

# Hepatitis associated with amoxicillin-clavulanic acid combination report of 15 cases

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## Abstract

Fifteen cases of hepatitis related to a combination of amoxicillin and clavulanic acid are reported. Most patients were aged 60 years or more and there were more men than women (sex ratio 4:1). The amoxicillin-clavulanic acid had been given at doses ranging from 0.5 to 6 g/day (mean 2 g/day) for seven to 60 days (mean 18 days). In 11 cases, the first symptoms appeared one to four weeks after stopping treatment. Jaundice was observed in all patients and was frequently associated with pruritus. Serum aminotransferase activities were increased in all patients and were generally two to 10 times the upper limit of normal. Serum alkaline phosphatase activity was considerably increased, from two to seven times the upper limit of normal. Histological examination of the liver, performed in seven patients, showed centri- or panlobular cholestasis in all cases, associated with granulomatous hepatitis in one. The prognosis of amoxicillin-clavulanic acid induced hepatitis seemed to be good. None of the patients exhibited biological or clinical features of hepatic failure and the course of the disease was characterised by the resolution of jaundice within one to eight weeks and a complete recovery within four to 16 weeks. Taking into account the number of treated subjects and reported cases, we estimated the risk of developing hepatitis with this drug combination to be very low, probably below 1/100 000. Our data suggest that the risk of hepatotoxicity may be increased in elderly men given lengthy treatment. The association of hepatitis and signs of hypersensitivity may suggest an immunoallergic mechanism of hepatotoxicity in some patients.

Amoxicillin, a semisynthetic penicillin, has been combined with clavulanic acid, an inhibitor of bacterial  $\beta$ -lactamases, to decrease antimicrobial resistance. This combination, first marketed in France in 1984, is one of the most prescribed antibiotics worldwide.<sup>1,2</sup> In France, in each oral brand, the ratio of amoxicillin to clavulanic acid (w/w) is 4/1. The administration of amoxicillin-clavulanic acid is associated with a moderate and asymptomatic increase in serum aminotransferase activity in 23% of subjects.<sup>3</sup> Since 1989, 32 cases of acute hepatitis have been described.<sup>4,12</sup> In addition, the Australian Adverse Drug Reactions Advisory Committee recently noted (without individual details) the receipt of 30 reports of hepatic dysfunction after amoxicillin-clavulanic acid administration.<sup>13</sup> In most cases, hepatitis related to amoxicillin-clavulanic acid exhibited cholestatic patterns; hepatocellular or

mixed cholestatic and hepatocellular patterns have been described less frequently.<sup>4-13</sup>

These data prompted a study which aimed to assess amoxicillin-clavulanic acid hepatotoxicity in France, on the basis of cases observed in several hospital liver units or spontaneously reported to the regional centres of the French System of Drug Surveillance (Pharmacovigilance centres)<sup>14</sup> and to the manufacturer, Beecham Laboratories.

In this report, we describe 15 cases compiled during this collaborative study, including one case recently published<sup>11</sup> and one case accepted for publication as a letter.<sup>15</sup> Our data confirm that amoxicillin-clavulanic acid generally causes acute cholestatic hepatitis and show that this drug combination may also occasionally induce granulomatous hepatitis. In addition, this study shows that the risk of hepatotoxicity is low and is mainly associated with elderly men receiving lengthy treatment.

## Methods

Forty patients with hepatitis possibly related to amoxicillin-clavulanic acid administration were seen in several liver units or were reported to regional centres of the national drug surveillance network and Beecham Laboratories, France between January 1987 and June 1990. In all cases, clinical, biological, and pathological data were carefully reviewed.

In 25 cases the available data were considered to be insufficient to exclude other causes of hepatitis. In the remaining 15 patients (see Tables I and II), hepatitis was ascribed to amoxicillin-clavulanic acid administration on the following grounds. These patients had no history of liver or biliary tract disease or of drug addiction, transfusion of blood products, or surgery within the six months preceding the onset of hepatitis. Only one patient (case 9) was an abuser of alcohol. In all patients, IgM antibodies to hepatitis A virus and hepatitis B surface antigen were absent in serum. Serological tests for hepatitis C virus infection were negative in the six patients tested (patients 1, 2, 5, 7, 8, 11). Serological tests for recent infection with cytomegalovirus in nine cases (patients 1-8, 11), herpes simplex viruses in three patients (patients 1, 2, 8), and Epstein-Barr virus in six patients (patients 1, 2, 5, 7, 8, 11) were also negative in all patients tested. Ultrasonography of the liver and biliary tract was normal in all cases. Computed tomography of the liver and biliary tract, undertaken in five patients (patients 6, 9, 10, 11, 15) was normal, as was endoscopic retrograde cholangiography performed in eight patients (patients 1, 3, 4, 5, 6, 7, 11, 13). In all patients, there was a clear chronological relation between

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TABLE I Age, sex, and drug administration in 15 patients with amoxicillin-clavulanic acid induced hepatitis

Patient no	Sex/age (years)	Amoxicillin-clavulanic acid administration				Interval from onset of treatment to onset of hepatitis (days)	Interval from stopping treatment to onset of hepatitis (days)	Indication	Other administered drugs	Previous administration of amoxicillin
		Dosage (g/day)	Duration of treatment (days)	Total dose (g)						
1	M/48	0.5-0.75	21	13	29	8	Bronchitis asthma	Theophylline, terbutaline, salbutamol	Yes	
2	F/52	3.0	15	45	45	30	Upper respiratory tract infection	Ketoprofen, metronidazole, netromycin, ranitidine, bethamethasone	No	
3	M/50	1.0	7	7	7	0	Sinusitis	Hydroxyzine, carbocystein, framycetin	No	
4	M/73	6.0	24	144	42	17	Endocarditis	Netromycin, clonidine, furosemide, digoxine, lorazepam, clobazepam	No	
5	M/57	1.5	17	25.5	35	18	Bronchitis asthma	Prednisolone, salbutamol, theophylline, beclomethasone, sodium nedocromil, ipratropium bromide	No	
6	M/82	2.0-3.0	15	34	38	23	Bronchitis	Furosemide	No	
7	M/79	1.5	15	22.5	35	20	Urinary tract infection	Heptaminol, raubasine-dihydroergocristine	No	
8	M/50	1.5	12	18	13	1	Upper respiratory tract infection	Roxithromycin	Yes	
9	M/75	1.0-2.0	10	30	38	18	Ocular infection	Diclofenac, sucralfate, levodopa	No	
10	M/82	1.5-2.0	60	100	89	29	Bronchitis	Prednisolone, roxithromycin	Yes	
11	M/62	3.0	14	42	21	8	Unknown	Ketoprofen, paracetamol, enoxaparine	No	
12	M/67	2.0	10	20	22	12	Pneumonia	Diltiazem, pindolol, prednisolone, theophylline, acetylcystein	No	
13	M/81	2.0-3.0	33	71	33	0	Pneumonia	Digoxine, trinitrine, indapamine, nicardipine, ticlopidine, lisinopril	No	
14	F/63	1.5	7	10.5	29	3	Otitis	Niflumic acid	Yes	
15	M/39	Unknown	10	Unknown	28	20	Upper respiratory tract infection	Prednisolone, amphotericine B, nitrazepam, serrapeptase	Yes	

amoxicillin-clavulanic acid administration and the onset of hepatitis, as well as between withdrawal of the treatment and the resolution of liver dysfunction. The direct involvement of other drugs in the hepatitis could be eliminated on the basis of clinical or chronological data.

### Results

Age, sex, and drug administration as well as clinical, biological, and histological manifestations observed in our 15 cases are summarised in Tables I and II.

The ages of the patients with hepatitis ranged from 39 to 82 years (mean 64 years), and there were more men than women (12 *v* 3 cases; sex ratio 4:1). The amoxicillin-clavulanic acid had been given at doses ranging from 0.5 to 6 g/day (0.5-3 g orally; 2-6 g iv) (mean 2 g/day) with a duration of administration ranging from seven to 60 days (mean 18 days). The cumulative dose varied widely, between 7 and 144 g (mean 42 g). Hepatitis occurred seven to 89 days (mean 33 days) after starting the treatment. In 11 patients, amoxicillin-clavulanic acid had already been stopped for one to four weeks when the first symptoms of hepatitis were observed. In most cases, amoxicillin-clavulanic acid was given for mild or moderately severe infection of the upper respiratory tract or for moderate bronchitis. Only three patients were receiving treatment for severe infections: endocarditis, bronchitis, and pneumonia. Five patients had previously received amoxicillin alone, without adverse effect.

All patients had jaundice, which was intense (serum bilirubin > 100 µmol/l) in 12. It was associated with pruritus in 12, asthenia in seven, and with vomiting, nausea, hepatomegaly, and skin rash in one case each.

Serum alanine and aspartate aminotransferase activities were increased in all patients - they

ranged from two to 10 times the upper limit of normal in 11 cases, and were 10 to 20 times the upper limit of normal in four. Serum alkaline phosphatase activity was appreciably increased, with values ranging from two to seven times the upper limit or normal. Similarly, serum  $\gamma$ -glutamyl transpeptidase activity exceeded 10 times the upper limit of normal in eight of the 12 patients tested. The 15 patients did not exhibit any clinical or biological features of hepatic failure (data not shown in the two Tables). Hepatitis was associated with blood hyper-eosinophilia (eosinophils > 400/mm<sup>3</sup>) in five patients. Results of tests for serum antitissue antibodies were available in 10 patients. Positive results with low or moderate titres (< 1/100) were found for antinuclear antibodies in three, for antismooth muscle antibodies in one, and for antimitochondrial antibodies in one case.

A liver biopsy was performed in seven patients and histological examination showed centrilobular or panlobular cholestasis in all. It was associated with granulomatous hepatitis in one patient. The course of the hepatitis was generally characterised by prompt improvement of liver dysfunction. The long term outcome of hepatitis could be assessed in nine patients. In these cases, jaundice resolved within one to eight weeks and liver tests returned to normal within four to 16 weeks.

Amoxicillin or mezlocillin, another  $\beta$ -lactam closely related to amoxicillin, was given to three patients after hepatitis. In one patient (case 1), amoxicillin was administered for three weeks after complete recovery without relapse of hepatitis. In the two other patients (patients 4 and 7), amoxicillin or mezlocillin was given while jaundice was still present and was associated with inconclusive fluctuation in liver test abnormalities. In collaboration with Beecham Laboratories, we tried to estimate the prevalence of amoxicillin-clavulanic acid hepatotoxicity

TABLE II Clinical, biological, and histological manifestations in 15 patients with amoxicillin-clavulanic acid induced hepatitis

Patient no	Clinical manifestations	Serum bilirubin ( $\mu\text{mol/l}$ )	ALT ( $\times$ upper limit of normal)	AST	Alk Pho	GGT	Hypereosinophilia*	Serum antitissue antibodies	Histological lesions	Course of the disease	
										Duration of jaundice (weeks)	Duration of liver test abnormalities (weeks)
1	Jaundice, pruritus, vomiting	230	10	6	2	15	+	Anti-SM: 1/50e Anti-Nu - Anti-Mit - Anti-LKM -	Centrilobular cholestasis	8	12
2	Jaundice, pruritus, skin rash, asthenia	152	4	1	3	9	-	Anti-Nu: 1/100e Anti-SM - Anti-Mit - Anti-LKM -	Centrilobular cholestasis	Unknown	Unknown
3	Jaundice, pruritus	243	3	2	2,5	1,5	-	Anti-Nu - Anti-SM - Anti-Mit -	Cholestasis	8	Unknown
4	Jaundice, pruritus, asthenia	308	2	2	2	6	+	Anti-Nu: 1/160e Anti-SM: 1/40e Anti-Mit: 1/40e	Cholestasis	8	>12 <52
5	Jaundice, pruritus, asthenia	280	18	10	6,5	29	-	Anti-Nu - Anti-SM - Anti-Mit - Anti-LKM -	Panlobular cholestasis	2	8
6	Jaundice, pruritus, asthenia, hepatomegaly	317	2	2,5	2,0	ND	-	Anti-Mit -	Cholestasis	>4	<16
7	Jaundice	800	15	11	9	13	+	Anti-Nu - Anti-SM - Anti-Mit - Anti-LKM -	Cholestasis Granulomatous hepatitis	3	10
8	Jaundice, pruritus	77	5,5	3	3,5	4,5	-	ND	ND	4	8
9	Jaundice, pruritus	202	9	8	7	19	-	Anti-Nu - Anti-SM - Anti-Mit -	ND	3	5
10	Jaundice, pruritus	279	3	1,5	7	11	-	Anti-Nu - Anti-SM - Anti-Mit -	ND	8	>12
11	Jaundice, pruritus	438	2,5	14	2,5	13	+	Anti-Mit -	ND	8	>8
12	Jaundice	71	10	8	2	26	-	ND	ND	1	4
13	Jaundice	161	11	5	5	25	-	ND	ND	3	>6
14	Jaundice, pruritus, asthenia, nausea	57	4	2	5	ND	+	ND	ND	Unknown	<16
15	Jaundice, pruritus	156	6	3	4	ND	ND	ND	ND	3	2

ALT=serum alanine aminotransferase; AST=serum aspartate aminotransferase; Alk Pho=serum alkaline phosphatase; GGT=serum  $\gamma$  glutamyl transpeptidase; \*Blood eosinophils >400/mm<sup>3</sup>; Anti-SM=anti-smooth muscle antibodies; anti-Nu=anti-nuclear antibodies; anti-Mit=anti-mitochondrial antibodies; anti-LKM=anti liver/kidney microsome antibodies; +: present; -: absent; ND: not done

and to assess possible factors contributing to this adverse reaction.

Taking into account the number of cases of hepatitis ascribed to the amoxicillin-clavulanic combination, either reported<sup>4-13</sup> or collected in this study, and the estimated number of treated patients, the prevalence of symptomatic hepatitis was calculated to range from one to five/1 000 000 treated patients in several European countries including France, United Kingdom, Germany and Belgium. Obviously, these calculated values depend on the reporting rate for drug induced adverse reactions. Nevertheless, these data suggest that the risk of developing amoxicillin-clavulanic acid hepatitis is very low, probably below 1/100 000.

### Discussion

Analysis of our 15 cases confirms previous reports showing that the amoxicillin-clavulanic acid combination may induce acute hepatitis, mainly exhibiting cholestatic features, and, less frequently, acute cytolytic or mixed pattern hepatitis.<sup>4-13</sup> One patient was affected by granulomatous hepatitis. It is noteworthy that there was frequently a delay of one to four weeks between stopping treatment and the onset of hepatitis in our study (Table I). A similar observation could be made by analysing patients reported by Reedy *et al.*<sup>4</sup> Such a feature is uncommon in drug induced liver injuries and makes diagnosis more difficult.<sup>16,17</sup> The prognosis

of amoxicillin-clavulanic acid induced hepatitis seems to be good. Indeed, in our patients, as well as in previously reported cases,<sup>4,10,12</sup> there was no clinical or biological evidence of hepatic failure. Furthermore, after stopping the drug, the course of the disease was characterised by complete recovery within four months (Table II).<sup>4,12</sup>

The mechanism of amoxicillin-clavulanic acid hepatitis is unknown. However, the frequent association of hepatitis with hypersensitivity manifestations (skin rash, hypereosinophilia, presence of serum antitissue autoantibodies) and the low prevalence of liver damage suggest an immunoallergic mechanism (Table II).<sup>4,7,8</sup>

In addition, we identified several factors that may contribute to hepatotoxicity of this drug combination. Firstly, men were much more frequently affected than women (male/female sex ratio, 4:1 in our study). A similar predominance of men was also seen, albeit to a lesser extent (sex ratio 2:1), in other reported cases.<sup>4,10,12</sup> This difference was not related to significantly more frequent prescription of the drug in men: 58% in men *v* 42% in women for subjects of all ages and 50% in men and women older than 65 years (data provided by Beecham Laboratories). Hypothetically, this may reflect some sexual influence in amoxicillin-clavulanic acid hepatotoxicity. Secondly, amoxicillin-clavulanic acid hepatitis seems to be influenced by age - elderly subjects being more frequently affected. Nine of our 15 patients and 15 of the 31 other reported cases,<sup>4,10,12</sup> were 60 years old or

more. In contrast, hepatitis occurs exceptionally in children, only a single case having been reported in patients younger than 18 years.<sup>8</sup> Thirdly, hepatotoxicity may also be time dependent. Indeed, the mean durations of treatment in our 15 patients (18 days) and in the 18 patients reported by Reedy *et al* (14 days),<sup>4</sup> were about twice as long as the usual length of treatment calculated for all patients who have received the drug (8.4 days) (data provided by Beecham Laboratories). In addition, the proportion of subjects who were treated for more than 15 days is 33% in our series and 24% in the other reported cases,<sup>4-10,12</sup> whereas it represents only 1% for all treated patients (data provided by Beecham Laboratories). These findings strongly suggest that prolonged treatment may increase the risk of hepatotoxicity with this drug combination. Several hypotheses may be proposed for this latter feature. Protracted treatment may increase the rate of immunisation against the drug; alternatively, it may be consistent with a mechanism of hepatotoxicity partially related to formation or accumulation, or both, of putative toxic metabolites. These points deserve further investigation.

In amoxicillin-clavulanic acid hepatotoxicity, the relative contribution of each compound or the role of the drug combination is not fully elucidated. The direct involvement of amoxicillin alone is unlikely. As far as we know, there is only one reported case of hepatitis caused by this compound, although it has been widely used for more than 15 years.<sup>18</sup> Five of our patients had previously received amoxicillin alone without ill effect (Table I). Rechallenge with amoxicillin alone performed in three patients (and our first case) was not followed by a recurrence of hepatitis, whereas rechallenge with both compounds in two of these three cases resulted in relapse of liver injury.<sup>8</sup> This latter observation suggests an involvement of clavulanic acid in hepatotoxicity. This view is supported by a previous report that clavulanic acid in association with another  $\beta$ -lactam antibiotic, ticarcillin, may have been responsible for the worsening of pre-existing liver disease.<sup>19</sup> Whether clavulanic acid hepatotoxicity is promoted by amoxicillin is still unknown. The potential contribution of other drugs to amoxicillin-clavulanic acid hepatotoxicity is also unknown.

In conclusion, these data confirm that treatment with amoxicillin-clavulanic acid may lead to acute hepatitis, mainly exhibiting cholestatic

features. Occasionally, granulomatous hepatitis may be observed. A time interval of one to four weeks between stopping the treatment and the first manifestations is frequently present and may hinder diagnosis. Complete recovery occurs within 16 weeks. Hepatotoxicity caused by this drug combination might be mediated by an immunoallergic mechanism in some patients and seems to have a very low frequency. The risk of hepatotoxicity may be increased in elderly men receiving lengthy treatment.

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