ISSN: 0219 - 2152 May 2021 Vol.23 No.1

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

Scan / click the QR code to read the full issue online

Scan / click on the QR code

Risk of heart valve regurgitation with fluoroquinolones

- Recent findings from published literature have suggested a small increased risk of heart valve regurgitation associated with the use of systemic fluoroquinolones

Advisory

- For patients with pre-existing risk factors or predisposing conditions for heart valve disorders, healthcare professionals are advised to consider the availability of alternative therapeutic options to systemic fluoroquinolones
- Healthcare professionals are also encouraged to advise patients to seek medical attention if they experience acute dyspnoea, new onset of heart palpitations, or development of oedema, especially if they have started fluoroquinolone therapy recently

Analysis of adverse event (AE) reports for year 2020

- In 2020, HSA received a total of 21,694 valid reports. AE reporting rates have been healthy at more than 20,000 reports a year, which has been the trend in the last ten years
- Out of the 279 vaccine AE reports, 128 reports involved children. In children aged 12 years and below, the most commonly reported AEs were seizures (febrile and afebrile) with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* vaccine, pneumococcal conjugate or influenza vaccines. In adults, the most commonly reported AEs were allergic reactions such as rash, urticaria, angioedema, and injection site reactions with seasonal influenza, pneumococcal, tetanus, or MMR vaccines
- There were 104 AE reports involving complementary health products in 2020. Three reports were associated with adulterated products, of which two were detected with sibutramine

5-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio and Haemophilus Influenza

Local safety signals for year 2020

- HSA received 12 cases of haemolysis associated with intravenous immunoglobulin (IVIG) in children with Kawasaki Disease
- Haemolysis is an expected AE associated with IVIG. However, high anti-A or anti-B haemagglutinin levels in the product could increase the risk of haemolysis. HSA investigated the affected batches and found no evidence to suggest product quality issues. HSA's assessment is that haemolysis is an expected AE in these patients due to the presence of multiple risk factors

Advisory

- Healthcare professionals are encouraged to take into consideration these risk factors when using IVIG, and report cases of haemolysis with IVIG to HSA

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

HSA's survey on the ways healthcare professionals obtain drug safety information

Pg 7-8

- In 2020, HSA conducted a survey to understand the current and most preferred ways healthcare professionals obtain drug safety information and whether there were any barriers to the use of HSA's safety information
- Based on the 107 responses, safety communications from HSA, emails or SMS via the MOH Alert and media reports were the common sources of drug information. "Email" was the most preferred communication mode for important drug safety updates. Lack of awareness or time to access the information or preferences for alternative information sources were the main reasons cited for not accessing drug safety communications from HSA
- HSA will continue to evaluate the effectiveness of the ways we currently communicate drug safety information and work to raise awareness of healthcare professionals to safety information provided through our website and emails

AE Case in Focus: Test Yourself

What could have caused the severe hypophosphataemia in this patient?

Pg 6, 8

This is a case of a 70-year-old man who had iron-deficiency anaemia. After two weeks of treatment with parenteral ferric carboxymaltose (FCM), he presented to the emergency department with worsening lethargy and dizziness. He had a history of chronic recurrent gastrointestinal bleeding from gastric antral vascular ectasia (GAVE). Upon examination, there was no chest discomfort, breathlessness, focal weakness, vomiting, diarrhoea or evidence of gastrointestinal bleeding. His electrocardiogram results were unremarkable and there were also no focal neurological findings. His laboratory test results showed a low serum phosphate level of < 0.32 mmol/L (normal range 0.94 – 1.50 mmol/L) and he was hospitalised for intravenous (IV) phosphate replacement. His renal function, magnesium, calcium and creatinine kinase levels were normal. There was no clinically apparent cause for his hypophosphataemia. Despite IV and oral phosphate replacement, he continued to be hypophosphataemic and his lethargy and dizziness persisted.

HSA would like to thank all past and present members of the HSA ADR News Bulletin Editorial Board for their valuable contribution and expert advice all these years. As we bid farewell to our two retired members, Clinical Prof. Chng Hiok Hee, Senior Consultant, Tan Tock Seng Hospital (TTSH) and Clinical Prof. Gilbert Lau Kwang Fatt, Director, Applied Sciences Group (ASG), HSA, we would like to welcome on board our two new members, Adjunct Assoc. Prof. Bernard Thong, Divisional Chairman (Medicine), Senior Consultant, TTSH and Dr. Belinda Lee, Consultant Forensic Pathologist, ASG, HSA.

Thank You!

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.

How to report suspected AEs to HSA?

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

@ HSA_productsafety@hsa.gov.sg

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

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

All website references were last accessed on 1 May 2021.

RISK OF HEART VALVE REGURGITATION WITH FLUOROQUINOLONES

Key Points

- Recent findings from published literature have suggested a small increased risk of heart valve regurgitation associated with the use of systemic fluoroquinolones
- For patients with pre-existing risk factors or predisposing conditions for heart valve disorders, healthcare professionals are advised to consider the availability of alternative therapeutic options to systemic fluoroquinolones
- Healthcare professionals are also encouraged to advise patients to seek medical attention if they experience acute dyspnoea, new onset of heart palpitations, or development of oedema, especially if they have started fluoroquinolone therapy recently

HSA would like to inform healthcare professionals about a small increased risk of heart valve regurgitation associated with the use of systemic fluoroquinolones. Fluoroquinolones are known to increase the risk of collagen-related disorders such as tendonitis, tendon rupture, and aortic aneurysm and dissection. Recently, these antibiotics have been found to be associated with regurgitation of the heart valves, another collagen-associated adverse event.

There are seven systemic fluoroquinolones registered locally, namely ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, levofloxacin, moxifloxacin and pefloxacin. There are no inhaled fluoroquinolone-containing products registered locally.

About heart valve regurgitation[1]

Heart valve regurgitation occurs when there is backflow of blood through the valve as the leaflets are closing or when there is leakage of blood through the leaflets that do not close completely. This subjects the heart to higher levels of stress and may lead to other morbidities or mortality if the condition is left untreated. Severe forms of aortic and mitral regurgitation can be life-threatening and may require surgical intervention. Causes of valvular regurgitation include degeneration, calcification, fibrosis or infection of the valve, or alteration of the valvular support structure.

Scientific literature on fluoroquinolone-induced collagen-related disorders

(a) Potential mechanisms of collagen-related disorders associated with fluoroquinolones

Fluoroquinolones have been associated with collagen-related disorders such as tendonitis, tendon rupture, and aortic aneurysm and dissection. While the mechanism behind these disorders has not been fully elucidated, *in vitro* studies have showed that fluoroquinolones exert various effects on different cell types, including reduced expression of extracellular matrix (ECM) proteins, upregulation of matrix metalloproteinase (MMP) expression, and inhibition of tendon cell proliferation.[2,3] It has been hypothesised that fluoroquinolone-induced collagen-related disorders may be due to an increased MMP expression, resulting in damage to the collagen fibrils that are found in the Achilles tendon, aorta and heart valves.

In a recently published *in vitro* study, human aortic myofibroblasts were exposed to ciprofloxacin to assess the capacity for ECM dysregulation.[4] The authors found that fluoroquinolone (ciprofloxacin) exposure resulted in decreased tissue inhibitors of matrix metalloproteinase (TIMP) expression and an increase in the MMP/TIMP ratio, as well as an attenuation of collagen-1 expression. These findings suggested that fluoroquinolone exposure induces human aortic myofibroblast-mediated ECM dysregulation through increased collagen degradation and impaired compensatory collagen deposition, which is in agreement with data from earlier studies.

(b) Disproportionality analysis and case-control study on risk of aortic and mitral regurgitation with fluoroquinolones[5]

Etminan *et al*. investigated the potential risk of heart valve regurgitation with fluoroquinolones, drawing from two sources of data to conduct a disproportionality analysis and case-control study.

The disproportionality analysis, which used data from the US Food and Drug Administration (FDA) adverse event reporting system (FAERS) database between 2004 and 2018, found an increased risk of valvular regurgitation with fluoroquinolone exposure (102 cases) compared to all other drugs in the database (6,099 cases), with a reported odds ratio (ROR) of 1.45 (95% CI: 1.20 – 1.77) (Table 1). Although a reduced risk was observed for moxifloxacin, the confidence interval was too wide to allow a meaningful interpretation of the data.

Table 1. Results of the disproportionality analysis of the FAERS database

Drug	Number of Cases	ROR	95% CI
Ciprofloxacin	44	1.67	1.24 – 2.25
Gatifloxacin§	6	2.87	1.29 – 6.39
Levofloxacin	52	1.80	1.37 – 2.37
Moxifloxacin	11	0.73	0.41 – 1.32
Lomefloxacin	0	-	-
Gemifloxacin§	0	-	-
Norfloxacin	0	-	-
Combined*	102	1.45	1.20 – 1.77

§Not registered locally
**The combined number is smaller than the total number of cases as one patient could have been prescribed multiple fluoroquinolones*

To further confirm the findings from their disproportionality analysis, the authors conducted a matched nested case-control study that included 12,502 cases of valvular regurgitation and 125,020 controls from a US health claims database between 2006 to 2016. The study found that current users of fluoroquinolones had a 2.4-fold and 1.75-fold increase in risk of combined aortic and mitral valve regurgitation compared to current amoxicillin and azithromycin users, respectively (Table 2). This risk remained elevated (albeit of a lower magnitude) for recent and past fluoroquinolone users. The authors added that their choice of comparator antibiotics was due to their overlapping indications (e.g. urinary tract infections and respiratory infections), which served to control for confounding by indication.

Table 2. Adjusted RRs for combined aortic and mitral valve regurgitation among fluoroquinolone users compared to amoxicillin and azithromycin users across different exposure periods^

Drug	Adjusted RR (95% CI)†		
	Current users	Recent users	Past users
Fluoroquinolone	2.40 (1.82 – 3.16)	1.47 (1.03 – 2.09)	1.06 (0.91 – 1.21)
Amoxicillin	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Fluoroquinolone	1.75 (1.34 – 2.29)	1.37 (0.95 – 1.98)	1.18 (1.01 – 1.38)
Azithromycin	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

^ Current users – Active prescription up to 30 days prior to the event
Recent users – Use within 31 to 60 days prior to the event
Past users – Use within 61 to 365 days prior to the event

†RRs were adjusted for variables such as sex, age, atrial fibrillation, diabetes, hypertension, coronary artery disease, stroke, chronic heart failure, chronic renal failure, and drugs that might increase the risk of valvular regurgitation, including statins, cabergoline, pergolide, and phentermine

Regulatory actions taken by overseas regulatory agencies[6,7]

In September 2020, the European Medicines Agency (EMA) assessed that fluoroquinolone use may increase the risk of heart valve regurgitation. Their review considered the information from published literature, reports of fluoroquinolone-associated valvular regurgitation reported to the European Union adverse events database and the assessments conducted by the pharmaceutical companies. In view of the common features in aortic aneurysm and dissection and heart valve regurgitation,

the EMA recommended that the existing warnings on aortic aneurysm and dissection in the package inserts (PIs) of systemic and inhaled fluoroquinolone-containing products should be expanded to include heart valve regurgitation. A Dear Healthcare Professional Communication was also distributed in the EU to highlight this new safety concern.

Following the European review, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety update in December 2020 warning healthcare professionals of the risk of heart valve regurgitation linked to the use of systemic and inhaled fluoroquinolones. Warnings were added to the PIs for these medicines and a letter was sent to relevant healthcare professionals in the UK.

Local situation

To date, HSA has not received any local reports of heart valve-related disorders associated with fluoroquinolone use. In 2019, HSA published an article to inform healthcare professionals about an update to the local PIs of all systemic fluoroquinolones to warn about the risk of aortic aneurysm and dissection.[8]

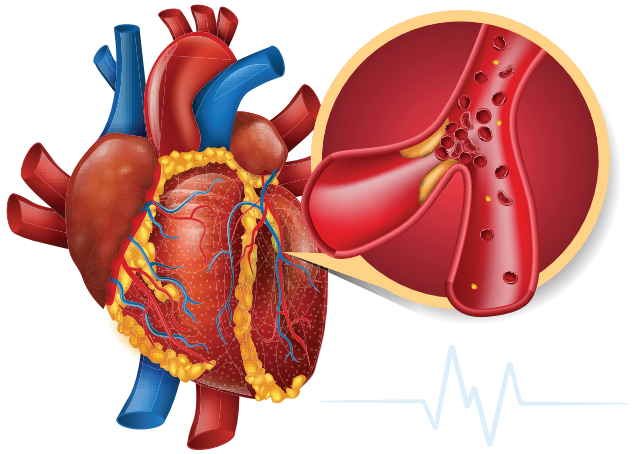
HSA has reviewed the available information, taking into account the scientific literature, the biological plausibility of collagen-related disorders with fluoroquinolones, and the regulatory actions taken by EMA and UK MHRA. HSA's assessment is that the existing warnings on aortic aneurysm and dissection should be expanded to include heart valve regurgitation as these safety issues are likely related, and is working with the pharmaceutical companies to strengthen the local PIs for all systemic fluoroquinolones to reflect this risk.

HSA's advisory

Healthcare professionals are advised to take into consideration the above safety information when prescribing systemic fluoroquinolones and the availability of other therapeutic options for patients with pre-existing risk factors such as heart valve diseases, or predisposing conditions such as connective tissue disorders (e.g., Marfan syndrome, Ehlers-Danlos syndrome), Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis, and infective endocarditis. Healthcare professionals are also encouraged to advise patients to seek medical attention if they experience acute dyspnoea, new onset of heart palpitations, or development of oedema, especially if they have started the fluoroquinolone therapy recently. In addition, healthcare professionals may wish to consider counselling their patients on other adverse effects associated with fluoroquinolones as appropriate, such as those involving the tendons, muscles and joints, and the nervous system.

References

1. *J Am Soc Echocardiogr 2003;16:777–802*
2. *Toxicology 2005; 212: 24–36*
3. *Chang Gung Med J 2011;34:461–7*
4. *J Thorac Cardiovasc Surg 2019;157:109–19*
5. *J Am Coll Cardiol 2019;74:1444–50*
6. *https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-31-august-3-september-2020-prac-meeting_en.pdf*
7. *https://www.gov.uk/drug-safety-update/systemic-and-inhaled-fluoroquinolones-small-risk-of-heart-valve-regurgitation-consider-other-therapeutic-options-first-in-patients-at-risk*
8. *HSA ADR News Bulletin 2019 May; 21; 2*



ANALYSIS OF ADVERSE EVENT (AE) REPORTS FOR YEAR 2020

Key Points

- In 2020, HSA received a total of 21,694 valid reports. AE reporting rates have been healthy at more than 20,000 reports a year, which has been the trend in the last ten years
- Out of the 279 vaccine AE reports, 128 reports involved children. In children aged 12 years and below, the most commonly reported AEs were seizures (febrile and afebrile) with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* vaccine, pneumococcal conjugate or influenza vaccines. In adults, the most commonly reported AEs were allergic reactions such as rash, urticaria, angioedema, and injection site reactions with seasonal influenza, pneumococcal, tetanus, or MMR vaccines
- There were 104 AE reports involving complementary health product in 2020. Three reports were associated with adulterated products, of which two were adulterated with sibutramine

This review analyses the AE reports received by HSA in 2020. The scope of this review includes pharmaceuticals (i.e. chemical or biologic drugs and vaccines) and complementary health products, and highlights reporting patterns which may be of interest.

Report analysis for 2020

(a) Volume of reports

In 2020, HSA received a total of 21,694 valid⁺ reports. AE reporting rates have been healthy at more than 20,000 reports a year, which has been the trend in the last ten years (except in 2013 when the figure dipped slightly) (Figure 1).

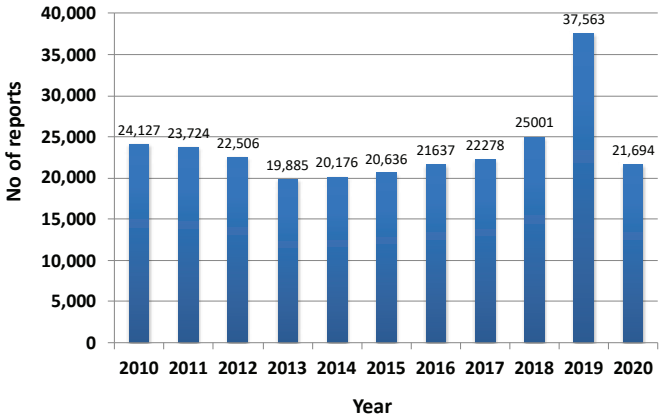


Figure 1. Number of valid reports captured in the AE database from year 2010 to 2020 based on date of receipt

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

(b) Source and types of reports

Majority of reports received were associated with pharmaceuticals (99.5%) which included biologics (1.7%) and vaccines (1.4%). The AE reports related to complementary health products (CHPs) comprised 0.5% , which included Chinese Proprietary Medicines, health supplements, traditional medicines and cosmetics.

Public hospitals and institutions contributed the most reports (57.8%), followed by polyclinics (27.6%). The proportion of reports received from General Practitioner (GP) clinics was 5.9%. The remaining reports were from public specialist clinics (4.2%), product registrants (2.4%), and private hospitals and specialist clinics (0.6%). Doctors (88.9%) contributed the highest number of reports, followed by pharmacists (6.7%). Reports from dentists, nurses and research coordinators have also been received.

(c) Demographics

Majority of the patients reported in the AE reports were Chinese (49.9%), followed by Malays (10.6%) and Indians (6.8%). The rest were Caucasians (0.3%), Eurasians (0.3%) and patients whose ethnicity was

not reported (32.1%). There were more AE reports received for females (59.8%) than in males (39.4%) The highest number of reports comprised elderly patients aged 60 to 69 years old (14.4%) followed by patients aged 50 to 59 years old (12.8%).

(d) Suspected drugs

The top 20 suspected drugs were from the following pharmacotherapeutic groups: nonsteroidal anti-inflammatory agents (NSAIDs) (22.7%), antibiotics (19%), analgesics and antipyretics (9.5%), cardiac therapy agents (4.6%), and contrast agents (2.3%) (Figure 2).

(e) Adverse events

More than half of the AEs reported were associated with skin reactions (54%), followed by those affecting the body as a whole (e.g. oedema, anaphylaxis) (16.6%), and respiratory system disorders (5.7%), with most being non-serious reactions (e.g. rash, periorbital oedema, nausea and vomiting). Selected serious AEs and their suspected drugs are summarised in Table 1.

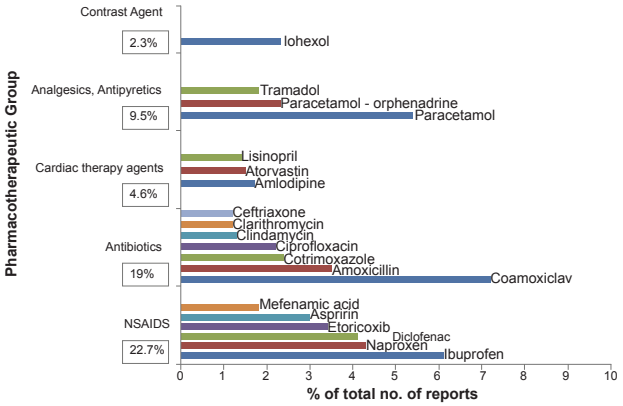


Figure 2. Top 20 drugs (by active ingredients) suspected of causing AEs

Table 1. Drugs suspected of causing serious AEs

Description	WHO preferred terms	Suspected active ingredient(s) (number in bracket denotes the number of times the drug has been implicated in 2020#)	Top 10 suspected active ingredient(s) from 2016- 2020 (number in bracket denotes the cumulative number of times the drug has been implicated from 2016 to 2020^)
Skin disorders	Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN)	Allopurinol (7), Coamoxiclav (5), Cotrimoxazole (4), Etoricoxib (3), Omeprazole (4), Clarithromycin (2), Doxycycline (2), Nivolumab (2), Paracetamol (2), Piperacillin and Tazobactam (3)	Allopurinol (39), Cotrimoxazole (32), Etoricoxib (26), Omeprazole (24), Coamoxiclav (21), Carbamazepine (15), Diclofenac (11), Piperacillin and Tazobactam (10), Amoxicillin (8), Ciprofloxacin (8)
Body as a whole	Anaphylactic reaction	Coamoxiclav (29), Paracetamol (20), Diclofenac (16), Ceftriaxone (15), Ibuprofen (14), Naproxen (14), Aspirin (14), Cefazolin (12), Etoricoxib (11), Piperacillin and Tazobactam (11)	Diclofenac (97), Ibuprofen (89), Coamoxiclav (88), Paracetamol (79), Naproxen (63), Ceftriaxone (52), Aspirin (51), Amoxicillin (45), Cefazolin (41), Ciprofloxacin (36)
Renal disorders	Azotaemia, Creatinine clearance decreased, Renal tubular disorder/necrosis, Renal failure acute/chronic, Nephritis interstitial, Renal function abnormal	Losartan (10), Diclofenac (9), Ciprofloxacin (6), Enalapril (7), Valsartan (2), Lisinopril (3), Ibuprofen (4), Pembrolizumab (4), Etoricoxib (3), Alpelisib (3)	Ciprofloxacin (47), Losartan (39), Lisinopril (27), Enalapril (26), Ibuprofen (20), Etoricoxib (20), Hydrochlorothiazide (19), Cotrimoxazole (16), Omeprazole (13), Valsartan (11)
Hepatic disorders	Jaundice, Hepatitis, Hepatitis cholestatic, Hepatic failure, Hepatocellular damage, Liver injury, Coma hepatic	Atorvastatin (24), Coamoxiclav (12), Cotrimoxazole (4), Azathioprine (5), Fenofibrate (3), Pembrolizumab (3), Losartan (3)	Atorvastatin (44), Coamoxiclav (35), Azathioprine (18), Cotrimoxazole (11), Fenofibrate (8), Diclofenac (7), Allopurinol (6), Methotrexate (6), Clarithromycin (5), Valproic Acid (5), Isoniazid (5)

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

Vaccine adverse event reports

HSA received 279 vaccine adverse event (VAE) reports in 2020. Of these, 151 (54.1%) reports involved adults, 4 (1.5%) reports involved children from 12 to 18 years old and 124 (44.4%) reports involved children aged 12 years old and below. Majority of the reports in children aged 12 years and below were from the active surveillance site at KK Women's and Children's Hospital (n=91), which HSA partners to screen paediatric hospital admission for AEs post-vaccination.

The most commonly reported AEs in children aged 0-12 years old were seizures (febrile and afebrile) with measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1* vaccine, pneumococcal conjugate or influenza vaccines. Other reported AEs included urticaria, meningitis, vaccine failure, Kawasaki disease, thrombocytopenia and injection site reactions associated with various types of vaccines. Vaccine-specific AEs received were intussusception with rotavirus vaccines, apnoea in premature infants with 6-in-1× vaccines and lymphadenitis and osteomyelitis with BCG vaccines. The AEs reported in children above 12 years include single reports of injection site reaction and seizure with Human Papillomavirus (HPV) vaccine, and rash with hepatitis B vaccine.

The most commonly reported AEs in adults were allergic reactions such as rash, urticaria, angioedema, and injection site reactions with seasonal influenza, pneumococcal, tetanus, or MMR vaccines. Isolated reports received were cellulitis or vasculitis with pneumococcal vaccination, erythema multiforme with hepatitis-B vaccine and Guillain-Barre syndrome and complex regional pain syndrome with influenza vaccines.

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

×6-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio, Haemophilus Influenza Type B and Hepatitis B

Overall, our review of the VAE reports in 2020 did not identify any new safety concerns with the reported vaccines. Compared with 2019, there were numerically higher number of reports on suppurative lymphadenitis and anaphylaxis with seasonal influenza vaccines. These events, as well as other VAEs received in 2020 were within the expected AE frequencies listed in the vaccine package inserts or in literature.

Complementary health products adverse event reports

There were 104 AE reports involving CHPs in 2020. Sixty-five reports involved products which were classified as health supplements while six were classified as cosmetic products. The rest were classified as Chinese Proprietary Medicines and/or complementary medicines. Forty-one (39%) reports were associated with glucosamine-containing products, describing mostly hypersensitivity reactions (rash and pruritus). There were 13 reports of hepatic reactions (e.g. transaminitis and jaundice) involving mostly CHPs with multiple ingredients. Most of the patients who experienced these AEs have recovered or were recovering at the time of reporting.

With reports from astute clinicians, HSA detected three adulterated products suspected to cause AEs in persons who had taken them. Two of these products, Freaky Fitz and Clinic K, were adulterated with sibutramine and the AEs reported included palpitations, insomnia and hallucinations. The third product, Lung Tan Tsao, which was labelled for eczema, allergies, fatigue and arthritis, was adulterated with dexamethasone and chlorpheniramine. Press releases were issued to alert the public on these products.

Acknowledgement

HSA would like to thank all healthcare professionals for actively reporting AEs to HSA.

LOCAL SAFETY SIGNAL FOR YEAR 2020

Key Points

- HSA received 12 cases of haemolysis associated with intravenous immunoglobulin (IVIG) in children with Kawasaki Disease
- Haemolysis is an expected AE associated with IVIG. However, high anti-A or anti-B haemagglutinin levels in the product could increase the risk of haemolysis. HSA investigated the affected batches and found no evidence to suggest product quality issues. HSA's assessment is that haemolysis is an expected AE in these patients due to the presence of multiple risk factors
- Healthcare professionals are encouraged to take into consideration these risk factors when using IVIG, and report cases of haemolysis with IVIG to HSA

HSA conducts regular individual and aggregated reviews of all AE reports to identify safety concerns associated with health products. The following was one of the potential local safety signals reviewed in 2020.

Haemolysis following intravenous immunoglobulin therapy in children treated for Kawasaki Disease

In 2020, HSA received 12 cases of haemolysis associated with intravenous immunoglobulin, or IVIG (Intragam® P, Blood Services Group, HSA) in children with Kawasaki Disease, occurring over a period of eight months from November 2019 to June 2020.

Haemolysis is an expected AE associated with IVIG. The incidence of haemolysis has been reported to range from 1.6% in adult patients[1] to as high as 16% in younger patients with Kawasaki Disease.[2] Haemolysis typically occurs within ten days of IVIG administration,[1,3] and is characterised by a drop in haemoglobin (Hb) following IVIG infusion, with laboratory evidence supporting haemolysis, including positive direct antiglobulin test (DAT), elevated unconjugated bilirubin, elevated lactate dehydrogenase and the presence of spherocytes and polychromasia on the peripheral blood film.[4] The majority of haemolytic episodes are self-limiting, although severe consequences may rarely occur, such as severe anaemia requiring transfusion, renal failure, and disseminated intravascular coagulation. A two-hit mechanism has been suggested for the development of haemolysis. The first step involves the passive transfer of anti-A and anti-B haemagglutinins, and the second step involves the enhanced activity of the immune system in patients with an underlying inflammatory state, resulting in accelerated removal of sensitised red blood cells from the circulation.[1,4]

The 12 cases were reported as a cluster from one hospital for HSA's investigation as the reporter was concerned about possible quality issues for the four affected batches, because high anti-A or anti-B haemagglutinin levels in the product (which is made from human plasma pooled from blood donors) could increase the risk of haemolysis. The children were aged four months to five years old and the time-to-onset of the suspected AE ranged from three to ten days. Of the 12 cases, eight of them were supported by laboratory evidence of red blood cell (RBC) destruction, with both having a positive DAT and a drop in Hb ≥ 1 g/dL. Two cases had a positive DAT, but the drop in Hb was less than 1 g/dL. One case had a drop in Hb of 3.6 g/dL on Day 9 and the blood film test showed haemolysis and reticulocytosis. However, the DAT performed on day 12 showed negative results. The last case was confounded by the presence of gastrointestinal bleeding. All the 12 patients recovered, with six treated with steroids and none requiring blood transfusion.

HSA investigated the affected batches and found no evidence to suggest product quality issues. Other plausible explanations for haemolysis include patient risk factors and the high cumulative doses of IVIG used. Patients with an underlying inflammatory state and those with non-O blood groups are at greater risk of developing haemolysis.[4] All the 12 patients had Kawasaki Disease causing them to be in a hyperinflammatory state. The blood group was reported for six of the patients, of which five were in the non-O blood groups. The patients were also treated with high doses of IVIG for Kawasaki Disease, with eight of the 12 patients requiring a second dose of IVIG due to inadequate response from the first dose. HSA's assessment is that haemolysis is an expected AE in these patients due to the presence of multiple risk factors. Healthcare professionals are encouraged to take into consideration these risk factors when using IVIG and report cases of haemolysis with IVIG to HSA.

References

1. *Transfusion 2008; 48:1598-601*
2. *Pediatric Rheumatology 2012; 10:10*
3. *Canadian Adverse Reaction Newsletter 2009; 19: 1-3*
4. *Transfus Apher Sci 2012; 46:93-96*
5. *Singapore package insert for Intragam® P. Approved 1 April 2015*

About intravenous immunoglobulin

Intravenous immunoglobulin, or IVIG (Intragam® P, Blood Services Group, HSA) is manufactured from human plasma donated by Singapore's voluntary and non-remunerated donors. It is made by chromatographic fractionation of large pools of human plasma.[5] It is indicated for replacement IgG therapy in primary immunodeficiency, myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections and congenital or acquired immune deficiency syndrome with recurrent infections. It is also indicated for immunomodulatory therapy in Idiopathic Thrombocytopenic Purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count, allogeneic bone marrow transplantation and Kawasaki disease.[1] IVIG in combination with aspirin is the mainstay of therapy for Kawasaki Disease, and has been shown to significantly reduce the incidence of coronary artery aneurysms.[2]

AE CASE IN FOCUS: TEST YOURSELF

A 70-year-old man presented to the emergency department with worsening lethargy and dizziness two weeks after receiving parenteral ferric carboxymaltose (FCM) for iron-deficiency anaemia. He had a history of chronic recurrent gastrointestinal bleeding from gastric antral vascular ectasia (GAVE). There was no chest discomfort, breathlessness, focal weakness, vomiting, diarrhoea or evidence of gastrointestinal bleeding. His clinical examination and his 12-lead electrocardiogram results were unremarkable. There were also no focal neurological findings.

The patient's laboratory test results showed a low serum phosphate level of < 0.32 mmol/L (normal range 0.94 – 1.50 mmol/L) and he was hospitalised for intravenous (IV) phosphate replacement. His renal function, magnesium, calcium and creatinine kinase levels were normal. There was no clinically apparent cause for his hypophosphataemia. As his haemoglobin levels remained low (7.5 g/dl), he was given a second dose of FCM.

Despite IV and oral phosphate replacement, he continued to be hypophosphataemic and his lethargy and dizziness persisted. The ratio of tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR) was low at 0.36 mmol/L based on the Walton and Bijvoet nomogram1 (normal age-based range 0.8 – 1.35), indicating renal phosphate wasting. The 25-hydroxyvitamin D level was normal at 29.3 ng/ml. Serum fibroblast growth factor 23 (FGF23), a phosphaturic peptide hormone secreted by osteocytes, was elevated at 220 relative units (RU)/ml (normal range ≤ 180 RU/ml).

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

HSA would like to thank Dr Kevin Teh Kim Jun, Senior Resident, Department of Gastroenterology and Hepatology, Changi General Hospital and Dr Joan Khoo, Senior Consultant, Department of Endocrinology, Changi General Hospital for contributing this article. This case report is also published in the EJCRIM 2020; 7: doi:10.12890/2020_001860.

Answers can be found on page 8.

HSA'S SURVEY ON THE WAYS HEALTHCARE PROFESSIONALS OBTAIN DRUG SAFETY INFORMATION

Key Points

- In 2020, HSA conducted a survey to understand the current and most preferred ways healthcare professionals obtain drug safety information and whether there were any barriers to the use of HSA's safety information
- Based on the 107 responses, safety communications from HSA, emails or SMS via the MOH Alert and media reports were the common sources of drug information. "Email" was the most preferred communication mode for important drug safety updates. Lack of awareness or time to access the information or preferences for alternative information sources were the main reasons cited for not accessing drug safety communications from HSA
- HSA will continue to evaluate the effectiveness of the ways we currently communicate drug safety information and work to raise awareness of healthcare professionals to the safety information provided through our website and emails

HSA would like to update healthcare professionals on the results from our survey which was conducted in 2020 to understand the current and most preferred ways healthcare professionals obtain drug safety information. The usage and potential barriers to using drug safety information from HSA were also assessed.

Survey

A survey was developed using the FormSG* platform and circulated to healthcare professionals through announcements published in the May and September 2020 issues of the HSA Adverse Drug Reaction News Bulletin as well as through virtual roadshows conducted for healthcare professionals by HSA in 2020.

**FormSG is a form builder tool developed by GovTech to enable public officers to create digital government forms to replace paper forms.*

Demographics

As of 31 December 2020, 107 survey responses were received. Most of the survey respondents were doctors (58%), followed by pharmacists (33%) and dentists (7%). Among the doctors, majority were either general practitioners (36%) or physicians from public hospitals (34%). The rest practised mainly at private hospitals/specialist clinics (13%) or polyclinics (12%). Among the pharmacists, 50% practised at public hospitals, while the rest were from retail pharmacies (18%), or from other fields such as regulatory and education. Half of the respondents had more than 20 years of experience in practice.

Information sources used by healthcare professionals

a) Overall

The median number of drug safety information sources used by each survey respondent was five (range: 1 to 10). The top three regular information sources on major drug safety issues (e.g. cancer, sudden cardiac death or suicidal behaviour) used by survey respondents were the safety communications from HSA, emails or SMS via the MOH Alert+ and media reports (e.g. local or wired news, TV, radio, social media, etc.). When the responses were analysed by the respondents' professions, this trend remained for dentists and doctors but drug databases such as Uptodate® and Micromedex®, replaced emails or SMS via MOH Alert+ as one of the top drug safety information sources used regularly by pharmacists.

+Alert service which allows medical professionals, licensees and healthcare partners to receive and read medical alert notification and circulars from the Ministry of Health (MOH).

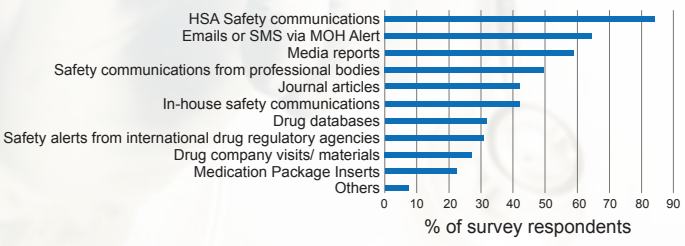


Figure 1. Information sources for major drug safety issues used by survey respondents on a regular basis∞

∞Survey respondents could select more than one option

b) Drug safety communications from HSA

Among HSA's drug safety communication tools, the HSA ADR News Bulletin and the Dear Healthcare Professional Letter (DHCPL) were the most commonly tools used. The other forms of drug safety communication from HSA that were used (in order of preference) included medication package inserts, and safety articles on the HSA website and the HSA website subscription for announcement updates. Five (4.6%) survey respondents did not use any of the drug safety communications from HSA. The main reasons for not referring to one or more of them included lack of awareness or time to access the information or preferences for alternative information sources. Other reasons included that "other sources reported the same information", "preference for bite-sized information" as well as "difficulty in retrieving the DHCPL from MOH Alert".

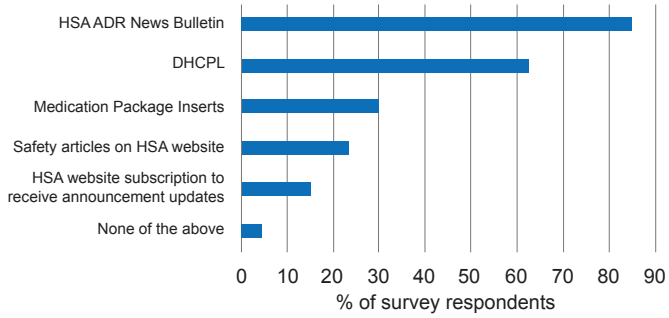


Figure 2. HSA Drug Safety Communications used by survey respondents∞

∞Survey respondents could select more than one option

c) Most preferred mode of communication

The survey respondents' most preferred mode of communication to receive important drug safety updates was "Email" (70%), followed by "Whatsapp" (17%). (Figure 3)

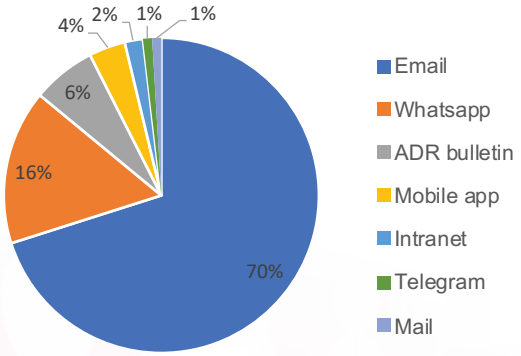


Figure 3. Most preferred communication mode for important drug safety updates^

^Survey respondents could select one option only

Discussion

Since we had received limited number of survey responses as invitations to the survey were sent out mainly through announcements in the HSA ADR News Bulletin, we acknowledge that the results presented may not be fully representative of the community of healthcare professionals in Singapore. Further feedback will need to be sought through other platforms such as future outreach programmes to healthcare institutions. Nonetheless, based on the current survey results, safety communications from HSA as well as the emails sent via the MOH Alert system were among the most commonly used drug safety information sources by the surveyed healthcare professionals. This could be attributed to the ease of access to these materials. Both the DHCPL and the HSA ADR News Bulletin are posted on the MOH Alert system, which is accessible via the Health Professionals Portal; they are also emailed directly to healthcare professionals through their email addresses registered with their respective professional boards. Abstracts of the DHCPLs and all issues of the HSA ADR News Bulletin are also accessible from the HSA website.

Notably, only 15% of the survey respondents indicated their use of the HSA website subscription function for announcement updates, possibly due to the lack of awareness. Healthcare professionals who are interested to receive updates on the latest HSA news and regulatory updates may log on to https://www.hsa.gov.sg/subscribe to subscribe. Subscribers will receive email notifications alerting them to the latest postings of their topic of interest.

To address the concerns from healthcare professionals who do not access HSA's drug safety information, HSA is open to reviewing the format of our current communications and its accessibility. In addition, new communication tools such as "Whatsapp" texts can be explored to alert healthcare professionals or prompt them to check their emails for latest safety updates.

HSA will continue to evaluate the effectiveness of the ways we currently communicate drug safety information periodically and work to raise the awareness of healthcare professionals to the safety information provided through our website and emails.

HSA would like to thank all the healthcare professionals who had participated in the survey.

ANSWER TO AE CASE IN FOCUS: TEST YOURSELF

Ferric carboxymaltose (FCM) was the likely cause of severe hypophosphataemia in this patient. His iron replacement was switched from FCM to high-dose oral iron, along with the addition of daily calcitriol 0.25 µg, cholecalciferol 1000 IU, and oral Fleet phospho-soda containing 515 mg of phosphate. His serum phosphate levels normalised and oral phosphate replacement was stopped 11 weeks later, without any need for further replacement.

A review of the patient's medication history showed that he had received 26 doses of parenteral FCM in the past three years, with admissions for non-specific symptoms (i.e. palpitations, chest discomfort, lethargy) which were attributed to anaemia. These symptoms could have been exacerbated by undiagnosed hypophosphataemia.

Parenteral iron preparations and hypophosphataemia

Parenteral iron preparations are indicated for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The locally registered parenteral iron preparations include ferric carboxymaltose (Ferinject®, Vifor Pharma Asia Pacific Pte Ltd), ferric derisomaltose (Monofer®, Compai Pharma Pte Ltd) and iron sucrose (Venofer®, Baxter Healthcare (Asia) Pte Ltd).

Hypophosphataemia secondary to parenteral iron preparations is a common adverse event and is usually asymptomatic and transient. Severe, symptomatic and prolonged cases of hypophosphataemia have also been reported.[2,3] The risk is greater in those with pre-existing disorders in phosphate homeostasis (i.e. low vitamin D, phosphate and calcium levels),[2] and those receiving prolonged, high doses of intravenous iron.[4] In some cases, these symptoms may be non-specific and resemble anaemia, resulting in continued treatment with parenteral iron while the hypophosphataemia remained undiagnosed. Severe hypophosphataemia can result in complications such as metabolic encephalopathy, rhabdomyolysis, impaired myocardial contractility, cardiac arrhythmias and respiratory failure due to diaphragmatic weakness, which will have impact on patient's morbidity, mortality and quality of life.[5]

The exact mechanism by which intravenous iron causes hypophosphataemia is not known, but what is known is that FGF23 is a potential mediator.[6,7] FGF23 is a hormone secreted by osteocytes that regulates phosphate and vitamin D homeostasis[2,8] by enhancing urinary phosphate excretion and suppressing 1,25-dihydroxyvitamin D levels.[6] When parenteral iron is administered, FGF23 levels increase via an inhibition of its degradation,[7,8,9] thereby resulting in hypophosphataemia.

There are reports in the literature that parenteral iron preparations have been associated with severe hypophosphataemia.[6,7,9] Hardy *et al*.[9] reported transient hypophosphataemia in 38 out of 78 (49%) patients who received FCM, of which five were severe (<0.32 mmol/L). In contrast, only 22 out of 52 (22%) patients who received parenteral iron sucrose developed hypophosphataemia, none of which were severe. There were no differences between patients who developed hypophosphataemia and those who did not, in terms of ferritin, vitamin D and haemoglobin levels, other than a higher cumulative iron dose in the former. The development of hypophosphataemia may be related to the carbohydrate moieties (e.g. carboxymaltose, sucrose, dextran) used in the parenteral iron preparations,[8] with a possible dose-dependent relationship.

Local situation

As of 1 March 2021, HSA has received seven local reports of hypophosphataemia associated with intravenous iron preparations, specifically FCM. The age of the patients ranged from 55 to 77 years old. Hypophosphataemia was assessed by the reporting doctor as serious in five of the reports, of which four involved hospitalisation. Of these, two were reported as asymptomatic, with one being persistently hypophosphataemic for two months after receiving intravenous FCM, despite improved vitamin D levels.

HSA's advisory

Healthcare professionals are advised to consider the possibility of hypophosphataemia in patients receiving parenteral iron replacement, and to report any suspected adverse events to the Vigilance and Compliance Branch of HSA.

References

1. *Lancet 1975; 2(7929): 309–310*
2. *Endocrinol, Diabetes & Metab Case Rep; 2019; 19-0065*
3. *Therapeutics and Clinical Risk Management 2020; 16: 245-259*
4. *Singapore package insert for Ferinject® (approved 17 May 2019)*
5. *EJCRIM 2020; 7: doi:10.12890/2020_001860*
6. *J Bone Miner Res 2010; 25(10): 2091–2097*
7. *J Clin Endocrinol Metab 2009; 94(7): 23322337*
8. *J Bone Miner Res 2013; 28(8): 17931803*
9. *Int J Rheumatol 2015; 2015: 468675*

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 1111
Fax : (65) 6478 9069

Website: http://www.hsa.gov.sg
Email: HSA_productsafety@hsa.gov.sg