Agranulocytosis Associated with Ticlopidine: A Possible Benefit with Filgastim*

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ABSTRACT

Ticlopidine is an oral antiplatelet agent frequently utilized in the treatment of cerebrovascular disease and is rarely associated with severe bone marrow suppression, typically aplastic anemia. Reports in the literature of isolated agranulocytosis are few, although they may be associated with significant morbidity and mortality. A case is reported of an elderly woman who developed febrile agranulocytosis several weeks after commencing ticlopidine but who had a favorable outcome after cessation of that drug and treatment with filgastrim.

Introduction

Drug-induced neutropenia is a relatively uncommon clinical occurrence which typically resolves soon after the implicated drug is discontinued. Neutropenia may occur in the context of aplastic anemia or as an isolated event.1 Agranulocytosis is typically defined as an absolute neutrophil count of less than 500 cells/mm³ and represents a true medical emergency owing to an increased risk of infection.2 Ticlopidine is an anti-platelet drug recently introduced for the treatment of stroke, transient ischemic attacks, and in the setting of intravascular coronary stents.3,4 Neutropenia occurs in approximately 0.8 to 1.0 percent of patients, usually within the first three months of therapy, and typically resolves once the drug is discontinued.3,5 Most cases of severe neutropenia reported in the literature have occurred in the setting of aplastic anemia. A case is reported of an elderly woman who developed isolated agranulocytosis with fever but had normalization of her neutrophil count several days after cessation of ticlopidine and treatment with filgastrim (G-CSF).

Case Report

An 82-year-old woman with a history of atrial fibrillation, diabetes mellitus, hypertension, and cerebrovascular disease was admitted to the hospital with a five day history of pyrexia, chills, and gingival ulcerations. Five weeks previously, therapy with ticlopidine 250 mg twice daily was commenced for drop-attacks presumably owing to posterior circulation ischemia. Serial blood counts were not ordered upon discharge.

Approximately five days prior to the current admission, she noted daily pyrexia to 103°F, associated with occasional shaking chills. She complained of painful ulcerations over her upper and lower gingiva but denied headache, neck stiffness, cough, sputum production, abdominal pain, diarrhea, dysuria, skin rash, or joint swelling. Other medications included digoxin, glipizide, and dipyridamole; she denied intake of any non-prescription drugs. There was no prior personal or family history of hematologic or collagen vascular disorders. She denied alcohol ingestion or previous blood transfusions.

Physical examination revealed a temperature of 102.6°F, pulse 129, respirations 18, and blood pressure 132/76 mm/Hg. Significant physical findings included only diffuse gingival ulcerations and irregular tachycardia. There was no pharyngeal exudate, cervical adenopathy,
hepatosplenomegaly, or petechiae. Complete blood count revealed: leukocyte count 800 cells/mm³ with 0 percent neutrophils, 72 percent lymphocytes, and 28 percent monocytes; haemoglobin 12.6 g/dl; platelets 393,000 cells/mm³.

Serum chemistries, liver function tests, coagulation studies, and urinalysis were normal as was a chest radiograph. Broad spectrum antimicrobial therapy with piperacillin and gentamicin was immediately instituted for febrile neutropenia after blood and urine cultures were obtained. Ticlopidine was discontinued. On hospital day 2, severe agranulocytosis persisted, and therapy with G-CSF (filgrastim) 300 mcg daily subcutaneously was begun. By hospital day 7, the absolute neutrophil count was approximately 5,000 cells/mm³ and G-CSF was discontinued.

Three sets of blood cultures and the urine culture remained sterile. Antinuclear antibody was negative, and thyroid function studies were normal. Serology was negative for hepatitis B and parvovirus. There was evidence of previous exposure to cytomegalovirus, Epstein-Barr virus, and hepatitis C virus, although liver transaminases were normal. The patient defervesced and felt symptomatically improved as well. She was discharged on all of her prehospital medications, with the exception of ticlopidine, with a normal white blood cell count.

Discussion

Drug-induced neutropenia occurs in approximately 10 cases per 100 million persons annually and has been associated with a myriad of agents, of which include captopril, cimetidine, trimethoprim-sulfamethoxazole, phenothiazines, and penicillins.6,7 Ticlopidine, a novel anti-platelet agent that inhibits adenosine diphosphate induced platelet aggregation, has been associated with neutropenia in approximately 1 percent of patients and typically occurs during the first three months of therapy.3,4,8,9 Neutropenia usually resolves within several days upon cessation of the drug,3,4 but it may take up to six weeks, usually in the setting of pancytopenia.5,10,11,12 Deaths owing to ticlopidine-induced bone marrow suppression have been reported and have usually occurred in the setting of aplastic anemia.14,15

Fever is a common manifestation of ticlopidine-induced neutropenia,5,10,13,14,15,16,17 and patients taking ticlopidine who develop fever should have a complete blood count obtained to exclude myelosuppression. Febrile neutropenia is a medical emergency, and patients should receive empiric antimicrobial therapy for coverage of skin and bowel flora.18 Blood cultures are often sterile in the setting of ticlopidine-induced febrile neutropenia, but on occasion they are positive, typically yielding gram-negative organisms.11,13,19 Fever often resolves once the neutrophil count increases, as was noted in the case of the patient reported.

As noted previously, ticlopidine-associated neutropenia may occur in the setting of aplastic anemia,14,15 in conjunction with thrombocytopenia or anemia (bicytopenia),11,19 or as an isolated event;5,15,16 however, case reports are few. The etiology of ticlopidine-associated neutropenia may be due to a direct toxic effect on myeloid precursors. Inhibition of bone marrow colony forming units in culture (CFU-C) has been demonstrated when ticlopidine in concentrations similar to therapeutic plasma levels is added to bone marrow cultures.19,20 This toxicity may be due to local increases in prostaglandin E1 levels that occur with ticlopidine.17 Some patients may have an inborn sensitivity of marrow precursors to ticlopidine, perhaps predisposing them to myelosuppression.20

Immunologic mechanisms have also been suggested.11,16,20 The formation of the reactive metabolites thiopene-S-oxides has been proposed as another mechanism of ticlopidine myelotoxicity, and patients with inability to detoxify these metabolites may be at an increased risk.21 Patients with renal failure may be at increased risk for hematologic toxicity since 30 percent of the drug is renally eliminated.16

Coexistent causes for neutropenia, such as overwhelming sepsis, viral infections, autoimmune disease, hematologic malignancy, and other drugs, need to be excluded in all patients.1 This patient had no clinical evidence of infection other than pyrexia, had negative cultures, and was continued on all of her other drugs with the exception of ticlopidine, with resolution of neutropenia. However, antibodies to the hepatitis C virus were present (HCV), but there was no clinical or laboratory evidence of active hepatitis.

A patient with antibodies to HCV without apparent active infection, who developed
agranulocytosis with ticlopidine was previously reported, as was a patient with active HCV infection and cirrhosis who died of complications owing to aplastic anemia. The HCV has been associated with many extrahepatic manifestations, including autoimmune phenomena as well as abnormal lymphoid tissue proliferation. However, it is unclear whether or not infection with HCV predisposes patients to neutropenia when taking ticlopidine.

A bone marrow biopsy was not obtained in this patient owing to the temporal association of neutropenia with commencement of the drug, no strong clinical evidence to implicate an underlying infection or other disease process, and rapid recovery of the neutrophil count after cessation of the drug. Bone marrow biopsy typically reveals absence of granulocytic precursors possibly associated with aplasia or hypoplasia of platelet and red cell precursors when aplastic anemia is present. Treatment of ticlopidine-associated neutropenia entails meticulous general supportive care, aggressive treatment with broad spectrum antibiotics in the presence of fever, and discontinuation of the drug. Patients with pancytopenia have generally been treated with platelet and red cell transfusions in addition to prednisone and supportive care as mentioned. In the case of drug-induced agranulocytosis, the average time to neutrophil recovery is approximately 12 days once the offending drug is discontinued.

Injection of G-CSF was utilized in a patient with pancytopenia owing to ticlopidine; however, the patient died of severe pneumonopathy. Another patient with pancytopenia had continued neutrophilic hypoplasia despite several weeks of therapy with G-CSF. Injection of G-CSF was utilized in a patient with pancytopenia owing to ticlopidine; however, the patient died of severe pneumonopathy. Another patient with pancytopenia had continued neutrophilic hypoplasia despite several weeks of therapy with G-CSF. The patient in this report had a brisk response in her neutrophil count four days after commencing G-CSF. Whether or not this response was due to G-CSF is difficult to prove since ticlopidine was discontinued six days prior. However, it is likely she did experience some benefit, since her neutrophil count increased significantly to non-neutropenic range after four days of treatment. It is interesting to note that the patient had a monocytosis upon presentation (28 percent). Monocytosis in the setting of agranulocytosis is felt to be a favorable indicator of impending neutrophil recovery. Hematopoietic growth factors such as G-CSF and GM-CSF exert their effect directly on bone marrow progenitor cells and are widely used in patients undergoing chemotherapy and bone marrow transplantation. Some series have shown a potential decrease in the duration of drug-induced neutropenia with G-CSF by approximately three days, but this remains to be established.

In conclusion, agranulocytosis is a rare adverse effect of ticlopidine therapy, although it may be life-threatening if not aggressively treated. All patients should have regular monitoring of their blood counts once therapy begins, and immediately if fever or other evidence of infection or neutropenia develops. Treatment of ticlopidine-associated agranulocytosis consists of discontinuing the drug, excluding infection, administering empiric broad-spectrum antibiotics, and, as this case demonstrates, possible G-CSF therapy which may shorten the time to peripheral neutrophil recovery.

References