ISSN: 0219 - 2152 Dec 2020 Vol.22 No.3

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

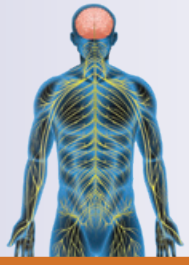
Scan / click the QR code to read the full issue online

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

AE Case in Focus: Test Yourself

What could have caused the constellation of the patient's neurological symptoms?

Pg 6-7



This is a case study of a 64-year-old Chinese man who presented with an acute onset of vertiginous dizziness of four days' duration. He developed right maxillary toothache seven days prior and self-medicated with levofloxacin for three days. He discontinued levofloxacin when he developed neurological symptoms. Upon examination, his deep tendon reflexes were absent in all four limbs despite *Jendrassik manuevre*, with bilateral flexor plantar responses. There was also impaired proprioception in both lower limbs. Based on his clinical presentation of ataxia, areflexia without ophthalmoplegia and positive anti-GQ1b antibody test, the patient was diagnosed with incomplete Miller Fisher Syndrome.

Reporting vaccine adverse events

Scan /click on the QR codes to read online

Vaccine safety monitoring is important to detect and mitigate potential safety concerns related to vaccines and to ensure that vaccines continue to be safe and effective for use. As vaccines are biologically-derived products, information that are useful for causality assessment of vaccine adverse events include:

(i) brand name of the vaccine
(ii) lot or batch number
(iii) route of administration
(iv) number of doses of vaccine given
(v) concurrent vaccinations

It is recommended that as much details are provided on the AEs as possible. Healthcare professionals are encouraged to report serious AEs suspected to be associated with vaccines to HSA. A robust vaccine monitoring system in Singapore to safeguard public health can be achieved with the active participation of healthcare professionals.

We want your feeback!

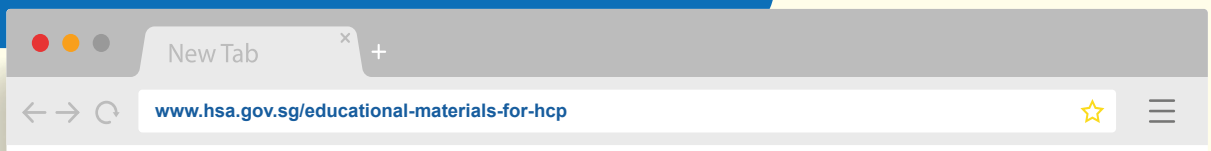
Your feedback is important to us. We encourage you to complete the two surveys by 31 January 2021.

Revamped layout of HSA ADR News Bulletin and its two-page hardcopy mailer
https://go.gov.sg/adrbulletin2

Electronic labelling (e-labelling) for Prescription-only Medicines
https://go.gov.sg/elabelsurvey

Dear Healthcare Professional Letters on safety concerns

Publication of HSA-approved educational materials



HSA is pleased to announce that HSA-approved educational materials that are produced by pharmaceutical companies are now available online.

Healthcare professionals can now access and download soft copies of Physician Educational Materials (PEM), Patient Medication Guides (PMG) and Patient Alert Cards (PAC) from the HSA website.

These materials are produced for selected medicinal products as part of the risk management plan to assure their safe use. They aim to communicate important treatment-related information, such as advice on the selection of the appropriate patient group and specific monitoring parameters (PEM), or self-monitoring by patients for early signs and symptoms of adverse events that require prompt medical attention (PMG/PAC).

Healthcare professionals who wish to obtain hard copies of these materials may request for them from the respective pharmaceutical companies.

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 December 2020.

ADVISORY ON RESTRICTION ON THE USE OF MONTELUKAST AND NEUROPSYCHIATRIC EFFECTS

Key Points

- HSA has completed a benefit-risk assessment of montelukast where additional precautionary measures are put in place to mitigate the known but rare risk of neuropsychiatric events
- These measures include restricting the use of montelukast in allergic rhinitis to patients who are inadequately treated or intolerant to alternative therapies and the strengthening of warnings on neuropsychiatric events in the package inserts of products containing montelukast
- Healthcare professionals (HCPs) are advised to consider the benefits of treatment and risks of neuropsychiatric effects before prescribing montelukast. HCPs are encouraged to discuss these with their patients and/or caregivers, alert them to look out for behavioural changes or new neuropsychiatric symptoms and to seek medical attention if these symptoms occur

HSA has completed a benefit-risk assessment of montelukast which concluded that the benefit-risk profile of montelukast remains favourable for its approved indication, if additional precautionary measures are put in place to mitigate the known but rare risk of neuropsychiatric events. 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 the strengthening of existing warnings on neuropsychiatric risks in the package inserts (PIs) of montelukast-containing products. Healthcare professionals are advised to consider the benefits of treatment and risks of neuropsychiatric effects before prescribing montelukast.

Background

Montelukast is a selective leukotriene receptor antagonist (LTRA) that has been registered in Singapore since 1998 for the prophylaxis and chronic treatment of asthma and the relief of symptoms of allergic rhinitis. Neuropsychiatric event is a rare but known adverse effect of montelukast and there are existing warnings on this risk in the PIs of locally registered montelukast products.

In March 2020, HSA initiated a safety review on montelukast in response to the regulatory actions taken by the US Food and Drug Administration (FDA)[1] to include a Boxed Warning on serious behaviour and mood-related changes with montelukast and to restrict the use of montelukast in the treatment of allergic rhinitis in patients with inadequate response or intolerance to alternative therapies. FDA's review did not identify new evidence regarding the known neuropsychiatric safety concern but highlighted a lack of awareness of healthcare professionals to this safety issue despite earlier communications by the agency.

Internationally, several regulatory agencies had also incorporated restrictions to the use of montelukast in allergic rhinitis.

In July 2020, Health Canada adopted similar measures as the US FDA.[2] In the United Kingdom, montelukast is only indicated for symptomatic relief of seasonal allergic rhinitis in patients with asthma.

International clinical practice guidelines on the use of montelukast [3,4,5]

International clinical practice guidelines on the treatment of allergic rhinitis recommend the use of intranasal steroid (e.g. mometasone, fluticasone) and/or oral antihistamines (e.g. cetirizine, loratadine) as primary therapies for allergic rhinitis. In particular, the American Academy of Otolaryngology- Head and Neck Surgery Foundation recommended against the use of LTRAs, including montelukast, as primary treatment therapy for allergic rhinitis, except in asthmatic patients. The British Society of Allergy and Clinical Immunology also recommended that LTRAs may have a place in therapy for asthmatic patients with seasonal allergic rhinitis. The Global Initiative for Asthma (GINA) guideline lists montelukast as an option for initial controller therapy in asthma.

Local reports of neuropsychiatric adverse events (AEs) associated with montelukast

HSA has received a small number of reports of neuropsychiatric events associated with the use of montelukast since its registration in Singapore in 1998. The events include aggressive behaviour, agitation, depression, tremor, hallucinations, hyperactivity, and sleep disturbances such as somnolence, insomnia and nightmares. There were no reports received for suicidal behaviour. The use of concomitant medicines and/or presence of comorbidities were not reported for most cases, limiting firm causality assessment.

HSA's benefit-risk assessment

HSA's benefit-risk assessment took into consideration the local safety data, current international clinical practice guidelines on the treatment of allergic rhinitis and asthma, the availability of alternative treatments for allergic rhinitis, inputs from local clinicians (including respiratory specialists, general practitioners and psychiatrists) and international regulatory actions.

Based on currently available information, HSA, in consultation with its Product Vigilance Advisory Committee, has concluded that the benefit-risk profile of montelukast remains favourable for its approved indications, if additional precautionary measures are taken to mitigate the risk of neuropsychiatric events. These additional measures include restricting the use in allergic rhinitis to patients who are inadequately treated or intolerant to alternative therapies and the strengthening of warnings on neuropsychiatric events in the PIs of products containing montelukast.

HSA's advisory and actions

Healthcare professionals are advised of the following, when considering the use of montelukast:

- To consider the benefits of treatment with montelukast and its risks of neuropsychiatric effects before prescribing montelukast
- To discuss with their patients and/or caregivers on the benefits and risks of treatment when prescribing montelukast. Healthcare professionals may make use of the patient educational material available for montelukast (e.g. article on MOH Health Hub[6]) for patient counselling
- To advise their patients and/or caregivers to be alert to changes in behaviour or new neuropsychiatric symptoms when taking montelukast and to seek medical attention if neuropsychiatric symptoms occur

HSA has issued a Dear Healthcare Professional Letter on 30 Octorber 2020 to inform healthcare professionals of the advisory on the new restriction on montelukast use and neuropsychiatric events[7]. HSA is working with the product registrants of montelukast-containing products to update the local PIs with the new recommendations on the indicated use of montelukast in allergic rhinitis and additional safety information on the risk of neuropsychiatric AEs.

Healthcare professionals are encouraged to report any suspected serious AEs related to montelukast to the Vigilance and Compliance Branch of HSA.

References

1. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug
2. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/august-2020.html
3. Otolaryngol Head Neck Surg 2015, 152(1S): S1-43
4. Clin Exp Allergy. 2017;47: 856–89.
5. www.ginasthma.org
6. https://www.healthhub.sg/a-z/medications/54/montelukast
7. https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/advisory-on-restriction-on-the-use-of-montelukast-and-neuropsychiatric-effects

CHARACTERISTICS OF SIBUTRAMINE-INDUCED ADVERSE EVENTS DUE TO ADULTERATED PRODUCTS

Key Points

- Serious adverse events (AEs), such as psychiatric and cardiovascular AEs, can occur in patients who unwittingly consume slimming products adulterated with sibutramine
- This review characterises the reported AE profile of sibutramine and serves to alert healthcare professionals of possible sibutramine-induced AEs in patients with similar clinical presentations who may have consumed adulterated products

Sibutramine was previously available in Singapore as a prescription-only medicine and was indicated as an adjunctive therapy for the management of obesity. Since 2010, it has been withdrawn in Singapore and other countries including the United States and the European Union due to an increased cardiovascular (CV) risk (e.g. myocardial infarction and stroke). Despite this, sibutramine continues to be used illegally in adulterated products, especially slimming products, which claim to be safe and effective for weight loss. Unfortunately, some consumers unwittingly fall prey to such products and experience adverse events (AEs) after consuming them. From January 2006 to October 2020, HSA has received 20 AE reports associated with sibutramine-adulterated products. Based on an analysis of these reports, we would like to present the characteristics of sibutramine-induced AEs, in particular psychiatric and CV AEs.

Mechanism of action of sibutramine

Sibutramine acts centrally to inhibit serotonin and norepinephrine reuptake to enhance satiety, and acts peripherally to increase metabolic rate, thermogenesis, and energy expenditure by stimulating β3-adrenergic receptors. This sympathomimetic activity of sibutramine causes a rise in heart rate and blood pressure, which can increase the risk of adverse CV outcome in susceptible patients.[1] To a lesser extent, sibutramine also inhibits the reuptake of dopamine. It has been suggested that the resultant accumulation of dopamine at the synaptic clefts, particularly when high doses are used, can increase dopaminergic transmission and lead to potential psychomimetic effects, in line with the dopamine hypothesis of psychosis.[2,3]

Adverse event reports with sibutramine

Of the 20 AE reports associated with products adulterated with sibutramine, the two most common AEs were psychiatric (eight reports) and CV (eleven reports) in nature. Five of these reports included both psychiatric and CV AEs. Other AEs that were reported include thyrotoxic symptoms, hypercortisolism and jaundice (one report each). The remaining three reports included hypoglycaemia, which was attributed to glibenclamide, another adulterant found in the products.

(a) Psychiatric AEs

In the cases which reported psychiatric AEs, the patients' ages ranged from 16 to 37 years old and most were females (75%). There was a wide range of symptoms and severity reported for these AEs, namely psychosis, insomnia, anxiety, labile mood (e.g. elation, irritability, fear), abnormal behaviour (laughing inappropriately, disorganised behaviour), obsessional thoughts and suicidal ideation. In cases where psychosis was reported, hallucinations were often auditory in nature and sometimes accompanied with delusions (e.g. grandiose delusions).

The time-to-onset of symptoms were also wide-ranging, from one day to 1.5 years, with a median of 22 days. In a case with relatively quick AE onset, a patient in her 20s experienced insomnia, palpitations and severe perspiration one day after taking the adulterated slimming product 'Bello Smaze'. She also experienced suicidal thoughts on the fourth day. She had recovered after stopping the product.[4] In another case, the onset of psychotic symptoms only became apparent three months after the patient started taking 'Freaky Fitz', another sibutramine-adulterated product. The patient had taken the product intermittently and had a genetic vulnerability with family history of psychosis.

The doses of sibutramine taken (where sibutramine quantification has been conducted by HSA) ranged from 9.3 to 49 mg daily. The recommended dose of sibutramine for adjunctive management of obesity was 10 to 15 mg daily. All the patients did not have any pre-existing psychiatric conditions, except for the above case where the patient had genetic vulnerability with a family history of psychosis. Five of the patients were treated for their AEs and the treatment involved antipsychotics, antidepressants and supportive therapy. Two of the patients recovered fully upon stopping the product, while the others were yet to recover from the AEs at the point of reporting to HSA.

(b) Cardiovascular AEs

In these reports, the patients' ages ranged from 21 to 52 years old and they were mostly female (81%). All the patients were reported not to have any comorbidities, except for one patient who had diabetes mellitus, hyperlipidaemia, hypertension, psoriasis and asthma. The most commonly reported CV AEs were palpitations, tachycardia, chest pain and tightness. The daily dose of sibutramine consumed in these cases ranged from 10 to 49 mg. The time-to-onset of the AEs was relatively short, with a median of 8.5 days (range: within hours to two years). In most of the cases, the symptoms experienced (e.g. sudden chest pain, tachycardia) were significant enough for the patients to consult a doctor. Four of the patients were hospitalised. In one particularly serious case, a patient in her 50s took an adulterated slimming product called 'BB Body' for three months and developed life-threatening ventricular tachycardia and loss of consciousness. She was intubated and underwent a cardioversion procedure. Subsequently, she was diagnosed with non-ischaemic cardiomyopathy, implanted with a defibrillator and managed with heart failure medications.[4,5]

Current trends in adulterated slimming products

With the increasing popularity of social media and e-commerce platforms, consumers can easily purchase slimming products online. Some of these products may be adulterated with sibutramine and claim to contain natural ingredients with promises of quick weight loss. Consumers may be misled to believe that these products are both effective and safe. Food-like presentations of adulterated slimming products such as chocolates and beverages also mislead consumers into thinking that such products are safe for consumption. Some of the adulterated products that were detected by HSA are shown in Figure 1 (page 5).[4]

HSA's advisory

This review characterises the reported AE profile of sibutramine and serves to alert healthcare professionals of possible sibutramine-induced AEs in patients with similar clinical presentations who may have unwittingly consumed sibutramine-adulterated products.

References

1. Int J Obes Relat Metab Disord 1998; 22 Suppl 1: S30-5; discussion S36-7, S42
2. Prog Neuro-Psychopharmacol Biol Psychiatry 2010; 34: 1359–1360
3. J Clin Psychopharmacol 2007; 27: 315–7.
4. https://go.gov.sg/hsa-press-releases
5. HSA ADR News Bulletin 2019 Dec; 21: 6-7

REMINDER TO VERIFY HLA-B*1502 STATUS IN NEW PATIENTS OF ASIAN ANCESTRY BEFORE STARTING CARBAMAZEPINE TREATMENT

Key Points

- Genotyping for HLA-B*1502 prior to treatment initiation with carbamazepine (CBZ) in new patients of Asian ancestry is the standard of care to identify individuals at risk of developing Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN), during treatment with CBZ
- Healthcare professionals are reminded to verify the HLA-B*1502 status prior to treatment initiation with CBZ in new patients of Asian ancestry. They are also to remain vigilant for CBZ-induced severe cutaneous adverse reactions (SCARs), including drug rash with eosinophilia and systemic symptoms (DRESS), especially during the first 12 weeks following treatment initiation with CBZ

HSA would like to remind healthcare professionals to verify the HLA-B*1502 status before starting carbamazepine treatment in new patients of Asian ancestry. Patients who are HLA-B*1502-positive are at an increased risk of developing severe cutaneous adverse reactions (SCARs), particularly SJS and TEN during treatment with CBZ.

CBZ is an anticonvulsant indicated for the treatment of epilepsy and other conditions such as diabetic neuropathy, trigeminal neuralgia and bipolar disorders. It has been registered in Singapore since 1988 and is currently available as Tegretol® (Novartis) and two other generic products.

About HLA-B*1502 genotype testing

Genotyping for HLA-B*1502 prior to treatment initiation with CBZ in new patients of Asian ancestry has been the standard of care in Singapore since 2013.[1] This one-time test helps distinguish high-risk patients who should avoid CBZ from low-risk patients who are able to continue to use this low-cost yet effective medicine. The implementation of this recommendation has contributed to a 92% reduction in the number of CBZ-associated SJS/TEN cases in Singapore, from 50 cases in the 5-year pre-implementation period (2008 - 2013) to four cases in the post-implementation period (2013-2018).[2]

The HLA-B*1502 genotyping test is available at the National University Hospital Molecular Diagnosis Centre, the Tan Tock Seng Hospital Molecular Diagnostic Laboratory, the DNA Diagnostic & Research Laboratory at Kandang Kerbau Women's and Children's Hospital, and the Tissue Typing Laboratory at the Health Sciences Authority of Singapore. The estimated turnaround time for the test result is one to four working days. Subsidised patients from the MOH-funded restructured hospitals and institutions would qualify for a flat rate subsidy of 75% of the cost of the test.

HSA's advisory

Healthcare professionals are advised to take note of the following:

- HLA-B*1502 genotype testing specifically identifies patients at risk of developing CBZ-induced SJS/TEN, but not CBZ-induced drug rash with eosinophilia and systemic symptoms (DRESS)
- HLA-B*1502 test results should be obtained prior to prescribing CBZ as SJS/TEN can develop and progress in susceptible patients, even after prompt discontinuation of the drug
- The use of CBZ should be avoided and treatment alternatives are strongly recommended in patients who are found to be positive for HLA-B*1502. As a precaution, these patients should also not be prescribed phenytoin, as there is preliminary data suggesting a suspected association between HLA-B*1502 and phenytoin-induced SJS/TEN
- Although reported to be rare, patients who test negative for HLA-B*1502 may still be at risk of developing CBZ-induced SJS/ TEN. The role of other factors, which may contribute to the development of SJS/TEN in these patients, such as drug dose, concomitant medications and co-morbidities, have not been studied
- Clinical vigilance for CBZ-induced SCARs including DRESS should continue, especially during the first 12 weeks following treatment initiation with CBZ

Healthcare professionals are encouraged to report any suspected serious adverse reactions related to CBZ use to the Vigilance and Compliance Branch of HSA.

References

1. https://www.hsa.gov.sg/announcements/safety-alert/recommendations-for-hla-b-1502-genotype-testing-prior-to-initiation-of-carbamazepine-in-new-patients
2. https://www.frontiersin.org/articles/10.3389/fphar.2020.00527/full

Continued from the article on page 4

Figure 1. Adulterated products containing sibutramine marketed as food products such as chocolates and beverages

"Freaky Fitz" and "Wholly Fitz" (marketed as Passion Lemon Tea)

"KiMiSo Dark Chocolate" and "Mone Macha Cocoa"

"LKS Coffee"

"Serifa Beauty SolidMolid", "Coco Curv" and "Choco Fit" (marketed as chocolate drinks)

VOLUNTARY WITHDRAWAL OF ESMYA™ (ULIPRISTAL ACETATE) TABLET 5MG IN SINGAPORE DUE TO RISK OF SERIOUS LIVER INJURY

Key Points

- The product registration of Esmya™ (ulipristal acetate) Tablet 5mg in Singapore has been voluntarily withdrawn by the company in October 2020
- This was due to concerns with overseas cases of serious liver injury requiring liver transplantation, and that it was not possible to identify which patients were most at risk for developing the liver injury or to identify measures that could further reduce the risk
- The withdrawal does not affect Ella® (ulipristal acetate) Tablet 30mg (Hyphens Pharma Pte Ltd) registered for use as an emergency contraception, as there is no signal of concern about liver injury with this product

Zuellig Pharma Pte Ltd, the product registrant of Esmya™ (ulipristal acetate) Tablet 5mg, has voluntarily withdrawn the product from the Singapore market in October 2020. This was due to concerns with overseas cases of serious liver injury requiring liver transplantation and that it was not possible to identify which patients were most at risk for developing liver injury or to identify measures that could further reduce the risk.

Esmya™ has been registered for use in Singapore since November 2014, for the pre-operative or intermittent treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age. In March 2020, HSA had temporarily suspended the sales of Esmya™ in Singapore as a precautionary measure, due to ongoing concerns of its association with liver injury reported overseas.

The withdrawal does not affect Ella® (ulipristal acetate) Tablet 30mg (Hyphens Pharma Pte Ltd) registered for use as an emergency contraception, as there is no signal of concern about liver injury with this product.

Background on the safety concern of liver injury[1-4]

Since 2017, HSA had been monitoring the safety concern of liver injury with Esmya™, following overseas reports of serious liver injury which had resulted in liver transplantation. HSA conducted a benefit-risk assessment and implemented additional risk mitigation measures in 2018 to minimise the risk of liver injury in patients taking Esmya™. These measures included prohibiting its use in patients with underlying liver disorders, restricting the use of multiple treatment courses in women who are not eligible for surgery, and increasing the frequency of liver function monitoring. The measures were communicated to healthcare professionals in April 2019 via the company's Dear Healthcare Professional Letter and published in the September 2019 issue of the HSA ADR News Bulletin.

In March 2020, following the report of another overseas case report of serious liver injury with Esmya™ requiring liver transplantation, HSA temporarily suspended the sales of Esmya™ in Singapore as a precautionary measure, while it continued its reassessment of the benefit-risk profile of Esmya™ for the local population. Another Dear Healthcare Professional Letter was issued for healthcare professionals to review the use of the medicine in their patients and to decide whether a switch to alternative therapies may be appropriate. Healthcare professionals were also advised not to start new patients on Esmya™ and to monitor existing patients for liver injury for two to four weeks after stopping treatment. To date, HSA has not received any local reports of serious liver injury related to treatment with Esmya™.

Local actions taken

The voluntary withdrawal of Esmya™ registration in Singapore by Zuellig Pharma Pte Ltd has been communicated to its purchasers and healthcare professionals in October 2020. HSA has also published an update on its website regarding the product withdrawal.[5] Healthcare professionals were advised to contact patients under their care who may have still been treated with Esmya™ to (i) stop Esmya™ and review alternative treatment options; (ii) monitor the liver function of these patients for two to four weeks after stopping treatment; and (iii) advise patients to monitor for signs and symptoms of liver injury (e.g. dark-coloured urine, yellowing

AE CASE IN FOCUS: TEST YOURSELF

A 64-year old Chinese gentleman presented with an acute onset of vertiginous dizziness of four days' duration. This was not associated with postural changes or head movements. There was no weakness of the limbs or neck muscles. He did not have any diplopia, dysarthria or dysphagia.

He developed right maxillary toothache seven days before and self-medicated with levofloxacin, a fluoroquinolone, for three days. He discontinued levofloxacin when he developed neurological symptoms. Initially, he took 500 mg of levofloxacin twice-daily, after which he increased the dose to 500 mg thrice daily for a total of eight doses. This amounted to 4000 mg cumulatively. He did not have any recent vaccinations and his past medical history included a well-controlled diabetes mellitus, hypertension and dyslipidemia.

On neurological examination, the patient had full power in all his limbs and neck muscles. His extraocular eye movements were intact, and there was no nystagmus or ptosis. However, deep tendon reflexes were absent in all four limbs despite *Jendrassik manuevre*, with bilateral flexor plantar responses. There was also impaired proprioception in both lower limbs. He had left-sided dysmetria and dysdiadochokinesia, with an ataxic gait. He was able to generate a negative inspiratory pressure of – 60 cm H_2O.

Magnetic resonance imaging of his brain was unremarkable, with no acute infarction. The patient's nerve conduction study done on day 4 of his symptoms was also unremarkable. Cerebrospinal fluid (CSF) analysis, also performed on day 4 of his symptoms, showed elevated protein at 0.90 g/L and WBC count of 17 cells/μL, after correction for a traumatic lumbar puncture. There was no evidence of infection found on a meningoencephalitis panel and dedicated HSV and VZV PCR (Polymerase Chain Reaction) testing. Serological testing for ganglioside antibodies showed anti-GQ1b IgG positivity and tested negative for anti-GM1 IgG and IgM. Based on his clinical presentation of ataxia, areflexia without ophthalmoplegia and positive anti-GQ1b antibody test, the patient was diagnosed with incomplete Miller Fisher syndrome.

The patient remained stable during his hospitalisation. As his illness was mild, with no bulbar symptoms, respiratory or motor involvement, he was not treated with intravenous immunoglobulin or plasma exchange. On a follow-up call made four weeks later, the patient had completely recovered with no residual symptoms.

Question: What could have caused the constellation of the patient's neurological symptoms?

HSA would like to thank Dr. Nicodemus Oey, Dr. Goh Yihui, and Dr. Aftab Ahmad at Ng Teng Fong General Hospital for contributing this article.

Answers can be found on page 7

continued from the article on the left column

of the skin, excessive tiredness, nausea and vomiting), and to contact their doctors immediately if they develop these signs and symptoms.

References

1. https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/esmya-(ulipristal-acetate)-and-risk-of-serious-liver-injury
2. https://www.hsa.gov.sg/announcements/adverse-drug-reaction-news-bulletin/2019-september-(volume-21-number-2)
3. https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/temporary-suspension-of-the-sales-of-esmya-(ulipristal-acetate)-tablet-5mg
4. https://www.hsa.gov.sg/announcements/adverse-drug-reaction-news-bulletin/adr-news-bulletin-2020-september-(volume-22-number-2)
5. https://www.hsa.gov.sg/announcements/safety-alert/voluntary-withdrawal-of-esmya-(ulipristal-acetate)-tablet-5mg-by-zuellig-pharma-pte-ltd

ANSWER TO AE CASE IN FOCUS: TEST YOURSELF

Based on his clinical presentation of ataxia, areflexia without ophthalmoplegia and positive anti GQ1b antibody test, the patient was diagnosed with incomplete Miller Fisher syndrome: a variant of Guillain-Barre Syndrome, which may have been related to his use of levofloxacin.

Levofloxacin-associated Miller Fisher Syndrome

Guillain-Barré Syndrome (GBS) is the most common autoimmune cause of acute peripheral neuropathy worldwide, affecting 1 in 100,000 people.[1] It has been widely accepted that GBS can be triggered by a preceding bacterial or viral infection, and pathogens such as *Campylobacter jejuni*, Epstein-Barr virus and Mycoplasma pneumonia have been identified as antecedent pathogens. The pathogenesis of GQ1b autoimmunity is thought to involve a process known as "molecular mimicry", where the infecting organism shares homologous epitopes to a component of the peripheral nerves, thereby causing a cross-reaction.[2]

Miller-Fisher Syndrome (MFS) is a GBS variant associated with antibodies to GQ1b, characterized by ataxia, ophthalmoplegia and areflexia. There can be incomplete forms of MFS, such as acute ataxic neuropathy or acute opthalmoparesis.[3] In this case report, the patient had developed incomplete MFS after exposure to the fluoroquinolone antibiotic levofloxacin, highlighting the need for healthcare professionals to be more vigilant when prescribing fluoroquinolones in view of a possible rare but potentially serious adverse effect of Guillain-Barré syndrome and its variants.

Cases of peripheral neuropathy and GBS occuring in patients associated with exposure to systemic fluoroquinolones have been reported in a pharmacovigilance study, which re-emphasises the previously purported link between fluoroquinolone use and peripheral nerve autoimmune-mediated damage.[4] However, as high as 30% of all GBS cases worldwide have been linked to no antecedent infections[1] which may point towards other possible pathophysiological mechanisms, such as the use of drugs. Fluoroquinolones have historically been associated with neurological adverse effects including peripheral nervous system (PNS) sensory and motor symptoms,[5] with a large case-control study reporting an increased risk especially in new users.[6] The time course at which neurological manifestations develop, ranges widely from as early as 24 hours upon initiation of treatment to the possibility of permanent peripheral neuropathy presenting at two months post-treatment.[7,8]

Overseas reports

Based on the WHO VigiLize#, as of October 2020, there were 91 GBS reports associated with fluoroquinolones worldwide. More males (58.2%) than females (34.1%) were implicated in the reports. Fluoroquinolones may not be the only suspected drug in many of these reports. Other co-suspects include influenza vaccine and antibiotics such as ceftriaxone, amoxicillin-clavulanic acid and meropenem. There were three fatalities.

There were two other MFS reports associated with fluoroquinolones. The first case involved a male patient of unknown age who took levofloxacin for an unknown indication. Treatment was withdrawn and he recovered. The second case involved a 39-year-old female patient who took ciprofloxacin for urinary tract infection. Outcome was not reported in this case.

#A search and analysis tool provided to medicine regulators by World Health Organisation, Uppsala Monitoring Centre (WHO UMC) for instant graphical overview of global AE reports.

Local situation

As of 1 October 2020, HSA has received more than 8,000 adverse event (AE) reports associated with the seven systemic fluoroquinolones that are registered in Singapore namely ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin and pefloxacin. The majority of fluoroquinolones AE reports (about 86%) were related to hypersensitivity reactions which ranges from non-serious e.g. mild rashes, angioedema to serious AEs such as anaphylaxis, Stevens-Johnson Syndrome and acute generalized exanthematous pustulosis.

This is our first reported case of fluoroquinolone-related GBS (MFS). Other local AEs specifically associated with the Nervous System Disorders System Organ Class that have been reported in association with fluoroquinolones include dizziness, headaches, hypoaesthesia, paresthesia, muscle contractions involuntary, convulsion, tremor, dysphonia, dysaesthesia, oculogyric crisis and myasthenic syndrome (Figure 1). These AEs are listed in the package inserts of locally registered fluoroquinolone-containing products.

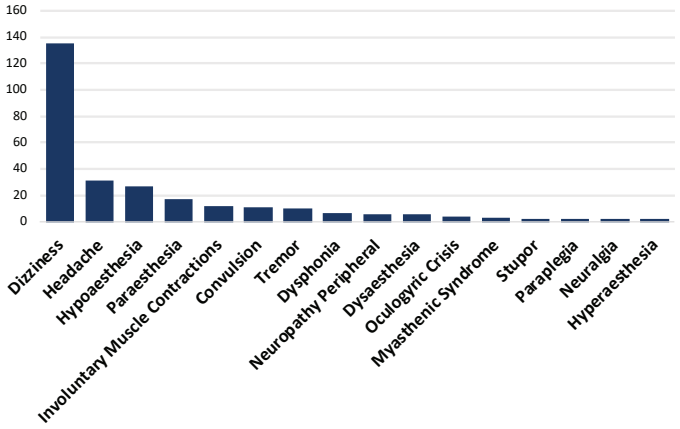


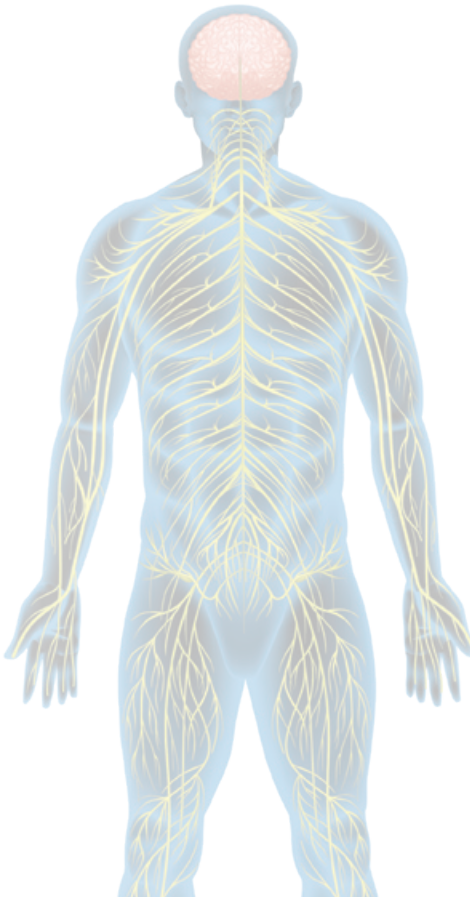
Figure 1. Fluoroquinolones-related AEs associated with the Nervous System Disorders SOC

Conclusion

Healthcare professionals are reminded to report suspected drug-induced AEs to the Vigilance and Compliance Branch of HSA. Your support towards the national adverse event monitoring programme is invaluable in safeguarding public health.

References

1. Neuroepidemiology 2009; 32 (2): 150-163
2. N Engl J Med. Jun 2012 14; 366(24): 2294-304
3. Nature reviews. Neurology 2014; 10 (9): 534-544
4. Annals of Epidemiology 2014; 24 (4): 279-285
5. Annals of Pharmacotherapy 2001; 35 (12): 1540-1547
6. Neurology 2014; 83 (14): 1261-1263
7. JAMA Neurology 2019; 76 (7): 827-833
8. Journal of Investigative Medicine 2014; 27 (2)



RISK OF DRUG-INDUCED LIVER INJURY ASSOCIATED WITH THE USE OF PIRFENIDONE

Key Points

- Overseas cases of drug-induced liver injury have been reported in patients treated with pirfenidone, including isolated cases with fatal outcome
- Healthcare professionals are advised to perform liver function tests prior to treatment initiation with pirfenidone, and subsequently at monthly intervals for the first six months, and then every three months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, with dose adjustment or treatment discontinuation as required

HSA would like to remind healthcare professionals about the risk of drug-induced liver injury (DILI) with the use of pirfenidone. This rare but potentially serious adverse event was highlighted in a Dear Healthcare Professional Letter (DHCPL) issued in November 2019 in response to overseas cases of DILI, including isolated cases with fatal outcome, reported in patients treated with pirfenidone. Healthcare professionals are advised to perform liver function tests prior to treatment initiation with pirfenidone, at regular intervals subsequently, and in the presence of clinical signs or symptoms that may indicate liver injury.

Pirfenidone (Esbriet®, Roche Singapore Pte Ltd) is an anti-fibrotic and anti-inflammatory agent. It has been registered in Singapore since 2016 and is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Overseas cases of pirfenidone-associated DILI

Pirfenidone has been known to be associated with transient and clinically silent elevation of liver enzymes, which are rarely associated with concomitant bilirubin increases. However, overseas cases of serious hepatic adverse events, including isolated cases with fatal outcome, have recently been reported in IPF patients treated with pirfenidone. Majority of the reported hepatic events occurred within the first few months of treatment. No alternative aetiologies or confounding factors were found in these reports, which were therefore deemed clinically relevant cases of DILI. In the absence of a plausible pharmacodynamic mechanism, these cases appeared to be possibly triggered by idiosyncratic reactions to pirfenidone. The frequency of clinically relevant DILI detected from post-marketing reports is estimated as rare (≥1/10,000 to <1/1,000).

Local situation and HSA's advisory

To date, HSA has not received any local report of DILI associated with pirfenidone use. In November 2019, a DHCPL was issued by the product registrant for Esbriet® to inform healthcare professionals about this safety concern.[1] The local package insert for Esbriet® has been strengthened to highlight the risk of clinically relevant DILI and recommend additional monitoring of liver function in the presence of clinical signs or symptoms suggestive of liver injury.

Healthcare professionals are advised to perform liver function tests prior to treatment initiation with pirfenidone, and subsequently at monthly intervals for the first six months of treatment, and then every three months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury. Recommendations on dose adjustment or discontinuation of pirfenidone therapy due to elevated liver enzymes are shown in Table 1.[2]

Table 1. Recommendations on dose adjustment or discontinuation of pirfenidone therapy due to elevated liver enzymes

Liver enzyme elevations	Recommendations
Aminotransferase elevation >3 to <5 x ULN* without bilirubin elevation	• Other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered • If clinically appropriate, the dose of pirfenidone should be reduced or interrupted • Once liver function tests are within normal limits, pirfenidone may be re-escalated to the recommended daily dose if tolerated
Aminotransferase elevation >3 to <5 x ULN* accompanied by hyperbilirubinemia or clinical symptoms indicative of liver injury	• Pirfenidone should be discontinued and the patient should not be rechallenged
Aminotransferase elevation ≥5 x ULN*	

** Upper limit of normal*

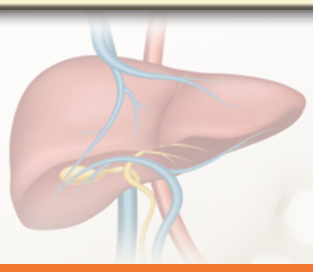
Healthcare professionals are also encouraged to report to HSA any suspected cases of DILI related to the use of pirfenidone.

References

1. https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/important-safety-update-on-esbriet-(pirfenidone)-and-drug-induced-liver-injury-(dili)
2. Esbriet® Singapore package insert (last approved 4th May 2020)

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.



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