Ticlopidine-Induced Cholestatic Hepatitis with Anti-nuclear Antibody in Serum

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Abstract: We describe a case of severe cholestatic hepatitis following administration of ticlopidine. A 57-year-old man without known liver disease developed jaundice approximately 3 weeks after initiation of ticlopidine for secondary prevention of stroke. Hyperbilirubinemia and abnormal liver function test values resolved 5 months after withdrawal of ticlopidine. The diagnosis of ticlopidine-induced cholestasis was made after thorough investigations had excluded other causes of jaundice. He was not retreated with ticlopidine. This case may serve to illustrate the possibility of ticlopidine hepatotoxicity, which has rarely been reported. Furthermore, to the best of our knowledge, ticlopidine-induced cholestatic hepatitis accompanied by autoantibody has not been previously reported. This case suggests that regular assessment of liver function should be performed in the initial 3 months of ticlopidine treatment due to the potential risk of adverse effects. In patients with abnormal biochemical test results, autoantibodies should be assessed.

Case Report

This 57-year-old man had a 10-year history of hypertension for which he had been taking enalapril 10 mg and benzyl hydrochlorothiazide 4 mg daily. One day before admission to our hospital, he was brought to a local hospital with unstable gait and vertigo. The diagnosis of cerebellar ischemic stroke was made on the basis of clinical and radiologic findings. He was then referred to our neurology department where ticlopidine 250 mg twice daily was started.

Three weeks after initiation of ticlopidine, he began to complain of progressively worsening nausea, yellow discoloration of the skin, and pruritis. He denied a history of alcohol abuse or having taken herbal medicines that may cause toxic hepatic injury [2]. Physical examination showed normal vital signs. His weight and height were 69 kg and 1.63 m, respectively. He appeared deeply jaundiced without apparent distress. Cardiac and chest examination revealed no abnormalities. The liver and spleen were impalpable and there was no shifting dullness. Laboratory data were as
follows: normal complete blood count; albumin, 4.3 g/dL; total bilirubin, 29.3 mg/dL (normal, < 1.3 mg/dL); direct bilirubin, 12.9 mg/dL (normal, < 0.4 mg/dL); serum aspartate transaminase (AST), 129 U/L (normal, < 34 U/L); serum alanine transaminase (ALT), 305 U/L (normal, < 36 U/L); serum alkaline phosphatase (Alk-P), 27.5 mg/dL (normal range, 16.35–65.4 mg/dL); gamma-glutamyl transpeptidase, 664 U/L (normal, < 26 U/L); serum prothrombin time, 11 s (control, 11.6 s); serum ceruloplasmin, 27.5 mg/dL (normal range, 16.35–65.4 mg/dL); and alpha 1 anti-trypsin, 143 mg/dL (normal range, 115.22–166 mg/dL).

Immunoglobulin (Ig) M antibody to hepatitis A virus and hepatitis B core antigen, and hepatitis B surface antigen were all negative by radioimmunoassay. IgM antibody to cytomegalovirus, IgM antibody to Epstein-Barr virus, antibody to hepatitis C virus (HCV), antibody to mitochondria, antibody to smooth muscle, and antibody to microsome were all negative by enzyme immunoassay, while antinuclear antibody (ANA) was positive (1:1280) in a discrete speckled pattern. Protein electrophoresis was normal with a gamma-globulin level of 0.7 g/dL (normal < 1.6 g/dL). HCV RNA was negative by Amplicor® (Roche Diagnostic Systems Inc. Asia, Singapore). Findings on both abdominal ultrasound and endoscopic retrograde cholangiopancreatography were normal.

Liver biopsy was performed 2 months after admission and disclosed marked cholestasis in hepatocytes and bile canaliculi. These features were prominent throughout the acinus but maximal in zone 3 (Fig. 1), and were accompanied by xanthomatous changes in hepatocytes and necroinflammation in zone 3 (Fig. 2). However, no bile duct injury was found. Ticlopidine was discontinued 3 weeks after institution of treatment. The patient’s hospital course was uneventful. Serum liver enzyme and bilirubin levels declined steadily after withdrawal of ticlopidine. Serum ALT concentrations decreased from 305 U/L to 120 U/L (> 50 % decrease) 1 week later and normalized within 1 month. The serum bilirubin concentration returned to normal 5 months after discontinuation of ticlopidine and remained normal on sequential determination (Fig. 3).

The patient was not retreated with ticlopidine. Serum ANA titer declined following discontinuation of ticlopidine from 1:1280 positive initially, to 1:640 positive at 12 months, and 1:320 positive at 24 months. He did not receive steroid treatment.

**Discussion**

Ticlopidine is an anti-platelet agent that suppresses adenosine diphosphate-induced platelet aggregation...
of severe adverse experience is not available. On the other hand, no hepatic adverse effects were reported in another large multicenter trial, the Ticlopidine Aspirin Stroke Study (TASS) [4]. Our case could serve to illustrate the probable causal relationship between ticlopidine and cholestasis, even though causality cannot be established in the absence of rechallenge.

Our patient had been taking benzyl hydrochlorothiazide and enalapril for several years without adverse experience. These agents are not commonly associated with cholestasis. However, ticlopidine has been suggested to have a causal role in drug-induced liver injury [5]. Male gender and the absence of stigmata of autoimmune hepatitis, including hypergammaglobulinemia, extrahepatic autoimmune symptoms, and piecemeal necrosis on histologic examination, suggest that the seropositivity of ANA in our patient was associated with drug autoimmunity rather than autoimmune hepatitis. Thorough investigations excluded other possible causes of cholestasis.

Our literature review found 30 published case reports describing 35 patients with probable ticlopidine-induced cholestasis [6-14]. These patients were predominantly elderly with a mean age of 69 years, ranging from 29 to 92 years. Men and women were equally affected. These patients developed symptoms 1 week to 3 months after administration of ticlopidine. The symptoms and laboratory abnormalities were all consistent with cholestasis. Typically, the serum Alk-P concentration was 5 to 10 times normal (mean, 707 U/L) while the serum bilirubin concentration varied widely, ranging from 0.7 mg/dL to 32.5 mg/dL (mean, 10.4 mg/dL). The serum ALT level ranged from 42 U/L to 2661 U/L (mean, 399 U/L). In all cases, resolution of cholestasis and normalization of liver enzyme concentrations occurred over a period of 10 days to more than 1 year after discontinuation of ticlopidine. There was no mortality or sequelae in these patients. The dosage of ticlopidine in the reported cases was less than or equal to the recommended dose (ie, 250 mg twice daily).

Biopsies were performed in 11 cases that predominately showed acinar cholestasis. Infiltration with lymphocytes in the portal area was observed in five cases, while spotty necrosis was seen in four cases. Granulomatous hepatitis [13] and bile duct injury with eosinophil infiltration in portal tracts have also been described [10]. None of these patients were retreated with ticlopidine. Ours is the 12th reported case of a patient with liver biopsy that revealed both cholestasis and spotty necrosis.

The mechanism of the hepatotoxicity of ticlopidine has not been established. Whether this drug causes cholestatic injury by inducing molecular changes in basolateral and canalicular transport systems needs further investigation [15]. The involvement of an immunoallergic mechanism is suggested by the apparent dose independence, the presence of tissue eosinophilia [10, 13], lymphocytic or plasma cell infiltration in the periportal area, granulomatous hepatitis [13], and bile duct injury [10]. On the other hand, results obtained using ticlopidine-induced cholestasis in rats suggest that the adverse effect might be caused directly by the drug or its metabolites rather than by hypersensitivity [10]. The apparently discrepant findings could be explained by the presence of more than one mechanism by which ticlopidine induces liver injury.

Various drugs can produce at least three types of acute cholestasis, including cholestasis without hepatitis (pure cholestasis, cholestasis with hepatitis, and cholestasis with bile duct injury [16]. In cases of pure cholestasis, the recovery is usually rapid and complete, while the reaction can be more severe and follow a prolonged course in cases with cholestatic hepatitis and cholestasis with bile duct injury. The present case is consistent with the previously reported cases of ticlopidine-induced cholestatic hepatitis. The various liver injury patterns and clinical courses in the reported cases and in the present case are similar to those caused by chlorpromazine, which is commonly cited as an example of drug-induced cholestatic hepatitis.

As previously mentioned, autoantibody in cases with drug-induced hepatitis may pose problems of differential diagnosis in practice. However, the differential diagnosis between autoimmune hepatitis and drug-associated autoimmunity should not be difficult. The autoantibodies can be the cause or effect of drug-induced liver damage. Furthermore, they may simply indicate the patient’s susceptibility or spontaneous disease that has been unveiled by the offending drug. The mechanisms involved remain unclear and hypothetical [17]. No common denominator of a pharmacologic, therapeutic, or chemical nature that links drugs with the capacity to induce autoimmune-like disease has been identified. These drugs include antibiotics (isoniazid, griseofulvin, streptomycin, tetracycline, sulfonamides, nitrofurantoin), anti-inflammatory agents (o-penicillamine, gold salts), and psychotropic drugs (chlorpromazine, lithium). The largest general pharmacologic category of drugs associated with autoimmune-like disease is related to treatment of cardiovascular diseases, but this is also a heterogeneous...
neous group and consists of anti-arrhythmics (procainamide, quinidine, acebutalol, practolol) and anti-hypertensives (hydralazine, methyldopa, some beta-blockers). Most of these drugs have one or two aromatic rings, but are otherwise chemically dissimilar. The amino group on procainamide is required for induction of autoimmunity [18], and other important functional groups are the hydrazide group on hydralazine and isoniazid and the sulfhydryl group on propylthiouracil. However, these reactive moieties are not components of other autoimmunity-inducing drugs [18]. It is still unknown whether ticlopidine induces autoantibodies through these mechanisms. However, it is evident that immunologic reactions may play a role in certain groups of drug-induced liver damage. The present case also supports the absence of correlation between signs of autoimmunity and the level of ANA. Therefore, seropositivity for autoantibodies might not be suspected in ticlopidine-induced hepatotoxicity, especially when the symptoms are mild and not suggestive of autoimmunity. The efficacy of immunosuppressants in such cases of autoimmunity that have been used in certain kinds of drug-induced hepatitis needs to be determined.

Cholestasis is a rare adverse effect of ticlopidine. It appears to be idiosyncratic and resolves without evident sequelae on timely withdrawal. In view of the potential hepatotoxicity of ticlopidine, attention to the monitoring of liver function tests in the initial 3 months of treatment is needed.

References