CASE REPORT

Ventricular tachyarrhythmia in a 78-year-old woman with essential thrombocythaemia

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SUMMARY

Anagrelide is a phosphodiesterase-3 inhibitor used in the treatment of essential thrombocythaemia. Cardiovascular side effects such as ventricular tachycardia and cardiomyopathy are rare but potentially fatal and should be made known to patients before starting the medication. It usually arises within the first 6 months after initiation of therapy and may be dose related. The elderly population are particularly susceptible. These cardiotoxicities result from an increase in cyclic AMP that induces positive inotropic and chronotropic effects and are often reversible with cessation of use. We report a case of a 78-year-old woman with essential thrombocythaemia and recently started on anagrelide who presented with syncope and multiple bruises and facial trauma and found to have developed ventricular tachyarrhythmia.

BACKGROUND

Anagrelide is a phosphodiesterase-3 (PDE3) inhibitor used in the treatment of essential thrombocythaemia. It decreases platelet production by inhibiting the maturation of megakaryocytes. Cardiovascular side effects such as ventricular tachycardia are rare but potentially fatal and should be made known to patients before starting the medication.

CASE PRESENTATION

A 78-year-old woman with a history of hypertension, dyslipidaemia and essential thrombocythaemia presented to the emergency department with multiple bruises following an episode of witnessed syncope. Witnesses reported that she fell face-first onto the pavement with a 30 seconds loss of consciousness. She mentioned having palpitations and feeling light-headed prior to the syncope. There were no associated postictal symptoms such as confusion, bowel and bladder incontinence, muscle rigidity, weakness or numbness. She denied chest pain, shortness of breath, recent illness, as well as any previous episodes of syncope. She was a non-smoker with no history of alcohol or illicit drug abuse. She has recently switched to anagrelide 3 weeks ago due to alopecia likely secondary to hydroxyurea. Vital signs were within normal limits with no orthostatic changes.

Physical examination revealed multiple facial haematomas, a right eyelid laceration and a depressed right maxilla. Cardiopulmonary, neurological and laboratory examinations were normal.

ECG showed normal sinus rhythm with a QTc of 0.458 ms (figure 1), and no signs of atrioventricular block, Q waves or ST-T wave changes. The patient was admitted to the cardiology floor under continuous cardiac monitoring which revealed multiple episodes of sinus arrhythmia and non-sustained ventricular tachycardia on the day of admission. Anagrelide was discontinued at the onset. Head CT showed a depressed fracture of the right frontal maxillary process and orbital floor fracture with extension to the infraorbital canal, right scalp haemorrhage but no intracranial haemorrhage. Brain MRI/MR angiography was negative for acute infarction or haemorrhage. Carotid Doppler showed no haemodynamically significant stenosis bilaterally. Electroencephalogram was normal. The echocardiogram revealed normal cardiac chamber size with normal systolic function and an ejection fraction of >55% with no wall motion abnormalities. Cardiac catheterization showed normal coronary arteries. An electrophysiology study was done with procainamide infusion which revealed no inducible ventricular tachyarrhythmia and no Brugada electrocardiographic provocation.

After this syncope event, likely secondary to cardiac toxicity due to anagrelide, the patient and haematologist discussed risk and benefits of restarting hydroxyurea again for the treatment of essential thrombocythaemia, and because the prior side effects were not significant and likely rare for this medication, the patient agreed to restart hydroxyurea for the treatment of essential thrombocythaemia and anagrelide was discontinued.

She was discharged home in stable condition. She has not had an episode of syncope for the past year since admission. The patient was never placed back on anagrelide, and her disease is currently being managed with hydroxyurea and regular phlebotomy.

DISCUSSION

The precise mechanism of action of the anagrelide is not well understood but is believed to be related to reduced expression of GATA-1 and FOG-1 transcription factors and subsequent suppression of megakaryocytopoiesis. Anagrelide effectively lowers platelet count in a spectrum of chronic myeloproliferative disorders, including essential thrombocythaemia and polycythaemia vera.^{1,2} Independent of this actions, it has also been found that anagrelide also inhibits cyclic nucleotide PDE3.³

Anagrelide is usually well tolerated. Reported side effects of this drug include nausea, dyspepsia,

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Figure 1 ECG on admission showing sinus rhythm with premature atrial complexes and QT prolongation (QTc 0.458s).

abdominal pain, diarrhoea, headache, fluid retention, anaemia and rash. These adverse events are related to the initiation of treatment, accumulative dosage, dosing interval and withdrawal.⁴

The mechanism of cardiotoxicity with the use of anagrelide is thought to be the results from inhibition of PDE3 which generate an increase in intracellular levels of cyclic AMP and triggering an increase in intracellular calcium level in the cardiomyocytes and vascular smooth muscle cells. This leads to a positive inotropic, chronotropic effects and vasodilator effects⁵ that translate to palpitation (26%), chest pain (8%) and tachycardia (8%). These can lead to congestive heart failure, cardiomyopathy, arrhythmia and syncope.⁶

Anagrelide absorption occurs rapidly and reaches maximum concentration in plasma within 1 hour after administration.⁷ After being absorbed, anagrelide is metabolised to the active metabolite 3-hydroxy-anagrelide in the liver primarily, by the cytochrome P450 1A2,⁷ which is further metabolised to an inactive metabolite, RL603. Anagrelide and the active metabolite 3-hydroxy-anagrelide have half lives of around 3 hours in healthy individuals.⁷

Anagrelide recommended starting dose is 0.5 mg twice daily, and this dose should be maintained at least for a week before adjusting the dose. Dose-dependent side effects like palpitation, diarrhoea and headaches had been reported, making patient compliance and titration of anagrelide difficult.⁴ Palpitations related to anagrelide has been reported to be more common during the first days or weeks of treatment.⁸

A clinical trial of anagrelide was conducted in 577 patients with myeloproliferative disorders.³ The study was conducted over 5 years, with a mean treatment duration of 65 weeks. The most common cardiovascular events were palpitations and tachycardia, which occurred in 209 patients (36.2%). These palpitations were usually benign and non-arrhythmia related and resolved over time. The incidence was later lower during the long-term therapy compared with the initial treatment phase.^{3,4,9}

Other severe cardiac adverse events described are as follows: congestive heart failure (14 patients/2.4%), fluid retention (132 patients representing 24%), cardiomyopathy (one patient), new or worsened angina (five patients) and sudden death (two patients).³ Case reports have been published regarding the association of anagrelide therapy with reversible cardiomyopathy and high-output heart failure and atypical Takotsubo syndrome.^{5,10-13}

In another a retrospective study, The Registro Italiano Trombocitemie (RIT) or Thrombocythaemia Italian registry, documented that 71 (30.6%) out of 232 patients with essential thrombocytosis experienced 88 cardiovascular adverse events during anagrelide treatment¹⁴ which included palpitations

(24%), angina (4.3%), systemic hypertension (3.5%), congestive heart failure (3.0%), arrhythmia (1.8%), acute myocardial infarction (0.9%) and pericardial effusion (0.4%). A significant relationship ($P < 0.01$) was found between adverse cardiovascular events' occurrence and a higher mean dose of anagrelide during induction phase.¹⁴ These findings suggest that the cardiovascular effects are dose related. The incidence of ventricular tachyarrhythmias reportedly ranges from 1% to 5%.¹⁴

Advanced age is associated with increased incidence of palpitations, but this is mainly to arrhythmia-related palpitations.¹⁵ The mechanism behind the aetiology of palpitations are scarring and myocyte hypertrophy, that can cause abnormalities in the conduction system, increasing the probability of rhythm disturbance and generation of arrhythmias, perceived as palpitations.¹⁶ For this reason, there is a possibility that cardiac rhythm side effects are more pronounced in the elderly population on treatment with anagrelide.⁷ The negative inducibility of ventricular tachyarrhythmia on electrophysiology study is expected for torsades de pointes.

Another significant cardiovascular adverse event associated with anagrelide is acute coronary syndrome, which has been reported in 1%–5% of patients under this drug.¹⁷ The mechanism related with coronary events and anagrelide might be related to the induction of coronary vasospasm through PDE inhibition. It has been proven in animal models that PDE inhibitor can increase transmitter release from sympathetic nerves and increase sympathetic tone.¹⁷ Also, another study showed lower levels of platelet factor-4 and vascular endothelial factors in relation to low platelet count. Because of the lower level of this growth factor, the possibility of coronary neoangiogenesis might be attenuate and further cause myocardial ischaemia in the setting of endothelial dysfunction.¹⁷

Although rare, anagrelide has also been associated with cardiomyopathy. Jurgens *et al*¹³, in a retrospective study, reported six patients with cardiomyopathy associated with anagrelide that improved symptomatically and objectively after discontinuation of the drug. The mechanism related with cardiomyopathy is unclear but could be related to positive inotropic activity, vasodilation and tachyarrhythmia.¹⁴

Despite knowledge of the cardiovascular adverse events reported under the use of anagrelide, it is still unclear whether a complete cardiovascular assessment is needed before or during the administration of the drug.

In summary, we described a case of cardiac syncope secondary to anagrelide. After an extensive negative cardiovascular and neurological work-up including an echocardiogram, cardiac catheterization, electrophysiology study, brain imaging and electroencephalogram, the concern for an arrhythmia as the trigger factor for this syncope episode was highly suspected. In our patient, ventricular tachyarrhythmia was not induced

Learning points

- Cardiovascular assessment would seem prudent before and during the first 6 months after initiation of anagrelide treatment.
- Attention should be given to elderly patients if anagrelide is used, especially in those with a history of cardiovascular disease, and those taking a higher dose of the drug.
- Adverse effects of anagrelide such as ventricular tachyarrhythmia occur and are potentially fatal but are rare and often resolve with cessation of use.

after procainamide which is expected in a patient with torsades de pointes. For this reason, and with the establishment of the temporal relationship between the recent initiation of anagrelide and the syncopal event as well as the disappearance of the symptom after withdrawal of the anagrelide, the team strongly believes that anagrelide was the causative agent.

Contributors MR-Z admitted and followed the patient on the cardiology service, participated in writing the case and review of the literature and development of the discussion and conclusion, got patient's consent, responsible for the overall content and guarantor. MR also followed the patient on the cardiology service, also participated in reviewing the discussion and conclusion. ML: critical revision of the manuscript and final approval of the version to be published, was the senior resident managing the patient on the cardiology service. AG: attending taking care of the patient, also did the electrophysiology studies, critical revision of the discussion, revision of the final version.

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