient care.

We want your feedback!

Dear Healthcare Professional,

HSA is conducting a short survey to understand how you access new drug safety information on a regular basis. Your feedback is important for HSA's evaluation of the effectiveness of our current drug safety communication channels. The survey will take about 2 minutes to complete and we hope to receive your reply by 30 June 2020

Please access this link (https://go.gov.sg/hsacomms), or scan this QR code for the survey.

Thank you

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

FIMASARTAN AND LOCAL REPORTS OF LIVER INJURY

Key Points

- Fimasartan, an angiotensin II receptor blocker (ARB), has been associated with four local cases of serious liver injury, two of which involved patients who had taken other ARBs in the past without any issues.
- Healthcare professionals are advised to take into consideration the local reports of liver injury when prescribing fimasartan and report any suspected cases to HSA.

HSA would like to inform healthcare professionals about local cases of serious liver injury reported in patients who were treated with Fimasartan. Fimasartan (Kanarb®, Boryung Pharmaceutical Co., Ltd) is an angiotensin II receptor blocker (ARB) that has been approved in May 2017 by HSA for the treatment of mild to moderate essential hypertension in Singapore.

Local cases

In 2019, HSA received four adverse event (AE) reports of liver injury suspected with the use of fimasartan, which were assessed to be serious by the reporting doctors. Three of the patients were hospitalised. The age of the patients ranged from 57 to 85 years old. Three were female and one was male. Other than hypertension, three patients had other underlying medical conditions including diabetes and hyperlipidaemia, and were taking other long term concomitant medicines. Two patients were reported to have taken other ARB in the past without any liver issues. Please refer to Table 1 for details.

All the patients were reviewed by gastroenterologists who assessed that the liver injuries could possibly be drug-induced, after ruling out other possible causes. The liver injuries reported were of varying severity, including two patients with elevated alanine aminotransferase (ALT) exceeding more than 1,000U/L and jaundice. The patterns of liver toxicity were either hepatocellular or mixed (hepatocellular and cholestatic). These cases of possible drug-induced liver injury (DILI) occurred between 51 to 151 days after the initiation of fimasartan.

All patients were reported to have recovered or were recovering after stopping fimasartan.

Table 1. Patients' profiles and concomitant medicines

Age	Gender	Onset (days)	Took other ARB previously	Concomitant medicines* & duration taken
65	F	132	Yes (olmesartan for 10 years)	None
85	F	151	Not reported	Linagliptin, amlodipine, atorvastatin, clopidogrel & trimetazidine (taken for a long time); Doxazosin (1 and a half months after fimasartan); Ginseng (once/month for a few years)
70	M	51	Yes (olmesartan)	Fenofibrate and atorvastatin (2 - 3 years); Po Chai Pills, a traditional medicine (took for 2 days one month before DILI)
57	F	52	Not reported	Metformin, sitagliptin and atorvastatin (a few years); Traditional Chinese Medicines for gastric discomfort (two weeks before DILI)

** Taken concurrently and three months before onset of AE*

Overseas cases

From 2012 to January 2020, there were 221 adverse drug reaction (ADR) reports associated with fimasartan captured in the World Health Organisation's (WHO's) global pharmacovigilance database describing liver AEs including increased hepatic enzymes such as ALT and aspartate aminotransferase (AST), increased blood bilirubin or gamma glutamyltransferase (GGTP) and hepatitis. The majority of the cases were from South Korea where the drug is primarily marketed. It is not marketed in countries such as the US or the EU.

A literature review of liver injury with fimasartan found one case report involving a 73-year-old man in South Korea reported by DH Park *et al*.[1] Other factors such as autoimmune diseases and infections were ruled out. Interestingly, the patient did not experience any AE with three other types of ARBs and DILI occurred only ten months after the first dose. Subsequently, the patient accidentally retook fimasartan for one month and the episode recurred. The authors commented that this strongly suggested that the cause of hepatotoxcity was fimasartan. The Roussel Uclaf Causality Assessment Method (RUCAM) scale score was eight for the first episode and 11 with the second episode of liver injury.

ARBs and DILI

An increase in hepatic enzymes (increased ALT, increased AST) was reported in the clinical trials of Kanarb® in the frequency of between 0.1% to less than 1%.[2]

ARBs as a drug-class have been associated with rare instances of acute liver injury, which more commonly presented as hepatocellular but occasionally cholestatic in nature.[3] Individual case reports of clinically apparent liver injury with various ARBs have also been published in literature. Bearing in mind the high volume of ARBs use in Singapore, to date, HSA has received 12 AE reports of liver injury with losartan (5), telmisartan (2), olmesartan (1) and valsartan (4).

Conclusion

As HSA continues to monitor reports of liver injury with the use of fimasartan closely, healthcare professionals are advised to take into consideration the above information when prescribing fimasartan. Some signs and symptoms of liver injury include fatigue or excessive tiredness, nausea and vomiting, abdominal pain and jaundice. Healthcare professionals are also encouraged to report any suspected cases of liver injury related to the use of fimasartan to HSA.

References

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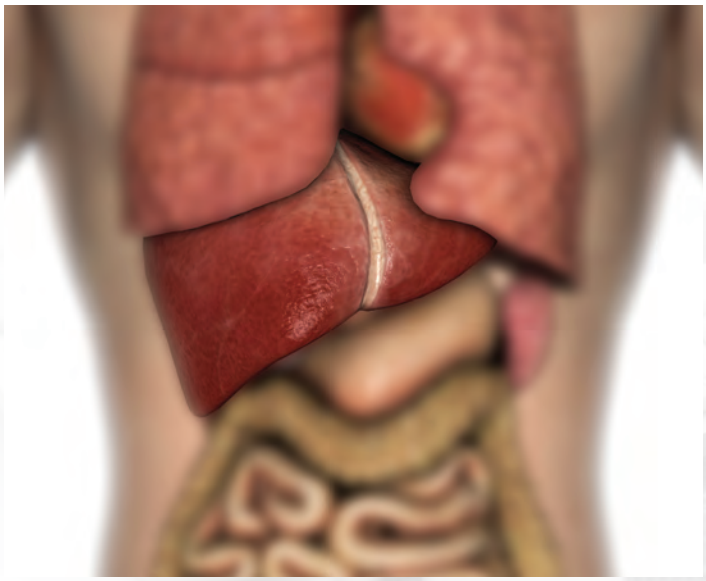

ANALYSIS OF ADVERSE EVENT REPORTS FOR YEAR 2019

Key Points

- In 2019, HSA received 37,563 adverse event (AE) reports. NSAIDs and antibiotics were the two highest reported pharmacotherapeutic groups of chemical drugs suspected to cause AEs.
- Two hundred and six of the 366 vaccine AE reports involved children. In children aged 12 years and below, the most commonly reported AEs were febrile and afebrile seizures with MMR, MMR and varicella, varicella, 5-in-1, pneumococcal conjugate or hepatitis B vaccines. In adults, the most commonly reported AEs were allergic reactions and injection site reactions with pneumococcal, tetanus, MMR or seasonal influenza vaccines
- There were 171 AE reports involving complementary health products and cosmetics. Ninety-nine (57.9%) reports involved hypersensitivity reactions associated with glucosamine-containing products

This review provides an analysis of the AE reports received by HSA in 2019. It covers pharmaceuticals (i.e. chemical, biologic drugs and vaccines) and complementary health products, and highlights the AE reporting patterns of interest.

Reports analysis of 2019

(a) Volume of reports

In 2019, HSA received a total of 37,563 valid+ AE reports suspected to be associated with health products. As of 2019, there were approximately 289,300 AE reports in the national safety database since data collection started in 1993.

+ Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid reports and were not captured into the national AE database as they could not be assessed for causality.

(b) Source and types of reports

Majority of the reports analysed were associated with chemical drugs (97.6%), followed by vaccines (1.1%), biologics (0.8%) and complementary health products (0.5%) which includes Chinese proprietary medicines, health supplements, traditional medicines and cosmetics.

Majority of the AE reports were from public hospitals (54.6%) and polyclinics (31.9%) and 5.1% were from private clinics/hospitals and 1.1% from drug companies. Healthcare professionals, i.e. doctors (88.3%) and pharmacists (6.7%), contributed to the majority of reports. Reports from dentists, nurses and research coordinators have also been received.

(c) Demographics

There were more AEs reports received for females (60.8%) than in males. Chinese patients constituted the highest proportion (52.6%) of AE reports, followed by Malays (9.95%) and Indians (6.2%). The age range of the patients with the highest frequency reported were ≥ 60 years of age (19.5%) followed by 50-59 years (9.8%).

(d) Suspected drugs

The top 20 suspected drugs commonly reported to cause AEs were from the following pharmacotherapeutic groups; nonsteroidal anti-inflammatory agents (NSAIDs) (24.3%), antibiotics (22.4%), analgesics and antipyretics (10.3%), cardiac therapy agents (5.8%) and contrast agents (1.7%). The most commonly reported AEs included rash, periorbital oedema and angioedema. This trend is similar to previous years.

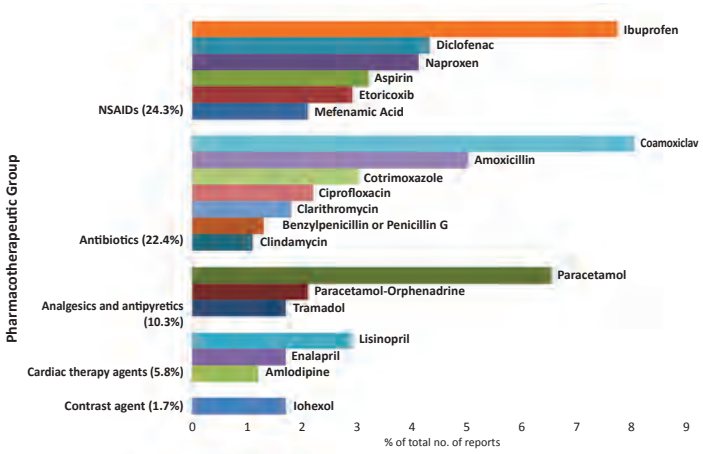

Figure 1. Top 20 drugs (by active ingredients) suspected of causing AEs

(e) Adverse events

The top System Organ Classes (SOC*) reported were skin-related disorders (57.4%) followed by those affecting the body as a whole (e.g. anaphylactic reaction) (17.1%) and respiratory system disorders (6.8%) (Figure 2).

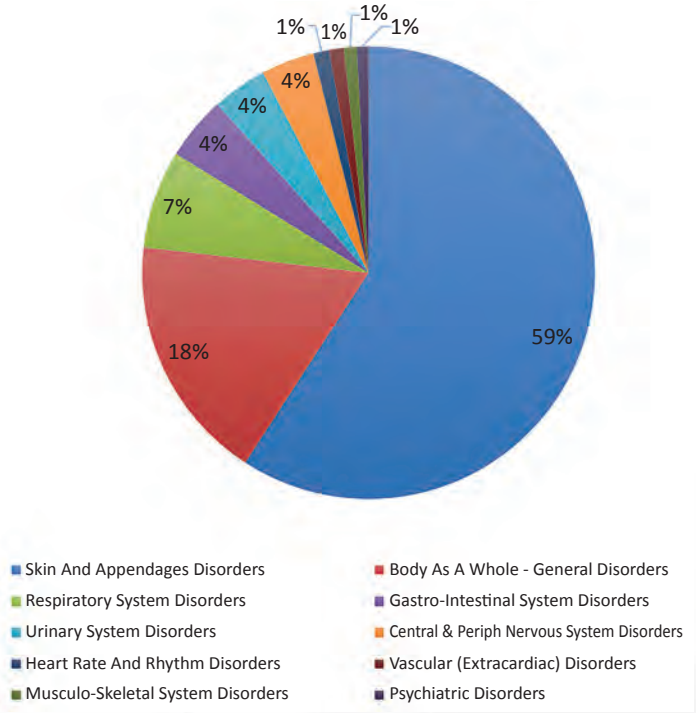

Figure 2. Top 10 AEs by System Organ Classes

** The System Organ Class refers to the adverse reaction terminology developed by the World Health Organisation (WHO).*

(N.B: More than one AE term may be described in an AE report)

(f) Serious AEs of interest

The drugs suspected to cause serious skin, body as a whole, renal and hepatic adverse reactions are listed in Table 1.

Table 1. Drugs suspected of causing serious AEs in 2019

Description	WHO preferred terms	Suspected active ingredient(s) (2019) (number in bracket denotes the number of times the drug has been implicated#)	Top 10 suspected active ingredients (number in bracket denotes the cumulative number of times the drug has been implicated from 2014 to 2018^)
Skin disorders	Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)	Cotrimoxazole (4), Omeprazole (4), Etoricoxib (4) Coamoxiclav (3), Amlodipine (3), Memantine (2), Ciprofloxacin (2), Carbamazepine (2), Nifedipine (2), Piperacillin and Tazobactam (2)	Allopurinol (34), Omeprazole (24), Etoricoxib (19), Coamoxiclav (17), Cotrimoxazole (16), Phenytoin (12), Lamotrigine (10), Ciprofloxacin (8), Doxycycline (7), Diclofenac (7), Cefazolin (7), Amoxicillin (7)
Body as a whole	Anaphylactic reaction	Diclofenac (15), Coamoxiclav (11) Iohexol (9), Piperacillin and Tazobactam (9), Cefazolin (8), Ibuprofen (8), Naproxen (7), Paracetamol (5), Paclitaxel (5), Ceftriaxone (5), Propofol (5)	Coamoxiclav (55), Diclofenac (44), Ibuprofen (39), Paracetamol (37), Naproxen (34), Ciprofloxacin (27), Aspirin (25), Amoxicillin (24), Ceftriaxone (23), Cefazolin (19)
Renal disorders	Acute/Chronic renal failure, Interstitial nephritis, Renal tubular disorder, Renal impairment	Ciprofloxacin (9), Etoricoxib (4), Losartan (2), Empagliflozin (2), Omeprazole (2), Naproxen (2)	Ciprofloxacin (22), Omeprazole (13), Cotrimoxazole (12), Diclofenac (10), Enalapril (9), Lisinopril (7), Hydrochlorothiazide (6), Coamoxiclav (5), Vancomycin (5), Metformin (4), Losartan (4), Fenofibrate (4)
Hepatic disorders	Hepatic failure, Hepatitis, Hepatitis cholestatic, Hepatocellular damage, Jaundice	Fimasartan (4), Azathioprine (3), Atorvastatin (3), Coamoxiclav (3), Meropenem (2), Carbimazole (2)	Coamoxiclav (13), Atorvastatin (9), Gabapentin (5), Isoniazid (4), Efavirenz (3), Paracetamol (3), Cotrimoxazole (4), Valproate (3), Pazopanib (3), Fenofibrate (3)

More than one suspected drug may be implicated in a single AE report. Only active ingredients implicated more than once are listed here.
^ Based on onset date of the AE

Vaccine adverse event (VAE) reports

HSA received 366 VAE reports in 2019. Of these, 206 reports involved children aged 18 years and below. Most were of the age group 12 years and below (92.2%) and corresponds to the age group of vaccinees under the National Childhood Immunisation Schedule. The active surveillance site at KK Women's and Children's Hospital, which HSA partners to screen paediatric hospital admission for post-vaccination AEs, captured the majority of these reports (87.4%).

The most commonly reported AEs in children aged 12 years and below were seizures (febrile and afebrile) with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1, pneumococcal conjugate or hepatitis B vaccines. Other reported AEs included meningitis, vaccine failure, Kawasaki disease, thrombocytopenia and injection site reactions associated with various types of vaccines. Vaccine-specific AEs received were measles-like syndrome with MMR vaccines, intussusception with rotavirus vaccines, and lymphadenitis and osteomyelitis with BCG vaccines. The AEs reported in children above 12 years of age were mainly suspected with Human Papillomavirus (HPV) vaccine and comprised events of headache, syncope and gastroenteritis. These reports were captured following the rollout of the national school-based HPV vaccination programme to secondary school children in 2019.

The most commonly reported AEs in adults were allergic reactions such as rash and angioedema, and injection site reactions, with pneumococcal, tetanus, MMR or seasonal influenza vaccines. Vaccine-specific AEs received were injections site reactions including cellulitis with pneumococcal vaccination, rubella rash with MMR vaccines and isolated reports of Guillain-Barre syndrome and cranial nerve palsy with influenza vaccines.

Analysis of the AE reports in 2019 compared with 2018 showed numerically higher number of reports for rubella rash with MMR vaccines, seizures (febrile and afebrile) with varicella vaccines, syncope with HPV vaccines and osteomyelitis with BCG vaccines. Overall, the VAE reports received in 2019 are within the expected incidences listed in the product package inserts or in literature.

Complementary health products reports

There were 171 AE reports involving CHPs and cosmetics. Ninety-nine (57.9%) reports were associated with glucosamine-containing products, describing mostly hypersensitivity reactions (rash and pruritus). There were eight reports of hepatic reactions (e.g. transaminitis and hepatitis) involving CHPs with multiple ingredients. Most of these patients have recovered or are recovering from the AE.

With the reports from astute clinicians, HSA detected eight adulterated products. The AEs of the six products adulterated with steroid (e.g. dexamethasone) included hirsutism, Cushing's syndrome and adrenal insufficiency. The remaining two products were marketed for weight loss and adulterated with sibutramine. One patient experienced palpitations and insomnia while the other patient who consumed a product called BB Body, required resuscitation and long-term treatment for heart failure. Three press releases were issued to alert to these products.

Acknowledgement

HSA would like to take this opportunity to thank all healthcare professionals for your active participation in the reporting of AEs.

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.

SAFETY UPDATE ON GENTIAN VIOLET ANTISEPTIC

Key Points

- Current evidence on the carcinogenicity of gentian violet (GV) has mainly been observed with high-dose oral exposure to GV in animal studies (rats and mice)
- Healthcare professionals are reminded that GV-containing antiseptic is limited to short-term external use only

HSA is aware that Health Canada had issued a safety alert in June 2019 to warn that gentian violet (GV)-containing antiseptic may potentially increase the risk of carcinogenicity. To ensure the safe use of GV-containing products in Singapore, HSA has conducted a benefit-risk assessment of these products.

About gentian violet[1-5]

GV is an antiseptic with antibacterial, antifungal and antihelminthic properties. The documented therapeutic uses of topical GV-containing products include the treatment of bacterial skin infections and fungal infections. Although GV's exact mechanism of action has not been elucidated despite its long history of use (more than a century), several mechanisms have been postulated, including the formation of free radicals and the induction of oxidative stress in bacteria. GV has been reported to be effective against *Candida albicans* and Gram-positive bacteria, particularly *Staphylococcus sp,* due to its ability to penetrate the bacterial cell wall. A systemic literature review also suggested that GV could be used to eradicate or disrupt biofilms in ear, nose, and throat (ENT) infections.

Safety alert from Health Canada[6-7]

In June 2019, Health Canada issued a safety alert on the potential risk of carcinogenicity with GV-containing products. The alert was based on Health Canada's review of available animal studies in the scientific literature, suggesting that oral exposure to GV in animals has been associated with the development of cancer.

In Canada, GV-containing products have been reported to be used on skin, mucous membranes (e.g. in nose, mouth and vagina), open wounds and on the nipple of a nursing mother to treat oral thrush in infants. Although Health Canada did not receive any cancer reports with the use of GV products, the agency highlighted its concerns over the potential oral exposure in infants as it had received adverse event reports (non-cancer) associated with the use of GV for oral thrush in two infants (aged two and five months). In response, the manufacturer of the only registered GV product (Gentiane Violet Liquid Topical) voluntarily discontinued the sale of the product in Canada.

Carcinogenicity of gentian violet[5, 8-12]

HSA has reviewed the available scientific literature and noted that current evidence on the carcinogenicity of GV has mainly been observed with high-dose oral exposure to GV in animal studies. Tumours were observed in various organs (e.g. liver, thyroid, reproductive organs) following two years of oral exposure to mid to high doses (up to 600ppm) of GV in rats and mice. There was insufficient evidence to suggest that the same cancer-causing effect with high-dose oral exposure to GV in animals could be extrapolated to the low-dose external application of GV in humans. To date, there have also been no local and international reports of cancer definitively linked with GV use in humans.

Local situation and HSA's advisory

In Singapore, GV is not a commonly used antiseptic, possibly due to the advent of newer and more effective antiseptics. However, there are some clinicians who use GV topically for the short-term management of certain acute conditions, such as skin erosion conditions, stoma care and ear infections, when other therapeutic options may not be as effective.

Based on available data, the current evidence on potential risk of carcinogenicity with GV appears to be mainly limited to high-dose oral exposure to GV in animal studies. Nonetheless, healthcare professionals need to be aware of this risk. As GV remains a useful therapeutic option for certain acute conditions, to ensure the safe use of the product, healthcare professionals are reminded that GV-containing antiseptic is limited to short-term external use only.

References

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AE CASE IN FOCUS: TEST YOURSELF

An 86-year-old Chinese male patient presented to the Dermatology Outpatient Clinic in July 2019 with maculopapular rash over the palms of both hands, which progressed to multiple small vesicles and small blisters which were tense, filled with clear fluid within 1 week (Figure 1).

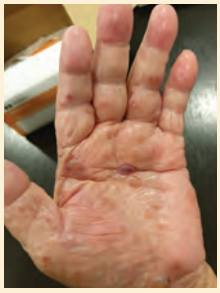

Figure 1. Multiple small vesicles and small blisters which were tense and filled with clear fluid on the palm

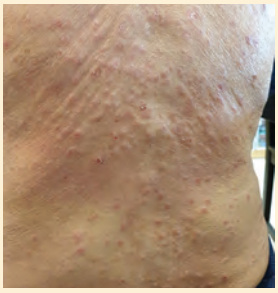

Figure 2. Scattered macular rashes on the body trunk

On closer examination, there were a few scattered pruritic macular rashes on the trunk (Figure 2). There were no other lesions and no oro-mucosal involvement. The patient was not febrile and was otherwise well.

His past medical history included cerebrovascular disease with expressive dysphasia, Type 2 diabetes mellitus, chronic obstructive pulmonary disease, osteoarthritis of the knees and hips, and dementia. In December 2018, he was admitted to a hospital with a severe viral pneumonia complicated by a secondary bacterial pneumonia, septic shock, multi-organ failure, non-ST elevation MI, atrial flutter and heart failure. He improved but developed acute kidney injury and anemia which persisted after discharge from hospital. His anemia improved in the following months, and oral anticoagulation (rivaroxaban) was started in April 2019. The patient was also on multiple medications**.

A differential of acral pompholyx, bullous pemphigoid-like (BP-like) lesions and scabies were considered, and the patient was empirically treated with topical permethrin for scabies, topical clobetasol for the palms, and 0.1% betamethasone for the macular pruritic rash on the trunk. In spite of the above treatment, the vesicles continued to evolve into large blisters on both palms (Figure 3).

** amiodarone, digoxin, furosemide, spironolactone, gliclazide MR, omeprazole, cholecalciferol, salbutamol inhaler, ipratoprium inhaler, salbutamol nebulising solution and ipratoprium bromide.

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RISK OF ADVERSE OUTCOMES WITH LIGHT-EXPOSED PARENTERAL NUTRITION PRODUCTS WHEN USED IN NEONATES AND CHILDREN BELOW TWO YEARS OLD

Key Points

- Exposure of parenteral nutrition (PN) products containing amino acids and/or lipids to light, especially in admixtures with vitamins and/or trace elements, may cause the formation of peroxides and photodegradation products
- Premature neonates are particularly susceptible to oxidative stress arising from PN photodegradation products, which can increase the risk of neonatal complications such as respiratory distress syndrome and bronchopulmonary dysplasia
- Healthcare professionals are advised to consider the importance of light protection measures when PN products containing amino acids and/or lipids are used in neonates and children below two years of age, to minimise the risk of adverse outcomes in this vulnerable population

Parenteral nutrition (PN) products are indicated for use in neonates when oral or enteral nutrition is not possible, insufficient or contraindicated. The use of light-exposed PN products containing amino acids and/or lipids might lead to adverse outcomes in neonates, particularly preterm neonates, due to their increased susceptibility to oxidative stress arising from PN photodegradation products. As such, it is important to provide light protection to PN products administered to neonates and children below two years old.

The locally registered PN products indicated for neonates or children below two years old include SMOFlipid, Vaminolact and Intralipid (Fresenius Kabi (Singapore) Pte Ltd); Clinoleic, Primene and Synthamin (Baxter Healthcare (Asia) Pte Ltd); and Lipidem, Lipofundin and Trophamine (B. Braun Singapore Pte Ltd).

Photodegradation products in PN products

In laboratory and clinical studies, light exposure to PN products has been shown to generate peroxides and other photodegradation products in quantifiable amounts, as early as 24 hours after exposure. PN products containing vitamins and lipids are the most susceptible, with lipid emulsions being prone to peroxidation due to their high polyunsaturated fatty acid content, and vitamins being prone to stability issues due to photodegradation oxidation (e.g. ascorbic acid, retinol, riboflavin).[1] While intense sunlight is most detrimental, exposure of PN products to ambient light, environmental light and phototherapy can also generate a significant oxidant load in patients.

The presence of high concentrations of photodegradation products in PN products can lead to oxidative stress, which causes damage to cell structures such as DNA, lipids and proteins.[2] Newborns, especially premature neonates, are at a higher risk of oxidative stress compared to children and adults, due to multiple risk factors such as weakened immunity, relative lack of antioxidant and free radical scavenger reserves, and use of oxygen therapy and phototherapy.[3,4] Oxidative stress has been shown to play a role in many neonatal complications, including respiratory distress syndrome, bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP).[2,3] In addition, premature neonates have high nutritional needs and require slow intravenous infusion rates, which further increase their risk of exposure to photodegradation products from light-exposed PN products.

Studies have shown that by implementing various light protection measures, the formation of PN photodegradation products can be slowed down or prevented. In a meta-analysis of four randomised trials, a total of 800 newborn premature neonates were evaluated for mortality at 36 weeks' gestational age or hospital discharge. Mortality in the light-protected group (where there was complete photoprotection of the PN admixture from compounding through delivery to the infant) was half of that in the light-exposed group (odds ratio 0.53; 95% CI 0.32 - 0.87), suggesting a reduced mortality at 36 weeks' gestational age when light protection for PN products was in place.[3]

European Medicines Agency's (EMA) review

In July 2019, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of this safety issue, taking into consideration non-clinical and clinical studies which provided evidence on the importance of light protection to reduce the risk of adverse outcomes in premature neonates.[4] While the data on harm primarily concerned premature neonates, the PRAC recommended that light protection of PN products should be extended to neonates and children below two years of age as a precautionary measure. A communication letter was also issued in the EU to raise awareness of this risk among healthcare professionals.

Local situation and HSA's advisory

To date, HSA has not received any local reports of adverse effects in neonates or children treated with PN products not protected from light. HSA is working with companies of affected products to update their local package inserts to reflect this risk.

Healthcare professionals are advised to consider the importance of light protection measures when PN products containing amino acids and/or lipids are used in neonates and children below two years of age, to minimise the risk of adverse outcomes in this vulnerable population.

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continued from page 6

New vesicles started to appear on the soles of his feet which evolved into large blisters (Figure 4). A working diagnosis of BP-like lesion was formed.

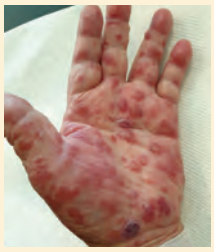

Figure 3. Large blisters on the palm

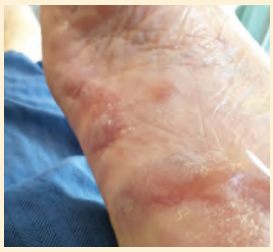

Figure 4. Large blisters on the sole of the foot

Blood tests, including serum indirect immunofluorescent, antibodies to bullous pemphigoid (i.e. BP180, BP230) were sent. The test for serum indirect immunofluorescent came back negative with BP180 <2.0 RU/ml and BP230 22.5RU/ml. Skin biopsy was considered but not performed as patient was clinically well and on oral anticoagulation.

Question: What could have caused the development of bullous pemphigoid-like lesions on the patient's palms and soles and macular pruritic lesions on his body trunk?

HSA would like to thank Dr. Samuel TH Chew, Senior Consultant Geriatrician and Dr. Shakil Chohan, Consultant Geriatrician from the Department of Geriatric Medicine at Changi General Hospital for contributing this article.

Answers can be found on page 8

ANSWERS TO AE CASE IN FOCUS

Possible causes of bullous pemphigoid (BP)

The patient's medication history was reviewed with regard to the timing and first onset of pruritus and rashes at home. The patient's caregiver noticed an increased in generalised scratching behaviour in him about 1 week after rivaroxaban was initiated in April 2019. The intensity of the pruritus gradually increased over time, and involved mainly the back and arms, leading to excoriations. Rivaroxaban was identified as the most likely offending drug that had caused acral BP-like lesions in the patient.

After a review of published literature of case reports on rivaroxaban-associated skin reactions,[1-5] rivaroxaban was stopped. This led to a complete resolution of pre-existing rash, vesicles and blisters by Week 3. The pruritus improved and resolved completely over the same period of time. The Naranjo Algorithm score (a causality assessment algorithm) was 7, suggesting that a probable relationship between rivaroxaban and the acral BP-like lesions.[6,7] The patient has been lesion and symptom free for the last seven months. The offending drug has not been restarted since.

Skin reactions are an expected adverse reaction with the use of rivaroxaban, and is listed in the Singapore package insert (PI) for rivaroxaban.[8,9]

The negative serum indirect immunofluorescent test, the negative BP180 test, the mildly elevated BP230 test and the rapid improvement of the rash, blisters and pruritic symptoms with the withdrawal of rivaroxaban is suggestive of a rivaroxaban-induced BP-like rash in our patient.

Immune-mechanism involved

It is likely that our patient developed a Type IV hypersensitivity reaction to rivaroxaban, given the history of gradual progressive onset and sequential development of generalised pruritus, macular rash, vesicles and tense blisters.

For BP disease, the underlying pathology is due to the autoimmune response to the hemidesmosomal proteins in the dermal-epidermal junction. These proteins have been identified as BP180 and BP230, with BP180 being the main antigen provoking the immune reaction.[10] IgG autoantibodies bind to these proteins in the cutaneous basement membrane, forming antibody-antigen complexes which are then responsible for the subsequent complement activation, degranulation of mast cells, and accumulation of neutrophils and eosinophils. Dermal-epidermal separation is effected by the release of proteases by activated granulocytes. Further neutrophil recruitment to the area also occurs as a result of the degranulation of the mast cells. The degree and number of infiltrating neutrophils determines the severity of the disease, due to their involvement in the initiation and progression of the inflammatory process.[11]

A variety of factors have been identified which may contribute to the loss of immune tolerance for these hemidesmosomal proteins, such as predisposing HLA allotype, Ultraviolet (UV) radiation, trauma and drugs.[10] There are two known types of drug-related BP disease, which are drug-induced BP and drug-triggered BP. Removal of the offending drug (systemic or topical) has been shown to lead to resolution of BP for the drug-induced category, but not for the drug-triggered category.[12] BP disease is also associated with neurological conditions such as stroke, dementia and Parkinson's Disease although the exact underlying pathophysiology for this association is still unknown.[11,12]

Drug-drug interactions

The patient is on long term amiodarone for fast atrial flutter, which is a moderate inhibitor of both CYP3A4 and P-gp. This is expected to lead to an increase of ≥ two-fold but ≤ five-fold increase of AUC for rivaroxaban.[13] In the setting of chronic kidney disease (CKD) approaching stage 4 for this patient, there will likely be further accumulation and increase in plasma rivaroxaban levels over time, which may then explain the subacute nature of the presentation of the pruritus, rash and BP-like lesions.

There are no known significant drug-drug interactions between rivaroxaban and omeprazole,[13] as omeprazole is metabolised predominantly via CYP2C19. There are no known significant drug-drug interactions between rivaroxaban and the rest of the patient's long-term medications.

Conclusion

As the use of direct oral anticoagulation may increase due to new guidelines, ease of use and increasing evidence of long-term safety,[14] it is important to increase awareness of the potential drug-drug (CYP4A and P-gp) and drug-disease (particularly CKD stage 4 and 5)[15] interactions in older patients.

As the development of drug allergy and skin reactions can occur insidiously, a high index of suspicion is required to identify these cases, particularly in the elderly patients with multiple comorbidities, poly pharmacy and cognitive/neurological impairments. Early detection and diagnosis are important for best outcomes, and complete resolution of BP-like skin reaction is possible upon withdrawal of the offending drug alone. Healthcare professionals are encouraged to report suspected drug-induced adverse events to the Vigilance and Compliance Branch of HSA.

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