Case report

Cholestatic hepatitis associated with amoxycillin – clavulanic acid combination. A case report

D. Dandakis[1], C. Petrogiannopoulos[1], G. Hartzoulakis[1], C. Flevaris[1], D. Lagoutari[1], G. Drakogiorgos[1], A. Zaharof[1] and K.Barbati[2]

SUMMARY

Several cases have been reported with amoxycillin – clavulanic acid induced hepatic illness. Most of them had cholestatic hepatitis but there were also cases with hepatocellular or mixed type. We report a case of cholestatic hepatitis in a 73-year-old woman with sinusitis who took this drug combination for 12-days and developed cholestatic hepatitis about 60 days later. This case is unusual because the patient was a woman with no other health problems and there was a long period before the onset of the symptoms. We also make a review in the literature.

Key words: Cholestatic hepatitis, Augmentin, Amoxicillin, pharmaceutical jaundice.

INTRODUCTION

Drug induced hepatotoxicity is a major cause of iatrogenic diseases. More than 900 compounds including herbal medicines are involved and can produce the full spectrum of liver injuries.

Numerous case reports and case series have been published[1-19]. Most of them involve acute cholestatic hepatitis, some acute hepatocellular and some mixed pattern hepatitis[6-8].

Risk factors for liver injury from this drug combination include age>55 years[2,7,8,12], male gender[7,8], serious medical illness, alcohol intake, repeated courses of amoxycillin – clavulanic acid combination therapy and combination of consumption with other hepatotoxic drugs. The prognosis seems to be good. Only one patient died[9].

[1]2nd Department of Internal Medicine and [2]Department of Pathology, Hellenic Red Cross Hospital, Athens, Greece

CASE REPORT

A 73-year-old woman received a 12-day course of amoxicillin–clavulanic acid combination for acute sinusitis. About 9 weeks later she presented with anorexia, jaundice, pruritus, and pale-coloured stools. She had no history of exposure to any potential hepatotoxic drug or infection and no use of alcohol. There was no past history of liver disease.

Physical examination revealed icterus, a mild hepatomegaly, no splenomegaly or stigmata of chronic liver disease.

Results of initial laboratory evaluation showed markedly elevated serum bilirubin levels, elevated liver enzymes and alkaline phosphatase. (The results are documented in the Table 1).

All other biochemical and haematological exams were normal.

Results of tests for hepatitis viruses (HAV, HBV, HCV, HIV, EBV, CMV, Echo, Coxsackie), autoimmune diseases (AMA, ANA, SMA, Anti-DNA, ANCA), metabolic diseases and hepatic toxins were unremarkable.

Ultrasonography, CT of the abdomen, and MRCP were normal.

Liver biopsy showed centrilobular cholestasis and chronic portal inflammation, extended at ducts epithelium. There were a few eoshinophils and neutrophils. There were no granulomas or elements of malignancy. The findings suggested pharmaceutical cholestasis.

The patient was discharged 20 days later with good improvement of the clinical and laboratory picture. Now, one and a half years later, she is healthy, in good condition and with normal liver function tests.

DISCUSSION

Since 1988, that first reported hepatitis due to the amoxycillin – clavulanic acid combination, several cases have been reported. Amoxycillin very rarely causes liver disturbances[1-3]. It was suggested that clavulanic acid or the combination with amoxycillin could be responsible for this adverse reaction[4]. In some cases the causal relationship was confirmed by a recurrence of hepatic injury after readministration of the drug even four years after the first episode[5].

Hepatic reactions have been mainly cholestatic but there are also some cases with hepatocellular or mixed cholestatic-hepatocellular hepatitis[6-8]. The onset of the symptoms appear at the end of the therapy[8] to 7 weeks after[7]. The prognosis seems to be good[8]. Only one patient died due to Augmentin – induced cholestatic hepatitis[9] and one patient developed chronic liver disease with persistence abnormal liver function tests[10]. The course of the disease was characterized by complete recovery within 4 to 16 weeks[8] .

The estimated rate for acute liver injury from amoxycillin – clavulanic acid combination is much higher than that for amoxycillin alone (1,7 vs 0,3 per 10.000 prescriptions).

The administration of this combination is associated with a moderate and asymptomatic increase in serum aminotransferase activity in 23%[11].

The risk of liver injury is greater in men (men/female qender ratio was 4:1 in one study[8] and 2:1 in others[7]). It is suggested that this might reflect some sexual influence in amoxycillin – clavulanic acid hepatotoxicity[8]. Older people seems to be affected more frequently,[2,7,8,12] but there are case reports of a 23-year-old man with an acute hepatocellular injury by amoxicillin–clavulanic acid combination[1,3], of a 4-year-old boy with spherocytosis[5] and a 3-year-old boy who had uncontrollable pruritus, failure to grow and extensive xanthomatosis, and on a liver transplantation was successfully performed 8 months after the onset of his symptoms[14]. Duration of treatment is another important risk factor[2,8,12]. Liver biopsies were performed on the majority of the patients but not on all. Most of them had centrilobular or panlobular cholestasis. There was portal inflammation in many cases[7,8]. One patient had granulomatous hepatitis[8].

Table 1. Liver function tests of the patient during her hospitalisation

	1st day of admission	10th day of admission	20th day of admission (discharge)
Bilirubin (mg/dl)	5,9	12,2	6,1
Direct Bilirubin	3,8	7,4	3,2
Indirect Bilirubin	2,1	4,8	2,9
AST (u/l)	87	170	62
ALT (u/l)	210	154	77
ALP (u/l)	268	228	55
GGT (u/l)	382	285	89
5'-N (u/l)	18		11
LDH (u/l)	410	315	345

The mechanism of hepatitis by amoxicillin – clavulanic acid combination requires further study. The frequent association with hypersensitivity manifestations such as skin rash, hypereosinophilia, antitissue antibodies suggest an immunoallergic mechanism[5,8,12,15-17]. Others believe that the reaction could be labelied as an idiosyncratic response to the drug[2,7] or more uncommonly to specific autoantibodies (anti-mitochondrial type 6, anti-LKM2, anti-LM antibodies)[6].

Apart from the symptomatic treatment with Cholestyramine, ursodeoxycholic acid (UDCA) was administrated to some patients[18,19]. UDCA probably did not influence the prognosis. It improved hepatic biochemical parameters and especially pruritus, malaise and fatigue.

This case is unusual in that this patient was female (ratio men to women is 4:1), she had no comorbid illness, there was no other apparent explanation for this disease and the onset of the symptoms appeared two months after stopping the drug.

In conclusion, the amoxicillin–clavulanic acid combination may cause hepatitis (mainly cholestatic) especially in elderly men who are receiving long-term therapy. The mechanism is not clear yet but it is suggested to be an immunoallergic or an idiosyncratic reaction. The clinical course is benign with good prognosis and the symptoms could appear a long time after the discontinuation of the drug.

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