Agranulocytosis Immediately after Oral Administration of Cibenzoline and Dabigatran in a Patient with Paroxysmal Atrial Fibrillation

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Abstract

This case report describes agranulocytosis immediately after oral administration of cibenzoline and dabigatran in a 70-year-old woman with paroxysmal atrial fibrillation (AF). No blasts were found in peripheral blood and bone marrow, and the white blood cell count increased abruptly by intravenous administration of granulocyte colony-stimulation factor, suggesting an allergic response caused by cibenzoline or dabigatran, or both. Though antiarrhythmic drugs with anticoagulation therapy are commonly used to treat paroxysmal AF, caution has to be paid to drug-induced agranulocytosis.

Key words: atrial fibrillation, anti-arrhythmic drug, anti-coagulation therapy, agranulocytosis, granulocyte-colony stimulation factor

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Introduction

Antiarrhythmic drugs are used to treat atrial fibrillation (AF). In addition to maintaining sinus rhythm, anticoagulation therapy is necessary for the prevention of stroke and systemic embolism. Recently, a direct thrombin inhibitor, dabigatran, has become available in clinical practice. Therefore, the combination therapy of antiarrhythmic drug and dabigatran is becoming popular for the management of paroxysmal AF. We report a case who developed agranulocytosis immediately after oral administration of cibenzoline and dabigatran.

Case Report

A 70-year-old woman underwent a total knee arthroplasty operation for the treatment of deformed knee joint at the Hospital of Shiga University of Medical Science. After the surgery, she developed paroxysmal AF. Cibenzoline (50 mg) twice daily and dabigatran (110 mg) twice daily were prescribed for the treatment of PAF. On the first day of administration, she took cibenzoline (50 mg) and dabigatran (110 mg) just after supper. On the morning, she felt chilly and had general malaise. Regarding past history, she had a surgical closure of secundum atrial septal defect at the age of 50 years. She did not have any allergic history.

On physical examination, her body temperature was 37.5°C at that time. Her blood pressure was 166/96 mmHg, pulse rate 88 beats/min. Her heart sound was normal without heart murmur, and respiratory sound was also normal. No lymphadenopathy was noted. The remainder of the physical examination was normal. Twelve-lead electrocardiogram showed inverted T wave in leads V₁-4 with normal sinus rhythm (Fig. 1). A chest radiograph showed clear lung fields with a cardiothoracic ratio of 53% (Fig. 2). A transthoracic echocardiogram showed normal wall motion and normal-sized chambers with a left ventricular ejection fraction of 61%. Table 1 shows laboratory data of peripheral blood one day after the oral administration of cibenzoline and dabigatran. The white blood cell (WBC) count was 1.6×10⁹/μL (35.5% neutrophils). No blasts were observed in peripheral blood. Mild normocytic and normochromic anemia was present. Results of other laboratory tests were normal,
including plasma levels of electrolytes, tests of renal and liver functions, and coagulation. Serum levels of thyroid hormone were normal, as were tests of renal and liver function.

Fig. 3 shows clinical manifestations. She suffered from repetitive episodes of PAF after the orthopedic surgery. Cibenzoline 50 mg and dabigatran 110 mg was orally administered after supper on a day in mid-June. Both drugs were withdrawn because she became symptomatic in the morning on the following day. On that day, WBC count was 1,600/μL and neutrophil count 568/μL. WBC count and neutrophil count dropped to 1,500/μL and 30/μL, respectively, on the 4th day after the administration of cibenzoline and dabigatran. Bone marrow biopsy was obtained from the pelvic bone. Pathological examination of the core-biopsy specimen revealed a hypocellular marrow for the patient’s age but no findings suspicious of myelodysplasia or leukemia. Table 2 shows the differential counts of bone marrow aspirate. There were no morphologic abnormalities in the granulocytic series. After the intravenous administration of granulocyte-colony stimulation factor (G-CSF, filgrastim 75 μg) on the 4th day, the number of WBC increased drastically from 1,500 (2% neutrophil) to 10,600 (78.1% neutrophil). After the cessation of cibenzoline and dabigatran, she has never experienced agranulocytosis. The patient has been treated with warfarin for 8 months without agranulocytosis.

Discussion

AF is one of the most common rhythm disorders in cardiac practice and causes thromboembolism. Anti-arrhythmic drug is widely prescribed to maintain sinus rhythm for the management of symptomatic AF (1). Anti-coagulation therapy is essential for the prevention of thromboembolism (2). In the present case, cibenzoline and dabigatran were orally administered to treat repetitively occurring AF. Immediately after the administration of these drugs, agranulocytosis developed. However, the WBC count and granulocyte count were soon increased after the intravenous administration of filgrastim and the intake cessation of cibenzoline and dabigatran. No recurrence of agranulocytosis has been observed since then. Therefore, this case had drug-induced agranulocytosis in the process of AF treatment.

Non-chemotherapy drug-induced agranulocytosis is a rare adverse reaction that is characterized by a decrease in the peripheral neutrophil count to less than 0.5×10⁹ cells/L. Pathogenic mechanisms for drug-induced agranulocytosis are: 1) immune-mediated destruction of granulocytes or granulocytic precursors, 2) dose-dependent inhibition of granulopoiesis, and 3) direct toxic effect on myeloid precursors or the marrow microenvironment. Immune-mediated drug-induced agranulocytosis occurs when drugs act as a hapten to induce antibody formation, complement fixation, and neutrophil destruction. In this drug-induced agranulocytosis, the time of onset is rapid (3, 4) and antineutrophil antibodies are often identified (5, 6). In contrast, drug-induced agranulocytosis due to dose-dependent inhibition of granulopoiesis and direct damage to the bone marrow microenvironment or myeloid precursor cells often has delayed onset of agranulocytosis (7, 8). Although we did not investigate antineutrophil antibodies, cibenzoline or dabigatran, or both could be offending drug(s) for the immune-mediated agranulocytosis of the present case.
Table 1. Next-day Laboratory Data of Peripheral Blood Following Oral Administration of Cibenzoline and Dabigatran

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>White blood cell</td>
<td>1600 /μL</td>
<td>Total protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>35.5 %</td>
<td>6.7 g/dL</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2.1 %</td>
<td>Albumin</td>
</tr>
<tr>
<td>Basophils</td>
<td>1.4 %</td>
<td>Aspartate</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>55.3 %</td>
<td>transaminase</td>
</tr>
<tr>
<td>Monocytes</td>
<td>5.7 %</td>
<td>18 U/L</td>
</tr>
<tr>
<td>Red blood cell</td>
<td>331×10^6/μL</td>
<td>Lactate</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>31 %</td>
<td>dehydrogenase</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9.9 g/dL</td>
<td>185 U/L</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>94 /μL</td>
<td>Alkaline</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>29.9 pg</td>
<td>phosphatase</td>
</tr>
<tr>
<td>Platelet</td>
<td>29.9×10^9/μL</td>
<td>270 U/L</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>321 mg/dL</td>
<td>γ-glutamyl</td>
</tr>
<tr>
<td>Prothrombin time (control)</td>
<td>11.5 sec</td>
<td>transferase 11 U/L</td>
</tr>
<tr>
<td>Prothrombin time (patient)</td>
<td>13.2 sec</td>
<td>Hematocrit 31 %</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (control)</td>
<td>29 sec</td>
<td>Total billirubin 0.55 mg/dL</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (patient)</td>
<td>41.9 sec</td>
<td>Direct billirubin 0.1 mg/dL</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>2.78 mg/mL</td>
<td>141 mmol/L</td>
</tr>
</tbody>
</table>

Figure 3. Clinical course.
AF: atrial fibrillation, WBC: white blood cell.

Drugs responsible for agranulocytosis are antibiotics, antithyroid drugs, antiplatelet agents, non-steroidal anti-inflammatory drugs, and other drugs (9, 10). In elderly patients with non-chemotherapy, drug-induced agranulocytosis presents commonly with severe infections, and thus results in a high mortality rate (11). In the present case, agranulocytosis developed during the hospital stay. The peripheral blood examination was performed immediately after the symptoms developed. Subsequently, G-CSF was administered. With rapid recovery of WBC count after the administration of G-CSF, she did not develop infection. Compatible with drug-induced agranulocytosis, the marrow was hypoplastic, with decreased cellularity, depression of all hematopoietic lineages, and almost complete disappearance of granulocyte precursors.

It is known that anti-arrhythmic drugs cause agranulocytosis. The manifestation of agranulocytosis after cibenzoline is a rare adverse effect of the drug. The frequency of agranulocytosis by cibenzoline is reported to be <0.1% (12). In a systemic review, it was reported that the median duration of agranulocytosis averaged 8 days and the nadir of WBC count averaged 0.18×10^9 cells/L (10). In the present case, the duration of agranulocytosis was much shorter than that in previous reports and the nadir of WBC count was much lower than that in previous reports.

Dabigatran, a new oral direct thrombin inhibitor, is similar or superior to warfarin in terms of prevention of stroke and systemic embolism in patients with AF (13). Since dabigatran has recently emerged in clinical practice (14), whether or not dabigatran causes agranulocytosis is unclear. In fact, the frequency of agranulocytosis by dabigatran is yet to be reported. Because both drugs were simultaneously ad-
Table 2. Differential Counts of Bone Marrow Aspirate

<table>
<thead>
<tr>
<th>Neutrophilic series</th>
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| Myeloblast                          | 0.9  
| Promyelocyte                        | 1.1  
| Neutrophil                          | 7   
| Eosinophilic                        | 0.6  
| Basophilic                          | 0   
| Metamyelocyte                       | 6.4  
| Eosinophilic                        | 0   
| Basophilic                          | 0   
| Band                                | 14.9 
| Segmented                           | 11.9 
| Eosinophilic series                 | 1.5  
| Basophilic cells                    | 0   
| Monocytes                           | 4.9  
| Lymphocytes                         | 10.4 
| Small                               | 26.9 
| Atypical                            | 0.3  
| Plasma cells                         | 0.8  
| Reticuloendothelial cells           | 0.3  
| Megakaryocytes                      | +   
| Myeloid-to-erythroid ratio          | 4.05 

ministered in the present case, we do not know which drug was causative for agranulocytosis. It is thought that a combination of dabigatran and anti-arrhythmic drug would prevail in the treatment of AF in the future. Thus, attention needs to be paid to new side effects of dabigatran. Whether the agranulocytosis in the present case was caused by a combination of these 2 drugs is unclear. However, it is speculated that the incidence of adverse effects may increase as the number of oral medicines used in combination increases.

It is reported that G-CSF, a hematopoietic growth factor that shortens the duration of neutropenia, is useful for the treatment of agranulocytosis (9). The present patient attained complete hematologic recovery after the removal of the causative drugs. This patient did not develop symptoms of infection because of the quick recovery by G-CSF administration, thus that we did not use antibiotics. We observed much faster hematologic recovery in patients treated with G-CSF, despite significantly lower initial neutrophil counts. Similarly, the duration of antibiotic use and length of hospital stay were also reduced with G-CSF treatment (15-17).

We encountered agranulocytosis after oral administration of cibenzoline and dabigatran. It is important to be aware of adverse effects when AF is pharmacologically treated.

The authors state that they have no Conflict of Interest (COI).

References


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