

Contents

- | | | | |
|---|-----|---|-----|
| ❖ Sodium-glucose cotransporter-2 (SGLT2) inhibitors and risk of serious diabetic ketoacidosis (DKA) | 1-2 | ❖ HMDP training course by expert on healthcare data analytics: Learning from the experience of the US FDA Mini-Sentinel | 6-7 |
| ❖ AE CASE IN FOCUS: Test yourself | 2-3 | ❖ List of Dear Healthcare Professional Letters | 7 |
| ❖ Analysis of adverse event (AE) reports for the year 2015 | 4-6 | ❖ Risk of potentiation of radiation toxicity associated with vemurafenib | 8 |

SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS AND RISK OF SERIOUS DIABETIC KETOACIDOSIS (DKA)

Key Points

- The benefit-risk profile of SGLT2 inhibitors remains favourable for their approved indications although the possibility of an increased risk of DKA cannot be excluded, particularly in the presence of predisposing factors
- SGLT2 inhibitors should be used with caution in patients at risk of developing DKA
- Patients presenting with metabolic acidosis during treatment with SGLT2 inhibitors should be assessed for ketoacidosis and tested for blood ketones, even when the blood glucose levels are not high



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In the September 2015 issue of the HSA Adverse Drug Reaction News Bulletin, HSA issued an interim safety update on the potential risk of DKA with SGLT2 inhibitors while evaluating this safety signal.¹ Subsequently, in February 2016, HSA issued a Dear Healthcare Professional Letter to communicate its benefit-risk assessment outcomes and recommendations.² This article serves to remind healthcare professionals on HSA's recommendations to minimise the risk of SGLT2 inhibitor-associated DKA.

Background

There are three SGLT2 inhibitor-containing products registered in Singapore since 2014. They are Invokana™ (canagliflozin, Johnson & Johnson Pte Ltd), Forxiga® (dapagliflozin, AstraZeneca Singapore Pte Ltd) and Jardiance® (empagliflozin, 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 or as an add-on combination therapy with other glucose-lowering agents including insulin. Forxiga® is also indicated as an initial combination therapy with metformin.

HSA's benefit-risk assessment

HSA's review took into account the findings from scientific publications as well as information from local and overseas cases of DKA associated with SGLT2 inhibitors. The review of the published clinical studies noted that although SGLT2 inhibitors use was associated with an increase in blood ketone body levels, the vast majority of patients with ketonaemia were clinically asymptomatic.^{3,4} For the patients on SGLT2 inhibitors who developed DKA, it was noted that they had contributory risk factors, such as recent surgery, infection, low caloric/carbohydrate intake, late-onset type 1 diabetes mellitus, long standing T2DM and pancreatic insufficiency.⁵⁻⁹ In a number of cases, euglycaemic DKA have also been observed in patients treated with SGLT2 inhibitors. Hence, this highlights the importance of blood ketone testing even when the blood glucose levels are not high, should ketoacidosis be suspected during treatment with SGLT2 inhibitors.

Local case reports of DKA

As of 1 February 2016, HSA has received five local cases of DKA and one case of ketonaemia associated with SGLT2 inhibitors use, all of which had resulted in the patients being hospitalised. Four cases were associated with canagliflozin and two cases were





associated with dapagliflozin. The time-to-onset of DKA from the initiation of treatment with SGLT2 inhibitors ranged from 11 to 169 days while that of ketonaemia was unknown. In two cases, the patients presented with euglycaemic DKA (blood glucose level less than 13.9 mmol/L). Similar underlying and/or concomitant risk factors as those reported in publications, such as infection, reduction in insulin dose, late-onset type 1 diabetes mellitus and long standing T2DM, were also observed in these local cases, which could have precipitated the development of DKA.

In consideration of the expert opinions from local endocrinologists and HSA's Pharmacovigilance Advisory Committee (PVAC), as well as the regulatory developments in other international jurisdictions, HSA has assessed that while the benefit-risk profile of SGLT2 inhibitors remains favourable for their approved indications, the possibility of SGLT2 inhibitors leading to an increased risk of DKA cannot be excluded, particularly in the presence of predisposing factors.

International regulatory actions

The United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA) and Health Canada have also initiated safety reviews on SGLT2 inhibitors following reports of ketoacidosis with the use of SGLT2 inhibitors.¹⁰⁻¹² To date, both the EMA and US FDA have completed their respective reviews. The EMA's Pharmacovigilance Risk Assessment Committee advised healthcare professionals to be aware of possible euglycaemic DKA cases.¹³ The US FDA added a new warning to the US package inserts for SGLT2 inhibitors to warn of the risk of ketoacidosis.¹⁴ Manufacturers of SGLT2 inhibitors are also required by the US FDA to conduct post-marketing studies to collect and analyse spontaneous reports of ketoacidosis with SGLT2 inhibitors and follow-up data for a period of 5 years.

HSA's advisory

Healthcare professionals are advised on the following to minimise the risk of SGLT2 inhibitor-associated DKA:

- SGLT2 inhibitors should be used in accordance to its approved indications
- SGLT2 inhibitors should be used with caution in patients at risk of developing DKA. Predisposing factors for DKA include a low beta-cell function reserve resulting from pancreatic disorders (e.g. Type 1 diabetes mellitus, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery, and alcohol abuse
- Patients should be advised on the possible signs and symptoms of metabolic acidosis, such as tachypnoea or hyperventilation, anorexia, abdominal pain, nausea, vomiting, lethargy or mental status changes, and to seek medical attention promptly upon experiencing such symptoms
- Atypical or euglycaemic DKA presentations were observed in some patients (i.e. blood glucose levels lower than usually associated with DKA) while in other cases, no alternative explanation for metabolic acidosis could be identified
- Patients presenting with metabolic acidosis should be assessed for ketoacidosis and tested for blood ketones, even when the blood glucose levels are not high
- If ketoacidosis is suspected, treatment with SGLT2 inhibitor should be discontinued

HSA is working with the product licence holders to strengthen the local package inserts of the SGLT2 inhibitor products, to warn of the risk of developing DKA during treatment with these medications. HSA has also required the product licence holders to submit Periodic Benefit-Risk Evaluation Reports. HSA will continue to closely monitor the local and international developments regarding the risk of DKA with SGLT2 inhibitors use and will update healthcare professionals of any new significant findings.

Healthcare professionals are encouraged to report any suspected serious adverse reactions relating to SGLT2 inhibitors use to the Vigilance and Compliance Branch.

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AE CASE IN FOCUS: TEST YOURSELF

A middle-aged Asian patient was diagnosed with invasive lung adenocarcinoma. After receiving three cycles of chemotherapy, the CT scan showed progression of the pulmonary nodules. The patient was then switched to crizotinib in view of ROS1 positivity*. Five months later, a repeat PET-CT scan showed complete remission. All renal imaging scans till this point were normal, and the patient had no underlying renal disease.

After one year of crizotinib therapy, the patient remained in remission, but large renal cysts were detected via CT scan and MRI. The patient was asymptomatic at this point, with normal renal function and unremarkable urinalysis. Six months later, the patient felt pain and discomfort and had an abdominal mass. A repeat CT scan showed a significant increase in the size of the renal cysts.

Question:

What could have caused the renal cysts in this patient?

HSA would like to take this opportunity to thank Dr Tan Yew Oo, Medical Oncologist, SOC Clinic @ Farrer Park for his contribution to this article.

Answers to the case study can be found on page 3

* ROS1 gene rearrangement (ROS1 positivity) occurs in about 1% of non-small-cell lung cancer (NSCLC) patients. This rearrangement can serve as a therapeutic target for crizotinib, which is an inhibitor of receptor tyrosine kinases including ROS1.¹

Reference

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ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

The renal cysts could possibly be induced by crizotinib.

In this case, the patient underwent CT guided retroperitoneal fluid drainage and cytology of fluid showed no malignancy. Crizotinib was stopped after the procedure and a repeat CT scan three months later showed residual renal cysts which continue to be closely monitored. Figure 1 shows the CT scans of this patient at baseline, when the cysts were detected, and three months after aspiration of the cysts.

About crizotinib and renal cysts

Crizotinib (Xalkori®, Pfizer Pte Ltd) is approved locally in October 2012 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an accurate and validated assay. It is an inhibitor of several receptor tyrosine kinases, including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON).

Renal cysts are common incidental radiographic findings, and can be simple or complex.¹ The latter carries a risk of complications such as haemorrhage, rupture, infection or malignancy.^{1,2} The incidence of crizotinib-associated complex renal cysts has been reported as 4% in the Xalkori® package insert. It is still unclear if these cysts arise de novo, from existing simple renal cysts, or both,^{2,3} and the mechanism of the formation of crizotinib-associated renal cyst is still not well elucidated.^{1,2}

Local reports

To date, HSA has received two reports of renal cysts associated with the use of crizotinib. The second case involved an elderly Asian patient who developed complex renal cysts after seven months of crizotinib therapy. The patient initially was treated with antibiotics, and underwent percutaneous drainage of the renal cysts which was negative for malignancy and infection. Subsequently, due to further enlargement of the renal cysts and concern for abscess formation, the patient underwent open drainage. Crizotinib was discontinued after exclusion of other aetiology and postoperative CT scans demonstrated resolution of abscess and complex renal cysts.

Literature findings

Crizotinib-associated renal cysts have been reported in literature. A retrospective Taiwanese study⁴ showed that out of 32 ALK-positive NSCLC patients who received crizotinib, seven had significant renal cyst change (22%, six with baseline renal cyst and one without), and four (13%) developed new complex renal cysts. The median time from initiation of crizotinib therapy to first detection of significant renal cyst change was 77 days. In two of the patients, the cysts regressed upon stopping crizotinib, and restarting of crizotinib was associated with progression of renal cysts.

In another study which involved a blinded, retrospective, independent radiologic review, out of 255 patients in the crizotinib arm evaluated at six months,² 9% had developed new cysts, and five patients with pre-existing cysts (2%) had both new cysts and size increases in existing cysts of more than 50%. In contrast, the 17 patients in the chemotherapy arm with available scans did not develop any new cysts, suggesting a causal role of crizotinib in renal cyst formation.

Related case reports have also been published. One case reported complex renal cysts appearing six months after initiation of therapy, which spontaneously regressed 22 months later despite continuous crizotinib treatment.³ In another case, a patient with a pre-existing simple renal cyst developed infected complex renal cysts 10 months into crizotinib therapy. This was managed via cessation of crizotinib treatment, cyst drainage and antibiotic administration.¹

Discussion

Treatment with crizotinib appears to be associated with an increased risk for the development and progression of renal cysts in patients with ALK-positive NSCLC.² It is the first tyrosine kinase inhibitor associated with renal cyst development,² and it is still inconclusive whether renal cyst formation is a class effect of ALK inhibitors.⁴ In one case report, a patient's complex renal cysts regressed significantly upon switching from crizotinib to another ALK inhibitor.⁴ As crizotinib-treated patients are likely to require repeated imaging studies, observation is probably the best approach to the management of asymptomatic renal cysts.³

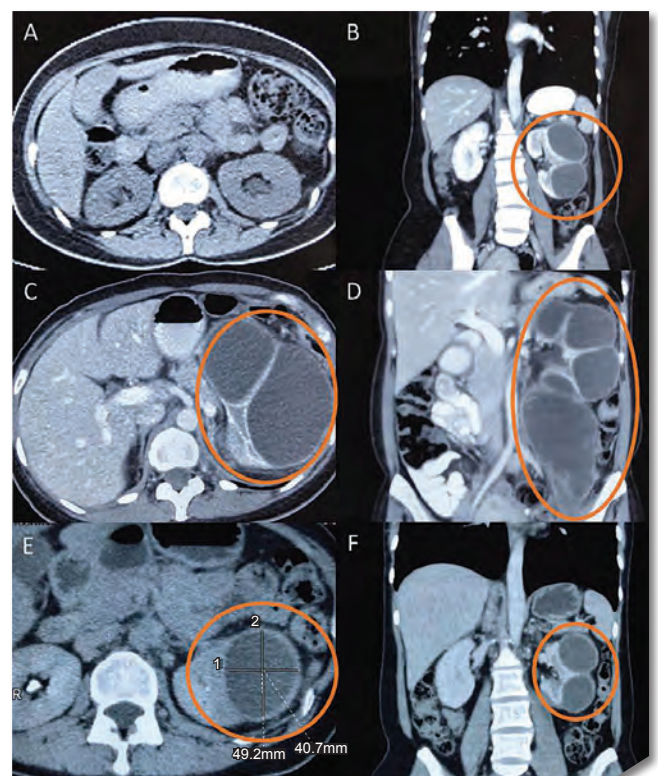
HSA's advisory

Healthcare professionals are advised to closely monitor patients on crizotinib and to report any adverse events suspected to be associated with crizotinib to the Vigilance and Compliance Branch of HSA. Your support towards the national safety monitoring programme is invaluable in safeguarding public health.

Reference

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Figure 1. CT scans of the patient (A) five months after starting crizotinib therapy showing normal kidneys, (B) 12 months after starting crizotinib therapy showing left renal cysts (circle), (C, D) 18 months after starting crizotinib therapy showing renal cysts which significantly increased in size (circle) and (E, F) three months after aspiration and cessation of crizotinib therapy, showing residual cysts (circle)





ANALYSIS OF ADVERSE EVENT (AE) REPORTS FOR YEAR 2015

Key Points

- NSAIDs and antibiotics were the two highest reported pharmacotherapeutic groups of western drugs suspected to cause AE
- The more commonly reported vaccine AEs in children under 12 years were seizures (febrile and afebrile seizures) or thrombocytopenia associated with a number of vaccines and suppurative lymphadenitis or injection-site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine
- Hypersensitivity reactions (e.g., rash, pruritus, periorbital oedema) were most frequently reported with the use of complementary health products

This review provides an analysis of the adverse events (AEs) reported to HSA in 2015 on the different health products (namely western drugs, vaccines and complementary health products) and highlight significant ones that would be of interest to the practising healthcare professional.

Report analysis for 2015

(a) Volume of reports

The number of valid* reports has grown over the years, with a sharp increase in 2006 when HSA started receiving electronic reports transmitted via the Critical Medical Information Store (CMIS). However, since 2010, the number of reports received yearly has plateaued to an average of 21,842 per year (Figure 1).

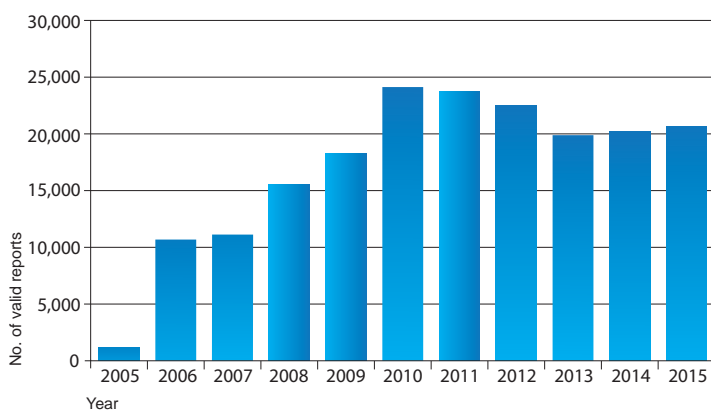
Singapore has been the world lead in terms of the number of valid reports per million inhabitants submitted to the World Health Organization (WHO) global pharmacovigilance database since 2011.

Please refer to WHO's chart:

<http://www.who-umc.org/graphics/31668.png>

In 2015, HSA reviewed 20,636 valid local AE reports suspected to be associated with health products. This is about 2.3% higher than the number of reports reviewed in 2014.

Figure 1. Number of valid reports captured in the AE database from year 2005 to 2015 based on date of receipt



(b) Source and types of reports

The majority of the reports analysed were associated with pharmaceutical drugs (96.7%). The other reports were associated with vaccines (1.5%), biologics (1.1%), and complementary health products (CHPs) (0.7%), which included Chinese Proprietary Medicines (CPM), health supplements, traditional medicines, and cosmetics. Almost all the reports were contributed by the public hospitals/healthcare organisations (57.5%) and polyclinics (39.8%), while the remaining reports were from private hospitals/clinics, retail pharmacies (1.1%) and pharmaceutical companies (1.7%). In the last four years, there has been a slight decrease in the percentage of reports received from the polyclinics by about 5%. Doctors (84.9%) contributed most to the number of reports in 2015, followed by pharmacists (11.1%). The other contributors were dentists, nurses, research coordinators and consumers (4%).

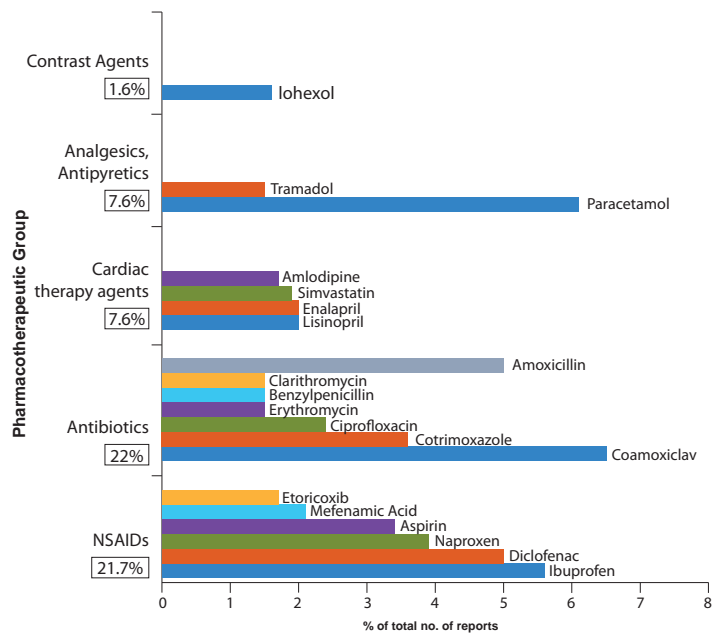
(c) Demographics

Chinese patients constituted the highest proportion (62.4%) of AE reports, followed by Malays (11.2%) and Indians (7.8%). There were more reports of AEs occurring in females (56.5%) than in males. The age range of the patients with the highest frequency reported was 50 to 59 years of age (16%).

(d) Suspected drugs

The top 20 suspected drugs commonly reported to cause AEs were from the following pharmacotherapeutic groups; nonsteroidal anti-inflammatory agents (NSAIDs) (21.7%), antibiotics (22%), cardiac therapy agents (7.6%), analgesics and antipyretics (7.6%) and contrast agents (1.6%) (Figure 2). This constituted more than half of the total volume of reports received. The most commonly reported AEs included rash, periorbital oedema, angioedema and face oedema.

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



(e) Adverse events

The two major System Organ Classes (SOC*) reported were skin-related disorders (50.4%) and those affecting the body as a whole e.g., anaphylactic reaction, malaise, fever, pain (18.9%) (Figure 3). AEs classified in these two SOC comprised about 70% of the reported AEs in 2015. Out of all the active ingredients suspected to have caused skin-related disorders, 22.5% reported were associated with NSAIDs while 35.6% were associated with antibiotics. This finding was also congruent with the two major pharmacotherapeutic groups of drugs for the top 20 suspected drugs reported for 2015.

* The System Organ Class refers to the adverse reaction terminology developed by the WHO. (N.B: More than one AE term may be described in an AE report)

+ 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.

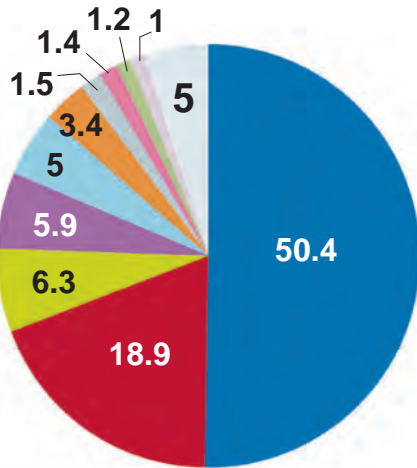


Figure 3. Top 10 AEs by System Organ Classes

System Organ Class (no. of reports)

Skin And Appendages Disorders (12,057)	Musculo-Skeletal System Disorders (363)
Body As A Whole - General Disorders (4,517)	Vascular Disorders (340)
Respiratory System Disorders (1,495)	Heart Rate And Rhythm Disorders (276)
Gastro-Intestinal System Disorders (1,410)	Psychiatric Disorders (231)
Central & Peripheral Nervous System Disorder (1,194)	Others (1,195)
Urinary System Disorders (825)	

Table 1. Drugs suspected of causing serious AEs

Description	WHO preferred terms	Top 10 suspected active ingredient(s) (number in bracket denotes the cumulative number of times the drug has been implicated from 1993 to 2015 [^])	Suspected active ingredient(s) (number in bracket denotes the number of times the drug has been implicated in 2015 [^])
Skin disorders	Stevens Johnson Syndrome (SJS)	Carbamazepine (145) [∞] , Cotrimoxazole (95), Allopurinol (79), Phenytoin (65), Amoxicillin (45), Coamoxiclav (43), Omeprazole (31), Etoricoxib (26), Lamotrigine (23), Cloxacillin (19)	Cotrimoxazole (8), Allopurinol (6), Phenytoin (3), Amoxicillin (1), Coamoxiclav (5), Omeprazole (4), Etoricoxib (6), Lamotrigine (2)
	Epidermal Necrolysis (Toxic Epidermal Necrolysis/TEN)	Allopurinol (27), Omeprazole (27), Ceftriaxone (21), Carbamazepine (19), Amoxicillin (16), Ciprofloxacin (16), Cotrimoxazole (16), Phenytoin (16), Vancomycin (14), Coamoxiclav (13)	Allopurinol (2), Ceftriaxone (2), Omeprazole (2)
Body as a whole	Anaphylactic Reaction/ Anaphylaxis	Diclofenac (128), Ibuprofen (73), Aspirin (69), Paracetamol (67), Amoxicillin (58), Naproxen (57), Ceftriaxone (53), Coamoxiclav (52), Benzylpenicillin/ Penicillin G (37), Cotrimoxazole (36)	Diclofenac (11), Aspirin (11), Paracetamol (11), Ibuprofen (10), Coamoxiclav (10), Naproxen (7), Iohexol (7), Benzylpenicillin/ Penicillin G (6), Ceftriaxone (6), Amoxicillin (5), Ciprofloxacin (5), Cotrimoxazole (5), Benzathine Benzylpenicillin (4), Mefenamic Acid (4)
Renal disorders	Acute renal failure	Diclofenac (17), Ciprofloxacin (8), rofecoxib (8), Etoricoxib (5), Allopurinol (4), Enalapril (4), Mefenamic Acid (4), Metformin (4), Hydrochlorothiazide (3), Losartan (3), Simvastatin (3)	Diclofenac (3), Cotrimoxazole (2), Enalapril (2)
Hepatic disorders	Hepatitis/Hepatitis Cholestatic/Jaundice	Azathioprine (38), Simvastatin (41), Cotrimoxazole (39), Isoniazid (38), Rifampicin (27), Phenytoin (25), Pyrazinamide (26), Fenofibrate (14), Carbamazepine (14), Allopurinol (14)	Azathioprine (4), Atorvastatin (4), Cotrimoxazole (4), Fenofibrate (2), Ketoconazole (2), Ceftriaxone (3), Coamoxiclav (2), Pyrazinamide (2)

[^] Based on onset date of the AE.

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

[∞] After the implementation of HLA-B*1502 genotype screening as standard of care for new carbamazepine (CBZ) patients of Asian ancestry on 30 April 2013, HSA has not received any reports of SJS/TEN associated with the use of CBZ in patients screened for the HLA-B*1502 allele.

Drug-AE pairs of interest

(a) Omeprazole : Risk of acute interstitial nephritis

Omeprazole is indicated for the treatment of duodenal ulcer, gastric ulcer and NSAID-associated gastric and duodenal ulcers or erosions.

To date, there were five reports of acute interstitial nephritis (AIN) associated with omeprazole received from 2013 to 2015. All the AE reports listed omeprazole as the only suspected drug except for one report, which listed cefepime as the other suspected drug. All reports involved male patients except two reports which did not list the gender of the patients. Their ages ranged from 63 to 76 years old. Three of the patients were Chinese and one was Indian. The ethnicity of the fifth patient was not reported.

AIN is a rare but serious adverse effect of omeprazole, a proton-pump inhibitor (PPI) which could potentially develop into renal failure if the patients are not managed properly. PPI-induced interstitial nephritis is triggered by a hypersensitivity immune reaction to the drug or one of its metabolites. It is idiosyncratic but potentially reversible when diagnosed early and if the inducing agent is withdrawn promptly. Renal biopsy remains the gold standard for diagnosis of AIN where histological demonstrations of interstitial infiltrations of lymphocytes and eosinophils along with macrophages and plasma cells, associated with interstitial oedema or tubulitis are observed.¹ Other common symptoms include fatigue, malaise, weakness, nausea, vomiting, anorexia and weight loss. AIN may present as early as one day (in the case of intravenous administration or drug re-challenge) or as late as

nine months after initiation of PPI therapy. Typical laboratory features include hematuria, proteinuria, pyuria, eosinophilia and anemia.¹ Prompt recognition and treatment of omeprazole-induced AIN may help to prevent renal complications and renal failure as approximately 15% of acute renal failure cases are a result of AIN.^{1,2}

(b) Tacrolimus (Prograf®): Risk of thrombotic microangiopathy

Tacrolimus is approved locally for the primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents.

In the past year, HSA received a cluster of four reports of thrombotic microangiopathy (TMA) associated with tacrolimus from a local hospital where tacrolimus was indicated as an immunosuppressant for either stem cell transplant or graft-versus-host disease secondary to donor lymphocyte infusion. The patients in these reports ranged from 36 to 63 years old and time-to-onset ranged from approximately two weeks to two months. Other than the use of tacrolimus, there were also other risk factors such as renal impairment, graft-versus-host disease, use of IV cyclosporin prior to AE and cytomegalovirus infection in these patients. The outcomes at time of reporting included one death, two patients recovering and one patient with uncertain outcome.³

TMA is an expected adverse event as calcineurin inhibitors (e.g., cyclosporin A, tacrolimus) can cause dose-dependent endothelial dysfunction and increased platelet aggregation possibly by inhibiting prostacyclins and thus causing toxicity-mediated drug-induced TMA.^{4,5}



(c) Etoricoxib (Arcoxia®): Risk of fixed drug eruption

Etoricoxib is an NSAID and a selective inhibitor of cyclooxygenase-2 (COX-2). Etoricoxib (Arcoxia®, MSD Pharma (Singapore) Pte Ltd) was approved in 2002 and has been registered in Singapore for 13 years. It is a commonly prescribed analgesic.

In 2015, HSA received 31 AE reports of fixed drug eruption (FDE) associated with the use of NSAIDs. Of these, 25 of the reports were associated with the use of etoricoxib. All patients were Chinese except for two Malays, two Indians and three of whom their race was not reported. Seventeen of the patients were male and eight were female. Their ages ranged between 20 to 77 years old. In four of the cases, the onset date of the AE occurred within the same day or the next day upon initiation of the drug.

FDE which is a form of cutaneous drug reaction, constitute about 10% of all drug reactions and NSAIDs are among the most common causes of FDE.⁶ Common sites of occurrence of FDE include the lips, genitalia, hands and feet. Lesions may be single, or less commonly, few or multiple (generalized FDE). They appear one to two weeks after initial exposure to the drug.

Based on a retrospective local study of patients with suspected FDE seen at a tertiary dermatology hospital between 2008 and 2012, etoricoxib was found to be the most common cause of the AE, accounting for 24 (38.7%) of the 62 FDE patients.⁷ The data collected for this study was based on the largest group of patients with FDE in Southeast Asia in recent years. This differs from the last FDE study in Singapore in 1988 in which Chan et al⁸ reported that tetracycline was the commonest cause.

This finding is consistent with the number of FDE cases reported in the WHO global pharmacovigilance database. There was a total of 113 case reports (as of 31 Dec 2015) with event terms of 'fixed eruption' and 'drug eruption' associated with etoricoxib (Arcoxia®) internationally; namely Americas, Asia and Europe. Eighty-six of the reports originated from Southeast Asia. Out of these, 78 reports (90.7%) were from Singapore while the rest of the 8 reports were from Malaysia. The Singapore reports involved 49 male and 29 female patients with the majority of the patients' age ranging from 18 to 44 years old (51.3%).

Vaccine adverse event (VAE) reports

There were 286 AE reports suspected to be associated with vaccines. Two hundred and forty two (242) of the reports (85%) involved children aged 12 years and below, which corresponded to the age group of vaccinees under the National Childhood Immunisation Schedule. Of the reports involving children, 81% of them (n=195) were captured by KK Women's and Children's Hospital (KKH) active surveillance sentinel site.

The more commonly reported AEs and the implicated vaccines in children aged 12 years and below included seizures (febrile and afebrile seizures) or thrombocytopenia with the measles, mumps and rubella (MMR), MMR and varicella (MMRV), varicella (VAR), 5-in-1, hepatitis B or pneumococcal conjugate (PNC) vaccines, and suppurative lymphadenitis or injection-site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine. Fever, allergic reactions such as rash, Kawasaki disease, and vaccine failure were also reported with a variety of vaccines. Reports of intussusception and diarrhoea with the rotavirus vaccine were also received. Overall, the number of reported AEs remained consistent with the expected frequencies of AE occurrence listed in the package inserts of these vaccines or in literature.

Other commonly reported vaccines suspected to cause AEs in adults and children above 12 years of age were the seasonal influenza, tetanus toxoid, varicella and human papillomavirus (HPV) vaccines. The majority of these reports described non-serious events such as hypersensitivity reactions, fever and injection-site reactions. Serious AEs included isolated reports of syncope with the HPV vaccine and vaccine failure with the varicella vaccine.

Complementary health products (CHP) AE reports

A total of 140 AE reports involving complementary health products (CHPs) were received in 2015. Of these, 79 reports were hypersensitivity reactions associated with glucosamine and included adverse events such as rash, pruritus and periorbital oedema.

There were 11 reports of hepatic reactions (e.g., raised liver enzymes and jaundice) associated with CHPs. However, it was difficult to ascertain the ingredient which might have caused the hepatic reaction as the CHPs were often used in various combinations, at different doses and for varying duration. Through reports received from astute clinicians, HSA detected eight adulterated CHPs. Common adulterants detected included corticosteroids (e.g., dexamethasone), analgesics (e.g., NSAID, such as ibuprofen) and antihistamines (e.g., chlorpheniramine). Most of the adulterated CHPs were marketed as capsules/pills for pain relief and general well-being. As a result of these findings, four press releases were issued to alert the public to the dangers of the illegal health products.

The press releases are available in the following hyperlink: http://www.hsa.gov.sg/content/hsa/en/News_Events/Press_Releases.html

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. Our goals of detecting potential safety signals and taking the necessary actions to safeguard public health would not have been possible without your vigilance and support.

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HMDP TRAINING COURSE BY EXPERT ON HEALTHCARE DATA ANALYTICS: LEARNING FROM THE EXPERIENCE OF THE US FDA MINI-SENTINEL



In November 2015, the Vigilance and Compliance Branch of HSA hosted MOH Health Manpower Development Plan (HMDP) Visiting Expert Professor Jeffrey Stuart Brown and organised a one-week course on healthcare data analytics. Professor Brown holds the appointment of Associate Professor and Director of Scientific Systems in the Department of Population Medicine at Harvard Pilgrim Health Care Institute as well as Associate Director of the Mini-Sentinel pilot project. His primary area of research involves the development of



healthcare analytics to facilitate multi-institutional safety surveillance of medical product data, including sequential analytics and data mining methodologies.

The Mini-Sentinel pilot project led by Prof Brown was initiated as part of the US Food and Drug Administration's (FDA) Sentinel Initiative, in response to a US congressional mandate to create a national public health active surveillance system to monitor the safety of regulated medical products such as drugs, biologics and devices¹. Since initiation of the pilot project in 2009, the Mini-Sentinel has established an active post-market risk identification and analysis system, and has created methodologies to access and analyse large volume of healthcare data.

Key topics covered

The course was attended by participants from academia, healthcare institutions and public health organisations. Pertinent topics on healthcare analytics were covered, including the development of the infrastructure, governance of the system and the data model used in Mini-Sentinel. Of interest, the common data model enables extraction and analysis of existing healthcare data from different data partners,

which facilitates rapid identification and evaluation of any potential safety issues. Prof Brown also shared case examples where routinely collected electronic healthcare data was used to assess the impact of regulatory actions in Mini-Sentinel.

Conclusion

In line with international developments, HSA is also exploring the use of healthcare analytics data for public health active surveillance activities. This course provided HSA staff as well as other interested parties a good learning opportunity to continue to develop expertise in this fast growing area. Other key research areas in utilising healthcare data analytics for drug safety surveillance include the use of quantitative data mining tools and text mining of de-identified hospital electronic medical records for early detection of adverse drug reactions in Singapore. HSA will continue to work with relevant stakeholders to explore methodologies to enhance its active surveillance system of drug safety signal detection and verification.

Reference

1. <http://www.mini-sentinel.org/>

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS (DHCPL) ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES BETWEEN 1 DECEMBER 2015 AND 31 MARCH 2016

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

Therapeutic products

5 Feb 2016 **Genotropin (Somatropin)**
Potential manufacturing defect in the dosing mechanism of some GoQuick pre-filled pens used to administer Genotropin, which may result in a small increase in the dosage administered compared to the preset dose

15 Feb 2016 **Epilim® (sodium valproate, valproic acid)**
Important advisory on the risk of congenital malformations and serious developmental disorders in children exposed in utero to Epilim®

24 Feb 2016 **Sodium-glucose cotransporter-2 inhibitors**
Potential risk of developing diabetic ketoacidosis (DKA), some of which are euglycaemic DKA, particularly when used in patients with predisposing factors

14 Mar 2016 **CellCept® (mycophenolate mofetil)**
Important advisory on teratogenicity risk and the need for pregnancy prevention in women and men taking CellCept®

14 Mar 2016 **Avandia (rosiglitazone tablets)**
Voluntary recall of selected lots due to a tablet dissolution quality issue

23 Mar 2016 **Allopurinol**
Recommendation that routine genotyping for HLA-B*5801 allele prior to initiation of allopurinol therapy is not required as standard of care in the local context.

24 Mar 2016 **Metoclopramide-containing products**
Amendments to the DHCPL dated 23 July 2015 on "Restrictions on the use of metoclopramide-containing products"

28 Mar 2016 **Glivec® (imatinib)**
Important advisory on the need to screen patients for hepatitis B virus (HBV) infection before treatment due to risk of HBV reactivation

28 Mar 2016 **Tasigna® (nilotinib)**
Important advisory on the need to screen patients for hepatitis B virus (HBV) infection before treatment due to risk of HBV reactivation

Medical devices

7 Dec 2015 **Birmingham HIP™ Modular Head (BHMH), monoblock version**
Important advisory concerning an increased risk of revision surgery for patients implanted with the monoblock BHMH device

7 Dec 2015 **Absorb™ and Absorb GT1™ Bioresorbable Vascular Scaffold Systems**
Update to the procedure techniques in the Instructions for Use to facilitate optimal clinical outcomes and reduce the likelihood of thrombosis

15 Dec 2015 **Ethicon GYNEMESH PS and TVT Devices**
Changes to the Instructions for Use to include additional information on adverse reactions, warnings, precautions and patient selection

18 Dec 2015 **Laparoscopic power morcellators (LPMs)**
New contraindication and cautionary statements on the risk of spreading unsuspected uterine sarcoma in the device labelling of locally registered LPMs used in gynaecological procedures

23 Dec 2015 **Expert™ Tibial Nail Ø 9.0 mm, cannulated, length 270 mm**
Voluntary recall of selected lots as the affected devices were erroneously anodized green instead of blue

4 Jan 2016 **Kirschner Wire 1.6mm w/Drill Tip, L 200mm**
Notification on incorrect labelling of product material. The device was indicated to be made of stainless steel instead of cobalt based alloy which contains 35% nickel

4 Jan 2016 **Samarys™ Peek Anterior Cervical Cage**
Voluntary recall of selected lots due to a non-conformity relevant to the gold wire markers. Missing or improperly secured/incorrectly positioned gold wire markers may protrude 1-2mm inside or outside the cage

20 Jan 2016 **HeartWare® Ventricular Assist System batteries**
Voluntary recall of selected lots due to potential deterioration of battery capacity

25 Jan 2016 **Proximal Femoral Nail Antirodation (PFNA) Nails, PFNA-II Nails, Distal Femoral Nails (DFN) & Proximal Femoral Nails (PFN), PFNA & PFNA-II Blades, and PFNA & PFNA-II End Cap Extensions**
Voluntary recall of selected parts and lots of products due to incorrect anodized colour coding

26 Jan 2016 **Dental abutment products and accessories from Biomet 3i**
Voluntary recall of selected lots as a limited number of product pouches may not have been sealed during packaging

27 Jan 2016 **Zimmer Universal Locking System Locking Reconstruction Plate Part number 00-4936-011-13 and Locking Dual Compression Plate Part number 00-4936-008-07**
Voluntary recall of specific lots due to incorrect package labelling

29 Jan 2016 **Nova T Copper Intrauterine Device**
Voluntary recall of specific batches due to an increased device breakage rate, which can be traced back to a change in the T-body mould in combination with the use of a specific raw material batch

10 Feb 2016 **RESTORIS MCK Baseplates**
Voluntary recall of selected lots due to potential for the sterile barrier of the affected products to be breached

16 Mar 2016 **Specify™ 5-6-5 Surgical Lead (model 39565-30, 39565-65) and Specify™ 2x8 Surgical Lead (model 39286-30, 39286-65)**
Labelling update of specific models to clarify that they are not intended for interoperative trial evaluation use

29 Mar 2016 **Reveal LINQ™ Insertable Cardiac Monitor model LNQ11**
Important notification on the sensitivity of an algorithm used in the affected product that may prematurely trigger the Recommended Replacement Time alert



RISK OF POTENTIATION OF RADIATION TOXICITY ASSOCIATED WITH VEMURAFENIB

Key Points

- Serious cases of radiation recall and radiation sensitisation have been reported overseas in patients who have received radiation treatment before, during, or after vemurafenib therapy
- Healthcare professionals should be aware of the risk of potentiation of radiation toxicity when vemurafenib is given concomitantly or sequentially with radiation treatment

Vemurafenib (Zelboraf®, Roche Singapore Pte Ltd) is a low molecular weight inhibitor of the BRAF serine-threonine kinase. It has been registered locally since February 2013 for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The risk of potentiation of radiation toxicity, such as radiation recall and radiation sensitisation, has been known to be associated with the use of certain chemotherapeutic agents in combination with radiation therapy. Radiation recall is an uncommon and unpredictable phenomenon which is characterised by acute inflammatory reactions confined to the previously irradiated area. Radiation sensitisation refers to greater than expected severity of the reaction for local radiation injuries. This article highlights serious overseas cases of radiation recall and radiation sensitisation in patients who were treated with radiation before, during, or after treatment with vemurafenib and the international regulatory actions taken.

International regulatory actions

(a) UK MHRA

In November 2015, the UK MHRA issued a drug safety update highlighting the European Medicines Agency (EMA)'s review of serious global cases of radiation recall and radiation sensitisation associated with the use of vemurafenib in patients receiving radiation treatment.¹ The EMA review concluded that vemurafenib is associated with the potentiation of radiation toxicity. As a result, the product labelling was subsequently strengthened to highlight this safety issue and a communication letter was issued to raise awareness of this risk among healthcare professionals.²

Cases of radiation recall and radiation sensitisation

In the review, a total of eight cases of radiation recall and 12 cases of radiation sensitisation have been reported globally, of which majority had received radiotherapy regimens greater than or equal to 2 gray/day.

The eight cases of radiation recall occurred in patients treated with vemurafenib following completion of radiotherapy. Of these, five were associated with cutaneous reactions such as erythema, hyperkeratosis, as well as eczematous, vesicular, or ulcerative lesions. Of the remaining three cases, two patients developed

pneumonitis and one patient had cystitis. The time-to-onset of radiation recall after the initial dose for vemurafenib ranged from 7 to 21 days (mean 12 days) for cutaneous reactions, 24 days for pneumonitis, and one day for cystitis.

The cases of radiation sensitisation occurred in patients treated with radiation before, during, or after treatment with vemurafenib. Of the 12 cases, nine involved the skin, three involved the oesophagus (including two fatal cases of radiation oesophagitis), and one each involving liver (fatal case of radiation necrosis of the liver) and the rectum. Except for one case, all cases received vemurafenib either concomitantly with radiation or within three days after completion of radiotherapy. When reported, the time-to-onset of radiation sensitisation following initiation of radiation therapy or treatment with vemurafenib ranged from 3 to 27 days (mean 10 days).

(b) Health Canada

In December 2015, Health Canada also issued a communication to warn healthcare professionals of the risk of radiation sensitisation or radiation recall reactions with vemurafenib. This communication was in response to a safety review conducted by Health Canada on the 20 global cases of radiation toxicity involving vemurafenib. Health Canada concluded that vemurafenib is associated with the potentiation of radiation toxicity. Consequently, a warning concerning this serious risk was included in the product monograph for Zelboraf®.³

Local situation and HSA's advisory

HSA has not received any local reports of radiation-related injuries associated with vemurafenib. The local package insert for Zelboraf® will be strengthened to warn of this risk.

Healthcare professionals are advised to take into consideration the above safety information when prescribing vemurafenib concomitantly or sequentially with radiation treatment.

Reference

1. *Drug Safety Update 2015 Nov; 9:2*
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Contributing Authors

Belinda Foo, BSc (Pharm) Hons
Adena Lim, BSc (Pharm) Hons, MPharm
Anna Lim, BSc (Pharm)
Dr M Limenta, BSc (Pharm) Hons, PhD
Patricia Ng, BSc (Pharm)
Sally Soh, BSc (Pharm) Hons
Tham Mun Yee, BSc (Pharm) Hons, MPH
Dr Dorothy Toh, BSc (Pharm) Hons, MPH, PhD

Photography

Saw Huiping

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
Helios, Singapore 138667

Tel : (65) 6866 3538

Fax : (65) 6478 9069

Website: <http://www.hsa.gov.sg>

Email: HSA_productsafety@hsa.gov.sg

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