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Cholestasis Associated with Ampicillin / Sulbactam Therapy ： A Case Report

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Abstract

Ampicillin/sulbactam is one of the most widely used antibiotics. Ampicillin/sulbactam related hepatotoxicity is very rare. We report a case of a 49-year-old male who suffered from cholestasis after receiving nine days of ampicillin/sulbactam treatment for diabetic foot infection. Jaundice subsided one month after withdrawal of the drug. Clinicians should be aware of this adverse side effect and should take ampicillin/sulbactam into consideration during diagnostic work up for drug induced liver injury. (J Intern Med Taiwan 2006; 17: 87-90)

Key Words ： Ampicillin, Sulbactam, Cholestasis

Introduction

It is well known that therapeutic drugs may cause liver damage. Antibiotics have been reported to cause hepatotoxicity. Ampicillin/sulbactam however has rarely been associated with hepatic injury. We report a case of cholestasis following ampicillin/sulbactam use. Since this is a commonly used antibiotic we hope that clinician will be aware of such side effect.

Case Report

A 49-year-old male consulted our emergency room due to general weakness and fever. He also complained of erythematous swelling of bilateral lower legs for three weeks. Patient is a case of type 2 diabetes mellitus for seven years. He was treated with oral antidiabetic agents glimepiride 2 mg and dimethylbiguanide 500mg twice a day. He denied us-

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ing herbal medicine or over-the-counter drugs. There was no history of recent surgery or blood transfusion. He smokes one half pack of cigarette per day for thirty years. He took one to two cans of beer every day for twenty years but he did not take alcohol for about one week prior to admission.

On examination he appeared acutely ill. He was febrile with body temperature of 38℃. The heart, lung and abdominal examination were within normal. There was non- pitting swelling over both legs below the knees. Both lower legs were erythematous, tender and warm on palpation. Pertinent laboratory data included elevated blood sugar up to 427mg/dL(normal 70-110). There was leukocytosis with white blood cell 20.89x10^3/m μL(normal 3.8-10.4). His renal and liver functions were normal. There was no proteinuria but serum albumin level was subnormal 3.1 gm/dL(normal 3.4-4.8).

On admission, patient was started on antibiotic treatment with prostaphyllin 1 gram intravenously every 6 hours. Multiple insulin injections were given for blood sugar control. On the third hospital day, leukocytosis became worse, white blood cell 25.39x 10^3/m μL(normal 3.8-10.4) and leg swelling did not improve. Antibiotic was shifted to ampicillin/sulbactam 3 grams intravenously every 8 hours. Patient noted yellowish discoloration of skin and tea colored urine on the ninth day of ampicillin/sulbactam treatment. He also suffered from malaise, anorexia and generalized itching. His serum direct and total bilirubin levels were 6.6mg/dL(normal 0-0.3) and 9.1 mg/dL(normal 0-1.1) respectively. Serum alkaline phosphatase was 1041IU/L(normal 40-129), γ -glutamyl transpeptidase was 163 IU/L (normal 8-61 IU/L), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and prothrombin time were normal. There was no other routine medication that may cause jaundice. We discontinued ampicillin/sulbactam on the ninth day of treatment. Complete blood count showed leukocytosis with white blood cell 28.3x10^3/m μL (normal 3.8-10.4), neutrophil 85%, lymphocyte 10%, monocyte 5%. Hemoglobin was 11.8gm/dl with normal mean cell volume. Platelet count was 151000/mm^3. Abdominal ultrasound was arranged showing liver cirrhosis, moderate splenomegaly and the presence of ascites. Since the etiology of liver cirrhosis and jaundice cannot be determined, viral and autoimmune hepatitis markers were done. Serologic tests for viral hepatitis including HBsAg, IgM anti-HBc, IgM anti-HAV, anti-HDV, anti-HCV, cytomegalovirus, Epstein-Barr virus and herpes simplex virus were negative. Direct and indirect Coombs tests, antinuclear and antimitochondrial antibodies were also negative. The possible etiology of his liver cirrhosis may be due to alcoholic liver disease. Paracentesis was done. Ascitic fluid analysis showed red blood cell=207/ μL, white blood cell=63/ μL, protein=2g/dL and was negative for malignant cells. Patient requested for discharge against medical advice because he wanted to seek second opinion at a medical center.

Patient refused any invasive investigation at medical center. Supportive measures were given. He was discharged after one week when jaundice improved. Jaundice resolved completely after one month.

Discussion

Drug-induced hepatotoxicity can be categorized as hepatocellular or cholestatic [1]. Drugs cause liver injury either via intrinsic toxicity (dose-dependent or predictable) or host idiosyncrasy (dose-independent or unpredictable)[2]. The kind of liver injury in our case can be designated as idiosyncratic "cholestatic" type because there is a more than two folds increase in alkaline phosphatase and bilirubin levels but ALT and AST levels were within normal [2].Causality-assessment methods provide a uniform approach to determine the likelihood of drug involvement in a suspected episode of hepatitis [3]. Our patient developed jaundice on the ninth day after exposure to ampicillin/sulbactam and resolved one month after with-

drawal of the drug. The temporal relationship is consistent with usual observation. The reported onset of symptoms was between 5 and 90 days and improvement usually occurred within weeks after withdrawal of the drug [4]. In our case, other possible hepatotoxic agents have been excluded. Serologic tests for viral and autoimmune hepatitis were negative. Ultrasonography of liver and biliary tract did not show cholelithiasis and biliary tract abnormalities. Jaundice subsided gradually upon withdrawal of ampicillin. Rechallenging with the suspected agent is usually not recommended [4].

Erythromycin was the prototype drug that cause cholestatic hepatic injury [4]. However, according to the report of Spanish registry, amoxicillin-clavulanate was the most common drug related to liver injury accounting for 12.8% of the whole series over a ten year period [5]. Among the 59 reported cases of amoxicillin-clavulanate induced liver injury, 22 cases were of hepatocellular type, 16 cases were cholestatic and 21 cases were mixed type[5]. In the above study, 5% of patients had underlying liver disease including liver cirrhosis and alcoholic hepatitis. In Taiwan, we have a high prevalence of chronic liver disease and clinicians should be cautious about drug induced liver injury. Erythromycin hepatotoxicity has been a classic example of drug-induced hepatitis [4,6]. Other rarely reported antibiotics included penicillinase-resistant penicillins, fluoroquinolones, cephalosporin and sulfamethoxazole/trimethoprim [6]. In the English literature three cases of ampicillin induced cholestasis has been reported [1, 7, 8]. Of these three cases, two were reported as probable ampicillin induced cholestasis [1, 7]. One report described cholestasis with hematologic and immunologic problems manifested as red cell aplasia and Steven-Johnson syndrome [8].No reports on hepatic injury have been published for sulbactam.

Cholestasis is characterized by the retention of bile in canaliculi. Drugs that affect transport proteins at the canalicular membrane will disable the bile salt export protein and interrupt bile flow [4]. Canaliculus is the specialized portion of the cell responsible for bile excretion. In cholestatic disease, there is disruption of actin filaments next to the canaliculi. This may lead to loss of villous process and the interruption of transport pumps such as multidrug-resistance-associated protein 3 (MRP3) thus prevent the excretion of bilirubin and other organic compounds [4]. Genetic defects in transporters may predispose a patient to drug induced cholestasis. Therapy for hepatotoxic effects of drugs consists of immediate withdrawal of suspected drugs. Ursodeoxycholic acid (UDCA) may be tried if cholestasis persisted after the discontinuation of the suspected drug [9]. The postulated mechanism by which UDCA protects the hepatocytes from cholestatic injury is by inducing hypercholeresis [10].This process prevents the retention of more hepatotoxic bile acids such as chenodeoxycholic acid and lithocholic acid [10].

Ampicillin is a commonly used antibiotic. We report this case to remind clinician about its possible hepatic injury and to take ampicillin into consideration during work up for drug induced liver injury.

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Ampicillin / Sulbactam 引起的膽汁滯留 — 一病例報告

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摘 要

Amipcillin/sulbactam 是屬於最常被廣泛使用的抗生素之一。使用 ampicillin/sulbactam 而引起肝毒性病變非常少見。我們報告一個 49 歲的男性病人因糖尿病腳部感染接受 9 天的 ampicillin/sulbactam 治療後產生膽汁滯留，而停藥一個月後黃疸消失。臨床醫師應該對此嚴重的副作用有所警覺，在考慮藥物引起的肝臟傷害時應該把 ampicillin/sulbactam 列入考慮。