Ticlopidine Induced Anemia and Agranulocytosis

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ABSTRACT

A 63-year-old man with a history of transient ischemic attack had been treated with ticlopidine for 2 months. He presented with a 6-day history of fever, sore throat, and generalized weakness. Agranulocytosis and anemia due to ticlopidine was diagnosed, and the ticlopidine was discontinued. Broad-spectrum antibiotics and granulocyte colony stimulating factor were administered. The recovery of the granulocyte count and an improvement of the clinical condition were noted on the 6th day of the admission.

Key Words: Ticlopidine, Agranulocytosis, Anemia, G-CSF.

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INTRODUCTION

Ticlopidine is a platelet agregation inhibitor that is used to decrease the occurrence of atherothrombotic arterial events such as cerebral infarction, cerebral transient ischemic attack, myocardial infarction and peripheral arterial disease[1]. Hematologic effects, including pancytopenia, thrombotic thrombocytopenic purpura, leukopenia, and agranulocytosis, are the most serious adverse reactions. Sporadic cases were reported in which anemia and leukopenia developed simultaneously, or leukopenia and thrombocytopenia[2-5]. We report an additional case of agranulocytosis and anemia due to ticlopidine with a favorable outcome, after the cessation of the drug and treatment with G-CSF and broad-spectrum antibiotics.

CASE REPORT

A 63-year-old man was admitted with a 6-day history of generalized weakness, sore throat, and fever. Ticlopidine had been used at a daily dose of 500 mg for 2 months prior to admission due to transient ischaemic cerebral stroke. The concurrent drug used was glipizide 5 mg/day for type 2 diabetes mellitus. At the time of the initiation of the ticlopidine therapy, the leukocyte count was 7.5 x 10^9/L, the hemoglobin level was 16 gr/dL and the

platelet count was 150 x 10^9/L. On physical examination, the patient appeared ill and pale. His temperature was 39°C and his blood pressure was 110/75 mmHg. The tonsils were red. Lymphadenopathy or hepatosplenomegaly were not found. The lungs were clear. The results of the neurological al examination was normal. On admission, the hematologic data was as follows: leukocyte count 1.1 x 10^9/L (10% neutrophils, 90% lymphocytes), hemoglobin 12.5 gr/dL and platelet count 185 x 10^9/L. The bone marrow was slightly hypocellular with a near absence of the granulocytic lineage. Serological studies for hepatitis B, hepatitis C, the human immunodeficiency virus, the Epstein-Barr virus and the cytomegalovirus were negative. The kidney and liver function tests were normal. The Iron, iron binding capacity, ferritin, vitamin B_{12} and folic acid serum lanels were normal. Ccultures were done, but no infectious agent could be identified. Agranulocytosis was diagnosed and the ticlopidine was discontined. Empiric antibiotic therapy (amikacin and ceftazidime) was started. G-CSF at 5 microgram/kg subcutaneously was administered over a period of 6 days. By the forth day of therapy, the patients temperature had returned to normal. He remained afebrile for the remainder of the hospitalization. During this time, the leukocyte count progressively improved, and the values on days 4 and 6 after admission were 2.2 x 10^9/L (30% neutrophils), and 3.2 x 10^9/L (50% neutrophils), respectively. He was discharged in stable condition on the 8 th day of hospitalization. Two months later, the WBC was 6.7 x 10^9/L, the Hg was 16.7 gr/dL and the platelet count was 147 x 10^9/L. All hematologic investigations were fully normal at a follow-up visit one year later.

DISCUSSION

Ticlopidine is an effective antiplatelet agent that inhibits the binding of adenosine 5-diphospate to its platelet receptor[6]. The platelet inhibition persists for 7 to 10 days after therapy is stopped. Ticlopidine is used for the secondary prevention of strokes, transient ischemic attacks, peripheral vascular disease and unstable angina. The Ticlopidine Aspirin Stroke Study (TASS) demonstrated that ticlopidine was somewhat more effective than aspirin in preducing the risk of death from any cause or the risk of a nonfatal stroke in patients with recent transient ischemic attack or mild stroke[7,8].

Ticlopidine is known to cause diverse severe hematological side effects including agranulocytosis, and, more rarely, thrombocytopenia or severe aplastic anemia[9-12]. Sporadic cases were reported, in which anemia and leukopenia developed simultaneously or leukopenia and thrombocytopenia[2,4]. Agranulocytosis occurs 1-3 months after treatment began and resolves within three weeks of ticloplidine discontinuation[7]. In our patient, agranulocytosis occurred 2 months after the start of ticlopidine therapy. Ticlopidine was administered with glipizide, which is unlikely to have been involved in the development of hematologic toxicity. He had been treated with glipizide for 2 years and this drug was continued during agranulocytosis and neutrophil recovery, suggesting that this drug was not the cause of hematologic toxicity. He continues to take glipizide and has had no further episodes of neutropenia. Certain viral infections, for example, infectious mononucleosis, infectious hepatitis and human immunodeficiency virus infection may cause neutropenia and pancytopenia due to infection of hemopoietic precursor cells. But in this case, screening was negative for viral agents.

Agranulocytosis is a potentially lethal toxic effect of ticlopidine, especially in older patients who are the usual population treated with ticlopidine[3,4]. The episode of neutropenia is associated with the arrest of the maturation of the granulocytic cell line. When agranulocytosis is detected, ticlopidine should be discontinued permanently. Great efforts should be directed at preventing and managing infection accompanying agranulocytosis, since it is the major cause of death. Admission to the hospital is advised for febrile patients and those exhibiting systemic infection. G-CSF regulates hematopoietic neutrophil progenitor colony growth and stimulates the release of bone marrow neutrophil storage pools resulting in an apparent rise in circulating neutrophils. G-CSF is now widely used to overcome neutropenias of various origins[12,13]. There are some reported cases of successful use of G-CSF in ticlopidine-induced neutropenia and pancytopenia[14,17]. Altho-

ugh ticlopidine induced neutropenia resolves after the discontinuation of the drug, G-CSF may speed neutrophil recovery, decrease the duration of hospitalization and reduce the risk of infectious diseases and sepsis. Our patient was treated with broad-spectrum iv antibiotics and G-CSF. He became afebrile and reached a leucocyte count greater then 2 x 10/L within 4 days after initiation of broad-spectrum antibiotics and G-CSF treatment.

The bone marrow toxicity pathogenesis due to ticlopidine remains at present uncertain. Directly toxic and immunological effects have been proposed. Quaglino et al. reported a marked inhibition of colony forming unit culture after the addition of ticlopidine to the culture[18]. Ono et al. also demonstrated that bone marrow toxicitiy is due to a direct cytotoxic effect of ofticlopidine[19].

Because of the risk of severe hematological adverse effects, such as agranulocytosis and aplastic anemia, seen with ticlopidine, it is recommended to use aspirin as the first line anti-platelet agent for patients with a history of ischemic events. Ticlopidine use should be limited to patients who are intolerant of aspirin and to patients in whom aspirin therapy has failed. It should be used carefully especially in aged people with underlying diseases. Patients receiving ticlopidine should be warned about its adverse effects. Complete blood cell counts must be performed before and during the first 3 months of ticloplidine therapy, in order to recognize the first signs of hematological toxicity[1].

REFERENCES

1. Haynes RB, Sandler RS, Larson EB, Pater JL, Yatsu FM. A critical appraisal of ticlopidine, a new antiplatelet agent. Effectiveness and clinical indications for prophylaxis of atherosclerotic events. Arch Intern Med 1992;152:1376-80.
2. Guerciolini R, Giordana G, Aversa F, Del Favero A. Anemia and agranulocytyosis associated with ticlopidine therapy. Acta Haemat 1985;73:232-4.
3. Szto GY, Linnemeier TJ, Ball MW. Fatal neutropenia and thrombocytopenia associated with ticlopidine after stenting. Am J Cardiol 1999;83:138-9.
4. Carlson JA, Maesner JE. Fatal neutropenia and thrombocytopenia associated with ticlopidine. Ann Pharmacother 1994;28:1236-8.
5. Gur H, Wartenfeld R, Tanne D, Solomon F, Sidi Y. Ticlopidine-induced severe neutropenia. Postgrad Med J 1998;74:126-7.
6. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. Ann Intern Med 1998;129:394-405.
7. Hass WK, Easton JD, Adams HP, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high risk patients. N Engl J Med 1989;321:501-7.
8. Harbison JW. Ticlopidine versus aspirin for the prevention of recurrent stroke. Analysis of patients with minor stroke from the Ticlopidine Aspirin Stroke Study. Stroke 1992;23:1723-7.
9. Kao TW, Hung CC, Chen YC, Tien HF. Ticlopidine-induced aplastic anemia: Report of three Chinese patients and review of the literature. Acta Haematol 1997;98:211-3.
10. Mallet L, Mallet J. Ticlopidine and fatal aplastic anemia in an elderly woman. Ann Pharmacother 1994; 28:1169-71.
11. Mataix R, Ojeda E, Carmen Perez M, Jimenez S. Ticlopidine and severe aplastic anaemia. Br J Haematol 1992;80:125-6.
12. Gabrilove J. The development of granulocyte colony stimulating factor in its various clinical applications. Blood 1992;80:1382-5.
13. Spiekermann K, Roesler J, Emmendoerffer A, Elsner J, Welte K. Functional features of neutrophils induced by G-CSF and GM-CSF treatment: differential effects and clinical implications. Leukemia 1997; 11:466-78.
14. Korkmaz ME, Cekin AH. Bone marrow suppression and klebsiella pneumonia septicemia due to ticlopidine and successful treatment with filgrastim; a case report. Int J Cardiol 1998;66:317-8.
15. Nguyen BH, Parker RB, Geraci SA. Use of filgrastim for ticlopidine induced neutropenia following coronary stenting. J Invas Cardiol 1998;10:226-8.
16. Ruiz-Irastorza G, Alonso JJ, Iglesias JJ, Aguirre C. Granulocyte colony-stimulating factor for neutropenia secondary to ticlopidine. Acta Haematol 1994; 91:106-7.
17. Thomson LE, Stewart JT. Ticlopidine induced agranulocytosis managed with granulocyte colony stimulating factor. N Z Med J 1998;111:81-2.
18. Quaglino D, Salladini G, Ricciotti M. Possible mechanism of action of ticlopidine on committed granulocyte-macrophage precursor. Haematologica 1984; 69:257-62.
19. Ono K, Kurohara K, Yoshihara M, Shimamoto Y, Yamaguchi M. Agranulocytosis caused by ticlopidine and its mechanism. Am J Hematol 1991;37:239-42.

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