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HSA Health Sciences Authority

ADVERSE DRUG REACTION NEWS

Contents

RECALL OF THREE BRANDS OF LOSARTAN PRODUCTS FOUND TO CONTAIN N-NITROSO-N-METHYL-4-AMINOBUTYRIC ACID (NMBA)

Key Points

- Three brands of losartan products, Hyperten, Losagen and Losartas, have been recalled as they were found to contain trace amounts of a nitrosamine impurity above internationally acceptable limits.
- Healthcare professionals have been advised to stop prescribing the three affected brands of losartan products and to review the treatment needs of patients currently on the affected losartan products.

On 28 March 2019, HSA recalled three brands of losartan products, Hyperten, Losagen and Losartas as they were detected to contain trace amounts of a nitrosamine impurity, N-nitroso-N-methyl-4-aminobutyric acid (NMBA) that exceeded internationally acceptable limits.

List of recalled losartan products

Product name	Active ingredient	Strength	Local supplier
Hyperten Tablet	Losartan Potassium	50mg	Goldplus Universal Pte Ltd
		100mg	
Losagen Tablet	Losartan Potassium	50mg	Medicell Pharmaceutical (S) Pte Ltd
		100mg	
Losartas Tablet	Losartan Potassium	50mg	Apotheca Marketing Pte Ltd
		100mg	

Not all losartan medicines are affected by the recall. Seven brands* of single-ingredient losartan products and five brands* of combination losartan products are not affected by NMBA contamination based on HSA's testing and available information to-date.

**Cozaar 50mg & 100mg, Losartan Hexal 50mg & 100mg, A-Losartan 50mg & 100mg, Rosart 50mg & 100mg, Myotan 50mg, Sartocad 50mg & 100mg and Lozarsin 50mg, Hyzaar Tablet, Hyzaar Forte, Hyzaar Plus 100/12.5, Cozaar XQ 5mg/50mg & 5mg/100mg, Losartan + HCT Mevon 50/12.5mg & 100/25mg, Rosart HCT 50mg/12.5mg & 100mg/25mg and Losarb Plus 100mg/25mg.*

Background

Since June 2018, there have been several overseas recalls of angiotensin II receptor blocker (ARB) medicines due to the presence of two nitrosamine impurities, N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA). Following the initial discovery of these impurities, HSA has been testing the registered ARBs that were available in Singapore. To date, no ARB medicines have been found to contain unacceptable levels of these 2 nitrosamine impurities.

Recently, several losartan products were recalled overseas due to the presence of a new nitrosamine impurity, NMBA, in the losartan active ingredient manufactured by Hetero Labs Limited, India. In March 2019, HSA developed the test methodology and proceeded to conduct testing of all losartan products in the Singapore market for the presence of the new impurity. Hyperten, Losagen and Losartas brands of losartan medicines were found to contain NMBA at levels above the internationally acceptable levels. The tests were part of HSA's ongoing investigations into the potential contamination of ARB medicines by nitrosamine impurities All the other brands of losartan medicines and ARBs (namely candesartan, irbesartan, valsartan, telmisartan, olmesartan, fimasartan) have been tested and were not found to contain NMBA.

Nitrosamine impurities

Nitrosamine impurities, including NDMA, NDEA and NMBA, are potential human carcinogens based on the carcinogenic effects observed in animal studies. These compounds may also be found in very small quantities in certain food (e.g. pickled vegetables, salted fish and processed meat products) and tobacco products. The potential risk of cancer is associated with the long-term exposure to unacceptable levels of the impurities.

Preliminary evaluation suggests these impurities could be generated when specific chemicals and reaction conditions are present during the manufacturing of the ARB active ingredients, particularly during chemical synthesis of the tetrazole ring structure in ARB medicines. The tetrazole ring structure is a common structure in ARBs, except for telmisartan and eprosartan.

HSA's benefit-risk assessment

The presence of carcinogenic impurities is generally unacceptable in medicines. In circumstances where these impurities are unavoidable, stringent limits are set based on international harmonised guidelines. The internationally acceptable daily intake level is determined based on a cancer risk of 1 in 100,000 for exposure over a lifetime (i.e. over 70 years). HSA had previously convened an Expert Panel comprising specialists in the fields of toxicology, pharmacology, oncology and cardiology to advise on the regulatory approach for products detected with these impurities. The panel had reviewed and recommended that products found to contain nitrosamine impurities that exceeded the acceptable limits should be recalled from the market.

The levels of NMBA detected in the three affected brands of losartan products were in trace amounts which exceeded the acceptable limit of 96 ng/day. HSA has advised patients not to stop taking their affected medicines unless replacement medicines have been provided as the health risks of stopping the medicines is higher than the potential risk of cancer.

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FLUOROQUINOLONES AND RISK OF AORTIC ANEURYSM AND DISSECTION

Key Points

- Data from epidemiological studies and overseas case reports suggest an increased risk of aortic aneurysm and dissection after treatment with systemic fluoroquinolones
- Conditions predisposing to this risk include a family history of aneurysm disease, pre-existing aortic aneurysm or dissection, genetic predisposition (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome), atherosclerosis, hypertension and the elderly
- Healthcare professionals are advised to take into consideration the potential risk of aortic aneurysm and dissection when prescribing fluoroquinolones, especially in patients with pre-existing risk factors

HSA would like to bring to the attention of healthcare professionals the potential risk of aortic aneurysm and dissection associated with fluoroquinolones for systemic use. This rare risk was highlighted by the European Medicines Agency (EMA) and the US Food and Drug Administration (US FDA) following their review of overseas cases of aortic aneurysm and dissection in patients who received fluoroquinolones, and data from epidemiological and non-clinical studies which suggest an increased risk of aortic aneurysm and dissection after treatment with systemic fluoroquinolones. Patients at increased risk included those with a history of pre-existing aneurysm, atherosclerosis, hypertension and the elderly.

Fluoroquinolones are a class of broad spectrum antibiotics that interfere with bacterial DNA replication and exert bactericidal activity by inhibiting the activity of DNA gyrase and topoisomerase. There are seven systemic fluoroquinolones registered locally, namely ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, levofloxacin, moxifloxacin and pefloxacin.

About aortic aneurysm and dissection

Aortic aneurysm is defined as a localised or diffuse dilation of the aorta, while aortic dissection occurs when there is separation of the layers within the aortic wall. These conditions are associated with alterations in collagen content, concentrations and structure. Since the Archilles tendon and the aorta are composed of the same type of collagen, it has been postulated that drugs which contribute to tendon ruptures could also cause or aggravate aortic aneurysm and dissection via a similar mechanism.[1] Fluoroquinolones can destroy the collagen and connective tissue along the aortic wall by upregulating multiple matrix metalloproteinases and causing degenerative changes in tenocyte cells, resulting in reduction in the diameter and amount of certain type of collagen fibrils. As such, they may contribute acutely to aneurysm progression and rupture although the exact mechanism remains to be confirmed.

The background risk of aortic aneurysm or dissection can vary depending on the population reports which ranged from nine aortic aneurysm events per 100,000 people per year in the general population to 300 aortic aneurysm events per 100,000 people per year in individuals at highest risk (e.g. those over the age of 85 years).[2] Conditions predisposing to this risk include a family history of aneurysm disease, pre-existing aortic aneurysm or dissection, genetic predisposition (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome), atherosclerosis, hypertension and the elderly.

Findings from epidemiological studies

Across multiple epidemiological studies published between 2015 to 2018,[1,3-5] there appears to be consistent evidence pointing to an approximately two-fold increased risk over the baseline risk of aortic aneurysm or dissection observed with fluoroquinolone use. However, study limitations such as confounding by indication and small sample sizes precluded determination of a definite causal association for this risk.

In a retrospective cohort study by Pasternak *et al*[4] to evaluate the risk of aortic aneurysm or dissection with oral fluoroquinolone use compared to amoxicillin use in patients aged 50 years or older, the fluoroquinolone group had a 1.66-fold increased risk (95% CI 1.12 - 2.46) within a 60-day risk period, with the increased risk occurring mainly in the first ten days after the start of treatment. Another self-controlled study by Lee *et al*[5] in elderly patients with a mean age of 71 years old showed an increased risk of aortic aneurysm or dissection associated with exposure to fluoroquinolones (odds ratio 2.71; 95% CI 1.14 - 6.46).

International regulatory actions

(a) EMA

In September 2018, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there was a risk of aortic aneurysm and dissection associated with the use of systemic and inhaled fluoroquinolones. Their safety review took into consideration evidence from epidemiological[1,3,4] and non-clinical studies,[6] spontaneous reports and responses from marketing authorisation holders (i.e. pharmaceutical companies). The PRAC subsequently recommended that the package inserts (PIs) of systemic and inhaled fluoroquinolones be updated to include the risk of aortic aneurysm and dissection, and a Dear Healthcare Professional Letter be distributed to communicate on this safety concern.

(b) US FDA

In December 2018, the US FDA issued a drug safety communication to warn about the risk of aortic aneurysm and dissection associated with fluoroquinolones. In addition to the published observational studies,[1,3-5] their review also included 56 cases of aortic aneurysm or dissection reported to US FDA during or after treatment with fluoroquinolones from 2015 to 2018. However, the agency noted that all patients from these cases had at least one risk factor for aortic aneurysm and dissection and the cause of these specific events could not be determined. Based on their review, the US FDA recommended a class-wide labelling update to the PIs of systemic fluoroquinolones to include warnings on the risk of aortic aneurysm and dissection.

Local situation and HSA's advisory

To date, HSA has not received any local reports of aortic aneurysm or dissection associated with fluoroquinolones. The Singapore PIs for systemic fluoroquinolones are being updated to include the risk of aortic aneurysm and dissection.

Healthcare professionals are advised to take into consideration the above safety information when prescribing fluoroquinolones, especially in patients who are at risk of aortic aneurysm and dissection. This includes patients with a history of peripheral atherosclerotic vascular disease, hypertension, certain genetic disorders that involve blood vessel changes (such as Marfan syndrome and Ehlers-Danlos syndrome), and the elderly.

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The contamination of ARB medicines with nitrosamine impurities is a new and evolving issue. HSA is closely monitoring the situation and working with the companies and international regulatory authorities to identify the root causes of the contamination and the corresponding measures to address the issue.

System-wide co-ordinated effort to ensure continued access of medicines

HSA completed the testing of all the losartan products marketed in Singapore prior to instituting the product recall so that healthcare professionals would know which alternative products they could consider switching their patients to.

The public healthcare family worked closely together to proactively reach out to affected patients and ensured that there were sufficient supplies of replacement medications for these patients. Moving forward, to assure the continued safety of the medicines supplied in Singapore, HSA has required companies supplying ARBs to test their products and ensure that they do not contain unacceptable levels of nitrosamine impurities.

UPDATE ON THE RECENT STUDY FINDINGS ON THE RISK OF NON-MELANOMA SKIN CANCER WITH PROLONGED USE OF HYDROCHLOROTHIAZIDE

Key Points

- Two recent Danish pharmacoepidemiological studies have suggested a cumulative dose-dependent association between the prolonged use of hydrochlorothiazide-containing medicines and non-melanoma skin cancer (NMSC)
- High cumulative usage of hydrochlorothiazide (i.e. ≥50g, corresponding to 12.5mg daily for 11 years) was found to be associated with an increased risk of basal cell carcinoma (BCC) (adjusted odds ratio [OR] 1.29, 95% CI 1.23-1.35) and squamous cell carcinoma (SCC) (OR 3.98, 95% CI 3.68-4.31)
- HSA is currently assessing the available data on this potential risk in the local context and will provide an update on our regulatory recommendations upon the completion of our review
- Meanwhile, healthcare professionals may wish to consider the recent findings from the two Danish studies when prescribing hydrochlorothiazide to their patients

HSA would like to update healthcare professionals on two recent pharmacoepidemiological studies using data from Danish registries which suggested a cumulative dose-dependent association between the prolonged use of hydrochlorothiazide-containing medicines and non-melanoma skin cancer (NMSC).

Hydrochlorothiazide is a diuretic that is commonly used alone or in combination with other antihypertensives for the treatment of hypertension.

From 2011 to 2015, the incidence rates of skin cancer in Singaporean men and women were 19.3 and 14.4 per 100,000 person-years, respectively.[1] The most common type of skin cancer is NMSC, which consists mainly of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[2] The known risk factors for NMSC include, but are not limited to UV exposure, immunosuppression, photosensitising medications, and fair or light skin complexion.[3]

High cumulative usage of hydrochlorothiazide (i.e. ≥ 50g, corresponding to 12.5mg daily for 11 years) was found to be associated with an increased risk of BCC (OR 1.29, 95% CI 1.23-1.35) and SCC (OR 3.98, 95% CI 3.68-4.31).

The possible mechanism of NMSC attributed by hydrochlorothiazide was postulated to be due to the photosensitising actions of hydrochlorothiazide, which might influence cancer risk at sun-exposed sites, as well as induce a chronic inflammatory reaction.[4,5]

HSA is currently assessing the available data on this potential risk, including the two studies and its relevance to the local context, and will provide an update on our regulatory recommendations upon the completion of our review.

Findings from Danish pharmacoepidemiological studies

Two recent pharmacoepidemiological studies using data from Danish registries had found a cumulative dose-dependent association between hydrochlorothiazide use and NMSC.

One study included 71,533 patients with BCC and 8,629 patients with SCC, who were matched with population controls in a 1:20 ratio by age and sex.[6] Patients with organ transplantation, HIV diagnosis or use of immunosuppressive agents were excluded, as these might predispose to skin cancer. High cumulative usage of hydrochlorothiazide (i.e. ≥50g, corresponding to 12.5mg daily for about 11 years) was found to be associated with an increased risk of BCC (OR 1.29, 95% CI 1.23-1.35) and SCC (OR 3.98, 95% CI 3.68-4.31). The respective ORs were based on high use of hydrochlorothiazide in 2.7% of patients and 2.1% of controls in the BCC group, and 10% of patients and 2.8% of controls in the SCC group. Notably, a clear dose-response pattern was observed in this study for both BCC and SCC, with a more than 7-fold increased risk of SCC for cumulative use of ≥ 200g hydrochlorothiazide (BCC: OR 1.54, 95% CI 1.38-1.71, SCC: OR 7.38, 95% CI 6.32-8.60).

In another Danish study, which included 633 cases with SCC of the lip, matched with 63,067 population controls,[7] a cumulative dose-response relationship between the use of hydrochlorothiazide and SCC of the lip was also demonstrated. The adjusted OR with ever-use of hydrochlorothiazide was 2.1 (95% CI 1.7-2.6), which increased to 3.9 (95% CI 3.0-4.9) and 7.7 (95% CI 5.7-10.5) with high cumulative hydrochlorothiazide use of ≥ 25,000mg and ≥ 100,000mg, respectively.

International regulatory actions

Following the publication of the two Danish case control studies, the European Medicines Agency (EMA)[8], Health Canada[9] and New Zealand Medsafe[10] conducted safety reviews on the risk of NMSC associated with the use of hydrochlorothiazide. EMA had considered that there was a biologically plausible mechanistic model supporting the increased risk of NMSC following higher cumulative doses of hydrochlorothiazide, while Health Canada concluded NMSC is a potential risk of prolonged hydrochlorothiazide treatment. However, uncertainty remains due to limitations noted in the reviewed studies. All three agencies recommended that the package inserts (PIs) of hydrochlorothiazide-containing products be strengthened on the risk of NMSC. Patients taking hydrochlorothiazide were also encouraged to practise preventive measures such as limiting the exposure to sunlight and ultraviolet (UV) rays to minimise risk of skin cancer.

Local situation and HSA's advisory

To date, HSA has not received any local reports of NMSC suspected to be associated with the use of hydrochlorothiazide. Three product registrants of hydrochlorothiazide-containing products have sent out Dear Healthcare Professional Letters to inform healthcare professionals about this safety issue as part of their global safety action plans. These companies have also begun updating the Singapore PIs for hydrochlorothiazide-containing products to include information on the observed increased risk of NMSC reported in the pharmacoepidemiological studies, as well as preventive measures to consider for patients taking hydrochlorothiazide.

As the incidence rates of NMSC vary across different countries and the baseline risks are dependent on factors such as skin phenotypes, HSA is reviewing the evidence from the study findings and other relevant data to assess the safety risks in the local context to determine if other regulatory actions are needed.

While HSA's safety review is ongoing, healthcare professionals should consider the findings from the two Danish pharmacoepidemiological studies when prescribing hydrochlorothiazide to their patients. HSA will provide an update on the outcome of our review when it is completed. Healthcare professionals are encouraged to report any suspected cases of NMSC related to hydrochlorothiazide to HSA.

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ANALYSIS OF ADVERSE EVENT REPORTS FOR THE YEAR 2018

Key Points

- The total number of adverse event (AE) reports increased above 20,000 reports per year in the last five years (2014 to 2018), with a significant increase in AE reports from general practitioners (GPs) in 2018
- More than 70% of the 340 vaccine-related AE reports involved children aged 12 years and below. In these reports, febrile and afebrile seizures were the most commonly reported AE linked with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* and pneumococcal conjugate vaccines
- Seven adulterated complementary health products (CHPs) were detected and press releases were issued by HSA The common adulterants found were dexamethasone and chlorpheniramine

This review provides an analysis of the AE reports received by the HSA in 2018. It covers therapeutic products, vaccines and complementary health products, and highlights the AE reporting patterns of interest.

Report analysis of 2018

(a) Volume of reports

In 2018, HSA received a total of 25,001 AE reports, reflecting a gradual increasing trend in AE reports over the past five years (Figure 1). While the increments in previous years were approximately 1,000 reports, 2018 saw an increase of more than 2,500 additional reports compared to 2017. This increase was attributed to more reports from General Practitioners (GPs).

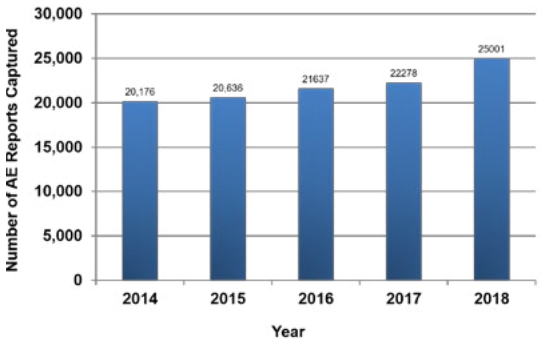

Figure 1. Number of valid reports captured in the AE database from year 2014 to 2018

(b) Source and types of reports

The majority of reports received were associated with pharmaceutical drugs (including biologics) (98.1%), followed by vaccines (1.4%), and complementary health products (0.6%) which includes Chinese Proprietary Medicines (CPM), health supplements, traditional medicines and cosmetics. Public hospitals and institutions contributed the highest proportion of reports (53.3%), followed by the polyclinics (32.7%). There has been a continued rise in reporting from GP clinics this year, from 0.4% in 2016 to 3.6% in 2017 and 8.2% in 2018 as more GP clinics signed on to GPConnect*, an integrated IT system. The remaining reports were from product registrants (1.5%), private hospitals (0.4%), and private specialist clinics (0.5%). Doctors (85.3%) contributed the most number of reports, followed by pharmacists (10.6%). Reports from dentists, nurses and research coordinators have also been received.

(c) Demographics

The patient profile reported in the AE reports closely reflect the local racial distribution, with the Chinese population constituting 70.3% of AE reports, followed by the Malays (13.5%) and the Indians (8.2%). Of those with gender reported, females accounted for 60.4% of the reports. Patients above the age of 60 accounted for 28% of the reports received.

(d) Suspected drugs

The top 20 suspected drugs have remained mostly similar from previous years. New entrants of suspected drugs into the top 20 list include etoricoxib and paracetamol-orphenadrine (Figure 2). These top 20 drugs have at least 250 implicated reports each and the highest number of reports involved coamoxiclav (1,900). It is to be noted that these figures do not take the drug utilisation rates into consideration and therefore do not inform on the relative safety profile of agents.

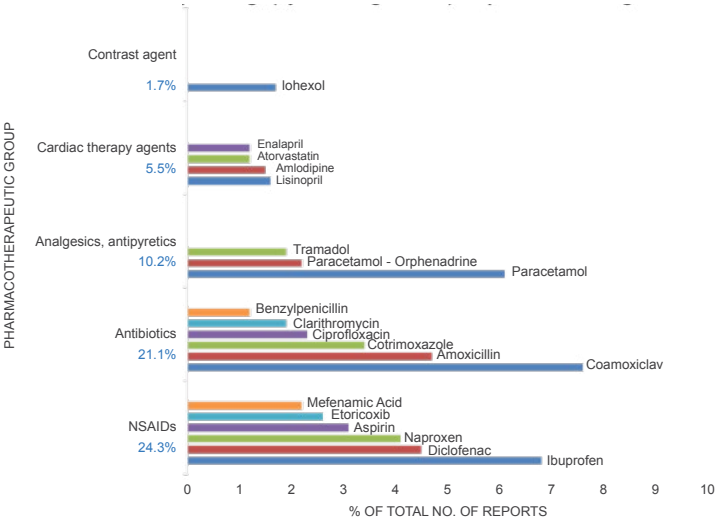

Figure 2. Top 20 drugs (by active ingredients) suspected of causing AEs

(e) Adverse events

The vast majority of serious AEs reported in 2018 are associated with drugs commonly known to cause these AEs as listed in Table 1. NSAIDs, anti-epileptic drugs, anti-microbial agents as well as omeprazole and allopurinol have been implicated in several serious AEs. Details of suspected drugs and the number of reports received for serious kidney, liver, skin and whole-body AEs are provided in Table 1.

** GP Connect is an IT service that allows GP clinics and authorised clinical staff to share and view GP practice clinical information and data between IT systems.*

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AE CASE IN FOCUS: TEST YOURSELF

A female patient in her 30s presented with a cough which lasted for two weeks. When she developed haemoptysis, she admitted herself to the A&E.

Upon medication history-taking, she revealed that she had been taking a traditional medicine in a capsule form containing black seed oil since 2016 to enhance her general well being. She had also started inhaling an essential oil blend four months ago using an atomizing diffuser. When she was well, she would inhale the vapour mist for four to five hours a week. During periods when she felt sick or had a fever, she would intensify the frequency of use to a daily basis and for similar number of hours during each session. She recalled doing the latter during two periods i.e. two months prior to her current presentation and during her latest bout of upper respiratory tract infection two weeks prior.

Her medical history included a five pack-year history of smoking (ten sticks/day for ten years), exposure to petroleum fuel inhalation where she had worked for three years in a petroleum company, doing field work for ten months and early childhood asthma. She had stopped using inhalers for more than 20 years and denied heavy exposure to smoke, fumes, chemicals or dust. She had no personal or family history of tuberculosis, lung cancer or any airway diseases.

During her hospitalisation, she continued to have a few episodes of small-volume haemoptysis which subsequently resolved with symptomatic treatment. She was discharged from the hospital and reported no further cough or any episodes of haemoptysis.

Question: What could have caused the patient's cough with haemoptysis?

Answers can be found on page 6

Table 1. Drugs suspected of causing serious AEs in 2018

Description	WHO preferred terms	Suspected active ingredient(s) (number in bracket denotes the number of times the drug has been implicated in 2018#)	Top 10 suspected active ingredient(s) (number in bracket denotes the cumulative number of times the drug has been implicated from 2013 to 2017)
Skin disorders	Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)	Allopurinol (11), Coamoxiclav (7), Cotrimoxazole (6), Phenytoin (6), Piperacillin and tazobactam (4), Omeprazole (4), Etoricoxib (2), Diclofenac (2), Sulfasalazine (2)	Allopurinol (34), Cotrimoxazole (29), Omeprazole (28), Etoricoxib (20), Carbamazepine (19), Phenytoin (17), Coamoxiclav (16), Lamotrigine (15), Ceftriaxone (15), Ciprofloxacin (13).
Body as a whole	Anaphylactic reaction	Ibuprofen (18), Coamoxiclav (17), Diclofenac (16), Naproxen (13), Ceftriaxone (11), Amoxicillin (10), Paracetamol (14), Benzylpenicillin or Penicillin G (8), Ciprofloxacin (8), Atracurium (7), Iohexol (7), Cefazolin (6), Aspirin (5), Lidocaine (5), Moxifloxacin (5), Piperacillin and Tazobactam (5)	Diclofenac (62), Paracetamol (54), Ibuprofen (53), Coamoxiclav (50), Naproxen (45), Aspirin (39), Ceftriaxone (32), Benzylpenicillin or Penicillin G (27), Ciprofloxacin (27), Amoxicillin (25)
Renal disorders	Azotaemia, Creatinine clearance decreased, Diabetes insipidus nephrogenic, Renal tubular disorder/ Necrosis, Acute/chronic renal failure, Interstitial nephritis, Nephropathy toxic, Abnormal renal function	Ciprofloxacin (7), Ibuprofen (7), Cotrimoxazole (4), Diclofenac (3), Losartan (3), Vancomycin (3), Cefazolin (2), Enalapril (2), Etoricoxib (2), Hydrochlorothiazide (2), Omeprazole (2), Piperacillin and Tazobactam (2)	Ciprofloxacin (28), Enalapril (27), Losartan (24), Diclofenac (17), Cotrimoxazole (17), Etoricoxib (15), Lisinopril (14), Hydrochlorothiazide (14), Omeprazole (12), Coamoxiclav (10)
Hepatic disorders	Jaundice, Hepatitis, Hepatitis Cholestatic, Hepatic failure, Hepatocellular damage, Liver injury, Hepatic coma	Atorvastatin (10), Coamoxiclav (6), Isoniazid (4), Methotrexate (3), Allopurinol (2),Cloxacillin (2), Diclofenac (2)	Azathioprine (23), Coamoxiclav (19), Atorvastatin (14), Cotrimoxazole (11), Simvastatin (8), Valproic acid (7), Isoniazid (6), Regorafenib (6), Fenofibrate (6), Pyrazinamide (6)

More than one suspected drug may be implicated in a single AE report. Only active ingredients implicated more than once are listed here.

Vaccine adverse event (VAE) reports

There were 340 AE reports suspected to be associated with vaccines, of which 248 reports (73%) involved children aged 12 years and below, which corresponds to the age group of vaccinees under the National Childhood Immunisation Schedule. The majority of these reports (n=224) involving the paediatric population were captured by the active surveillance site at KK Women's and Children's Hospital (KKH), which screens all paediatric hospital admissions for possible relationship to recent vaccination.[1]

The most commonly reported AE in children aged 12 years and below was seizures (febrile and afebrile seizures) with the measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* and pneumococcal conjugate vaccines. Other reported AEs included injection-site reactions, rash, Kawasaki disease, meningitis, thrombocytopenia and vaccine failure involving a variety of vaccines. For vaccine-specific AEs, there were reports of intussusception with the rotavirus vaccine, measles or measles-like rash with the MMR or MMRV vaccines, suppurative lymphadenitis as well as isolated reports of osteomyelitis and disseminated Bacillus Calmette-Guérin(BCG) disease with the BCG vaccines. Based on yearly trend analysis, the number of reports of VAEs in 2018 were comparable to 2017, with the exception of measles or measles-like rash with the MMR or MMRV vaccines where more reports were received in 2018.

The commonly reported vaccines suspected to cause AEs in adults and children above 12 years of age were the human papillomavirus (HPV), pneumococcal, seasonal influenza, MMR and tetanus toxoid vaccines. The commonly reported AEs included rash, periorbital oedema and injection-site reactions associated with a variety of vaccines. For vaccine-specific AEs, there were isolated reports of syncope with the HPV vaccine, parotitis and Bell's palsy with the MMR vaccine. Compared to 2017, there were more reports of injection-site reactions with pneumococcal vaccines in adults, describing injection-site cellulitis, erythema or swelling.

Overall, the number of reported AEs in children and adults remained consistent with the expected frequencies of AE occurrence listed in the package inserts of the vaccines or in literature.

Complementary health products (CHP) AE reports

There were 148 AE reports involving CHPs. Sixty-two (41.9%) reports were associated with glucosamine-containing products, describing mostly hypersensitivity reactions (rash and pruritus).

There were 25 reports of hepatic reactions (e.g. transaminitis), including seven AE reports of liver injury suspected to be associated with the consumption of mahogany seeds, also known as *Swietenia macrophylla* seeds. The fruit of the mahogany seed is commonly known as "sky fruit", "buah tunjuk langit" (in Malay) or "向天果" in Chinese. For details on this safety concern, please refer to the article published in the Dec 2018 issue of the HSA's Adverse Drug Reaction News Bulletin titled "Adverse event reports of liver injury suspected with the use of mahogany seeds".

With the help of astute clinicians, HSA detected seven adulterated CHPs. The reported AEs were expected and mainly associated with endocrine disorders such as Cushing's syndrome and adrenal crisis. The common adulterants detected were dexamethasone and chlorpheniramine. Other reported AEs associated with CHPs include renal function abnormalities, hypersensitivity and skin reactions. In 2018, there were four press releases issued related to CHP AE reports, including the press release on reports of liver injury after the consumption of mahogany seeds.

Acknowledgement

The Vigilance and Compliance Branch would like to take this opportunity to thank all healthcare professionals for your active participation in the reporting of AEs. It has been heartening to see the increase in AE reports from the General Practitioners and we are looking forward to receive more reports with the enhanced IT connectivity and advancements. Your continual support has helped us to detect potential safety signals and enabled the relevant regulatory actions to be taken to safeguard public health.

**5-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio and Haemophilus Influenza Type B vaccine*

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ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

Based on the case presentation and differential diagnosis explained below, the patient was diagnosed with lipoid pneumonia.

About lipoid pneumonia

Lipoid pneumonia results from an accumulation of lipids in the alveoli. It could be due to endogenous or exogenous causes. Endogenous causes include bronchial obstruction, chronic pulmonary infections, pulmonary alveolar proteinosis or fat storage diseases. Exogenous causes include inhalation or aspiration of animal/vegetable fat or mineral oil.[1] Lipoid pneumonia is rare, with an autopsy study in the US reporting a frequency of 1 – 2.5%.[2]

The degree of lung parenchyma injury is affected by the type, amount, frequency, exposure duration and route (aspirated versus inhaled) of the causative agent.[3] Mineral oil and vegetable oil tend to cause mild inflammatory reactions and commonly manifesting as fibrous tissue encapsulating the intra-alveolar oil forming a nodule (paraffinoma). Animal fats are hydrolysed into free fatty acid which triggers intense inflammatory reaction which usually presents as oedema and alveolar haemorrhage and may potentially progress to end-stage fibrosis.[3]

Common signs and symptoms of lipoid pneumonia

The common clinical presentations of lipoid pneumonia are cough and dyspnoea. Fever, haemoptysis, chest pain and weight loss have also been reported, which may be related to acute inflammatory reaction or superimposed infection.[4] Usually, physical examinations can be normal, with occasional findings of crackles, wheeze or dullness on percussion. In addition, pulmonary function test may show restrictive pattern in advanced and chronic cases.[4]

An area of fat attenuation within the nodules and consolidation is a diagnostic feature of lipoid pneumonia on radiology. Unfortunately, this is rarely seen. More commonly observed is the imaging of acute exogenous lipoid pneumonia which is non-specific, showing ground-glass opacities and consolidation that may predominantly involve the middle and lower lobes.[3] Crazy paving pattern, interlobular septal thickening and airspace nodules have been reported. In acute exogenous lipoid pneumonia, these features may be present within 30 minutes of exposure. Chronic exogenous lipoid pneumonia characteristically manifests as fat-containing nodules, though they can be non-fat containing as well. These nodules may be fluorodeoxyglucose (FGD) avid on positron emission tomography (PET) scan, mimicking lung cancer.[3] Other radiological findings include pneumatoceles, pneumomediastinum, pneumothorax and pleural effusions. Pneumatoceles usually develop within regions of ground-glass opacity or consolidation and manifest within two to 30 days of exposure. In acute exogenous lipoid pneumonia, the radiological features typically improve or resolve over a period of two weeks to eight months; while in chronic exogenous lipoid pneumonia, these changes may persist over time even after removal of the causative agent.[2]

The detection of fat-laden (foamy) macrophages in respiratory specimens (sputum, bronchoalveolar lavage or lung tissue) has been used as a diagnostic marker for exogenous lipoid pneumonia.[4] However, doubt has been raised on their specificity, where lipid-laden macrophages have been detected in the absence of lipoid pneumonia. The histology of lung tissue showing intra-alveolar lipid and alveolar fill-in by lipid-laden macrophages, in the presence of normal alveolar walls and septae structures (in acute cases), is a more reliable marker for exogenous lipoid pneumonia; especially if extracellular oily droplets are also demonstrable. Rarely, fat globules can be seen on inspection of BAL specimens, which often appears grossly whitish or turbid when haemoptysis is absent.[2]

Case review

In the case above, the patient had no fever or other associated symptoms otherwise. Pertinent review of the various organ systems was negative. She was hemodynamically stable, normoxic and did not demonstrate any signs of active bronchospasm. While her lung examination revealed only some crackles, the rest of her physical examination test results were normal. Her chest X-ray (CXR) showed patchy shadowing in both lower zones of the lung fields and her computer tomographic (CT) scan of the chest (Figures 1, 2 and 3 on page 7) revealed bilateral, peripheral, diffuse and non-specific ground glass opacification and airspace changes. Her haemoglobin level, coagulation profile and renal function were normal and her serum autoimmune markers including anti-nuclear cytoplasmic antibody (ANCA) were negative. She underwent a bronchoscopic airway inspection which did not show any localised bleeding source or any endobronchial lesion. A bronchoalveolar lavage (BAL) was performed during the bronchoscopy procedure which showed only a bloody return. Transbronchial lung biopsy was not carried out due to the recent episodes of haemoptysis. Microbiological testing of the BAL was conducted to test for infective organism including mycobacterium. Cytologic examination of the specimen showed an increased number of foam (lipid-laden) macrophages and no haemosiderin-laden macrophage.

The patient had been taking black seed oil since 2016 which makes it an unlikely causative agent and was inhaling the essential oil blend four months ago, which has a stronger temporal association to the AE. The essential oil blend used by the patient contained clove, trans cinnamaldehyde (cinnamon bark), limonene (lemon), and eucalyptol (Eucalyptus radiate and Rosemary). Pulmonary AEs such as pulmonary oedema, irritation of the mucosa membrane, bronchospasm have been reported with the ingestion or aspiration of these individual components.[5] The labelled directions recommended use of up to ten minutes each time, three times daily. The patient had been inhaling the essential oil blend beyond the recommended dose and it is postulated that these air-borne oil particles could have caused acute exogenous lipoid pneumonia complicating an upper respiratory tract infection, presenting with symptoms of cough and haemoptysis. The patient recovered upon discharge from hospital which could be due to a change in her usage pattern after being warned against excessive aspiration by the treating physician.

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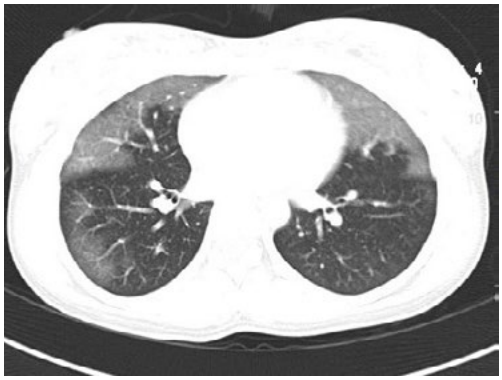

Figure 1. Sagittal cut of the CT thorax showing bilateral, peripheral ground glass opacities

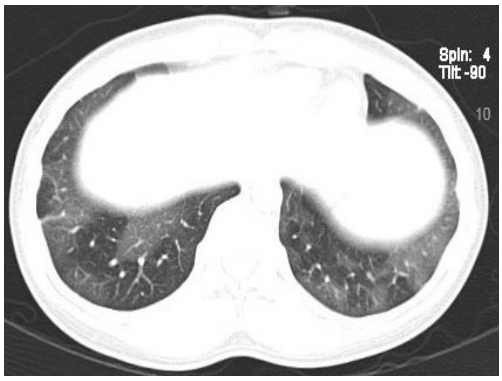

Figure 2. Sagittal cut of the CT thorax showing lung bases

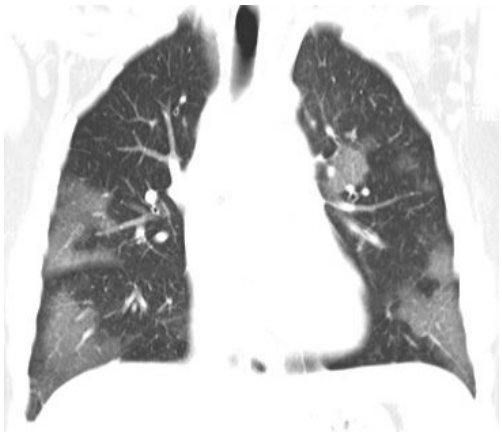

Figure 3. Coronal cuts of CT thorax showing bilateral, peripheral ground glass opacities

HSA would like to thank Dr. Chua Ai Ping, Senior Consultant and Dr. Valencia Lim, Senior Resident from the Respiratory Division, Department of Medicine at Ng Teng Fong General Hospital for contributing this article.

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.

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 DEC 2018 TO 30 APRIL 2019)

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

Therapeutic products

3 Dec 2018	**Hydrochlorothiazide** Cumulative dose-dependent association with non-melanoma skin cancer
22 Feb 2019	**Tecentriq® (atezolizumab)** New risk of immune-related myositis
1 Mar 2019	**Thyrozol® (thiamazole; synonym: methimazole)** New risk of acute pancreatitis and update on risk of congenital malformations
18 Mar 2019	**Benlysta® (belimumab)** New risk of serious depression and/or suicidal ideation, behaviour or self-injury
28 Mar 2019	**Hyperten, Losagen, Losartas (losartan)** Recall of 3 brands of losartan products found to contain N-nitroso-N-methyl-4-aminobutyric acid (NMBA)
2 Apr 2019	**Esmya (ulipristal acetate)** Update of local package insert to include warnings on risk of serious liver injury and to inform of the need for liver function monitoring before, during and after treatment with Esmya
11 Apr 2019	**Actemra® (tocilizumab)** Risk of hepatotoxicity (serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplant) associated with the use of Actemra®

Medical devices

*23 Nov 2018	**BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent** Update on the restenosis rate as complaint rate for restenosis exceeds the listed rate
5 Dec 2018	**Nellix® EndoVascular Anerysm Sealing System** Important update on usage following complaints of caudal migration of the stent-graft-Endobag
14 Jan 2019	**CERAMENT™|BONE VOID FILLER, CERAMENT™|GENTAMICIN or CERAMENT™|VANCOMYCIN** Additional safety precaution in patients treated for Aneurysmal Bone Cysts or other bone cysts prone to producing large volumes of fluid
28 Jan 2019	**Medtronic Dual Chamber Pacemakers** Voluntary recall and distribution suspension affecting a subset of affected device susceptible to circuit error
31 Jan 2019	**Nellix® EndoVascular Aneurysm Sealing System** Voluntary recall of all models and serial numbers due to AEs including migration, Type 1 endoleak, and aneurysm enlargement, which was attributed to use outside of the current indications
4 Mar 2019	**Raindrop Near Vision Inlays** Increased risk of corneal haze in patients implanted with affected device
21 Mar 2019	**Cook Inferior Vena Cava (IVC) Filter** Update on sections 'Precautions, Potential Adverse Events and References' in product label and reinforcement on routine follow-up and IVC Filter retrieval
9 Apr 2019	**Ethicon Intraluminal Staplers** Voluntary recall of affected lots of due to occurrences of uncut washers and malformed staples which can compromise staple line integrity
12 Apr 2019	**Geistlich Bio-Oss Pen®** Potential for the presence of particulates on the outer barrel of affected device

*DHCPLs not published in Dec 2018 issue

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS AND RISK OF NECROTISING FASCIITIS OF THE PERINEUM (FOURNIER'S GANGRENE)

Key Points

- Overseas cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in patients who have received SGLT2 inhibitor therapy
- Healthcare professionals are advised to consider the possibility of Fournier's gangrene in SGLT2 inhibitor-treated patients who present with pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise

HSA would like to inform healthcare professionals about overseas cases of necrotising fasciitis of the perineum reported in patients who were treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors. This rare but serious soft tissue infection of the genital, perineal, and/or perianal regions, also referred to as Fournier's gangrene, is a potentially life-threatening event that requires urgent surgical intervention and broad-spectrum antibiotic therapy.

Background

SGLT2 inhibitors are oral glucose-lowering agents that increase the renal excretion of glucose (i.e. glycosuria) through the inhibition of SGLT2-mediated renal glucose reabsorption. Three SGLT2 inhibitors have been registered in Singapore since 2014, either as single ingredient or fixed-dose combination products. They are canagliflozin (Invokana™; Johnson & Johnson Pte Ltd), dapagliflozin (Forxiga®, Xigduo XR®; AstraZeneca Singapore Pte Ltd) and empagliflozin (Jardiance®, Jardiance Duo®, Glyxambi®; Boehringer Ingelheim Singapore Pte Ltd). These drugs are indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus (T2DM), as monotherapy and as an add-on combination therapy with other glucose-lowering agents including insulin. In addition, Forxiga® is indicated as an initial combination therapy with metformin, and Jardiance® and Jardiance Duo® are indicated as an add-on combination therapy to reduce the incidence of cardiovascular death in T2DM patients with established cardiovascular disease.

Fournier's gangrene usually presents as a polymicrobial infection with common clinical features of swelling of the external genitalia, fever and pain that may rapidly progress to skin necrosis if not treated promptly. It occurs almost exclusively in males with an estimated male:female ratio of 10:1. A US study, based on hospitalisation data, reported an estimated incidence rate of Fournier's gangrene of 1.6-3.3 per 100,000 males annually and overall fatality rate of 7.5%.[1] The identified predisposing factors for Fournier's gangrene include diabetes mellitus, obesity, older age, and other conditions leading to impaired microcirculation and/or immunosuppression.[2]

Overseas cases of Fournier's gangrene with SGLT2 inhibitors

In September 2018, the US Food and Drug Administration (FDA) issued a drug safety communication warning that cases of Fournier's gangrene have been reported in SGLT2 inhibitor-treated patients.[3] The agency conducted a search of its adverse event reporting system database (FAERS) from March 2013 to February 2018 as well as the medical literature through 2018, and identified a total of 12 cases of Fournier's gangrene associated with SGLT2 inhibitors. In contrast, the agency identified only six cases of Fournier's gangrene (all in men) associated with several other antidiabetic drug classes (insulins, biguanides, sulfonylureas, and dipeptidyl peptidase-4 inhibitors) in the search of the FAERS over a period of 34 years.

Of the 12 SGLT2 inhibitor-associated Fournier's gangrene cases, seven cases involved men and the remaining five cases involved women, with ages ranging from 38 to 78 years. The average time from the initiation of a SGLT2 inhibitor to the onset of Fournier's gangrene was 9.2 months (range 7 days to 25 months).

Patients in all 12 cases were hospitalised and required surgical debridement, of which five cases required multiple surgeries and one case required skin grafting. The clinical course for four cases was complicated by diabetic ketoacidosis, acute kidney injury, and septic shock, which prolonged the patients' hospitalisation or led to death. The SGLT2 inhibitor was discontinued in eight cases; one patient had died; and information on drug continuation or discontinuation was not included in the remaining three cases.

International regulatory actions

Following assessment of the available data, the US FDA[3] and the European Medicines Agency (EMA)[4] had requested for the package inserts of SGLT2 inhibitor products to be updated on the warning concerning the risk of Fournier's gangrene.

Local situation and HSA's advisory

HSA has not received any local reports of Fournier's gangrene associated with SGLT2 inhibitors. The local package inserts for SGLT2 inhibitor-containing products are being updated to warn about this risk.

Healthcare professionals are advised to take into consideration the above safety information when prescribing a SGLT2 inhibitor, and to consider the possibility of Fournier's gangrene in SGLT2 inhibitor-treated patients who present with pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If Fournier's gangrene is suspected, healthcare professionals should consider the discontinuation of SGLT2 inhibitor with the initiation of prompt treatment.

Healthcare professionals are also encouraged to report any serious adverse reactions, including Fournier's gangrene, related to SGLT2 inhibitors to the Vigilance and Compliance Branch of HSA.

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