Isotretinoin (13-cis-retinoic acid)-associated premature ventricular contractions

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Isotretinoin (13-cis-retinoic acid), a synthetic vitamin A derivative, is used to treat a wide variety of dermatologic conditions including severe acne. Isotretinoin can trigger premature ventricular contractions (PVCs). We describe a 17-year-old boy who presented with PVCs on electrocardiogram during isotretinoin (Roaccutane, Roche) treatment for nodular facial acne. Presence of documented PVCs -on electrocardiogram and Holter monitoring- and the disappearance of these PVCs after cessation of the treatment strongly suggest isotretinoin-related PVCs in our case. The impact of isotretinoin on ventricular rhythm can not be ruled out in our case as we have revealed the presence of the temporal association of isotretinoin and documented PVCs. Thus, clinicians should be aware of possible arrhythmogenic effect(s) of isotretinoin.

Key words: isotretinoin, ventricular arrhythmia, acne.

Isotretinoin (13-cis-retinoic acid) is a synthetic vitamin A derivative. It reduces production of sebum, stabilizes keratinization, and prevents comedones formation. Alike other retinoids, isotretinoin works by altering DNA transcription, although the exact mechanism of action is unknown. Isotretinoin has been used to treat a wide variety of dermatologic conditions including severe acne[1]. It has been used orally at 0.5-1 mg/kg/day for 4-6 months. Isotretinoin has a high level of lipophilicity, and is primarily (99.9%) bound to plasma proteins, mostly albumin. Isotretinoin is metabolized by the liver, and metabolites of isotretinoin are excreted with urine and feces. The mean elimination half time is 21 hours. Adverse drug reactions associated with isotretinoin include dryness of skin, lips and mucous membranes, cheilitis, skin fragility, skin peeling, rash, flushing, photosensitivity, nose bleeds, dry eyes, eye irritation, conjunctivitis, reduced tolerance to contact lenses, raised liver enzymes, headaches, stroke, hair thinning, fatigue, weakness, dizziness, gastrointestinal disturbances, abdominal pain, raised blood glucose and lipid levels, raised liver function levels, palpitations, tachycardia, and abnormal cardiac rate or rhythm (rare). Isotretinoin treatment is contraindicated in pregnancy[1-3]. Cardiac side effects have been rarely reported with isotretinoin treatment; there have been a few reports of isotretinoin-related sinus or atrial tachycardias[2,4,5]. Herein, we report a case with ventricular arrhythmia possibly related with isotretinoin.

Case Report

A 17-year-old boy admitted with a chief complaint of easily tiring during exercise with the school football team. His past medical history revealed bronchoscopy for popcorn aspiration and adenoidectomy at the ages of 2 and 3, respectively. He started that he had been on isotretinoin (Roaccutane, Roche) 30 mg per day for the treatment of nodular facial acne for six months. Shortly after the initiation of the treatment he developed cheilitis. He had never experienced any episodes of palpitations or other symptoms such as chest pain, dizziness or skipped beat feeling, but his heart sounds were arrhythmic on cardiovascular examination.

Twelve-lead electrocardiogram (ECG) showed premature ventricular contractions (PVCs) (Fig. 1). Transthoracic echocardiography showed normal left and right ventricular size and function. Twenty-four-hour Holter monitoring showed frequent single, bigeminy, trigeminy, quadrigeminy uniform PVCs. The PVCs disappeared during exercise testing. When he was readmitted to the Cardiology Department three months after cessation of isotretinoin treatment, his cardiovascular examination was normal. There were no PVCs on 12-lead ECG and 24-hour Holter monitoring or during exercise testing. We believe the temporal relationship between the isotretinoin treatment and the patient's documented arrhythmia on ECG and Holter suggest a drug-related cause.

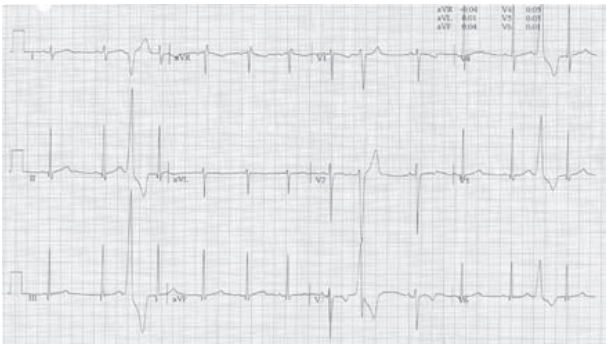

Fig. 1. The patient's 12-lead ECG during isotretinoin use.

Discussion

Isotretinoin-associated cardiac side effects have been rarely reported. Hasdemir et al.[4] described a 16-year-old boy who presented with palpitations and non-sustained episodes of atrial tachycardias on 24-hour Holter monitoring associated with isotretinoin treatment. Charalabopoulos et al.[5] reported an 18-year-old man who developed sinus tachycardia with transient right bundle branch block after three months of isotretinoin treatment. Bigby and Stern[2] described a 26-year-old woman who developed symptomatic episodes of sinus tachycardia after each dose of isotretinoin.

Premature ventricular contractions (PVCs) are characterized by an early beat with a wide and abnormal QRS complex, without a preceding P wave. T wave axis is usually opposite to the QRS. PVCs are relatively common findings in children, especially in adolescents. PVCs are reported in about 1-2% of all pediatric patients and in 50-60% of healthy teenagers with normal hearts. In the pediatric populations, PVCs commonly result in an irregular pulse as in our patient. PVCs can result from hypoxia, hypovolemia, electrolyte abnormalities, medications, or irritation from intracardiac monitoring or pacing catheters, or it can be idiopathic in nature. An exact evaluation of children presenting with PVCs is necessary to denote that they have "benign ventricular ectopy". This evaluation is initially done by echocardiography, 24-hour Holter monitoring and exercise test. In order to be considered benign, the PVCs should be uniform in morphology, should be suppressed with exercise, should produce no significant effects, and should not be associated with any anatomical or electrical heart disease. In our patient, documented PVCs were benign in nature with uniform morphology, with suppression by exercise and with no symptoms, and with normal echocardiographic findings[6]. We think that the benign ventricular ectopy in our patient was related to isotretinoin treatment. Presence of documented PVCs -on ECG and Holter monitoring- and their disappearance after cessation of the treatment strongly suggest isotretinoin-related PVCs. The temporal relationship between isotretinoin treatment and documented arrhythmia of the patient suggests a drug-related cause. As a result, clinicians should be aware of the possible arrhythmogenic effect(s) of isotretinoin.

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