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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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AE Case in Focus: Test Yourself

What could have caused the acute kidney injury in this patient?

Pg 7 - 8

This is a case study of a 70-year-old woman with a past medical history of hypertension, hyperlipidemia and cervical cancer. She had a hospital admission for changes in her bowel habit, loss of appetite and weight, and was readmitted due to abdominal discomfort, bloatedness and constipation. A colonoscopy revealed a recto-sigmoid stricture secondary to previous exposure to radiotherapy. Her repeat abdominal CT scan showed rectosigmoid stenosis with upstream faecal loading at the descending colon and her X-rays were suggestive of intestinal obstruction. She was administered laxatives, including oral lactulose and sodium phosphate enemas. Prior to her surgery for loop colostomy, she developed sudden tachycardia, hypotension, desaturation and oliguria. Her blood test results showed marked electrolyte derangement and she developed acute kidney injury with hypernatremia, hypokalemia with a high anion gap metabolic acidosis.

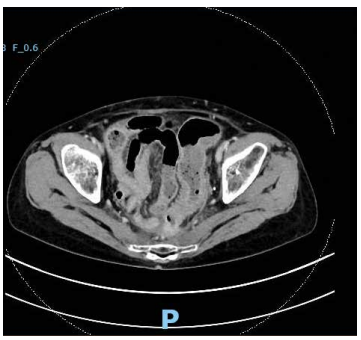

Figure 1. CT scans of the abdomen/pelvis

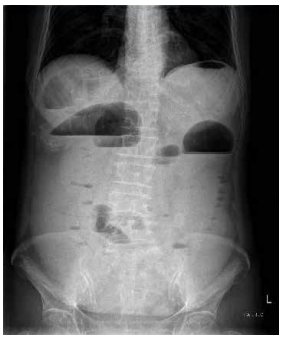

Figure 2. Abdominal X-ray (erect)

We want your feedback!

Dear Healthcare Professional,

HSA is conducting two short surveys to seek your feedback.

Revamped layout of HSA ADR News Bulletin and its two-page hardcopy mailer
https://go.gov.sg/adrbulletin2
We would like to gather feedback to assess if the recent changes made to the HSA ADR News Bulletin has helped to improve the readability and uptake of information by busy healthcare professionals.

Drug safety communication channels
https://go.gov.sg/hsacomms
Thank you to those who have completed this survey in its first run in the May 2020 issue. For those who have not submitted your feedback, we urge you to do so by scanning the QR code or clicking the weblink.

Your feedback is important to help us improve our communication of drug safety information. Each survey takes about 2 minutes to complete and we look forward to receiving your responses by 30 October 2020.

Did you miss a HSA safety alert email? This could be why...

We have received feedback that emails from HSA ended up in the junk email folder in some of your mailboxes. We understand that such occurrences do happen occasionally.

To avoid missing important emails from us, we would like to remind you to check your junk email folder periodically for HSA's safety alerts. Alternatively, you can set email rules in your mailbox to ensure that emails from HSA goes into your Inbox.

We hope this tip is useful.Thank you for your partnership.

Dear Healthcare Professional Letters on safety concerns

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 September 2020.

CONDITIONAL APPROVAL OF REMDESIVIR (VEKLURY®) FOR COVID-19 INFECTION IN SINGAPORE

Key Points

- HSA granted a conditional approval for remdesivir (Veklury®) for the treatment of COVID-19 patients in Singapore on 10 June 2020 following an expedited review due to the urgent public health need during the COVID-19 pandemic
- Taking into consideration the limited data on its efficacy and safety, remdesivir has been restricted to use by Infectious Diseases physicians. Healthcare professionals should refer to the interim treatment guideline for remdesivir published by the National Centre for Infectious Diseases (NCID) for clinical recommendations on the use of remdesivir
- Healthcare professionals are required to report any suspected serious adverse events observed with the use of remdesivir to help HSA better understand the benefit-risk profile of the drug

On 10 June 2020, HSA granted a conditional approval for remdesivir (Veklury®, Gilead Sciences Singapore Pte Ltd) for the treatment of COVID-19 patients in Singapore. The data on the efficacy and safety of remdesivir submitted for registration to HSA was limited. However, given the urgent public health need during the COVID-19 pandemic, HSA expedited the review for remdesivir and has required data from on-going manufacturing and clinical studies to be submitted by the company post-approval to ensure the continued efficacy and safety of the product.

Indication of remdesivir (Veklury®) with the conditional approval

Remdesivir (Veklury®) is indicated for the treatment of COVID-19 infection caused by SARS-CoV-2 in adult patients with oxygen saturation of ≤ 94% (room air), or those requiring oxygen inhalation, under invasive mechanical ventilation (IMV), or under extracorporeal membrane oxygenation (ECMO). The approved treatment regimen is 200 mg IV injection on Day 1 of treatment, followed by 100 mg IV injection once daily from Day 2 up to Day 10. The optimal duration of treatment of remdesivir has not been established. As a guide, the total duration of treatment is up to ten days in patients under IMV or ECMO, up to five days in patients who are not under IMV or ECMO, and up to ten days if these patients do not improve. As no studies in children and pregnant women were presented to HSA, no recommendation for use were made in these special populations.

HSA's scientific considerations for efficacy and safety of remdesivir (Veklury®) in COVID-19 patients

The conditional approval of remdesivir (Veklury®) was based on preliminary clinical data from two Phase 3 trials, i.e. the U.S. National Institute of Allergy and Infectious Diseases (NIAID-ACTT1)[1] and Gilead's SIMPLE-severe trial,[2] and an abbreviated manufacturing data set. Singapore had participated in both clinical trials and enrolled around 100 patients.

The efficacy of remdesivir was based primarily on the results from the NIAID-ACTT[1] trial which showed a faster time to recovery compared to placebo (11 days vs. 15 days), and a higher recovery rate of 32% (rate ratio: 1.32, 95% CI: 1.12–1.55, p<0.001). The results did not show a statistically significant survival benefit, although the death rate was numerically lower with remdesivir treatment compared to placebo (5.9% vs. 10.4%, hazard ratio: 0.70, 95% CI: 0.47–1.04, p=0.059).

The observed favourable results were driven primarily by the higher recovery rate in patients who had oxygen saturation of ≤ 94% (room air) and required oxygen supplementation. In patients with very severe disease such as those who required IMV or ECMO, there was no significant difference between remdesivir and placebo. Nonetheless, preliminary results from the SIMPLE-severe trial suggested that patients who progressed to requiring IMV or ECMO may have a lower death rate with a 10-day course of remdesivir compared to a 5-day course (17% vs. 40%). This observation was inconclusive as it was based on an exploratory analysis in a very small number of patients and was not statistically powered.

In the absence of adequate data in this subgroup of severely ill patients who required IMV or ECMO, the appropriate use of remdesivir must be carefully assessed and considered only when the benefit clearly outweighs the risk.

The safety analysis comprised data from more than 1,000 patients who had received at least one dose of remdesivir. The clinical studies[1,2] excluded patients with elevated liver enzymes or impaired renal functions at baseline, as measured by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels > 5 times upper limit of normal, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 or serum creatinine clearance < 50 ml/min. The adverse events (AEs) of clinical interest reported with remdesivir included liver enzyme elevation, renal-related AEs (acute kidney injury, increased serum creatinine, decreased glomerular filtration), infusion-related reactions (hypotension, nausea, vomiting), respiratory failure, prothrombin time prolongation, and thrombocytopenia.

Given the limited experience with remdesivir, healthcare professionals should consider appropriate clinical and laboratory monitoring, which includes liver, renal and blood tests to allow early detection of any abnormalities or potential AEs.

Restrictions on the use of remdesivir (Veklury®)

Taking into consideration the limited data on its efficacy and safety, the use of remdesivir has been restricted to Infectious Diseases (ID) physicians. Notwithstanding the approved indications for remdesivir, healthcare professionals should refer to the interim treatment guideline for remdesivir published by the NCID for clinical recommendations on the use of remdesivir.[3]

A Dear Healthcare Professional Letter (DHCPL) was issued to ID physicians on 10 June 2020. Healthcare professionals may access the DHCPL by using their professional log in access to MOH Alert via their respective healthcare professional board or councils' websites.

HSA will continue to evaluate the situation, monitor the benefit-risk profile of remdesivir and provide updates to healthcare professionals as necessary. Healthcare professionals are required to report any suspected serious AEs observed with the use of remdesivir to the Vigilance and Compliance Branch. Your reports are important to help us better understand the benefit-risk profile of remdesivir and will contribute significantly to patient safety.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al., (2020) *Remdesivir for the treatment of COVID-19 – Preliminary Report.* N Engl J Med
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3. NCID Interim Treatment Guidelines for COVID-19 (Version 3.0, dated 6 July 2020). Available from: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx (Accessed 31 Aug 2020)

TEMPORARY SUSPENSION OF SALES OF ESMYA™ (ULIPRISTAL ACETATE) TABLET 5 MG

Key Points

- The sales of Esmya™ (ulipristal acetate) tablet 5 mg has been temporarily suspended in Singapore since March 2020 as a precautionary measure, due to ongoing concerns of its association with liver injuries reported overseas
- The European Medicines Agency (EMA) has recently concluded from its review that the risks of serious liver injury associated with the use of ulipristal acetate 5 mg products for the treatment of symptoms of uterine fibroids outweighed its benefits, and has recommended the revocation of the marketing authorisation of these products in the European Union
- To date, HSA has not received any local adverse drug reaction reports of serious liver injury, or liver failure, associated with Esmya™ treatment in Singapore
- HSA is reassessing the benefit-risk profile of Esmya™ and will keep healthcare professionals updated on the outcomes of our review

The Health Sciences Authority (HSA) would like to inform healthcare professionals about the temporary suspension of the sales of Esmya™ (ulipristal acetate) tablet 5 mg, used for the treatment of symptoms of uterine fibroids. The sales of Esmya™ has been temporarily suspended in Singapore since March 2020 as a precautionary measure, while HSA conducts a reassessment on the benefit-risk profile of Esmya™.[1] This was due to ongoing concerns of its association with liver injury, including overseas reports of serious liver injury resulting in liver transplantations that were surfaced by the European Medicines Agency (EMA).

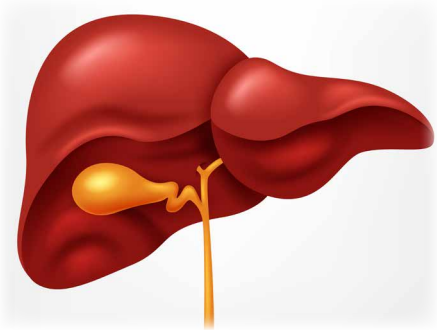
EMA's review and recommendation to revoke the marketing authorisation of ulipristal acetate tablet 5mg in the European Union

In 2018, the EMA had conducted a safety review on the risk of serious liver injury with Esmya™, which concluded that there was a risk of rare but serious liver injury with the product. As a result, additional measures, such as contraindicating the use of Esmya™ in patients with underlying liver disorders, more frequent liver function monitoring and restricting the use of multiple courses of the product in women who are not eligible for surgery, were put in place to manage this risk. As a new case of serious liver injury resulting in liver transplantation had occurred despite these measures, the EMA restarted a review in March 2020, to determine if the previous risk minimisation measures were adequate to manage this safety concern.[2]

The EMA's review was restricted only to ulipristal acetate 5 mg for the treatment of symptoms of uterine fibroids and did not affect the use of ulipristal acetate 30 mg as a single-dose medicine for emergency contraception, as there was no concern about liver injury with the latter. In September 2020, the EMA completed its review of this safety concern, and recommended the revocation of the marketing authorisation of all ulipristal acetate 5 mg products, including Esmya™. The EMA's review took into consideration the reported cases of serious liver injury, as well as the inputs of patient and healthcare professional representatives, including experts in gynaecology. As it was not possible to identify which patients were most at risk of liver injury, or the measures which could reduce this risk, the EMA concluded that the risks of using ulipristal acetate 5 mg for the treatment of symptoms of uterine fibroids outweighed their benefits. Therefore, the EMA recommended that these products should no longer be marketed in the European Union.[3]

Local situation

Esmya™ has been registered for use in Singapore since November 2014, for the pre-operative or intermittent treatment of symptoms



of uterine fibroids in adult women of reproductive age. Since 2017, HSA has been closely monitoring the overseas reports of rare but serious liver injuries associated with Esmya™.

In 2018, HSA conducted a benefit-risk assessment on the risk of rare but serious liver injury associated with the use of Esmya™ in the treatment of symptoms of uterine fibroids. It was assessed that the benefits of Esmya™ continued to outweigh the risks of serious liver injury (approximately 1 in 95,000 patients) for its locally approved use, with the implementation of additional risk mitigation measures. These measures include a) contraindicating the use in patients with underlying liver disorders; b) restricting the use of multiple treatment courses in women who are not eligible for surgical treatment and c) increasing the frequency of liver function monitoring. These measures were communicated to healthcare professionals via the company's Dear Healthcare Professional Letter in April 2019[4] and a publication in the September 2019 issue of the HSA ADR News Bulletin.[5] A patient information brochure was also developed and disseminated by the company to advise patients on the potential risk of serious liver injury and the signs and symptoms to look out for during treatment with Esmya™. To date, HSA has not received any local adverse drug reaction reports of serious liver injury, or liver failure, associated with Esmya™ treatment in Singapore.

HSA's regulatory actions

Following the notification of an overseas case report of serious liver injury with Esmya™ leading to liver transplantation despite the implementation of risk minimisation measures, HSA has worked with the company to implement the temporary suspension of the sales of Esmya™ in March 2020 as a precautionary measure, while HSA reassesses the benefit versus risk profile of the product. In the interim, HSA has also issued an advisory for healthcare professionals, including assessing if a switch to alternative therapies was appropriate for their patients, monitoring the liver function of patients who have been prescribed Esmya™, and not to start new patients on Esmya™.

HSA's reassessment of the benefit-risk profile of Esmya™ is currently ongoing, and our review will take into consideration the latest information from overseas developments. We will keep healthcare professionals updated on the outcomes of our review when completed.

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RISK OF VENOUS THROMBOEMBOLISM WITH TOFACITINIB

Key Points

- A dose-dependent increased risk of serious venous thromboembolism (VTE), including cases of pulmonary embolism and deep vein thrombosis, was observed in patients taking tofacitinib in a clinical study
- Healthcare professionals are advised to use tofacitinib with caution in patients with risk factors for VTE

HSA would like to bring to the attention of healthcare professionals the findings from a clinical study, which found a dose-dependent increased risk of serious venous thromboembolism (VTE) in patients with rheumatoid arthritis treated with tofacitinib.

Tofacitinib (Xeljanz, Pfizer Pte Ltd) is a Janus kinase (JAK) inhibitor that has been registered in Singapore since November 2014. It is approved for reducing the signs and symptoms of rheumatoid arthritis, in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate. The treatment consists of an oral dose of 5 mg administered twice daily.

Increased risk of venous thromboembolism with tofacitinib in study A3921133

Study A3921133 is an open-label clinical trial (n=4,362) evaluating the cardiovascular safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, compared with a tumour necrosis factor (TNF) inhibitor therapy, in patients with rheumatoid arthritis. The patients in the study were 50 years of age or older, with at least one cardiovascular risk factor (e.g. current smoker, high blood pressure, high cholesterol levels, diabetes mellitus, history of heart attack, family history of coronary heart disease). In 2019, an interim analysis of the study results identified a signal of pulmonary embolism (PE) and mortality with the tofacitinib 10 mg twice daily treatment arm. This triggered an in-depth European review of the interim results, which found a dose-dependent increased risk of serious VTE, including cases of deep vein thrombosis (DVT) and PE, in patients taking tofacitinib.

Compared to treatment with a TNF inhibitor, tofacitinib 5mg twice daily increased the risk of PE about 3-fold, while tofacitinib 10mg twice daily increased the risk by approximately 6-fold (Table 1). In a sub-group analysis, the risk of PE was found to be further increased in patients with risk factors for VTE, with a hazard ratio of 9.14 (2.11 – 39.56) and 3.92 (0.83 – 18.48) for the tofacitinib 10mg and 5mg arms respectively, compared to TNF inhibitors.

Incidence rates for DVT and all-cause mortality (within 28 days of last treatment) were also increased for patients treated with tofacitinib compared with TNF inhibitors (Table 1). Mortality was mainly due to cardiovascular events, infections, and malignancies.

Table 1. Incidence rates and hazard ratios of VTE events and all-cause mortality in patients treated with tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, versus TNF inhibitors.

	Tofacitinib 10 mg twice daily	Tofacitinib 5 mg twice daily	TNF inhibitors (Reference)
PULMONARY EMBOLISM			
Incidence rate per 100 patient-years	0.54 (0.32 – 0.87)*	0.27 (0.12 – 0.52)*	0.09 (0.02 – 0.26)*
Hazard ratio	5.96 (1.75 – 20.33)*	2.99 (0.81 – 11.06)*	1.0
DEEP VEIN THROMBOSIS			
Incidence rate per 100 patient-years	0.38 (0.20 – 0.67)*	0.30 (0.14 – 0.55)*	0.18 (0.07 - 0.39)*
Hazard ratio	2.13 (0.80 – 5.69)*	1.66 (0.60 – 4.57)*	1.0
ALL-CAUSE MORTALITY			
Incidence rate per 100 patient-years	0.89 (0.59 – 1.29)*	0.57 (0.34 – 0.89)*	0.27 (0.12 – 0.51)*
Hazard ratio	3.28 (1.55 – 6.95)*	2.11 (0.96 – 4.67)*	1.0

**Results are presented with 95% CI.*

European Medicines Agency's (EMA) review

Following a review of the data from study A3921133, data from earlier studies, as well as consultation with experts, the EMA concluded that tofacitinib could increase the risk of VTE in patients who are already at high risk. Consequently, the EMA recommended that tofacitinib should be used with caution in all patients with known risk factors for VTE. This included patients who have had a heart attack or have heart failure, cancer, inherited blood clotting disorders or history of blood clots, patients taking combined hormonal contraceptives or hormone replacement therapy, and patients undergoing major surgery or are immobilised. Other risk factors to be considered when prescribing tofacitinib included age, obesity, smoking status, diabetes and hypertension. Additionally, the EMA recommended against the use of tofacitinib 10 mg twice daily for maintenance treatment in patients with ulcerative colitis who have known risk factors for VTE, unless there is no suitable alternative treatment available. For the treatment of rheumatoid arthritis and psoriatic arthritis, the current approved dose of 5 mg twice daily should not be exceeded.

Local situation and HSA's advisory

In Singapore, tofacitinib has only been approved for the treatment of rheumatoid arthritis, at a dose of 5 mg twice daily. As of July 2020, HSA has not received any local adverse drug reaction reports of VTE associated with tofacitinib treatment. In light of the findings from study A3921133, HSA is working with Pfizer to update the Singapore package insert of Xeljanz with safety information regarding the increased risk of VTE events. Healthcare professionals are advised to use tofacitinib with caution in patients with risk factors for VTE. Healthcare professionals are also encouraged to report to HSA any suspected cases of VTE related to the use of tofacitinib.

References

1. https://www.ema.europa.eu/en/news/ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots
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RISK OF OROFACIAL MALFORMATIONS ASSOCIATED WITH THE USE OF ONDANSETRON IN EARLY PREGNANCY

Key Points

- Evidence from recent large epidemiological studies suggests that first trimester pregnancy exposure to ondansetron is associated with a small increased risk of orofacial malformations in infants. The evidence for cardiac malformations remains inconclusive
- Healthcare professionals are reminded on the approved indications for ondansetron, and to take into consideration information on the risk of orofacial malformations when prescribing ondansetron

HSA would like to update healthcare professionals on recent published epidemiological studies examining the risk of congenital malformations associated with the use of ondansetron in early pregnancy. A small increased risk of orofacial malformations was observed in infants of women administered ondansetron during the first trimester of pregnancy. However, conflicting results were obtained regarding cardiac malformations.

Ondansetron is an antiemetic agent and acts as a selective serotonin 5-HT3 receptor antagonist. It has been registered in Singapore since 1990, and is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, as well as for the prevention and treatment of post-operative nausea and vomiting.

Ondansetron has been used off-label as second-line therapy for the management of nausea and vomiting of pregnancy and hyperemesis gravidarum.[1] Studies in the US observed a marked increase in ondansetron off-label use, from less than 1% before 2000 to nearly one-quarter in 2014, and its use was most common in the first trimester of pregnancy.[2,3]

Findings from recently published large epidemiological studies

A number of studies, which have attempted to evaluate the risk of congenital malformations associated with the use of ondansetron during pregnancy, have yielded conflicting results. Two recent large epidemiological studies have added to the body of evidence, suggesting that exposure to ondansetron during the first trimester of pregnancy is associated with a small increased risk of orofacial malformations in infants.

The first study was a retrospective cohort study of US health insurance claims data that reviewed more than 1.8 million pregnancies with more than 88,000 exposed to ondansetron in the first trimester.[4] The study concluded that first trimester exposure to ondansetron was associated with a small but statistically significant increased risk of oral clefts in infants (adjusted relative risk 1.24, 95% CI 1.03-1.48), corresponding to a risk difference of 2.7 (95% CI 0.2-5.2) per 10,000 births. No apparent increase in the risk of cardiac malformations or overall congenital malformations was observed after accounting for measured confounders.

The second study was a nested case-control study using another US administrative claims database that included more than 860,000 mother-infant pairs.[5] Since antiemetics were prescribed prophylactically to be used on an "as-needed" basis, the authors sought to minimise the risk of exposure misclassification in prescription data by examining a subset of 5,557 pregnancies with confirmed medical administration of ondansetron in their primary analysis. Based on this subset, first trimester exposure to ondansetron was found to be associated with an increased risk of cardiac defects (adjusted odds ratio [OR] 1.43, 95% CI 1.28-1.61) in infants, compared to those with no exposure to antiemetic during pregnancy. A trend towards an increased risk of orofacial cleft defects was also observed, although it did not reach statistical significance (adjusted OR 1.30, 95% CI 0.75-2.25).

These two studies were among the 12 studies included in a recent meta-analysis which confirmed an increased risk of orofacial clefts associated with first trimester exposure to ondansetron (pooled OR 1.22, 95% CI 1.00-1.49; p=0.0496), without heterogeneity between the included studies.[6] The main analysis of overall cardiac malformations, however, did not reach statistical significance and the heterogeneity between studies was found to be substantial.

Regulatory actions taken by EMA and MHRA

In January 2020, the UK Medicines & Healthcare Products Regulatory Agency (MHRA) issued a safety communication regarding the risk of orofacial malformations with ondansetron, and cautioned on the use of ondansetron outside of its authorised indications.[7] This followed an earlier review of the above-mentioned epidemiological studies by the European Medicines Agency (EMA), which concluded that these studies were considered sufficiently robust to indicate that the use of ondansetron during the first trimester was associated with a small increased risk in orofacial malformations, despite some limitations inherent to the data sources.[8] As a result, the European product information for ondansetron-containing products were updated to highlight this risk, and that the available epidemiological studies on cardiac malformations showed conflicting results.

Local situation and HSA's advisory

To date, HSA has not received any local reports of congenital malformations associated with ondansetron use. The local package inserts for all ondansetron-containing products are being updated to highlight the findings of the studies mentioned above.

Healthcare professionals are reminded on the approved indications for ondansetron, and to take into consideration the above safety information when prescribing ondansetron. Healthcare professionals are also encouraged to report to HSA any suspected cases of congenital malformations related to the use of ondansetron.

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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.

AE CASE IN FOCUS: TEST YOURSELF

A 70-year-old woman with a past medical history of hypertension, hyperlipidemia and cervical cancer, presented in October 2019 with a month's history of changes to her bowel habit, loss of appetite and weight. Her computerised tomography (CT) abdomen scan report showed a focal segmental dilatation of the upper rectum as well as extensive atherosclerotic disease involving bilateral common iliac, internal and external iliac arteries. A colonoscopy revealed a recto-sigmoid stricture secondary to previous exposure to radiotherapy for cervical cancer. The stricture was traversable with the scope. Her biopsy was negative for malignancy and showed only fibrotic changes in keeping with radiotherapy. Her diet was modified and she remained clinically well. She was opening her bowels daily and there was no clinical evidence of obstruction. She was kept under review with a six-monthly follow-up visit.

Unfortunately, the patient was admitted back to the hospital as an emergency case on February 2020 with a week's history of abdominal discomfort, bloatedness and constipation. Blood test results were unremarkable with normal renal function. A repeat CT scan showed the same stenosis at the rectosigmoid junction with upstream faecal loading at the descending colon (Figure 1).

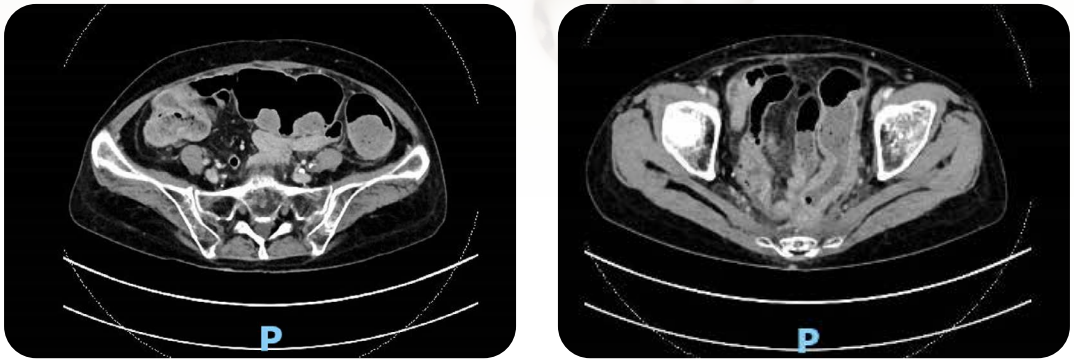

Figure 1. CT scans of the abdomen/pelvis: Rectosigmoid stenosis likely causing partial obstruction with distention of the large bowel proximally

She was still passing flatus with small amounts of stools. Laxatives were administered to her, which included oral lactulose and Macrogol. She was also administered two sodium phosphate enemas over a period of two days. Though she was still passing stools daily, her abdomen was soft but distended. She was counselled for a loop colostomy which was arranged for the next day. However, prior to her surgery, she developed sudden tachycardia, hypotension, desaturation and oliguria. Her arterial blood gasses showed mixed metabolic and respiratory acidosis (pH 7.186, pCO_2 49.9 mmHg, pO_2 88.3 mmHg, bicarbonate 16.7 mmol/l, BE -9.7, O_2 saturation 94.2%). Blood test results revealed marked electrolyte derangement, with profound hypocalcaemia (corrected calcium 1.25 mmol/l) and hyperphosphatemia (phosphate > 12.9 mmol/l). She also developed an acute kidney injury with hypernatremia, hypokalemia with a high anion gap metabolic acidosis (urea 22.7, sodium 154, potassium 2.9, chloride 95, bicarbonate 16.1 mmol/l and creatinine 357 umol/l). Lactate, magnesium and ketones levels were all within normal range. The ECG showed sinus tachycardia, 106 bpm, and prolonged QTc 570s. Erect chest and abdominal X-ray showed clear lung fields and distended bowel loops (Figure 2).

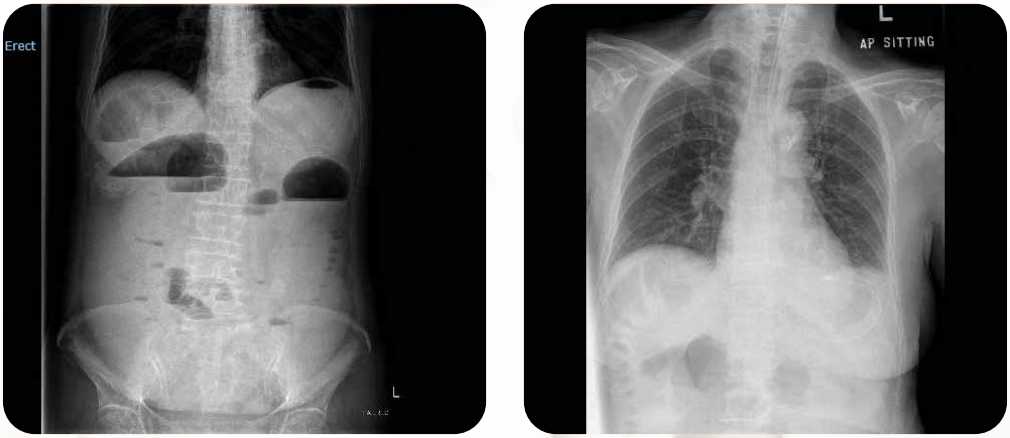

Figure 2. Abdominal X-ray (erect) and chest X-ray. A few prominent small bowel loops and the ascending and descending colon appearing prominent and opacified. The erect view shows fluid distended bowel loops with multiple fluid levels. Features are suggestive of intestinal obstruction. Vascular calcifications are also seen.

Question: What could have caused the acute kidney injury in this patient?

HSA would like to thank Dr. Yeoh Lee Ying, Senior Consultant, Department of Medicine, Dr. Sharmini Su A Sivarajah, Consultant, Department of Surgery and Ms Chew Tan Wei, Senior Pharmacist from Sengkang General Hospital for contributing this article.

Answers can be found on page 8

ANSWERS TO AE CASE IN FOCUS

The patient has oligo-anuric acute kidney injury (KDIGO 3)[1] with unusual electrolyte abnormalities secondary to sodium phosphate enema administration.

Causes of hyperphosphatemia

High blood phosphate levels can be of endogenous or exogenous origin. Organic phosphate stays mainly in the tissue and will be released from the cells in certain conditions such as tumour lysis and rhabdomyolysis that are generally associated with concomitant hyperphosphaemia and hyperkalemia. Dietary phosphate is absorbed in the small intestine (60 - 80%) and excreted by the kidney. Hyperphosphatemia from exogenous sources occurs when the absorption of phosphate exceeded the renal excretion capacity. This can happen with excess phosphate intake or absorption and renal insufficiency.

Sodium phosphate as laxatives

Sodium phosphate is an effective laxative which is available in oral and rectal form. Each 45 ml of Fleet® Phospho-soda oral solution contains sodium dihydrogen phosphate dihydrate 24.4 g and disodium phosphate dodecahydrate 10.8 g, which is equivalent to 4.82 mmol/mL of sodium and 4.15 mmol/mL of phosphate. Each single 118 mL dose of Fleet® Phospho-soda enema contains monobasic sodium phosphate monohydrate 19 g and dibasic sodium phosphate heptahydrate 7 g (~210 mmol of sodium and ~180 mmol of phosphate).[2,3]

The laxative effect of sodium phosphate is relatively quick through osmosis. It is generally well tolerated in healthy individuals and is frequently used for bowel cleansing. Sodium phosphate induced hyperphosphatemia is a consequence of both high phosphate intestinal absorption and decreased renal excretion. Commonly reported risk factors for the development of considerable hyperphosphatemia after administration of sodium phosphate medicines are multiple doses, extreme age, intravascular volume depletion, acute or chronic kidney disease, impaired bowel motility, bowel obstruction, active colitis or concomitant medications such as diuretics, NSAIDs, renin-angiotensin blockade and anti-cholinergic agents. [3-5] The severity of adverse events associated with the use of sodium phosphate medications is similar regardless of the route of administration.[2]

Reports of adverse events with sodium phosphate

Most of the adverse effects of sodium phosphate were published in case report series[3,6,7] and one systematic review report.[8] Electrolyte disturbances that occurred in more than half of the patients with risk factors following sodium phosphate administration include hypocalcemia, hyperphosphatemia, hypernatremia, hypokalemia, hypomagnesemia with QTc interval prolongation and high anion gap metabolic acidosis.

Acute phosphate nephropathy had been reported in patients who received oral sodium phosphate as part of bowel preparation.[4,5] These patients presented with crystal-induced acute kidney injury as a result of calcium phosphate precipitation and formation of hydroxyapatite crystals in the kidney tubules. A retrospective review of the case series from Columbia University from 2000 to 2004 revealed the patients' mean age was 64 years, with most of them hypertensive (76%) and on renin-angiotensin receptor blockade (87%).[9] The raise in their serum creatinine varied from days to months, with bland urinary sample and minimal proteinuria. Diffuse tubular injuries with calcium-phosphate deposition were seen in the renal biopsies. Some of these patients had progressed from chronic tubule-interstitial injuries to chronic kidney diseases.

Case review

The predisposing factors contributing to this patient's acute kidney injury were age, volume depletion, significant atherosclerotic disease burden and decreased bowel transit time. Increased contact between the bowel and enema promoted phosphate and sodium absorption, and the chelation of calcium and phosphate led to hypocalcemia. Intestinal potassium loss and inadequate kidney conservation contributed to hypokalemia that further impaired the gut motility. The management of acute phosphate nephropathy involves early recognition and cessation of sodium phosphate usage, intravascular volume repletion, correction of electrolyte abnormalities and dialysis support if clinically indicated. To prevent this adversity, one must have a high suspicion in recognising patients who are at risk by administering alternative laxatives, ensure close monitoring of electrolytes and providing adequate volume repletion.

Call for adverse event reporting

The development of acute kidney injury can occur suddenly as highlighted in this case report. Healthcare professionals are advised to consider the various risk factors that predispose patients to kidney injury when given sodium phosphate laxatives. Healthcare professionals are encouraged to report suspected drug-induced adverse events to the Vigilance and Compliance Branch of HSA. Your support towards the national adverse event monitoring programme is invaluable in safeguarding public health.

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