

Sustained-Release Procainamide-induced Reversible Granulocytopenia after Myocardial Infarction

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SUMMARY

A 71-year-old man with paroxysmal atrial fibrillation who had a previous anterior myocardial infarction exhibited granulocytopenia 8 days following the administration of oral sustained-release procainamide (750 mg/day). The plasma concentrations of procainamide and N-acetyl procainamide were at subtherapeutic levels. Discontinuation of procainamide led to complete recovery. A bone marrow aspiration showed slight hypoplasia with normocellular marrow. Lupus erythematosus (LE) and antinuclear antibody (ANA) tests were negative. The frequency and relationship of granulocytopenia caused by sustained-release procainamide in patients with tachyarrhythmias are briefly discussed, and prior reported cases are reviewed. Precautionary measures for the early recognition of this grave hazard in exposed patients are advocated. The physician should be aware of this complication before initiating treatment with this drug. (*Jpn Heart J* **36**: 483–487, 1995)

Key words: Procainamide Sustained-release Granulocytopenia
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SUSTAINED-RELEASE procainamide is effective and widely used in the treatment of cardiac tachyarrhythmias, especially those following myocardial infarction. It is well known that minor side effects including nausea, diarrhea, pruritus, urticaria, fever and chills may occur. However, these undesirable effects, which are minor in nature, should not prevent the use of procainamide in light of its specific value in controlling cardiac arrhythmias. In addition, cardiac toxicity is unusual when the drug is given orally and in a daily dose not exceeding 2 g.¹⁾ Granulocytopenia is a very rare complication of procainamide. In this article, we report a patient who had received oral sustained-release procainamide therapy (750 mg/day) for his paroxysmal atrial fibrillation, and developed reversible granulocytopenia.

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CASE REPORT

A 71-year-old man was admitted to our university's hospital on April 26, 1994 for treatment of acute anterior myocardial infarction. After 1 month cardiac catheterization was performed. The coronary arteriogram showed total occlusion in segment 7 and 25% stenosis in segment 2. Left ventriculogram showed akinesis in segments 2, 3 and 6. The patient had received medical therapy including nitroglycerine (25 mg/day), nisoldipine (5 mg/day), enalapril maleate (5 mg/day), and aspirin (81 mg/day). In the one month post-infarction period, he developed paroxysmal atrial fibrillation two or three times per day. Oral cibenzolin (300 mg/day), aprindine (40 mg/day) and propranolol (30 mg/day) were prescribed with poor results. Oral sustained-release procainamide 750 mg/day (T.I.D.) was started on June 21, 1994. His blood picture just before the administration of procainamide was almost normal; complete blood count revealed a hemoglobin count of 10.3 g/dl, white blood cell count of 6400/ μ l with 44.3% granulocytes, and platelet count of 227,000/ μ l (Table). In addition, blood creatinine, liver function, and renal function findings were normal. On June 28, 1994, 8 days following the initiation of oral procainamide therapy, his blood picture showed a markedly decreased white blood cell count of 3900/ μ l with 3% granulocytes. Hemoglobin and platelet counts after the administration of procainamide did not change compared to those before the start of procainamide therapy (11.4 g/dl, and 222,000/ μ l, respectively). He had no symptoms such as infection and fever. Plasma concentrations of procainamide and N-acetyl procainamide (NAPA) were measured. However, they showed low plasma concentrations (0.2 μ g/ml and 1.6 μ g/ml, respectively). Also, lupus erythematosus (LE) and anti-nuclear antibody (ANA) tests were negative. In addition, we could not find clinical evidence of a lupus-like syndrome. Procainamide was discontinued at a total dose of 5.25 g. Drip infusion of G-CSF and oral prednisolone were used to treat

Table

		May 25	June 14	June 21	June 28	July 4
WBC	(/ μ l)	5100	5900	6400	3900	4800
Neutro	(%)	51.4	56.0	44.3	3.0	38.0
Eos	(%)	10.0	8.0	8.6	8.0	8.0
Baso	(%)	1.6	1.0	1.3	0	1.0
Lymph	(%)	28.4	25.0	35.1	67.0	46.0
Mono	(%)	8.6	10.0	10.7	22.0	7.0
RBC	(g/dl)	376×10^4	392×10^4	369×10^4	393×10^4	377×10^4
Hb	(g/dl)	10.5	11.1	10.3	11.4	10.8
PLT	(/ μ l)	18.3×10^4	23.1×10^4	22.7×10^4	22.2×10^4	21.5×10^4

WBC = white blood cell; Neutro = neutrophil; Eos = eosinophil; Baso = basophil; Lymph = lymphocyte; Mono = monocyte; RBC = red blood cell; Hb = hemoglobin; PLT = platelet.

the granulocytopenia. During the one month following the withdrawal of procainamide, the patient's granulocyte count rose to that before the administration of procainamide. After recovery, a bone marrow aspiration revealed a hypoplastic, normocellular marrow.

DISCUSSION

Granulocytopenia and/or agranulocytosis are very rare complications of sustained-release procainamide therapy. Although fewer than 30 cases¹⁻¹⁸⁾ of procainamide-induced granulocytopenia and/or agranulocytosis have been reported, the exact incidence of this phenomenon is unknown. Review of the English-language literature reveals certain common features in patients developing agranulocytosis secondary to procainamide. The majority of patients (75%) survived; the mean age was 64 years; there was no sex predilection. Sustained-release procainamide is normally excreted by the kidney, the half-life being approximately 6-8 hours. About 40-70% is excreted unchanged; the remainder is biotransformed in the liver, predominantly by N-acetylation. Although there was a definite increase in the complication as patients received more drug over longer periods, as little as 36.5 gm was enough to cause agranulocytosis. The exact mechanism by which procainamide causes agranulocytosis is still unknown. Berger BE, et al¹⁹⁾ reported on the mechanism of the agranulocytosis and/or granulocytopenia induced by procainamide. They implicated antileukocyte antibody activity, as seen with aminopyrine, and a direct bone marrow toxic effect possibly mediated through inhibition of nucleic acid synthesis, as observed with the phenothiazines. The occurrence of a case of agranulocytosis secondary to a new sustained-release preparation of procainamide within months of its availability for clinical use merits attention. In a recent review of a sustained-release procainamide preparation, agranulocytosis was not reported. It has been suggested that slow acetylators (increased procainamide-to-NAPA ratio) are more prone to drug-induced side effects,²⁰⁾ but this has not been confirmed. Ellrodt AG, et al²¹⁾ reported 8 patients who had shown severe neutropenia induced by sustained-release procainamide. Their patients developed severe neutropenia within 3 months of initiation of sustained-release procainamide therapy and in addition showed impaired bone marrow reserves. Interestingly, 5 of the 8 patients had just had cardiovascular surgery. They caution that patients may be at particular risk after cardiovascular surgery and that the hematologic status of these patients should be assessed frequently, particularly during the first 3 months of therapy. In the present case, our patient had received a relatively low total dose of 5.25 g of procainamide, and in addition the plasma concentrations of both procainamide and NAPA were at subtherapeutic levels. These results sug-

gest that it was not direct suppression of bone marrow by procainamide. Another possibility exists in the present case. Procainamide causes granulocytopenia through an immunologic mechanism, which is thought to be the mechanism in its production of a lupus-like syndrome. However, leukocyte agglutinins, such as evidenced by a positive LE test, have never been found in our patient with granulocytopenia, strongly suggesting that there is no immunologic basis for this adverse effect.

In a study by Lawson and Jick²²⁾ of 488 hospitalized patients receiving procainamide, 45 had an adverse reaction to the drug, but not one developed agranulocytosis. As previously described, neither specific dose nor duration of therapy of procainamide nor age or sex of the patient will predict individuals who will develop procainamide-induced agranulocytosis. The physician should be aware of this potentially lethal complication before initiating treatment with this drug. Careful follow-up is needed in patients being administered procainamide.

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