Amoxicillin–clavulanic acid-induced hepatotoxicity

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INTRODUCTION

Amoxicillin–clavulanic acid-induced hepatotoxicity is a rare side effect with potential mortality. The product monograph reports transient cholestatic jaundice and hepatitis as adverse effects. We report a case of suspected amoxicillin–clavulanic acid hepatotoxicity which illustrates the morbidity associated with this reaction and adds to the previously described cases in the literature.

THE CASE

A 69-year-old male presented to his family doctor with complaints of diarrhea with pale stools, nausea and vomiting, a 10-lb. weight loss, dark urine, pruritus, jaundice, and general malaise. His medical history was remarkable for hypercholesterolemia and mild hypertension. He had a cholecystectomy in the 1970s and a Billroth II partial gastrectomy at age 30 for ulcers. During the onset of symptoms, his medications included hydrochlorothiazide/triamterene and lovastatin, both of which had been taken on a long-term basis. After the onset of symptoms, lovastatin, which the patient had been receiving for 5 years, was discontinued. The patient was a social drinker of no more than approximately 3 alcoholic drinks per week. He had no previous history of jaundice or liver disease.

On July 11, 1995, the patient had a benign cutaneous lesion removed from his back. Ten days following this procedure, a 10-day course of amoxicillin-clavulanic acid was prescribed. Ten days after completing the course, the patient noted jaundice. One month after starting the course of antibiotics he noted pale and loose stools in up to 4-5 bowel movements per day, and dark urine. On August 28, a week after the onset of diarrhea, he sought medical attention from his family doctor. His other symptoms included nausea and vomiting, a 10-lb. weight loss, pruritus, jaundice, and general malaise. His medical history was remarkable for hypercholesterolemia and mild hypertension. He had a cholecystectomy in the 1970s and a Billroth II partial gastrectomy at age 30 for ulcers. During the onset of symptoms, his medications included hydrochlorothiazide/triamterene and lovastatin, both of which had been taken on a long-term basis. After the onset of symptoms, lovastatin, which the patient had been receiving for 5 years, was discontinued. The patient was a social drinker of no more than approximately 3 alcoholic drinks per week. He had no previous history of jaundice or liver disease.

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The patient's total bilirubin increased to 325 mmol/L by the time of an endoscopic retrograde cholangiopancreatogram (ERCP) on September 19, 1995. This showed a normal common bile duct with no stones or obstruction, normal intrahepatic ducts and drainage, with a previous cholecystectomy. A second abdominal ultrasound and computed tomography (CT) scan also showed a normal upper abdomen.

Three days after the ERCP, a liver biopsy was performed which showed portal areas with concentric deposition of fibrous tissue which implied acute and chronic inflammation. There were signs of early bile duct proliferation and acute inflammation in the sinusoids. There was marked cholestasis, feathery degeneration of hepatocytes and mild focal fatty changes. This described a picture of cholestasis secondary to small bile duct inflammation. It appeared to be a toxic reaction possibly as a result from cholestyramine. The excretion of bile continued until October of 1996, his clinical symptoms improved significantly. In October of 1996, his clinical symptoms improved significantly.

DISCUSSION

Most cases of amoxicillin–clavulanic acid-induced hepatotoxicity have been cholestatic, with or without clinical symptoms of jaundice. In a case reported by Stow et al., a patient experienced acute liver failure as a result of amoxicillin–clavulanic acid. According to the product monograph, serious adverse effects including jaundice and anuria have been seen. In the case reported by Stow et al., the patient developed jaundice within 2–3 days of starting the drug.

In a more recent case report, a patient developed jaundice within 2–3 days of starting amoxicillin–clavulanic acid. The patient's liver enzymes returned to normal within 2 weeks, and he experienced no further complications.

In conclusion, amoxicillin–clavulanic acid-induced hepatotoxicity is a rare but potentially serious side effect. Healthcare providers should be aware of this adverse effect and monitor patients closely for signs and symptoms of liver injury, especially when using this medication for extended periods of time.
DISCUSSION

Most cases of amoxicillin-clavulanic acid-induced hepatotoxicity were cholestatic in nature but hepatocellular and mixed cholestatic-hepatocellular injuries have also been seen. In our patient's case, a predominantly cholestatic picture was seen as defined by an ALP increase of less than 8-fold, AST and ALT increase of less than 8-fold according to the criteria established by Lewis et al. 

Onset of symptoms varied from 2 days to 4 weeks after discontinuation of antibiotics. Recovery from symptoms was reported to be between 1-4 months. This patient became asymptomatic after 5 months. A point of interest is that this patient had an HIDA scan that confirmed good hepatocyte function but showed severe cholestasis. The severity and the protracted nature of his illness brought up the issue of a possible liver transplant. However, he continued to improve and became asymptomatic after 5 months. A point of interest is that our patient's case, a predominantly cholestatic picture was seen as defined by an increase of less than 8-fold, AST and ALT increase of less than 8-fold according to the criteria established by Lewis et al.

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Risk factors associated with amoxicillin-clavulanic acid-induced liver injury have been described by several articles. A number of risk factors have been identified and debated, including increasing age, male sex and duration of therapy. Studies have shown that with increasing age there was a greater risk of liver injury due to amoxicillin-clavulanic acid. One study reported an odds ratio of 16:1 for patients over 55 years of age vs. patients under 50 years old. Most adverse hepatic reactions have been reported in patients over 50 years of age, although use of this drug was seen mostly in the pediatric population. A general consensus is that patients over the age of 60 should be considered at increased risk. Postulated mechanisms included decreased drug elimination, altered drug metabolism or altered immunological function. Decreasing renal function with age might also affect the renal clearance of this drug since the drug is partially eliminated through the kidneys.

Male gender is a risk factor; the number of cases affecting males generally outnumber females by a 2:1 ratio. The relative risk ratios varied amongst studies, ranging from not significant to 4 times the risk. There was no explanation for this risk factor, and some authors dismissed this as a statistical error due to the small number of reported cases. However, 1 study in France which documented over 100 cases did report male sex as a risk factor.

Not all studies found duration of treatment to be a risk factor. One reported that with a second consecutive course of this antibiotic, the odds ratio increased 3-fold. However, other studies have categorized hepatotoxicity as idiosyncratic and hence the onset and duration of therapy were not felt to be risk factors.

Studies have examined other factors which may contribute to the hepatic injuries. It was found that alcohol consumption, previous amoxicillin-clavulanic acid exposure, and penicillin allergy were not risk factors. The relative risk of jaundice was increased 8-fold when compared to the use of amoxicillin alone. Most authors agreed that the clavulanic acid component was responsible for the adverse hepatic reactions.

In conclusion, this case adds to the reported cases that indicate amoxicillin-clavulanic acid might lead to hepatic injury. This patient fits the criteria for increased risk with his male gender and elderly age. There are many reported cases worldwide. However, the total number of cases is unknown at this point. There have been 3 reported fatalities. This reaction can be identified with liver enzyme elevation and may need further testing with ERCP and HIDA scan. The long lag time between the discontinuation of the antibiotic and the onset of symptoms should be kept in mind.

a result from drug ingestion. The patient was started on cholestyramine 4g twice a day, hydroxyzine 25mg four times a day, and loperamide 2mg as required.

The patient was followed through the gastroenterology clinic at regular visits. His symptoms of jaundice and pruritis became worse. A hepatobiliary scan (HIDA) scan was performed on October 6th, 1995, which showed poor liver uptake and no radiotracer was seen in the biliary tract or bowel. This implied a degree of hepatocellular dysfunction in addition to severe cholestasis. His symptoms of malaise, anorexia, vomiting, and jaundice continued until December despite improving liver function tests. On January 24th, 1996, his clinic visit showed no pruritis or jaundice, and the patient reported increased weight and appetite. On February 7th, 1996, a second HIDA scan showed excellent biliary excretion, with no evidence of bile obstruction in the biliary tract and bowel. His alkaline phosphatase finally normalized in October of 1996. The patient remained asymptomatic with normal blood work since then.
mind, as well as the long period of recovery. Hospitalization is usually not required. Clinicians and pharmacists should be aware of this adverse reaction, and observe for it in high risk patients.

REFERENCES


AN UPDATES ON REACTIONS

In the recent MedWatch presentation, MedWatch pointed out that patients who were taking drugs that inhibit the 3A4 isozyme after cardiac surgery had an additional 38% increase of sudden unexplained deaths. Physicians are urged to reassess the labelling of warnings, precautions, and pediatric use.

Cisapride, a drug used to treat gastrointestinal symptoms and disorders, has not been equally effective or available as prescribed, used and ingested. January 1–March 31, 2010 saw prescriptions for cisapride consumption. In the same period, physicians were also reminded of the increased risk factors. Patients who have a history of cisapride should be monitored closely.

1. Concomitant use of macrolide antibiotics, ketoconazole, itraconazole, and clarithromycin.

32

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