ISSN: 0219 - 2152 Dec 2019 Vol.21 No.3

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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Risk of cardiovascular events with febuxostat

- Pre-market clinical studies have suggested a modestly higher rate of serious cardiovascular (CV) events, including CV death, with febuxostat when compared with allopurinol
- A recently completed post-market clinical study has further characterised the CV profile of febuxostat by showing statistically significant greater risk of CV death and all-cause mortality among gout patients with established CV disease compared to allopurinol

Advisory

Healthcare professionals are advised that treatment with febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure

Update on hormone replacement therapy and breast cancer

- The risk of breast cancer with hormone replacement therapy (HRT) use has been previously highlighted by studies such as the Women's Health Initiative (WHI) and Million Women Study (MWS)
- A recent meta-analysis has added to this body of evidence by showing an excess breast cancer risk associated with the use of all types of HRT, except vaginal oestrogens. In addition, it also found that the risk of breast cancer persisted for more than 10 years after stopping HRT, which is longer than previously reported

Advisory

Healthcare professionals are reminded to use the lowest effective dose and the shortest duration of HRT for the treatment of menopausal symptoms in their patients and to review their patients regularly

AE Case in Focus

Ventricular tachycardia and non-ischemic cardiomyopathy – What could have caused this in the patient?

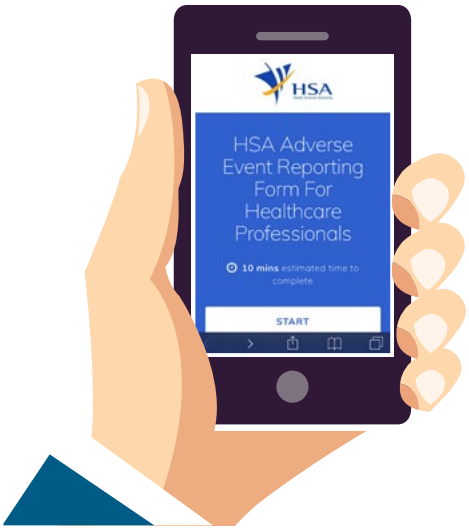
- A case study on ventricular tachycardia and non-ischemic cardiomyopathy in a patient which led to a loss of consciousness, requiring cardioversion and intubation to save her life. As a result, she now suffers from severe heart failure, and is implanted with a defibrillator. The patient had no prior medical illness, no family history of heart disease and was taking a slimming product bought over the internet.

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

Regulatory Updates

Launch of a new mobile-friendly adverse event reporting form

HSA is pleased to launch a new adverse event (AE) reporting form, which facilitates the submission of AE reports via mobile devices. This is in addition to our current modes of reporting, which includes the CMIS (Critical Medical Information Store) module, hardcopy forms, email and online form.



Announcement

- The HSA ADR News Bulletin editorial team is pleased to announce that we have revamped the layout to help busy healthcare professionals pick up topics for reading. The revamped layout will contain succinct eye-catching category headers, key points and QR codes for easy access to the online version via the mobile phone.

- With effect from 2020, as part of our efforts to be more environmentally friendly, we will be replacing the hardcopy 8-page bulletin with a 2-page version containing abstracts of the articles and QR codes that will direct the user to the full web-based articles (refer to first 2 pages of Dec 2019 bulletin as a example).

If you wish to receive the 8-page hardcopy bulletin, please email the following information to HSA_productsafety@hsa.gov.sg by **29 February 2020**:

- Full name
- Professional Registration Number e.g. MCR, SDC or PRN No.
- Mailing address

"Dear Healthcare Professional Letters" on safety concerns

(1 Sep 2019 to 30 Nov 2019)

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

RISK OF CARDIOVASCULAR EVENTS WITH FEBUXOSTAT

Key Points

- Pre-market clinical studies have suggested a modestly higher rate of serious cardiovascular (CV) events, including CV death, with febuxostat when compared with allopurinol
- A recently completed post-market clinical study has further characterised the CV profile of febuxostat by showing statistically significant greater risk of CV death and all-cause mortality among gout patients with established CV disease compared to allopurinol
- Healthcare professionals are advised that treatment with febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure

Febuxostat (Feburic®, Astellas Pharma Singapore Pte Ltd) has been registered in Singapore since 2016 and is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred. As pre-market studies had suggested its association with serious cardiovascular (CV) events, warnings that febuxostat is not recommended for use in patients with ischaemic heart disease or congestive heart failure were included in its product labelling when it was first approved. Recently, findings from a completed post-market study have further characterised the CV profile of febuxostat by showing that gout patients with a pre-existing major CV disease treated with febuxostat had a statistically significant higher risk of CV death and all-cause mortality compared to those on allopurinol.

Serious cardiovascular events associated with febuxostat[1]

Concerns about the CV risk of febuxostat first arose during the pre-market phase, where a numerical excess of serious CV events (including CV death, non-fatal myocardial infarction and non-fatal stroke) was observed among febuxostat-treated subjects compared to allopurinol-treated subjects (1.3 vs 0.3 events per 100 patient-years) in the phase 3 clinical studies, APEX and FACT. As a result, the product labelling for febuxostat had included warnings on possible CV events when it was first approved and the US Food and Drug Administration (FDA) had requested for the conduct of a large post-market clinical trial to further evaluate its CV safety. This study, known as the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) study, was recently completed in 2017.

About the CARES study[2]

The CARES study was a phase 4, multi-centre, randomised, double-blind CV outcomes study that involved 6,190 patients with gout who were treated with either febuxostat or allopurinol. The patients also had an established major CV disease, including a history of myocardial infarction, hospitalisation for unstable angina or transient ischaemic attack, stroke, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease. After a median follow-up of 32 months, the study found a statistically significant higher risk of CV-related death and all-cause mortality in the febuxostat group compared to the allopurinol group (Table 1). The primary endpoint, which was a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina with urgent revascularisation, occurred at similar rates between both groups.

Table 1. CARES study findings

Endpoint	Febuxostat (n=3,098)	Allopurinol (n=3,092)	Hazard ratio (95% CI)
	No. of patients (%)		
Primary composite end point: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or urgent coronary revascularisation due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.89-1.21)
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03-1.73)
Non-fatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72-1.21)
Non-fatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73-1.41)
Unstable angina with urgent revascularisation	49 (1.6)	56 (1.8)	0.86 (0.59-1.26)
All-cause mortality	243 (7.8)	199 (6.4)	1.22 (1.01-1.47)

International regulatory actions

Following a review of the CARES study, international regulatory agencies, namely the US FDA, the European Medicines Agency and the Australia Therapeutic Goods Administration concluded that the existing warnings on CV risk in the product labelling for febuxostat should be strengthened to reflect the key findings from the study.[3-5] In addition, the US FDA restricted the use of febuxostat as a urate-lowering agent to patients who have inadequate response to, or are intolerant to allopurinol.

Local situation

The imbalances in the incidence of serious CV events between febuxostat- and allopurinol-treated patients observed from the pre-market studies are currently highlighted in the local package insert (PI) of Feburic® to warn healthcare professionals about the potential risk of serious CV events, including CV deaths. The PI also included advice that treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. In response to the CARES study, the company has updated the local PI to highlight the study findings and to recommend that caution should be exercised for exacerbation and/or onset of CV disease when administering febuxostat.

HSA's advisory

Healthcare professionals are advised to take into consideration the above information when prescribing febuxostat, particularly to patients with a history of CV disease. In patients with ischaemic heart disease or congestive heart failure, treatment with febuxostat is not recommended.

References

1. *Singapore Feburic® package insert (approved 3 Dec 2019)*
2. *N Engl J Med 2018; 378: 1200-10*
3. *https://www.fda.gov/media/120418/download*
4. *https://www.ema.europa.eu/en/documents/procedural-steps-after/adenuric-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf*
5. *https://www.tga.gov.au/node/882032*

UPDATE ON HORMONE REPLACEMENT THERAPY AND BREAST CANCER

Key Points

- The risk of breast cancer with hormone replacement therapy (HRT) use has been previously highlighted by studies such as the Women's Health Initiative (WHI) and Million Women Study (MWS)
- A recent meta-analysis has added to this body of evidence by showing an excess breast cancer risk associated with the use of all types of HRT, except vaginal oestrogens. In addition, it also found that the risk of breast cancer persisted for more than 10 years after stopping HRT, which is longer than previously reported
- Healthcare professionals are reminded to use the lowest effective dose and the shortest duration of HRT for the treatment of menopausal symptoms in their patients and to review their patients regularly

A recent meta-analysis has shown that an increased risk of breast cancer was associated with the use of all types of hormone replacement therapy (HRT), except vaginal oestrogens. The analysis also found that the excess risk of breast cancer with systemic HRT persisted after stopping HRT for longer than previously reported. In view of the above, HSA would like to update healthcare professionals on these findings and the recommendations on the use of HRT.

About the meta-analysis[1]

The meta-analysis, published in The Lancet in August 2019, was conducted by the Collaborative Group on Hormonal Factors in Breast Cancer to assess the association between the type and timing of HRT use and the risk of incident invasive breast cancer in post-menopausal women. The main analysis used a nested case-control design, where 108,647 cases of breast cancer from prospective epidemiological studies were each matched with up to four randomly selected controls (i.e. women without breast cancer) by age, year of birth, and broad geographical region, as appropriate. The studies conducted mostly in early 2000s included long-term follow-up of women who were current users, past users, or never users of HRT. Among women who developed breast cancer, the mean HRT duration was 10 years in current users and seven years in past users. The mean age at HRT initiation and at menopause was the same, both at 50 years.

Key findings from the meta-analysis[1]

1) Effect on risk by type of HRT

All forms of HRT, except vaginal oestrogens, were associated with an increased breast cancer risk, regardless of the type (combined oestrogen-progesterone or oestrogen-only)

and route of delivery (oral or transdermal). Low doses of oestrogen applied directly via the vagina to treat local symptoms were not found to have an effect on breast cancer risk.

The relative risk of breast cancer in women taking HRT was greater for combined HRT than oestrogen-only preparations, when compared to never users of HRT. Among current users of combined HRT, the risk of breast cancer during years 5 - 14 was greater with continuous HRT (i.e. daily progesterone use) than with sequential HRT (i.e. intermittent progestogen use) (Relative risk (RR) 2·30, 95% CI 2·21, 2·40 vs RR 1·93, 95% CI 1·84, 2·01; heterogeneity p<0·0001).

2) Effect on risk by duration of use

The risk of breast cancer increased with longer duration of use. There appeared to be little or no excess risk of breast cancer with current or previous use of HRT for duration of less than one year. However, during years 1 - 4 of current use, an excess risk was found with both combined HRT (RR 1·60, 95% CI 1·52, 1·69) and oestrogen-only systemic HRT (RR 1·17, 95% CI 1·10, 1·26). This risk approximately doubled during years 5 - 14 of use (combined HRT: RR 2·08, 95% CI 2·02, 2·15; oestrogen-only systemic HRT: RR 1·33, 95% CI 1·28, 1·37). The relative risks for past users were lower than in current users, but some excess risk persisted for more than 10 years after stopping, and its magnitude depended on the duration of previous use. However, there was little information about breast cancer risk associated with past use that had ceased more than 15 years.

Similar findings from earlier studies

The risk of breast cancer associated with the use of HRT had been previously highlighted by large research studies such as the Women's Health Initiative (WHI)[2,3] in the US and the UK Million Women Study (MWS)[4] published in 2002 and 2003. Both studies found an increased risk of breast cancer associated with combined HRT use. In addition, the MWS also noted an excess breast cancer risk with oestrogen-only HRT use and increasing total duration of use in current users, regardless of HRT type. This recent meta-analysis adds to this body of evidence by confirming the earlier findings. However, contrary to the MWS which observed a decline in breast cancer risk after stopping HRT that reached the same level as never users of HRT by five years, the meta-analysis noted this risk to persist for more than 10 years when compared to never users.

Local situation

There are 16 HRT products registered in Singapore. These products are contraindicated for use in patients with known, past or suspected breast cancer. In response to the earlier studies, HSA had published a series of bulletin articles in 2002[5], 2004[6] and 2011[7] to update healthcare professionals on the benefits and risks of HRT. An advisory was also issued in 2002 by HSA, in consultation with medical experts in the management of HRT, to advise physicians not to use HRT for the prevention of coronary heart disease.[8]

HSA's advisory

Healthcare professionals are advised to use the lowest effective dose and the shortest duration of HRT for the treatment of menopausal symptoms in their patients wherever possible and to review their patients regularly. As the potential harm may outweigh the potential benefits for women who are using HRTs solely for the long-term prevention of osteoporosis, it may be beneficial for patients to be also made aware of other non-HRT therapies for the treatment and prevention of osteoporosis. In addition, HRT does not protect postmenopausal women against cardiovascular events and hence these products are not to be initiated or continued for the purpose of reducing cardiovascular risk or preventing coronary heart disease.

References

1. *http://dx.doi.org/10.1016/S0140-6736(19)31709-X*
2. *JAMA 2002; 288: 321-33*
3. *JAMA 2010; 304: 1684-92*
4. *Lancet 2003; 362: 419-27*
5. *HSA ADR News Bulletin 2002 Aug; 4: 1,4*
6. *HSA ADR News Bulletin 2004 July; 6: 2*
7. *HSA ADR News Bulletin 2011 April; 13: 8*
8. *https://www.hsa.gov.sg/announcements?contenttype=dear%20healthcare%20professional%20letters*

AE CASE IN FOCUS: TEST YOURSELF

A female in her 50s was brought by the ambulance to the Emergency Room following a loss of consciousness which caused facial injury. She had no prior symptoms or medical illness. She did not smoke or drink alcohol and had no family history of heart disease.

Upon examination by the doctor, the patient was found to be drowsy with a blood pressure of 98/60 mmHg, heart rate of 218 bpm and SpO2 of 100% on room air. The ambulance's electrocardiogram (ECG) documented ventricular tachycardia (VT) (Figure 1). She was sedated and intubated for airway protection, and then cardioverted with an external 100J synchronised shock to atrial fibrillation with right bundle branch block (Figure 2). Her serum troponin-T was elevated at 174.8 pg/ml. Her CT brain scan and coronary angiography results were normal. The echocardiogram showed severe left ventricular systolic dysfunction with a left ventricular ejection fraction (LVEF) of 30%, and moderate mitral regurgitation. Her cardiac MRI scan revealed late gadolinium enhancement of the mid-wall in the basal septum compatible with fibrosis.

She was diagnosed with non-ischaemic cardiomyopathy. The patient was prescribed amiodarone, bisoprolol and lisinopril. She subsequently underwent implantation of a cardiac resynchronisation therapy defibrillator (CRTD).

On further review of her history, she reported taking a slimming product called "BB Body" which she had purchased over the internet. She had been taking one sachet of the product daily for three months and had lost eight kg in weight. The product was sent to the HSA's laboratory for testing. The patient discontinued the product and six months after hospital discharge, the CRTD recorded non-sustained VT but no tachycardia. The echocardiogram showed persistent left ventricular dysfunction (LVEF 35%) and mild-moderate mitral regurgitation.

Question: What could have caused the patient's life-threatening cardiac condition?

HSA would like to thank Dr. Jennifer Joy Limpot Penalosa and Dr. Derek Chin Tze-En from the Department of Cardiology at Khoo Teck Phuat Hospital (KTPH) for contributing this article; and Dr. Ashish Chawla, Senior Consultant from the Department of Diagnostic Radiology at KTPH for contributing the cardiac images.

Answers can be found on page 7-8

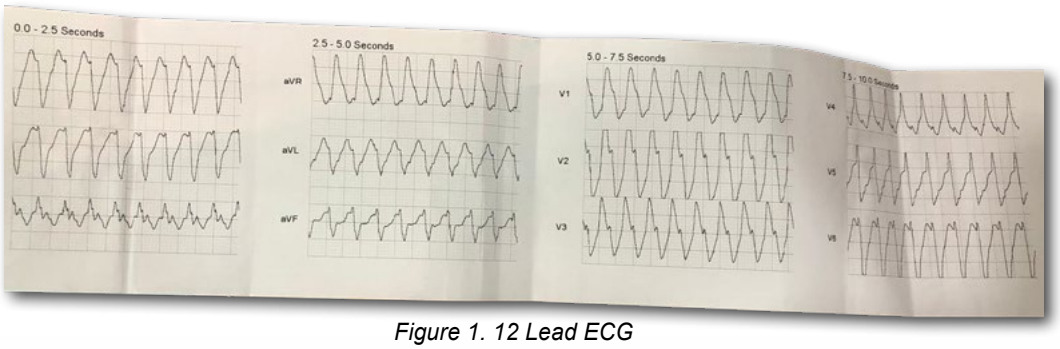


Figure 1. 12 Lead ECG

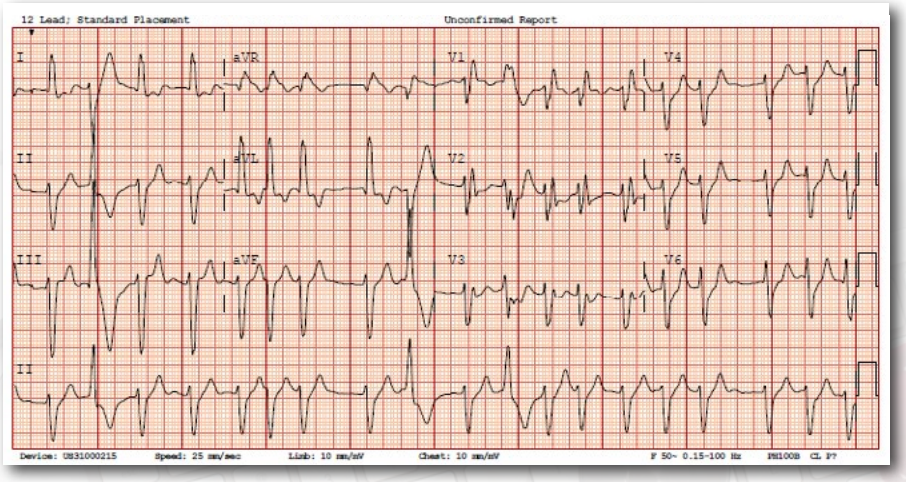


Figure 2. Post conversion 12 Lead ECG

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 SEP 2019 TO 30 NOV 2019)

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

Therapeutic products

14 Aug 2019*	**Romesec Capsule 20mg (Omeprazole)** Recall of affected product for batch number #3963179 and 19010069 due to unacceptable product degradation
16 Sep 2019	**Ranitidine-containing products** Retail level recall of eight brands of ranitidine products detected with nitrosamine impurity, N-nitrosodimethylamine (NDMA) that exceeded internationally acceptable level
16 Oct 2019	**Mitomycin-C Kyowa for Injection 2mg/vial and Mitomycin-C Kyowa for Injection 10mg/ vial** Retail level recall of affected products due to concerns that the products' sterility cannot be guaranteed due to manufacturing deviations
4 Nov 2019	**Kyprolis® (carfilzomib)** Risk of progressive multifocal leukoencephalopathy and Hepatitis B virus reactivation and patient monitoring advisories

Medical devices

2 Sep 2019	**EMBLEM™ S-ICDs (Model A209 and A219)** Earlier than expected device replacement (ERI/EOL) of affected device due to compromised performance of an electrical component causing accelerated battery depletion
4 Sep 2019	**PALACOS® LV+G, PALACOS® MV+G, PALACOS® R+G** Recommendations on the sterile removal of the primary cement powder bag
13 Sep 2019	**STRATAFIX™ Spiral PDS™ Plus Knotless Tissue Control Device** Voluntary recall of selected lots that do not meet certain internal testing specifications
19 Sep 2019	**Various legacy Biomet products** Recall of affected devices with elevated levels of bacterial endotoxin and residual debris. Locally, only Comprehensive RVS Mini Baseplate (Item No: 010000589) and Comprehensive RVS Baseplate - 28 MM (Item No: 115330) are supplied in Singapore
22 Oct 2019	**Blackwell Models and Orion Models of implanted cardiac devices** Advisory on the potential inaccurate display of remaining longevity estimate by Medtronic programmer and remote monitoring software applications
5 Nov 2019	**Allergan XEN Glaucoma Treatment System** Recall of unused lots affected by trace amounts of residual polishing compounds from the manufacturing process
6 Nov 2019	**WECK® Auto Endo5® Automatic Hem-o-lok® Clip Appliers** Recall of specific lots due to risk of misloading and/or jamming which may lead to clips falling out, clip breakage, or the jaws becoming locked in a partially closed position
19 Nov 2019	**SynchroMed™ II Implantable Infusion Pumps Models 8637-20, 8637-40** Voluntary recall of specific serial numbers of affected models due to presence of a foreign particle inside the pump motor assembly, which could interfere with motor gear rotation and lead to a permanent motor stall
26 Nov 2019	**STAR Total Ankle Replacement** Patients implanted with affected device distributed prior to 1 Aug 2014 may experience a higher than expected risk of polyethylene fracture due to potential increase in polyethylene oxidation prior to or after implantation

*DHCPLs not published in Sep 2019 issue

ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

HSA tested "BB Body" and found that it contained sibutramine. This drug is recognised to potentially cause serious adverse events such cardiac arrhythmia and cardiovascular death in patients taking the drug.

Slimming products and risk of adulteration

There are many different varieties of non-prescription slimming products and food supplements available in the market. Many claim to contain 100% natural ingredients. Buyers assume that they can safely consume these products and are free from side-effects. However, some of these products may be adulterated with medicinal ingredients or banned synthetic analogues which can potentially cause serious adverse events or even death. Sibutramine, a prescription-only weight loss drug, has been banned in Singapore since 2010 due to serious safety concerns. It is a common adulterant detected in many non-prescription slimming products by HSA.

Sibutramine and cardiovascular adverse events

Sibutramine was first approved for the treatment of obesity in the United States (US) in 1997 and in Canada in 2000. The prescription-only drug is a beta-phenylethylamine that inhibits the synaptic reuptake of both serotonin and norepinephrine. Developed initially as an anti-depressant, it had little effect on depression, but its use was associated with decreased appetite, reduced caloric intake and weight loss.[1] However, soon after its launch in the market, the use of sibutramine was associated with adverse effects. Between 1998 and 2001, the US FDA received 397 reports, including 143 cardiac arrhythmias and 29 deaths. There were a further 28 reports in Canada, 47 in Italy, 215 in the United Kingdom and 99 in France (including tachycardia, hypertension, arrhythmia and death), leading to contraindications in patients with established coronary heart disease, stroke, heart failure and cardiac arrhythmia.[2]

In 2010, the Sibutramine Cardiovascular Outcomes Trial (SCOUT), studied 10,744 obese patients aged ≥55 years with pre-existing cardiovascular disease and/or type 2 diabetes mellitus randomised to sibutramine 10-15 mg daily or placebo over a mean of 3.4 years.[3] The authors found increased risks for non-fatal myocardial infarction and non-fatal stroke, outweighing the benefit of weight loss. This led to the suspension of the drug in the European Union and Singapore, and its withdrawal from the US market.[4]

While the drug is no longer commercially available and banned in Singapore, it has been detected in illegal adulterated weight loss supplements and sold as herbal products on the internet. Cases of life-threatening cardiovascular events following the use of sibutramine-

containing products continue to be reported, including a case of refractory ventricular fibrillation in a 21-year-old woman,[5] and dilated cardiomyopathy and massive left ventricular thrombus in a 32-year-old man.[6]

Case review

In the case above, the patient developed life-threatening ventricular tachycardia and a non-ischaemic cardiomyopathy. She had no associated symptoms to suggest an inflammatory/endocrine cause or any family history that indicated a possible genetic etiology of her heart disease. There was also no evidence to suggest infiltrative causes based on the cardiac magnetic resonance images (MRIs). Upon medication-history taking, it was found that the patient took a slimming product 'BB Body'. The product 'BB Body' was sent for testing and found to be adulterated with sibutramine at doses recognised to cause cardiovascular disease. The patient underwent cardioversion and intubation and was implanted with a defibrillator.

Conclusion

The cause of the condition was made possible by revisiting the clinical history and obtaining the actual product for analysis by HSA's laboratory. Healthcare professionals are encouraged to enquire about the use of dietary/health supplements and to consider their role in causing adverse events. In such cases, the HSA's laboratory is an important resource for the analysis and identification of adulterated potent ingredients, facilitating the correct diagnosis and treatment of affected patients.

References

1. *Ann Pharmacother 1999; 33: 968-78.*
2. *Diabetes Care. 2011 May; 34(Suppl 2): S114–S119. doi: 10.2337/dc11-s205*
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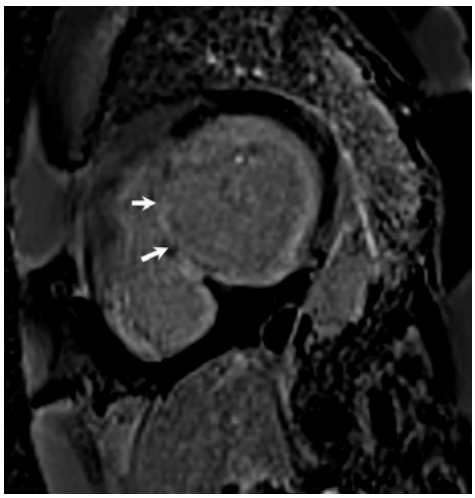
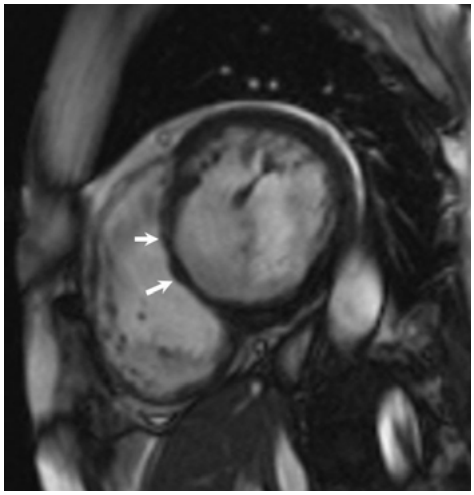


Delayed post contrast PSIR image shows transmural hyperenhancement of septal wall in basal region (white arrows)



Cine SSFP image in end-diastole shows thinning of septal wall in basal region (white arrows)

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:

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