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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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This is a case of a 63-year-old man who presented with two weeks' history of yellowing of the skin, tea-coloured urine and a recent onset of pruritus. These symptoms were preceded by a month of lethargy. On examination, he was found to be jaundiced with excoriation marks over both his upper limbs. His past medical history included type II diabetes mellitus, hyperlipidaemia and hypertension. He was on long term medication for his chronic conditions, which included vildagliptin/metformin 50mg/850mg (Galvus Met®). He was previously on linagliptin, but was switched to Galvus Met® about a year ago in view of his suboptimal diabetic control. The initial investigations revealed a cholestatic pattern of deranged liver enzymes, with alkaline phosphatase at 208 U/L, alanine transaminase at 70 U/L, aspartate transaminase at 56 U/L, and bilirubin at 689 µmol/L. Prothrombin time was prolonged at 12.7 seconds. He also had acute kidney injury with a creatinine level of 486 µmol/L and urea of 27.2 mmol/L. His presentation and initial investigations revealed possible acute liver and kidney injuries. A transjugular liver biopsy procedure was performed, and the histology of the liver specimen showed evidence of cholestatic hepatitis with prominent canalicular cholestasis and bile plugs, accompanied by prominent lobular inflammation.

What could have contributed to the patient's liver injury?

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

AE Case in Focus: Test Yourself

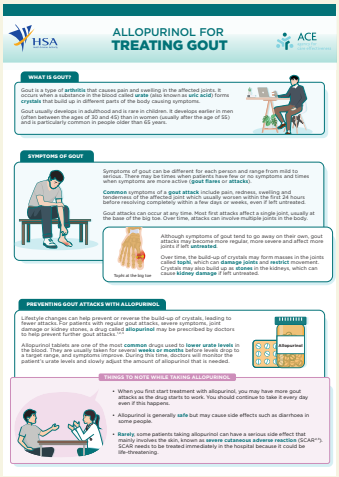
Pg 4

This is a case of a 50-year-old female with a history of poorly controlled eosinophilic asthma and was started on mepolizumab. However, her asthma remained poorly controlled and she was switched to subcutaneous dupilumab. She presented at the asthma clinic in her third month of dupilumab initiation with palpitations, heat intolerance, loss of appetite and hand tremors. Her last (4th) dose of dupilumab was given four weeks prior to her presentation at the clinic. On examination, she had a diffusely enlarged thyroid with a bruit. Laboratory tests showed she had primary hyperthyroidism with elevated thyrotropin receptor antibody (TRAb) levels. Her thyroid ultrasound scan revealed a heterogenous thyroid gland with increased gland vascularity consistent with Graves' Disease.

What could have caused Graves' Disease in this patient?

New patient factsheet on the safe use of allopurinol

A new patient factsheet on the safe use of allopurinol was published by HSA in June 2024 on the consumer guide webpage on HSA's website.[1] It was co-developed with the Agency of Care Effectiveness (ACE), Ministry of Health (MOH). The reader-friendly factsheet with summarised text and clear visuals, helps patients understand the use of allopurinol for gout, its potential risk of severe cutaneous adverse reactions (SCAR) and what to do if SCAR is suspected.



Healthcare professionals are encouraged to use this factsheet as an educational aid when they prescribe allopurinol especially to new patients, and to remain vigilant to these potentially life-threatening adverse reactions.

The factsheet can be downloaded via this link.[2] A video of this factsheet was also posted on HSA's social media channels: X (formerly Twitter)[3] and LinkedIn[4].

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1. https://www.hsa.gov.sg/consumer-safety/articles/safe-use-of-allopurinol
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3. HSA X https://twitter.com/HSAsg
4. HSA LinkedIn https://www.linkedin.com/company/health-sciences-authority/posts/?feedView=all

Dear Healthcare Professional Letters on safety concerns

Scan/click on QR code

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 Sep 2024.

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Analysis of adverse event reports in paediatrics from 2019 to 2023

Key Points

- From 2019 to 2023, HSA received 4,853 valid+ adverse event (AE) reports in the paediatric population (aged 17 years and below).
- The top five pharmacotherapeutic groups suspected of causing the AEs were antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, cough preparations and antihistamines.
- More than half of the AEs reported were skin reactions, followed by immune-mediated reactions, reactions affecting the body as a whole and respiratory disorders. Most of these reports were assessed as non-serious.

This is a review of the AE reports received by HSA in the paediatric population (individuals 17 years old and below) in the past 5 years from 2019 to 2023. The scope of this review includes pharmaceuticals (i.e., chemical drugs, biologics), cell, tissue and gene therapy products (CTGTP), complementary health products (CHPs) and cosmetic products. Vaccines were excluded in this review.

Report analysis in paediatrics (2019 to 2023)

(a) Volume of reports

From 2019 to 2023, HSA received a total of 4,853 valid+ reports. The number of reports received yearly for this period ranged from 652 to 1,353. There was a 40% fall in the number of reports received during the COVID-19 pandemic period (2020 and 2021) as compared to during the non-pandemic period. The proportion of paediatric reports out of the total number of reports received yearly ranged from 1.8% to 5.0%.

+Reports lacking important details e.g., names of suspected drugs and AE descriptions were regarded as invalid reports and not captured in the AE database as these reports could not be assessed for causality.

(b) Sources and type of reports

Majority of the reports were from hospitals (47.9%), followed by polyclinics (27.9%) and General Practitioner clinics (21.3%). Other reporting sources included product registrants (1.5%) and national specialty centres (1.3%). Most of the suspected products reported were chemical drugs (97.4%) and biologics (1.6%). This was followed by health supplements (0.4%), complementary medicines (0.3%), CTGTP (0.2%) and cosmetic products (0.1%).

(c) Demographics

Where patient demographics were reported (e.g., gender, ethnicity), there was an even distribution of reports received for females (51.1%) and males (48.9%) as compared to a slightly higher percentage of females (61.7%) in the overall population. Chinese patients constituted the highest proportion (67.5%) of reports, followed by Malays (16.3%) and Indians (7.8%).

The category of patients (by age) with the highest reported frequency was in children (2 to 11 years old) (44.7%), followed by adolescents (12 to 17 years old) (43.5%) and infants (less than 2 years old) (11.8%).

Analysis of reports by drugs and AE

The top five pharmacotherapeutic groups suspected of causing AEs were antibiotics (46.2%), non-steroidal anti-inflammatory drugs (NSAIDs) (35.0%), analgesics (11.2%), cough preparations (4.4%) and antihistamines (3.2%). Refer to Figure 1 for the top five drugs within each group. The top causative drugs are not unexpected as these are widely prescribed medications for common childhood illnesses such as fever, cough, colds and flu. It is important to note that the highest reported drugs are usually correlated to their high usage.

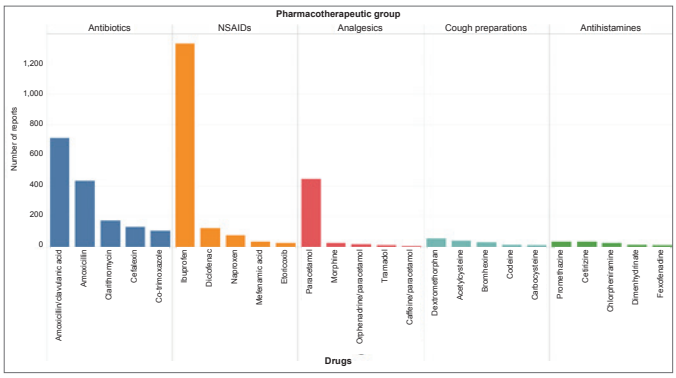

Figure 1. Top five pharmacotherapeutic groups and the top five drugs within each group suspected of causing AEs in paediatrics

Slightly more than half of the AEs reported were skin reactions (i.e., rash, pruritus, urticaria) followed by immune-mediated reactions (i.e., angioedema, anaphylaxis), reactions affecting the body as a whole (i.e., fever, oedema, tiredness, fatigue) and respiratory disorders (i.e., dyspnoea, wheezing). Majority of these AEs (except anaphylaxis) were assessed as non-serious.

Review of AE signals of interest

HSA conducts regular individual and aggregated reviews of local AE reports and would like to highlight some of these drug-AE reviews based on the cumulative analysis of spontaneous reports received from 2019 to 2023 in the paediatric population. Currently, these signals of interest are AEs known to be associated with the drugs and are not indicative of a new safety concern. HSA communicates such signals of interest to apprise healthcare professionals of our findings so that they can be vigilant of these AEs and report similar AEs to us. HSA will monitor any international developments and local AE reports associated with these drugs and inform healthcare professionals of any new significant findings.

(a) Intragam® P and haemolysis

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. These cases were reported as a cluster from one hospital due to concerns of quality issues of the affected batches. Seven cases were reported in females and five in males, with ages ranging from four months to five years old. All 12 patients recovered, with treatment. The latency period ranged from three to 10 days.

HSA investigated the affected batches and found no evidence to suggest product quality issues. Other plausible explanations for haemolysis in some of the patients include risk factors such as non-O blood groups and the high cumulative doses of IVIG used.[1] In addition, all 12 patients had Kawasaki Disease causing them to be in a hyperinflammatory state. The incidence of haemolysis has been reported to range from 1.6% in adult patients[2] to as high as 16.0% in younger patients with Kawasaki Disease.[3] HSA assessed that haemolysis is an expected AE in these patients due to the presence of multiple risk factors.

The cluster of events was also published in the May 2021 issue of the ADR News Bulletin[4] to increase healthcare professionals' awareness. Following this cluster of events,

no similar trend has been observed, and no reports were received from 2021 to 2023.

(b) Probiotics-containing health products and allergic reactions in children with cow's milk allergy

From 2019 to 2023, HSA received 11 reports of allergic reactions associated with probiotics-containing health products in the paediatric population, with more cases reported in 2022 and 2023 (six and three cases respectively). There were two cases of anaphylaxis and nine cases of allergic reactions (e.g., rash, angioedema, flushing). Five patients reported having a history of milk allergies (including the two anaphylaxis cases), and their ages ranged from 16 months to seven years old.

Probiotic products may contain cow's milk protein, a known food allergen, and these may be labelled as casein, whey, lactoglobulin, lactoferrin, or colostrum. Severe allergic reactions may occur if patients with cow's milk allergy consume these products. The local prevalence of cow's milk allergy is reported to be 0.51% based on a standardised questionnaire study of over 4,000 children at well-baby visits.[5] The most common presentation of children with milk allergy in a local retrospective study[6] was cutaneous reaction (e.g., angioedema, rash). Although most reactions are mild, cow's milk allergy can be severe and life-threatening.[7]

An 'AE case in focus' article regarding this safety concern was published in the December 2022 issue of the ADR News Bulletin.[8] Healthcare professionals are reminded to exercise care when prescribing or recommending health products labelled with food allergens to patients.

(c) Ceftriaxone and anaphylaxis

HSA received a cluster of six reports of anaphylaxis associated with ceftriaxone in the paediatric population from one hospital, occurring over a period of nine months in 2023. This comprised 38.5% of ceftriaxone-anaphylaxis reports received in 2023. These six reports constitute a 'higher-than-usual' trend observed in the preceding years from 2019 to 2022, where an average of one to two reports were received yearly.

Investigations by HSA did not find any evidence that suggested quality issues associated with the brand and batches of ceftriaxone used in these patients. HSA also worked closely with the hospital to conduct a review of these cases. Four patients were diagnosed with anaphylaxis and had positive tryptase and/or skin tests, while one patient was clinically diagnosed with anaphylaxis. The last patient was diagnosed with an allergic reaction to ampicillin and ceftriaxone due to other confounders. No risk factors were identified in these patients and other potential causes (e.g., change in brand or drug administration procedures) that could have contributed to the cluster of cases were also ruled out.

Following the review of this cluster, HSA has been closely monitoring the number of AE reports for this signal, and no unusual trends have been observed to date.

(d) Montelukast and neuropsychiatric events

Over the last five years (from 2019 to 2023), HSA received 17 reports of neuropsychiatric events with montelukast describing hallucinations, anxiety, behavioural changes and sleep disturbances. Eleven (64.7%) of these reports were in paediatrics, with ages ranging from one to 14 years old. Seven patients were females. Five of the patients had a medical history of asthma. It has been reported in the literature that neuropsychiatric events were more frequently reported for children than for adults.[9]

In March 2020, HSA initiated a benefit-risk assessment on the risk of neuropsychiatric events with montelukast.[10] HSA's review concluded that the benefit-risk profile of montelukast remains favourable for its approved indications with the implementation of risk mitigation measures. These measures include restricting the use of montelukast in the treatment of allergic rhinitis to patients who have inadequate response or are intolerant to alternative therapies and strengthening the existing warnings on neuropsychiatric risks in the package inserts (PIs) of montelukast-containing products. This was also in consideration of the regulatory actions taken by the US Food and Drug Administration to include a Boxed Warning on serious behaviour and mood-related changes in the PIs of montelukast products and to restrict the use of montelukast. HSA also issued a Dear Healthcare Professional Letter in October 2020 to inform healthcare professionals on our regulatory decisions and advisory on the use of montelukast.

HSA has been closely monitoring the situation and our review of the local AE reports with montelukast since the implementation of the risk mitigation measures in 2020 has not identified any new safety concerns regarding neuropsychiatric risk. Healthcare professionals are reminded to consider the benefits of treatment with montelukast and its risks of neuropsychiatric effects before prescribing montelukast. They are also encouraged to advise their patient and/or their caregivers to be alert to changes in behaviour or new neuropsychiatric symptoms and to seek medical attention if these symptoms occur.

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10. *https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/advisory-on-restriction-on-the-use-of-montelukast-and-neuropsychiatric-effects*

AE Case in Focus: Test Yourself

A 50-year-old female with a history of poorly controlled eosinophilic asthma was started on mepolizumab. However, her asthma remained poorly controlled and she was switched to subcutaneous dupilumab. The initial dose for dupilumab was 600mg, which was reduced to 300mg every two weeks thereafter.

She presented at the asthma clinic in her third month of dupilumab initiation with palpitations, heat intolerance, loss of appetite and hand tremors. Her last dose of dupilumab (4th dose) was given four weeks prior to her presentation at the clinic. She had defaulted on her two subsequent doses as she was not feeling well.

On examination, she was found with a diffusely enlarged thyroid with a bruit. Laboratory tests showed she had primary hyperthyroidism with elevated thyrotropin receptor antibody (TRAb) levels. Her thyroid ultrasound scan revealed a heterogenous thyroid gland with increased gland vascularity consistent with Graves' Disease.

Q: What could have caused Graves' Disease in this patient?

HSA would like to thank Dr. Wesley Loo from the Department of Respiratory and Critical Care Medicine at the Singapore General Hospital for contributing this article.

Answers can be found on page 8.

Summary of adulterated products reported to HSA from November 2022 to December 2023

Key Points

- The most common category of adulterated products detected by HSA in the period between November 2022 and December 2023 was those marketed for pain or inflammatory conditions, followed by weight loss products.
- Steroids were the most common adulterants found in products for pain or inflammatory conditions, while sibutramine was the most common in weight loss products.
- Healthcare professionals play an important role in detecting the use of illegal products through careful taking of their patient's medication history (including complementary health products and supplements) and being vigilant to potential AEs, and reporting them to HSA.

HSA issued seven press releases (*https://go.gov.sg/hsa-press-releases*) between November 2022 and December 2023 to warn the public of 22 adulterated products. These were alerted to HSA through adverse event (AE) reports from healthcare professionals and feedback from the public. HSA's Pharmaceutical Laboratory tested these products and found that they contained potent ingredients. Most of the products (46%) were marketed for pain or inflammatory conditions (including psoriasis and eczema) and were adulterated with steroids. About a third of the products (32%) were marketed for slimming or weight loss with the remaining products marketed for sexual enhancement and cough.

The adulterated products were mostly marketed on local e-commerce and social media platforms (91%). Other sources included neighbouring countries and retailers' websites. HSA worked with platform administrators to remove the affected listings on e-commerce platforms and websites and issued warnings to the sellers.

Products marketed for pain and inflammatory conditions adulterated with steroids

The most common category of adulterated products detected by HSA was for products marketed for pain and inflammatory conditions. Contrary to the label claims on the products, steroids (e.g., dexamethasone, clobetasol propionate, prednisolone and betamethasone) were detected in all the adulterated products. Non-steroidal anti-inflammatory drugs (NSAIDs) (such as diclofenac and salicylic acid) were the next most common adulterants. Other adulterants included antihistamines (e.g., chlorpheniramine), antibiotics (e.g., chloramphenicol), antifungals (e.g., ketoconazole) and statins (e.g., lovastatin, atorvastatin). Apart from potent medicinal ingredients, high levels of arsenic were also detected in one product ('Euzema Confidence Revival Cream').

a) Adverse effects of Cushing's syndrome or adrenal insufficiency with 'AlphaMiracHerbs', 'Shu Jin' capsules, 'Tao Ju Hui Yi Mei Li Shang Kou Hu Li Ruan Gao', D'Sihat Herba Gout & Sendi', 'DND Rx9', 'Pill Hua Luo Cin Tan'

- A four-year-old child was found to have Cushing's syndrome after using 'Tao Ju Hui Yi Mei Li Shang Kou Hu Li Ruan Gao' for four months. The cream was purchased from a local peddler at a makeshift stall in Eunos. Marketed as a "baby cream" and falsely labelled to "contain ingredients that cannot be absorbed by the body" with "no medicinal effects", tests revealed that it contained chloramphenicol, clobetasol propionate, dexamethasone and ketoconazole.
- A male in his 30s purchased 'DND Rx9' online from Malaysia and developed Cushing's syndrome after taking it for several months for gout. HSA tested 'DND Rx9' and found that it contained dexamethasone, prednisolone and diclofenac.
- A female in her 50s developed Cushing's syndrome and adrenal insufficency after taking 'D'Sihat Herba Gout & Sendi' for seven months for her knee pain. She also experienced weight gain, lower limb swelling and developed elevated blood sugar levels. The product was tested to contain dexamethasone and antihistamines. It was obtained from Malaysia through friends and was also sold online.
- A male in his 50s developed Cushing's syndrome after consuming 'Pill Hua Luo Cin Tan' for about a month. He also experienced a relapse of hepatitis, with a sudden increase in liver inflammation. Tests showed that the product contained dexamethasone, prednisolone and diclofenac. He had purchased the product for his wrist pain from a "traditional Chinese medicine shop" in Malaysia.
- A male in his 60s developed Cushing's syndrome after taking 'AlphaMiracHerbs' capsules for about four months for psoriasis. A female in her 60s who took 'Shu Jin' capsules regularly over ten years for joint pain was diagnosed with adrenal insufficiency and osteoporosis. The products were tested to contain dexamethasone, chlorpheniramine and statins and were obtained from Malaysia.

b) High level of arsenic in 'Euzema Confidence Revival Cream', and potential harm of 'Jolicare™' Creams

- A male in his 30s developed purpura after using 'Euzema Confidence Revival Cream' purchased online for eczema for a year. His doctor suspected that the adverse skin reaction was caused by 'realgar', a mineral containing arsenic. Despite claims that it "contain(s) 100% all-natural herbs" and "has no side-effects", HSA tested the cream to contain very high levels of arsenic, betamethasone and salicylic acid.
- HSA was alerted to the online sale of 'Jolicare™' creams (Baby, Collagen and Original) from multiple feedback. HSA detected clobetasol propionate, dexamethasone, chloramphenicol and ketoconazole in all three 'Jolicare™' creams. 'Jolicare™' products were falsely promoted as "natural, herbal" and that "the dose is approved by skin specialists and is safe for all, including babies and pregnant mums".

Euzema Confidence Revival Cream

Jolicare™ Original Cream

Products marketed for slimming or weight loss adulterated mostly with sibutramine

Similar to our previous update on adulterated products[1], the most common adulterant found in slimming products was sibutramine, a prescription-only weight loss medicine banned in Singapore since 2010 due to increased risk of heart attacks and strokes.

a) Adverse effects with 'Enru Plus+', 'Hkt Herba Kurus Tradisi' and 'FINOS'

- A female experienced breathlessness, heart palpitations and nausea while another experienced palpitations and dizziness after consuming 'Enru Plus+'. Another two females experienced severe insomnia and heart palpitations after consuming 'Hkt Herba Kurus Tradisi' and vomiting and headache after taking 'FINOS' respectively. All three products were available on local e-commerce platforms as slimming products and labelled to contain natural ingredients. Contrary to their claims, Enru Plus+' and 'Hkt Herba Kurus Tradisi' were tested to contain sibutramine, while orlistat and sennosides were detected in 'FINOS'.

b) Potential harm of 'Mofa Coffee', 'Fercy Dietary Supplement Product', 'Honey Q Dietary Supplement' and 'Slime 7D Advance Slimming Pill'

- Parcels of 'Mofa Coffee' were detected at Changi Airfreight Centre and referred to HSA for further investigation. Labelled to aid appetite suppression and to contain natural ingredients, tests revealed that it contained high levels of sibutramine.

- HSA was alerted to 'Fercy Dietary Supplement Product', 'Honey Q Dietary Supplement' and 'Slime 7D Advance Slimming Pill' based on feedback from the public. These products were falsely labelled to have "passed GMP audit", were "herbal and natural" and to contain "no banned substances". All three products were tested to contain sibutramine, with sennosides also found in 'Fercy Dietary Supplement Product'. Fluoxetine and diphenhydramine were also detected in 'Honey Q Dietary Supplement'.

Products marketed for sexual enhancement adulterated with sildenafil or tadalafil

a) Adverse effect with 'Lorenxo Delicious Pure Chocolate Supplement'

- A male in his 30s experienced severe headaches after taking 'Lorenxo Delicious Pure Chocolate Supplement' purchased from a local e-commerce platform. Contrary to its label to contain only natural ingredients, HSA tested the product to contain tadalafil.

b) High levels of sildenafil or tadalafil in 'Spinach Ginseng Herb Sugar', 'Tanduk Rusa Kuat Lelaki' and 'mentalk candy'

- On separate occasions, Immigration & Checkpoints Authority officers alerted HSA to parcels found to contain 'Spinach Ginseng Herb Sugar', 'Tanduk Rusa Kuat Lelaki' and 'mentalk candy'. These were also sold on local e-commerce platforms. All the products were tested by HSA to contain extremely high levels of either sildenafil or tadalafil.

Product marketed for cough adulterated with steroids and antihistamines

a) Adverse effect with 'Yanwo Chongcao Yanyin Qinfei Huatan Dan'

- A female in her 40s had abnormal blood cortisol levels after consuming 'Yanwo Chongcao Yanyin Qinfei Huatan Dan' (YCYQHD) for two months for chronic cough. Despite being marketed to be "100% Natural Pure Herbal", HSA tested YCYQHD to contain dexamethasone, prednisolone, promethazine and chlorpheniramine.

Conclusion

Healthcare professionals play an important role in detecting the use of illegal products through careful taking of their patient's medication history (including complementary health products and supplements) and being vigilant for potential AEs, and reporting them to HSA.

Reference

1. *HSA ADR News Bulletin December 2022 Vol. 24 No. 3*

Inappropriate use of modafinil and armodafinil

Press release issued on 6 November 2023

In 2023, three persons developed severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), after consuming modafinil or armodafinil obtained from friends or street peddlers in Geylang.

Modafinil and armodafinil are not registered in Singapore but are available in some countries as prescription medicines. Doctors can apply to HSA to bring in modafinil or armodafinil for their patients' medical conditions, such as narcolepsy, under the Special Access Route. Modafinil and armodafinil can cause serious adverse events such as heart problems, hypertension, and psychiatric conditions including anxiety, hallucinations or mania. Serious skin reactions including SJS and toxic epidermal necrolysis (TEN) have also been reported. Due to their stimulant effects on the brain, both drugs carry a potential risk of dependency.

HSA had published an ADR News Bulletin article on SCAR reports with modafinil and armodafinil in 2023.[1] As at June 2024, HSA has received 12 AE reports with modafinil or armodafinil. Of the three AE cases reported in 2024, two were SJS cases. The events occured in males, one in his 20s and the other in his 50s, who had likely obtained armodafinil/modafinil from unauthorised sources.

Healthcare professionals are advised to be vigilant of SCAR occurring with modafinil and armodafinil. Besides reporting these AEs to HSA (*https://www.hsa.gov.sg/adverse-events*), they are encouraged to clarify with patients on the source of the medication so that HSA can take the necessary regulatory and enforcement actions.

Reference

1. *HSA ADR News Bulletin December 2023 Vol. 25 No. 3*

AE Case in Focus: Test Yourself

A 63-year-old man presented at the clinic with two weeks' history of yellowing of the skin, tea-coloured urine and a recent onset of pruritus. These symptoms were preceded by a month of lethargy. On examination, he was jaundiced with excoriation marks over both his upper limbs. He was lucid and alert throughout his visit at the clinic, with no asterixis.

His medical history included type II diabetes mellitus, hyperlipidaemia and hypertension. He was on long term atorvastatin 40mg, amlodipine 5mg and valsartan 80mg. He was previously on linagliptin, but switched to vildagliptin/metformin 50mg/850mg (Galvus Met®) about a year ago in view of his suboptimal diabetic control. He had also taken a traditional Chinese medicine recently.

Initial investigations revealed a cholestatic pattern of deranged liver enzymes, with alkaline phosphatase at 208 U/L, alanine transaminase at 70 U/L, aspartate transaminase at 56 U/L, and bilirubin at 689 µmol/L. Prothrombin time was prolonged at 12.7 seconds. He also had acute kidney injury with a creatinine level of 486 µmol/L and urea of 27.2 mmol/L. His full blood count showed a haemoglobin level of 10.9 g/dL, white blood cell count of 12.4 x 10^9/L, and platelet count of 352 x10^9/L. His haemolysis screen was negative.

His presentation and initial investigations revealed possible acute liver and kidney injuries. Further investigations included viral workups for hepatitis A IgM antibody, hepatitis B core IgM antibody, hepatitis B DNA, hepatitis C RNA, hepatitis E PCR, Epstein-Barr Virus (EBV) PCR, cytomegalovirus (CMV) PCR, and herpes simplex virus (HSV) PCR, all of which were negative. Autoimmune screen for liver and kidney conditions were also negative. Ultrasound scans of his kidney and bladder showed possible chronic renal parenchymal disease changes without obstructive pathology. His magnetic resonance cholangiopancreatography scan did not show any biliary tree dilatation or significant space-occupying lesions to explain the current cholestatic derangement of liver enzymes.

A transjugular liver biopsy procedure was performed, and the histology of the liver specimen showed evidence of cholestatic hepatitis with prominent canalicular cholestasis and bile plugs, accompanied by prominent lobular inflammation.

Q: What could have contributed to the patient's liver injury?

HSA would like to thank Clinical Asst Prof Liou Wei Lun, Consultant and Clinical Asst Prof Thinesh Lee Krishnamoorthy, Senior Consultant from the Department of Gastroenterology and Hepatology at Singapore General Hospital for contributing this article.

Answers to AE Case in Focus: Test Yourself

This patient's liver biopsy suggested a drug-induced liver injury (DILI) aetiology. His medication history, which included vildagliptin, was carefully obtained and examined. Based on available evidence in literature, vildagliptin was the most likely

culprit drug. The patient's treatment with vildagliptin was stopped when DILI was suspected. In view of the cholestatic injury, he was started on ursodeoxycholic acid. Despite the significantly deranged liver enzymes and hyperbilirubinaemia (Table 1), his liver function remained stable.

As his kidney function was also worsening (Table 1), a kidney biopsy was performed to exclude drug-induced tubulointerstitial nephritis. The biopsy showed focal segmental glomerulosclerosis and bile cast nephropathy without evidence of immune complex-mediated glomerular disease, which suggested that the current deterioration in kidney function is secondary to his liver injury. He underwent two sessions of plasma exchange to treat his hyperbilirubinaemia and prevent further bile cast injury to the kidneys. Although he initially required dialysis support, his kidney function improved following plasma exchange and he was able to be weaned off dialysis support. His liver enzymes and bilirubin returned to normal levels within one year after the presentation.

Table 1. Trend of patient's liver and kidney function test results.

	Month 0	Month 1	Month 2	Month 3	Month 4	Month 6	Month 8	Month 10
Bilirubin (µmol/L)	689	473	240	165	89	47	37	15
Alkaline Phosphatase (U/L)	208	345	552	217	205	171	186	157
Alanine transaminase (U/L)	70	275	50	35	46	21	37	26
Creatinine (µmol/L)	486	361	552	261	176	104	145	110

Drug-induced liver injury (DILI) and Dipeptidyl peptidase-4 inhibitors

Diagnosis of DILI remains challenging for health care providers. In patients with polypharmacy, it is often difficult to establish the specific drug causing DILI. In an attempt to stop the clinical progression of the adverse event (AE) and identify the cause, the physician may need to discontinue treatments, which could result in suboptimal management of the underlying disease. DILI can be broadly categorised as intrinsic or idiosyncratic.[1] Drugs that induce liver injury in a predictable, dose-dependent manner are classified as intrinsic DILI, e.g., paracetamol overdose. This is commonly due to direct mitochondrial injury, oxidative stress, or alterations in bile acid homeostasis driven by the drug or its metabolites. Idiosyncratic DILI usually reflects an adaptive immune response targeting the liver, characterised by a prolonged latency, suggesting that time is needed for antigen-specific lymphocytes to be activated and to proliferate to sufficient numbers in order to mediate a DILI event.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are used for the treatment of type 2 diabetes mellitus (DM). They inhibit the degradation of incretin by DPP-4, resulting in improved glycaemic control by stimulating glucose-dependent insulin secretion and suppression of glucagon secretion. Some of the DPP-4 inhibitors include saxagliptin, linagliptin, sitagliptin and vildagliptin. Hepatotoxicity is a rare and known adverse effect of DPP-4 inhibitors, occurring in less than 1% of patients.[2] The specific mechanism by which it can cause liver injury is not well understood.

The similarity in activity among the DPP-4 inhibitors suggests that there may be cross-sensitivity to hepatic injury among the different agents, but this has not been reported. On the other hand, there have been case reports of successful switching from one DPP-4 inhibitor to another without complication. This could be due to differences in the pharmacokinetic profiles among these drugs.[3] Saxagliptin undergoes extensive hepatic metabolism in the liver by the cytochrome P450 system hence toxic or immunogenic metabolites may be produced and cause liver injury. Only a small proportion of linagliptin and sitagliptin are metabolised by the cytochrome P450 system. On the other hand, vildagliptin is mainly metabolised by hydrolysis mediated by DPP-4, with negligible contribution from the cytochrome enzymes. Linagliptin is mostly excreted into the bile, whereas the other DPP-4 inhibitors are excreted into the urine. All these drugs are substrates for P-glycoprotein drug transporter.

With regard to the patient in our case study, the long latency between the initiation of vildagliptin and liver injury is suggestive Pr of an idiosyncratic reaction, driven by an immune-mediated mechanism. The patient's liver injury associated with vildagliptin appears to be drug-specific in view that the patient was tolerating linagliptin well previously. A similar cholestatic injury has been reported in a published case report.[4] The patient was successfully switched to linagliptin without recurrence of liver injury. The New Zealand Centre of Adverse Reactions Monitoring (CARM) reported two cases of vildagliptin-related DILI, of which one patient developed liver failure and another developed deranged liver enzymes.[5] In a meta-analysis of more than 8,000 patients treated with vildagliptin, the incidence of hepatic AEs was low, mostly with mild and transient elevation of liver enzymes.[6]

DILI secondary to other DPP-4 inhibitors have been reported in literature. All these overseas cases responded well to drug withdrawal. Table 2 shows a summary of published overseas case reports of DPP-4 inhibitors related liver injury.

Table 2. Overseas case reports of liver injury associated with DPP-4 inhibitors.

Case publications	Patient information	DPP-4 inhibitor(s)	Type of liver injury	Treatment	Outcome
Toyoda-Akui M, et al[7]	58-year-old male, DM & chronic alcohol use	Sitagliptin	Hepatocellular injury with jaundice	Drug withdrawal and plasmapheresis	Resolved after 2 months
Shahbaz A, et al[8]	58-year-old male, DM	Sitagliptin	Hepatocellular injury	Drug withdrawal	Resolved; Injury recurred when drug was rechallenged
Shahbaz A, et al[9]	44-year-old female, DM	Sitagliptin	Hepatocellular injury	Drug withdrawal	Resolved
Kutoh E, et al[4]	58-year-old female, DM	Linagliptin	Cholestatic injury with jaundice	Drug withdrawal	Resolved after 2 months
Thalha AM, et al[9]	33-year-old male, DM	Saxagliptin	Hepatocellular injury	Drug withdrawal	Resolved after 7 weeks
Kurita N, et al[10]	65-year-old female, DM & end stage renal failure	Vildagliptin	Cholestatic injury	Drug withdrawal	Resolved after 4 months. Switched to linagliptin without injury

Local situation

As at 30 June 2024, HSA received ten AE reports of liver injury with DPP-4 inhibitors: three reports with linagliptin, four reports with sitagliptin, and three reports with vildagliptin. The median age was 62 years (range: 42 to 77 years). Five cases were reported in males, four in females, and one unreported gender in the remaining case. Latency period was reported in three cases, with the liver injury occurring between 83 and 111 days. Cholestatic hepatitis (four reports) was the most common AE reported, followed by raised liver enzymes (three reports), hepatitis (two reports) and acute liver failure (one report). Besides the case above, the other two reports associated with vildagliptin were acute liver failure with jaundice (latency was 111 days) and hepatitis (latency unknown).

Conclusion

Despite the long history of use of DPP-4 inhibitors, significant liver injury is rarely reported. Nonetheless, it is important for healthcare professionals to be aware of and to consider the risk of liver injury when prescribing these medications.

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Answers to AE Case in Focus: Test Yourself

Based on the temporal relationship of dupilumab and the development of Graves' Disease, and a Naranjo algorithm[1] score of 4 (indicative of a possible adverse drug reaction), the patient's Graves' Disease was assessed as possibly related to dupilumab.[2] Dupilumab was stopped and the patient was given treatment. The outcome of the patient was not known as she did not return for her follow-up visits at the clinic.

Dupilumab

Dupilumab (Dupixent, Sanofi-Aventis Singapore Pte. Ltd.) was registered in Singapore in April 2019. It is a biologic humanised monoclonal antibody indicated for use in several diseases such as atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis. For asthma, it is indicated as an add-on maintenance treatment for severe asthma with type 2 inflammation characterised by elevated blood eosinophils and/or elevated fractional exhaled nitric oxide (FeNO) and as maintenance therapy for oral corticosteroid-dependent asthma.[3,4] Dupilumab inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13), thereby controlling asthma through the reduction of cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide and immunoglobulin E (IgE). Some of the common adverse events (AEs) associated with dupilumab include injection site reactions, oropharyngeal pain, respiratory infections and joint aches and pain.[3] Hypersensitivity reactions have also been reported both in clinical trials and post-market setting.[4]

Graves' Disease and dupilumab

Graves' Disease is an autoimmune disorder affecting the thyroid gland. It involves the stimulation of the thyroid stimulating hormone (TSH) receptor by thyrotropin receptor antibodies (TRAb). Dupilumab's association with autoimmune disease development is not well characterised. Other than the case above, there has not been any other reported cases of Graves' Disease arising from the use of dupilumab.[2] However, other thyroid diseases (e.g., thyroiditis, transient hyperthyroidism and hypothyroidism) have been reported with dupilumab.[5]

The mechanism of Graves' Disease development with dupilumab is postulated to be related to the inhibition on the IL-4 and IL-13 pathways. Through the inhibition of these pathways, the T helper 2 (Th2) cells are suppressed which amplifies the type 1 T helper (Th1) cells pathway, leading to an increased Th1 cytokine production. This stimulates increased production of TRAb of the activating subtype, leading to Graves' Disease.[6] The inhibition of the IL-4 and IL-13 pathways also promote the development of inflammation towards interleukin-17 (IL-17)/interleukin-23 (IL-23) pathways, which have been implicated in the pathogenesis of autoimmune diseases such as psoriasis[6] and Graves' Disease.[7,8]

The presence of clinical features compatible with Graves' Disease and a thyroid panel of tests showing primary hyperthyroidism may be important clues to the diagnosis of biologic-associated Graves' Disease. To evaluate this AE further, one may adopt the approach by the European Thyroid Association, which involves the measurement of TRAb levels.[9] TRAb of the activating type binds to the TSH receptor, leading to an increase in intracellular cyclic AMP and the release of thyroid hormones. Elevated TRAb levels support the diagnosis of Graves' Disease. The guidelines also recommend performing an ultrasound examination of the thyroid gland with colour flow or power Doppler examination to evaluate other possible causes of thyrotoxicosis, particularly in the setting of a negative TRAb.[2,10] Clinical inputs from endocrinologists may also be sought.

Local situation

As at 30 June 2024, this is the only case of Graves' Disease suspected to be associated with the use of dupilumab that has been reported to HSA.[2] Four other immune-mediated AEs suspected to be associated with dupilumab have been reported. These included eosinophilic myocarditis, juvenile idiopathic arthritis, psoriasiform dermatitis, and colitis with diverticulitis. The median age of these five patients was 68 years old (range: 9 to 71 years). The latency period ranged from 28 days to approximately seven months. All five reports were assessed as serious by the reporting doctors. Other AEs included five reports of infections (e.g., eczema herpeticum, bacteraemia, pneumonia, bronchitis), two reports of eye-related AEs (keratitis, retinal detachment), two reports of joint/limb pain (arthralgia, pain in legs) and two reports of eosinophilia, one of which was associated with a severe flare of underlying atopic dermatitis.

Conclusion

Given the novelty of biologic-associated Graves' Disease, there are currently no formal guidelines for the diagnosis and management of this AE. Guidance on its management may be taken from existing guidelines on Graves' Disease, which typically involve anti-thyroid drugs such as propylthiouracil or carbimazole.[10] Other alternatives include radioactive iodine and thyroidectomy[10] but these may be less ideal in the context of a biologic-associated Graves' Disease given its potential reversibility.

Healthcare professionals are encouraged to be vigilant and look out for potential AEs associated with dupilumab and report these to the Vigilance and Compliance Branch of HSA.

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