J. Med. Toxicol. (2010) 6:420–423
DOI 10.1007/s13181-010-0019-4

TOXICOLOGY OBSERVATION

Corticosteroid Therapy in a Case of Severe Cholestasic Hepatitis Associated with Amoxicillin–Clavulanate

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Published online: 17 March 2010

Abstract Amoxicillin–clavulanate is the most common drug involved in drug-induced liver injury and the single most frequently prescribed product leading to hospitalization for drug-induced liver disease in Spain. The liver damage most frequently associated with amoxicillin–clavulanate is cholestasic type. The latency period between first intake and onset of symptoms is 3–4 weeks on average. A 76-year-old man developed fever, pruritus, and jaundice 3 weeks after having completed treatment with amoxicillin–clavulanate. Liver function tests showed cholestasic hepatitis (up to 50.75 mg/dL of total serum bilirubin level). The ultrasound-guided liver biopsy revealed severe canalicular cholestasis and portal and lobular eosinophilic infiltrates. Prednisone and ursodeoxycholic acid therapy were then prescribed. The patient became symptom-free with normal liver function tests. Amoxicillin–clavulanate can cause hepatocellular, cholestasic, or mixed liver injury. The presence of eosinophilic infiltrates in the liver biopsy and the clinical signs of hypersensitivity in some of the cholestasic cases suggest a pathophysiological immunoallergic mechanism. For this reason, corticosteroid treatment should be considered for patients with severe cholestasic liver injury.

Keywords Drug-induced liver injury · Hepatotoxicity · Amoxicillin–clavulanate

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Introduction

Amoxicillin–clavulanate is the most common drug involved in drug-induced liver injury and the single most frequently prescribed product leading to hospitalization for drug-induced liver disease in Spain [1–3].

The liver damage most frequently associated with amoxicillin–clavulanate is cholestasic type (with reported total bilirubin levels ranging between 0.6 and 36.9 mg/dL) [1], although hepatocellular injury and mixed patterns have also been described [4]. The pathophysiological mechanisms of this liver toxicity are unknown. Metabolic determinants may play a greater role in the origin of the hepatocellular injury, whereas immunological factors may be more important in the pathogenesis of cholestasis [4]. The latency period between first intake and onset of symptoms is 3–4 weeks on average [3]. Except for the withdrawal of the drug, there is no specific therapy for this condition [1]. Corticosteroid treatment has been suggested [5] and occasionally reported [6, 7].

We report a case of severe cholestasic hepatitis associated with amoxicillin–clavulanate in which bilirubin levels reached 50.75 mg/dL, and we describe its evolution following corticosteroid therapy.

Case Report

A 76-year-old man developed fever (39°C), weakness, pruritus, and jaundice 3 weeks after having completed treatment with amoxicillin–clavulanate (875/125 mg three times daily, p.o., for 7 days) for a respiratory infection. He denied nausea, vomiting, diarrhea, or abdominal pain. The patient had a previous history of hypertension treated with diet. He had no known drug allergies and denied alcohol,

Table 1 Liver function tests of a 76-year-old man who developed severe cholestasic hepatitis after receiving amoxicillin–clavulanate (875 mg three times daily, p.o., for 7 days) for a respiratory infection

	21 days from cessation of therapy with AC Hospital admission	26 days from cessation of therapy with AC	41 days from cessation of therapy with AC Steroid therapy onset[a]	46 days from cessation of therapy with AC	60 days from cessation of therapy with AC	74 days from cessation of therapy with AC	103 days from cessation of therapy with AC Recovery[b]	112 days from cessation of therapy with AC Steroid therapy cessation[c]
Laboratory levels[d]								
Total bilirubin (0.20–1.50 mg/dL)	2.21	16.62	50.75	9.76	3.2	1.32	1.20	0.9
Direct bilirubin (0.01–0.25 mg/dL)	1.75	10.25	26.82	0.70	0.72	0.2	0.10	1.22
AST (5–37 U/L)	295	325	199	71	50	50	38	35
ALT (5–40 U/L)	352	274	237	165	50	54	40	35
GGT (7–48 U/L)	399	640	427	439	161	76	52	42
LDH (250–500 U/L)	851	1,010	554	528	428	433	232	396
ALP (40–130 U/L)	266	718	909	455	162	120	114	110

AC amoxicillin–clavulanate, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *GGT* γ-glutamyltranspeptidase, *LDH* lactate dehydrogenase

[a] Steroid therapy**:** An initial dose of 1 mg/kg/day of prednisone (70 mg/day) for 15 days was administered; then, 10 mg/day was reduced from the previous dose every week until 10 mg/day was reached; then, 5 mg/day was administered for 1 week; afterwards, 5 mg every other day during 1 week, and then treatment was discontinued

[b] Recovery: The patient was symptom-free, with normal liver function tests

[c] Steroid therapy cessation: Day (counting from that in which therapy with amoxicillin–clavulanate was discontinued) when prednisone treatment was finalized (a total of 71 days of treatment with prednisone).

[d] Coagulation tests, serum albumin levels, hemogram numbers, and lipidic profiles were all into normal range during the evolution

illicit drug use, or recent travel. He received no other medications and he did not take mushrooms or medicinal herbs.

On physical examination at admission, the patient was jaundiced and showed skin scratching lesions without underlying rash, an axillary temperature of 39.3°C, an arterial blood pressure of 120/70 mmHg, and a heart rate of 80 bpm. There was no adenopathy and the exam of his thorax and abdomen was unremarkable (no visceromegaly nor tenderness or pain in the right upper quadrant was observed). Laboratory assessment showed the following: hemoglobin, 12.9 g/dL (normal, 12–16 g/dL); white blood cell count, 5,100/μL (normal, 4,500–10,000/μL; neutrophils, 63%; eosinophils, 8.3%); platelet count, 114,000/μL (normal, >130,000/μL); prothrombin time, 11.3 s (normal, 10.3–12.3 s); serum glucose 6.3 mmol/L (normal, 4.4–6.1 mmol/L); BUN 24 mg/dL (normal, 10–35 mg/dL); serum creatinine, 1.0 mg/dL (normal, 0.6–1.1 mg/dL); serum sodium, 133 mEq/L (normal, 135–145 mEq/L); serum potassium, 4.1 mEq/L (normal, 3.5–5.5 mEq/L); serum chloride, 102 mEq/L (normal, 95–105 mEq/L); C-reactive protein, 7.6 mg/L (normal, <7 mg/L); and serum albumin, 4 g/dL (normal, 3.5–5.2 g/dL). Liver function tests showed a cholestasic and cytolytic profile (Table 1). Complete laboratory evaluation included negative serologies for hepatitis A, B, C, Epstein–Barr virus, and cytomegalovirus and negative assays for anti-nuclear, anti-mitochondria, and anti-smooth muscle antibodies. Ceruloplasmin, alpha-1 anti-trypsin, and serum iron levels were all in the normal range. Chest roentgenogram was also normal, and serial blood and urine cultures were negative. Hepatic ultrasound, abdominal computed tomography, and magnetic resonance cholangiography did not show any significant abnormality.

Since the patient suffered a progression in cholestasis (up to 50.75 mg/dL of total serum bilirubin level; Table 1), an ultrasound-guided liver biopsy was performed at day41 from cessation of therapy with amoxicillin–clavulanate. The histological study of this sample revealed severe canalicular cholestasis with bile plugs in dilated bile canaliculi, ductopenia, fibrosis, giant cell transformation, steatosis, portal and lobular eosinophilic infiltrates, and necrosis predominating in the central zones, suggestive of drug reaction (Fig. 1).

Prednisone (1 mg/kg/day) and ursodeoxycholic acid (13 mg/kg/day) [8] were then prescribed (day 41 from cessation of therapy with amoxicillin–clavulanate). This treatment was promptly followed by an improvement in the clinical status of the patient and in the laboratory test results (in 5 days, total serum bilirubin levels descended from 50.75 to 9.76 mg/dL, Table 1). After 10 weeks of corticosteroid therapy (full dose of 1 mg/kg/day for 15 days followed by a progressive initial descent of 10 mg every week), the patient became symptom-free with normal liver function tests (Table 1).

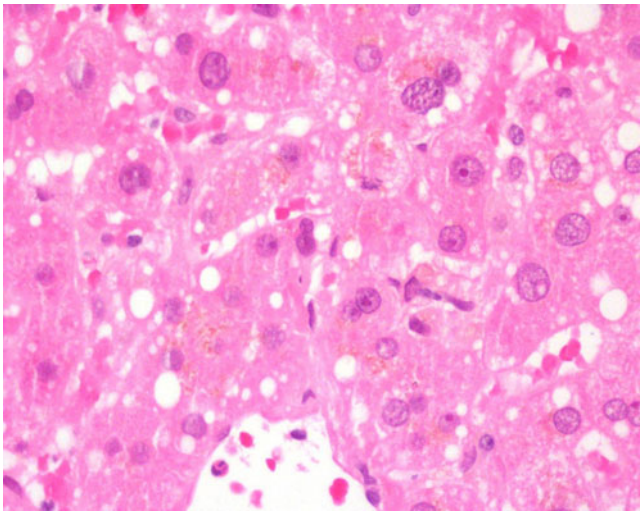

Fig. 1 Ultrasound-guided liver biopsy performed at day 41 from cessation of therapy with amoxicillin–clavulanate, revealing severe canalicular cholestasis with bile plugs in dilated bile canaliculi, ductopenia, fibrosis, giant cell transformation, steatosis, portal and lobular eosinophilic infiltrates, and necrosis predominating in the central zones, suggestive of drug reaction (H&E stain, ×250)

Discussion

Amoxicillin–clavulanate was first commercialized in 1984, and the first report of toxic hepatitis related to this drug was reported from the Netherlands [10]. The calculated incidence of amoxicillin-associated hepatotoxicity ranges between 1 and 17 per 100,000 prescriptions [11–13].

In this case, treatment with amoxicillin–clavulanate could "probably" be related to the observed hepatic injury, according to the scale ("definite or highly probable," "probable," "possible," "unlikely," and "excluded") of the Council for International Organizations of Medical Sciences/ Roussel Uclaf Causality Assessment Method [9].

Some studies suggest that higher doses [14] and longer duration of therapy [12] are predisposing conditions to develop amoxicillin/clavulanate-associated toxic hepatitis, whereas other reports contradict these findings and consider age a major risk factor [15]. On the other hand, duration of therapy and age seem to be linked to the cholestasic and mixed pattern of liver injury [1]. The evolution of this hepatotoxicity is usually self-limited, and 7% unfavorable outcomes (defined as death, need for transplantation, or persistent liver damage) have been reported [1]. Cholestasis generally resolves after 3 months [4], and high serum bilirubin levels are considered predictors for progression to fulminant liver failure [3].

The presence of eosinophilic infiltrates in the liver biopsy and the clinical signs of hypersensitivity (fever, rash) in 38% of the cases suggest a pathophysiological immunoallergic mechanism [1]. For this reason, and although no controlled trials have been performed to

ascertain its efficacy [16], corticosteroid treatment is considered for patients with severe jaundice [7]. In our case, we employed an initial dose of 1 mg/kg/day, similar to that recommended for autoimmune hepatitis [17], followed by a progressive descent guided by the clinical and laboratory test responses. The evolution of this case could support the use of corticosteroids in patients with severe cholestasic hepatitis associated with amoxicillin–clavulanate.

References

1. Lucena MI, Andrade RJ, Fernández MC, Pachkoria K, Peláez G, Durán JA et al (2006) Determinants of the clinical expression of amoxicillin–clavulanate hepatotoxicity: a prospective series from Spain. Hepatology 44:850–856
2. Agencia Española del Medicamento (2006) Uso de la asociación amoxicilina–clavulánico y riesgo de hepatotoxicidad. Boletín de la Tarjeta Amarilla 23:4.1
3. Andrade RJ, Lucena MI, Fernández MC, Peláez G, Pachkoria K, García-Ruiz E, et al (on behalf of the Spanish Group for the Study of Drug-Induced Liver Disease) (2005) Drug-induced liver injury: An analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 129:512–521
4. Gresser U (2001) Amoxicillin–clavulanic acid therapy may be associated with severe side effects—review of the literature. Eur J Med Res 6:139–149
5. Tajiri K, Shimizu Y (2008) Practical guidelines for diagnosis and early management of drug-induced liver injury. World J Gastroenterol 14:6774–6785
6. Ferrando J, Sanz P, Sevilla G, Figueras P, Martín I (2002) Insuficiencia hepática secundaria a hepatitis por amoxicilina-ácido clavulánico. Tratamiento con corticoides. Med Interna 19:551–552
7. Giannattasio A, D'Ambrosi M, Volpicelli M, Iorio R (2006) Steroid therapy for a case of severe drug-induced cholestasis. Ann Pharmacother 40:1196–1199
8. Katsinelos P, Vasiliadis T, Xiarchos P, Patakiouta F, Christodoulou K, Pilpilidis I, Eugenidis N (2000) Ursodeoxycholic acid (UDCA) for the treatment of amoxycillin–clavulanate potassium (Augmentin)-induced intra-hepatic cholestasis: report of two cases. Eur J Gastroenterol Hepatol 12:365–368
9. Danan G, Benichou C (1993) Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 46:1323–1330
10. Van den Broek JWG, Buennemeyer BLM, Stricker BHCh (1988) Cholestatische hepatitis door de combinatie amoxicilline en clavulaanzuur (Augmentin). Ned Tijdschr Geneeskd 132:1495–1497
11. Hussaini SH, O'Brien CS, Despott EJ, Dalton HR (2007) Antibiotic therapy: a major cause of drug-induced jaundice in southwest England. Eur J Gastroenterol Hepatol 19:15–20
12. Larrey D, Vial T, Micaleff A, Babany G, Morichau-Beauchant M, Michel M, Benhamou JP (1992) Hepatitis associated with amoxicillin–clavulanic acid combination: report of 15 cases. Gut 33:368–371
13. O'Donohue J, Oien KA, Donaldson P, Underhill J, Clare M, MacSween RN, Mills PR (2000) Co-amoxiclav jaundice: clinical and histological features and HLA class II association. Gut 47:717–720
14. De Abajo FJ, Montero D, Madruga M, García LA (2004) Acute and clinically relevant drug-induced liver injury: a population based case–control study. Br J Clin Pharmacol 58:71–80
15. Thomson JA, Fairley CK, Ugoni AM, Forbes AB, Purcell PM, Desmond PV et al (1995) Risk factors for the development of amoxcycillin–clavulanic acid associated jaundice. Med J Aust 162:638–640
16. Lee W (2003) Drug-induced hepatotoxicity. N Eng J Med 349:474–485
17. Luxon BA (2008) Diagnosis and treatment of autoimmune hepatitis. Gastroenterol Clin North Am 37:461–478