Propafenone-Induced Drug Fever in the Absence of Agranulocytosis

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Summary: Propafenone is an antiarrhythmic drug used in the treatment of life-threatening ventricular tachyarrhythmias. Adverse reactions necessitating discontinuation of the medication are common. Propafenone-induced drug fever has not been definitively proven. We present a case report of drug fever secondary to propafenone, confirmed with rechallenge.

Key words: propafenone, drug fever

Introduction

Propafenone (Rhythmol®, Knoll Pharmaceuticals, Whippany, N.J.) is a class IC antiarrhythmic drug used in the treatment of life-threatening ventricular tachyarrhythmias. Approximately 20% of patients discontinue this medication because of adverse reactions.¹ To date, there has been no report of a direct association between propafenone and a febrile reaction. We describe a case of drug fever secondary to propafenone, confirmed with rechallenge.

Case Report

The patient is a 56-year-old white man with a past medical history significant for hypertension, rectal carcinoma (status post abdominoperineal resection), and an anterior myocardial infarction suffered in October 1994.

In May 1995, the patient presented with sustained monomorphic ventricular tachycardia (VT), rate 180 beats/min, associated with dizziness. He underwent electrophysiologic testing which reproduced his clinical VT. Despite intravenous procainamide, quinidine, and mexilitene, sotalol, and propafenone, the patient remained inducible for VT. However, propafenone substantially reduced the rate of VT from 180 to 120 beats/min, which was hemodynamically well tolerated. The patient elected to proceed with a clinical trial of propafenone and was discharged on the following medications: enteric-coated aspirin 325 mg daily, Isordil® 10 mg three times a day, digoxin 0.125 mg daily, sublingual nitroglycerin as necessary, propafenone 300 mg three times daily, and ramipril 2.5 mg daily. The ramipril and propafenone were newly prescribed.

Ten days after discharge, the patient developed fatigue and a fever to 106°F associated with nausea, rigors, and chills. By the next morning, the symptoms resolved. However, over the ensuing four days, the patient noted recurrent fevers associated with rigors and nausea which seemed to occur each night at approximately 2 A.M. He also developed an evanescent rash on the dorsum of both hands which appeared after the onset of the febrile episodes. There were no symptoms to suggest a focal infection. He was admitted for work-up of his fever.

On admission, his vital signs were: blood pressure 108/60, heart rate 90 beats/min, respiratory rate 16/min, and temperature 39.2°C. Physical exam was normal except for the skin exam which revealed erythematous papules, approximately 2 to 3 mm in diameter, located on the dorsum of both hands. Laboratory data, including chest x-ray, were unremarkable except for thrombocytopenia (platelet count 79,000) and an elevated erythrocyte sedimentation rate (ESR = 90). The admission white blood count (WBC) was 4,100 (normal range: 4,000-10,000) with 42% polymorphonuclear cells, 40% bands, 12% lymphocytes, 5% monocytes, and 1% eosinophils.

The possibility of drug-induced fever was considered and the administration of ramipril and propafenone was stopped on admission. Since there was no definite source of infection, antibiotic therapy was withheld pending culture results. Blood, urine, and sputum cultures drawn on admission were negative. Subsequently, the patient defervesced on the second hospital day and remained afebrile, returning to his baseline status. Over the course of the hospitalization, laboratory data were significant for the development of pancytopenia, the

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Received: September 16, 1996

Accepted with revision: January 3, 1997

nadir of which occurred on Day 4 of his hospital stay (WBC 2,700, 58% polymorphonuclear cells, 22% lymphocytes, 12% monocytes, 6% eosinophils and 1% basophils, hemoglobin 10.8 gm/dl, and platelet count 70,000), returning to normal 2 days later. Dermatology evaluated the patient's skin rash and felt it was consistent with a drug-induced reaction. The rash subsequently resolved by the second hospital day.

It was not known whether the patient's drug reaction was secondary to ramipril or propafenone since both medications were started concomitantly. Although other options available to treat this patient's ventricular tachyarrhythmia included amiodarone or an implantable cardiac defibrillator (ICD), the patient opted to be rechallenged with propafenone. After four doses of propafenone (150 mg/dose), the patient's fever spiked again to 39.2°C (Fig. 1); however, he did not redevelop a rash. Propafenone was discontinued immediately and the patient defervesced. An ICD was subsequently implanted.

Discussion

Propafenone is a class IC antiarrhythmic agent that is used in the treatment of life-threatening ventricular tachyarrhythmias. The use of propafenone in our patient deserves comment in view of the CAST trials^{2,3} which showed excess mortality associated with the use of class I antiarrhythmics in patients with asymptomatic or mildly symptomatic ventricular arrhythmias detected by Holter monitoring after a myocardial infarction. Our patient differs from those enrolled in the CAST trials in three important ways. First, our patient had symptomatic life-threatening VT. Second, propafenone was chosen after careful electrophysiologic testing as the agent that best controlled the patient's VT. Third, in the CAST trials patients with sustained life-threatening VT were excluded.

The most common adverse drug reactions associated with propafenone involve the gastrointestinal tract (unusual taste, nausea, vomiting, anorexia, and constipation); the cardiovascular system (first-degree atrioventricular block, intraventric-

ular conduction delay, new or exacerbated congestive heart failure, and ventricular proarrhythmia); and the central nervous system (dizziness, headaches, blurred vision, paresthesias, and vertigo).^{1,4-6} Approximately 20% of patients have to discontinue the medication due to an adverse reaction.¹ To our knowledge, drug-induced fever directly linked to the administration of propafenone has not been previously reported. A computerized literature search using BRS Colleague[®] dating back to 1966 (two decades prior to the marketing of propafenone) located no reports of fever associated with the use of the medication. Personal contact with Knoll Pharmaceuticals confirmed that up to the present there have been no reported cases of fever directly caused by propafenone. Miwa and Jolson reported fever associated with propafenone in four patients;⁷ however, these patients all had agranulocytosis, and occult infection could not be excluded. In contrast, our patient's fever occurred in the setting of a normal granulocyte count and in the absence of infection.

Drug-induced fever can be caused by almost any medication. There are several potential mechanisms leading to drug-induced fever including the drug's pharmacologic action, its effect on thermoregulation, a local complication following injection, or an idiosyncratic reaction.⁸ However, the most common mechanism probably is an immunologic reaction (hypersensitivity reaction) mediated by drug-induced antibodies.⁸ Our patient had clinical features highly suggestive of a hypersensitivity reaction—occurrence of fever after 7 to 10 days of administration, presence of a rash, and resolution of fever within 48 h of stopping the medication. Immunologically associated drug fevers typically recur within a few hours after being rechallenged with the offending agent. In our patient, recurrence of fever occurred approximately 30 h after being rechallenged with propafenone. In addition, the presence of rigors was unusual because it typically signifies endotoxin release associated with infection and not with drug fever. Despite these atypical features, an immune-mediated mechanism was the most likely cause of our patient's drug-induced fever.

The clinician should also be aware of several other commonly used cardiac medications that can cause drug fever through an immune-mediated (hypersensitivity) reaction. These cardiac medications are the following: methyl dopa, procainamide, quinidine, and lasix; less commonly, hydralazine, streptokinase, and calcium antagonists.⁹

There are no specific diagnostic symptoms, signs, or laboratory data which can be used for a definitive diagnosis of hypersensitivity drug reaction; however, there are clinical findings which are suggestive of a drug-induced reaction. Although a wide range of individual variability exists, the patient typically appears well with intermittent rather than sustained fevers that may also be associated with dermatitis, urticaria, serositis, and eosinophilia.⁸ The most characteristic feature of a hypersensitivity drug reaction is resolution of the fever with cessation of the offending agent. While resolution of fever after withdrawal of the medication is suggestive of a drug fever, the only definitive evidence is recurrence of fever with rechallenge of the medication.

FIG. 1 The patient's temperature curve demonstrating recrudescence of the fever in response to rechallenge with propafenone on hospital Day 4.

To our knowledge, there has been no previous report of a definitive direct association between propafenone and fever. Although propafenone-induced drug fever is rare, physicians using this medication should be aware of its potential for causing a hypersensitivity reaction.

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