Severe Cholestatic Jaundice and Subsequent Pancytopenia Associated with Ticlopidine

Hae Seong Yoon, MD3, Hyeong Kweon Kim, MD2, Kwang Soo Cha, MD1, Uk Don Yoon, MD1, Sam Yong Ji, MD1, Joo Ho Kim, MD3, Shin Bae Joo, MD4, Young Dae Kim, MD1, Woo Weon Shin, MD1 and Jong Seong Kim, MD1

1Department of Internal Medicine, Dong-A University College of Medicine, Pusan
2Department of Internal Medicine, Veterans General Hospital, Pusan,
3Department of Internal Medicine, Kwanghye General Hospital, Pusan,
4Department of Internal Medicine, Hankook General Hospital, Kwangju, Korea

Ticlopidine 사용 후 발생한 심한 담즙울체성 황달과 범혈구감소증

Introduction

Ticlopidine, a potent antiplatelet agent, is widely used for the treatment of cerebrovascular disease. The combination of aspirin and ticlopidine is recently considered a standard regimen for the prevention of subacute stent thrombosis after coronary stent implantation. Neutropenia is the most worrisome adverse reaction to this agent, occurring in 1–2% of patients. Reversible abnormal liver function tests were reported in only 1% of patients receiving the drug in two large clinical trials. Severe cholestasis has rarely been reported, with approximately 12 case reports including only five from the English medical literatures.
We report the first case of severe cholestasis and subsequent pancytopenia associated with use of ticlopidine after coronary stent implantation.

**Case Report**

A 54-year-old male was transferred for painless jaundice of one week duration. There was no history of blood transfusion, jaundice, significant alcohol ingestion, hepatitis or gallstone disease. He had a previous history of unstable angina 1 month ago and underwent coronary stent implantation for critical stenosis of the proximal left anterior descending artery 15 days ago. Thereafter, he began to take aspirin (100 mg qd), ticlopidine (250 mg bid), isosorbide dinitrate (40 mg bid), and atenolol (25 mg bid). On clinical examination, he was deeply jaundiced and maculopapular rash was present on the whole body. His blood pressure and pulse rate were 110/70 mmHg and 80 beats per minute respectively. No other stigmata of chronic liver disease was present. His abdomen was soft, not tender and both liver and spleen were not palpable.

**Investigations**

Initial laboratory findings were as follows: hemoglobin level 8.1 g/dl, total white cell count \(6.8 \times 10^3/\text{ul}\), differential count-polymorphs 65%, lymphocytes 15%, monocytes 4% and eosinophils 10%, platelet count of \(590 \times 10^3/\text{ul}\), AST 114 U/L (10–35), ALT 141 U/L (0–35), total bilirubin 16.8 mg/dL (0.2–1.2), direct bilirubin 15.6 mg/dL (0–0.5), alkaline phosphatase 1082 U/L (70–290), r-GTP 266 U/L (11–53), LDH 540 U/L (120–520), total protein 4.2 g/dL (6.6–8.4), albumin 3.7 g/dL (4.1–5.2), prothrombin time 12s (control 12s), activated partial thromboplastin time 46s (control 43s). On the urine analysis, proteinuria, bilirubin, urobilinogen were detected. Skin tests for clonorchis sinensis and paragonimiasis westermani were negative and parasitic specific antibodies (Cysticercus, Paragonimiasis, Sparganum, Clonorchis) were not detected. No ova were present in the stool. Total Ig E level was 311 IU/ml (<200).

Serologic tests for hepatitis A, B, C and D were negative. Antimitochondrial, antinuclear, anti-smooth muscle, anti-DNA, antineutrophil cytoplasmic, anti-Scl 70, anticentromere, anti-RNP and anti-Smith antibodies were all negative. Serum 1-antitrypsin was 321 mg/dl (140–320) and serum copper was 134 mg/dl (70–130), and serum ceruloplasmin was 31.3 mg/dl (20–55).

Abdominal ultrasound and CT scan revealed a normal sized liver without any focal lesions. The intra and extraphepatic biliary ducts were not dilated and no gallstones were detected. Endoscopic retrograde cholangiopancreatography showed no abnormalities. All medications including ticlopidine were discontinued and supportive therapy including hepatotonic agents was done. A percutaneous liver biopsy was not carried out because his liver function tests were progressively deteriorated (Fig. 1) and pancytopenia (Fig. 2) was superimposed. Periperal blood smear (Fig. 3) showed that red cells were normocystic and normochromic, white blood cells decreased markedly in number with no blast or immature.
cells, and platelets also decreased markedly in number. Bone marrow aspiration and biopsy were done to investigate other causes of pancytopenia. The aspiration (Fig. 4) showed that megakaryocytes were mildly decreased in number with decreased platelet production and myeloid precursors moderately increased in number with left shift and erythroid precursors relatively decreased in number. The overall cellularity was about 60% in marrow biopsy (Fig. 5).

The causes of fever were investigated but not found. Blood and urine culture were negative. Widal titers for S. typhi O & H and S. paratyphi A & B were all 1 / 80. Prothrombin time was 10.5s (control 12s). Serum fibrinogen was 435 mg/dl (200~400) and antithrombin III was 29.1 mg/dl (22~39). Serum FDP was lower.

---

**Fig. 2.** Chronological change of complete blood counts. WBC, white blood cell; BM, bone marrow.

**Fig. 3.** Peripheral blood smear. Red cells are normocytic and normochromic anemia, white blood cells decreased in number with no blast or immature cells, and platelets markedly decreased in number.

**Fig. 4.** Bone marrow aspiration. Megakaryocytes are mildly decreased in number with decreased platelet production, myeloid precursors moderately increased in number with left shift, and erythroid precursors relatively decreased in number.

**Fig. 5.** Bone marrow biopsy. The section shows mildly hypercellular marrow and the overall cellularity is about 60%. Megakaryocytes are adequate in number, but myelopoiesis mildly increased and erythropoiesis moderately decreased.
than 10 μg/ml (2–8).

Platelets transfusion was ineffective. Prednisolone of 30 mg/day was tried and it was effective to raise the blood components. His blood components and liver function tests were slowly resolved and he was discharged at 113 days after coronary stent implantation. At the 17 days after discharge, his blood cells and liver function tests were much recovered and he felt better.

**Discussion**

Ticlopidine is an antiplatelet agent used worldwide for a variety of vascular disorders in which platelets play a prominent role. Studies in animals and human demonstrated that ticlopidine is a potent inhibitor of platelet aggregation induced by adenosine diphosphate (ADP), and variably inhibits aggregation by collagen, epinephrine, arachidonic acid, thrombin, and platelet activating factor. Its action is both dose- and time-related, with its onset of activity being 24 to 48 hours, its maximal activity occurring after 3 to 5 days, and its activity still being present 72 hours after a final dose. Overall, side effects occur in 10 to 15% of patients receiving ticlopidine. The most common side effects are gastrointestinal disturbances and skin rashes, neither of which necessarily require discontinuation of therapy in most patients. Neutropenia is the most worrisome and occurs in 1–2% of patients. As a result, complete blood counts with white cell differentials is recommended every 2 weeks during the first 3 months of therapy.

Reversible abnormal liver function tests were reported in only 1% of patients receiving the drug in two large clinical trials. Severe cholestasis has been reported rarely, with approximately 12 case reports including only five from the English medical literatures. From the available literature, ticlopidine induced cholestatic jaundice is characterized as follows. Patients ranged in age from 45 to 92 years and developed jaundice without prodromal symptoms at a mean of 32 days (range 1-12 weeks) after starting ticlopidine. Serum bilirubin usually exceeded 24 mg/dl (range 5.3–30.2 mg/dl). Alkaline phosphatase and transaminase were elevated and varied widely. Jaundice resolved over a period of 10 days to 3 months after drug withdrawal. The time taken for liver function to normalize after discontinuation of the drug ranged from 5 days to 8 months. Biopsies performed in four cases and demonstrated cholestasis. Centrilobular acidophilic necrosis and a portal lymphoplasmacytic infiltrate were seen in one case, and spotty moderate necrosis in another. Rechallenge has not been reported. None of the reported cases with ticlopidine induced cholestatic jaundice died from the condition.

We extensively investigated other common causes of jaundice and ruled out viral hepatitis, primary biliary cirrhosis, autoimmune hepatitis, hepatobiliary sepsis, cholangitis, gallstone disease, mixed connective tissue disease and systemic lupus erythematosus, Wilson's disease, genetic cause and viral infections such as cytomegalovirus or Epstein-Barr virus. Our patient was similar to the clinical features and latency period of severe cholestasis caused by ticlopidine in previously reported cases. However, it is unusual that pancytopenia occurred subsequently and it was responsive to steroid even though no evidence of autoimmune causes was noted. Besides neutropenia, anemia and thrombocytopenia were reported to be associated with the use of ticlopidine.

Cholestatic jaundice due to ticlopidine is a rare idiosyncratic side effect that resolves predictably with drug withdrawal without apparent sequelae. Adverse hepatic effects usually occur within the first 3 months of therapy. Patients should be informed to see a physician if they experience weakness, nausea, emesis, decreased appetite, weight loss, painless jaundice or icteric sclera, elevated liver enzyme. The clinician should be aware of this potentially reversible condition and undertake careful history taking, physical examinations, complete blood counts and liver function tests as well as white blood cell count, particularly because a favorable response to drug withdrawal may obviate the need for extensive investigations. The safety and efficacy of 2 weeks of ticlopidine therapy or new antiplatelet agents such as cilostazol and clopidogrel are now reported after coronary stent implantation.
REFERENCES