

Review

AMOXICILLIN-CLAVULANIC ACID THERAPY MAY BE ASSOCIATED WITH SEVERE SIDE EFFECTS – REVIEW OF THE LITERATURE

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Abstract:

Introduction: There is a growing body of evidence that amoxicillin-clavulanic acid may induce severe adverse effects in patients.

Methods: A medline search of case reports and reviews on amoxicillin-clavulanic acid induced adverse effects was performed. The criteria of a consensus conference on the reporting of drug-induced liver disease were applied.

Results: Amoxicillin-clavulanic acid has been associated with drug-induced cholestatic hepatitis in 208 reported patients. In 153 evaluable patients there were 106 males and 47 females with a mean age of 60 years (1-90). Liver associated co-morbidity and co-medication does not play a major part in the development of disease. In most instances respiratory tract infection and sinusitis were treated by amoxicillin-clavulanic acid with a mean treatment duration of 13.9 days and a reaction time until first onset of jaundice of 25.2 days average. Infection and cholestasis from other reason were ruled out in most patients. Liver injury was classified according to laboratory parameters to be hepatocellular in 35 patients, cholestatic in 24 patients and mixed in 83 patients. Normalization of liver enzymes was observed 11.5 weeks after onset of drug administration (average); three of 153 patients did not survive the adverse event.

Conclusion: Amoxicillin-clavulanic acid which is marketed for treatment of respiratory infections and sinusitis/otitis may in some cases induce severe adverse effects and death in patients of different age, especially if they are on multidrug regimens. In consideration of this fact many authors recommend to reflect carefully, whether amoxicillin-clavulanic acid is necessary in treatment of patients with localized or uncomplicated infections. If amoxicillin-clavulanic acid is prescribed, transaminase, alkaline phosphatase and bilirubin tests should be obtained within the first two weeks and after four to five weeks after beginning of treatment to recognize early enough undesired hepatic side effects.

Key words: Amoxicillin-clavulanic acid; drug-induced liver disorder; antibiotic-induced cholestatic hepatitis; severe adverse effects; respiratory tract infection; sinusitis; otitis; soft tissue infection

INTRODUCTION

It is well-known that therapeutic drugs may be asso-

ciated with side effects, often described as liver damage, manifested clinically as hepatitis or only as abnormal laboratory parameters. Certain drugs are obviously associated with liver cell necrosis, e.g., paracetamol, isoniazid, iproniazid, or halothane. Genetic differences in drug metabolism, e.g., isoniazid and phenytoin, and longterm treatment with methotrexate, chlorpromazine and androgens, are considered to be responsible for hepatotoxicity [1].

It is less known that antibiotics can induce abnormalities of liver function including cholestatic jaundice. Despite regulation for the introduction of new compounds into the market, many side effects are not detected during the phase III studies but during routine clinical use and are then reported in case reports. There is a growing body of evidence that amoxicillin-clavulanic acid, which is a widely used antibiotic, has been associated since marketing of the drug in 1984 with jaundice and biochemical abnormalities. Until 1993 the UK Committee on Safety of Medicines (CSM) has received 138 reports of hepatobiliary disorders (three fatal) with amoxicillin-clavulanic acid. 12% of all suspected adverse reactions reported with amoxicillin-clavulanic acid were in the hepatobiliary system. The reporting rate for hepatic disorders has increased from 1 case per 200000 prescriptions to 1 per 56000 prescriptions in 1991 [2]. The rate of hepatic adverse events associated with the treatment of amoxicillin-clavulanic acid, however, may be higher than suspected due to difficulties in recognizing the causal relationship in cases with long reaction time. The need for standard definitions of adverse drug reactions has been recognized and criteria for assessing the causality of these adverse reactions were outlined in 1990 [3]. The purpose of this study was to evaluate all available case reports on adverse liver reactions using standard criteria for assessing the causality of adverse drug reaction of amoxicillin-clavulanic acid.

MATERIAL AND METHODS

Case reports on side effects of amoxicillin-clavulanic acid were searched in medline. Reviews on antibiotic side effects or on amoxicillin-clavulanic acid were checked for literature cited. Then a questionnaire was constructed according to the guidelines of the Consensus meeting 1990 [3]. Information was collected on age, gender, liver associated comorbidity,

co-medication, indication for treatment with amoxicillin-clavulanic acid, daily dosage of amoxicillin-clavulanic acid and treatment duration. The time from treatment to the development of jaundice, histology and ultrasound examination and laboratory tests (ALT, AST, AP, TB, test for hepatitis, CMV or EBV) were retrieved. Time to normalization of transaminases and alkaline phosphatase, outcome and inadvertent re-challenge of the patient with co-amoxiclav were recorded for evaluation.

If not indicated in the text of the case report, the liver injury was classified according to the guidelines of 1990 for reporting adverse drug reaction. Liver injury is designated hepatocellular when there is an increase over 2N in ALT alone. Each activity is expressed as multiple of N. Liver injury is designated cholestatic when there is an increase of over 2N in AP alone. Liver injury is designated mixed when both ALT (above 2N) and AP are increased. According to the guidelines drug-induced acute hepatocellular, cholestatic or mixed liver injury is suggestive within 5-90 days reaction time from onset of drug administration. After cessation of the drug the course is sug-

gestive if reduction of at least 50% of the excess above the upper limit of normal ALT, AP and/or total bilirubin occurs within 6 months [3].

The data are presented as mean, min and max, standard deviation, and 95% CI. Statistical analysis was performed using the alternate t-test; results are considered significant when $p < 0.05$.

RESULTS

1987 to 2000 208 patients were reported to have amoxicillin-clavulanic acid induced liver injury of whom 153 patients could be evaluated (106 male and 47 female) with a mean age of 60 years (1-90 years range); in 55 patients there were not enough data for evaluation (Table 1). Most of these patients ($n = 46$) were from Belgium, followed by France ($n = 29$), USA ($n = 23$), Spain ($n = 11$), Australia ($n = 9$), United Kingdom ($n = 8$), Netherlands (8), Italy ($n = 7$), Poland ($n = 4$). Chile had two patients ; Saudi-Arabia, Germany, Canada, Republic of China Taiwan, Switzerland and Singapore reported one patient each. More than 50% of the patients are 60 years and older

Table 1. Case reports on side effects of co-amoxiclav treatment, evaluated in this study.

Author	Year	Nation	Number of patients	Author	Year	Nation	Number of patients
Alexander [17]	1991	Belgium	2	Julve [95]	1998	Spain	1
Ballester [75]	1998	Spain	1	Larrey [5]	1992	France	15
Barrio [76]	1998	Spain	2	Limauro [96]	1999	USA	1
Belknap [77]	1993	USA	1	Ma [97]	1997	Canada	1
Benjamin [78]	1999	USA	1	Maggini [33]	1999	Italy	7
Beurton [79]	1999	France	1	Michielsen [15]	1990	Belgium	1
Boucher [80]	1995	France	1	Nathani [39]	1998	USA	1
Bralet [81]	1996	France	5	Pedro-Botet [98]	1996	Spain	1
Bustamente [82]	1997	Spain	1	Pelletier [99]	1990	France	1
Caballeria [83]	1992	Spain	1	Perez Castrillon [100]	1997	Spain	1
Chawla [84]	2000	Chile	1	Permal [101]	1992	France	1
Chopra [85]	1992	Saudi-Arabia	1	Peroux [102]	1992	France	1
Cleau [86]	1990	France	1	Postema [103]	1998	Netherlands	1
Corbalan [87]	2000	Espania	1	Reddy [10]	1989	USA	18
Desgrandchamps [88]	1987	Switzerland	1	Richardet [104]	1999	France	1
Dowsett [13]	1989	UK	1	Rodriguez [105]	1991	Spain	1
Escallier [89]	1990	France	1	Ryley [106]	1995	UK	5
Frieß [90]	1995	Germany	1	Schippers [107]	1998	Netherlands	1
Galindo [91]	1995	Spain	1	Schneider [11]	1989	USA	1
Habior [92]	1994	Poland	2	Silvain [20]	1992	France	1
Hanssens [93]	1994	Belgium	4	Smith [108]	1991	UK	2
Hartleb [94]	1997	Poland	2	Soza [109]	1999	Chile	1
Hautekeete [18]	1995	Belgium	8	Stricker [14]	1989	Netherlands	5
Hautekeete [31]	1999	Belgium	27 (other patients are included in other reports)	Van den Broek [110]	1988	Netherlands	1
Hebbard [19]	1992	Australia	1	Verhamme [12]	1989	Belgium	2
Horsmans [59]	1994	Belgium	1	Watteeuw [111]	1995	Belgium	1
				Wong [16]	1991	Australia	8
				Yang [112]	1995	Taiwan	1
				Yap [113]	1993	Singapore	1

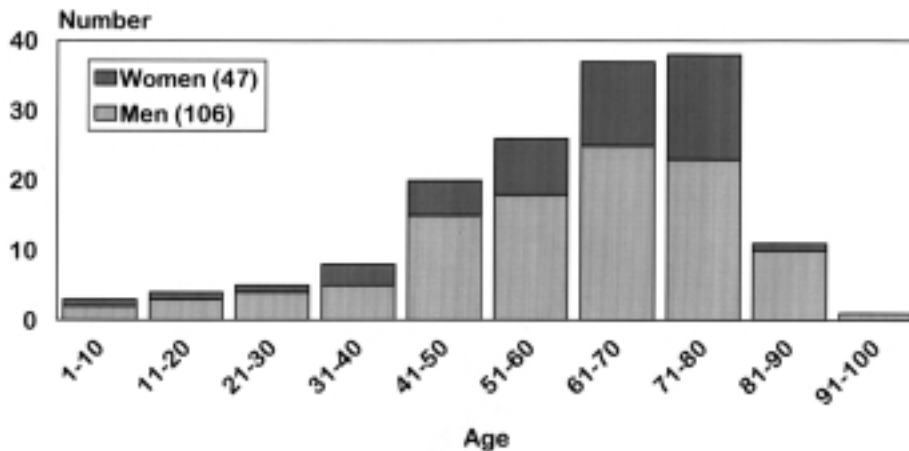


Fig. 1. Age distribution (n = 153) in men and women.

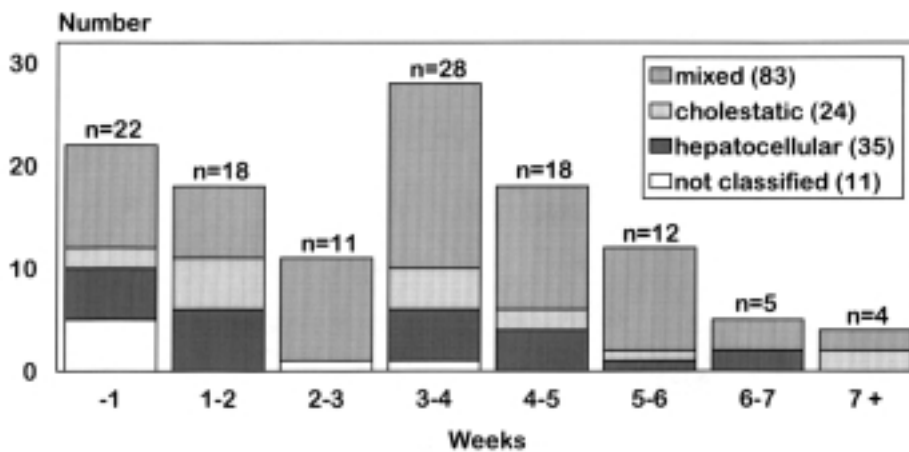


Fig. 2. Time of hepatic injury from onset of amoxicillin-clavulanic acid therapy to jaundice (n = 118).

(Fig. 1).

In 107 patients there was no comorbidity associated with liver, 3 patients were reported to have markers indicating that they had hepatitis in the past. In 43 patients the information on comorbidity was inconclusive.

In 131 patients there was sufficient information available on comedication; in 22 patients there was a lack of information. In a few patients drugs given concomitantly, e.g., cimetidin, danazol, diltiazem, erythromycin, ethinylestradiol, fenoterol, framycetin, indapamid, levodopa, levomepromazin, lisinopril, lorazepam, lovastatin, nifedipin, nitrazepam, nitrendipin, norfloxacin, ofloxacin, ranitidin, roxithromycin, thiamazol and zolpidem, are known to induce a transient increase of liver enzymes. However, in the majority of patients these substances were longterm medication (Table 2).

The indication for co-amoxiclav treatment was in most instances respiratory infection (n = 79) followed by ear-nose and throat infections (n = 32) (Table 3). The daily dosage was 1990 mg on an average (375 mg - 6000 mg). The treatment duration had a range from 1 to 112 days (mean 13.9 days). Symptoms were recognized after 25.2 days average. There seem to be two time peaks from initial treatment to apparent onset of reaction, one at less than one week and a second at three to four weeks, visible. Most cases of cholestatic liver injury occurred until 2-

3 weeks reaction time, whereas the majority of cases with mixed liver injury became obvious after 3-4 weeks (Fig. 2).

Histological examination of liver tissue has been performed in 101 patients. In 41 patients no histological examination was performed and in 12 patients the information is inconclusive. 126 patients had an ultrasound exam of liver and biliary tract system to exclude cholelithiasis as cause of cholestatic icterus, in 12 patients no exam took place, and in 15 patients the information is insufficient.

Liver injury was classified according to the guidelines of the consensus conference (1990) as hepatocellular in 35 patients, cholestatic in 24 patients and mixed in 83 patients. In 11 patients data did not allow classification. Hepatitis serology was negative in 136 patients. In 80 patients tests for CMV or EBV were performed; three of them were positive. Rechallenge with co-amoxiclav was inadvertently done in 14 of 154 patients followed by cholestatic icterus and liver enzyme increase. Normalization of liver enzymes was observed after 11.5 weeks (average) (1 - 108 weeks). Three of 153 patients did not survive the adverse event.

Distribution of age, daily dosage of co-amoxiclav and treatment duration were compared to the average of all countries. Patients in Belgium (66.4 ± 13.1) and France (63.7 ± 4.2) were older than the average patient (60 ± 17.9). The daily dosage of amoxiclav was

Table 2. Concomitant medication with potential liver side effects.

Substance	Possible side effects (rare)	Number of patients obtaining the drug*
Acetaminophen/Paracetamol	Liver cell injury	8
Allopurinol	Hepatitis, reversible increase of liver enzymes, acute cholangitis	1
Amikacin	Small transient increase of ALT, AST, AP	1
Cefaclor	Small transient increase of ALT, AST, AP, cholestatic icterus, hepatitis	1
Cefalexin	Small transient increase of ALT, AST, AP, cholestatic icterus, hepatitis	3
Chloramphenicol	Liver cell injury	1
Chlortalidon	Acute cholecystitis, icterus	1
Cimetidin	Liver cell damage	1
Clonazepam	Small transient increase of liver enzymes	1
Danazol	Liver enzyme increase; cholestatic icterus	1
Diazepam	Small transient increase of liver enzymes	1
Diltiazem	Transient increase of ALT, AST, or AP	1
Erythromycin	Transient increase of ALT, AST, AP or bilirubin	3
Ethinylestradiol	Cholestatic icterus	1
Fenoterol	Transient increase of liver enzymes	1
Framycetin	Transient increase of ALT, AST, AP	2
Gentamicin	Transient increase of ALT, AST, AP	4
Hydrochlorothiazid	Acute cholecystitis in case of cholelithiasis, icterus	1
Indapamid	Transient increase of liver enzymes, hepatitis or posthepatic cirrhosis	1
Indometacin	Increased liver enzymes	1
Ketoprofen	Increased liver enzymes	2
Levodopa	Transient increase of ALT, AST, AP	1
Levopromazin	Cholestasis	1
Lisinopril	Cholestatic icterus, hepatitis	1
Lorazepam	Transient increase of liver enzymes	5
Lovastatin	Transient increase of liver enzymes	1
Nicardipin	Intrahepatic cholestasis, increase of liver enzymes	1
Niflumic acid	Liver enzyme increase	1
Nitrazepam	Transient increase of liver enzymes	1
Nitrendipin	Intrahepatic cholestasis, increase of liver enzymes	1
Norfloxacin	Cholestatic icterus; increase of ALT, AST, AP; hepatitis	1
Ofloxacin	Cholestatic icterus; increase of ALT, AST, AP; hepatitis	1
Promethacin	Cholestasis	2
Ranitidin	Hepatitis, increased liver enzymes	2
Roxithromycin	Liver injury; increased ALT, AST, AP, bilirubin	2
Thiamazol	Liver injury (high dose treatment); hepatitis; transient cholestasis	1
Trimethoprim	Transient increase of liver enzymes, bilirubin	1
Zolpidem	Liver injury (high dose treatment), increase of liver enzymes, especially gamma-GT	1

* Patients may be listed several times when obtaining several drugs of this list

significantly less in Australia, Belgium, and USA when compared to the average patients (1990 ± 1031.3 mg). Treatment duration was shorter in the Netherlands (7.7 ± 3.5 days) and United Kingdom (9.6 ± 5.8 days) when compared to the average pa-

tient (13.9 ± 8.1 days) (Table 4).

DISCUSSION

The liver is a major site of metabolism of drugs and is an important site of adverse drug reactions. These ef-

Table 3. Indication for amoxicillin-clavulanic acid treatment.

Type of infection	Number of patients	%
Respiratory Tract	79	52
Ear-Nose-Throat	32	21
Urinary Tract	12	8
Soft tissue	12	8
Gastrointestinal	4	2.6
Dental	3	1.9
Bone	1	0.5
Biliary	1	0.5
Cardiovascular	1	0.5
Eye	1	0.5
Not indicated	7	4.5

fects can range from mild abnormalities in liver function tests to fulminant hepatic failure and death. Drugs may cause acute hepatocellular hepatitis, e.g., paracetamol, isoniazid, NSAIDs, and antidepressants, or acute cholestasis, e.g., estrogens. Phenothiazines, NSAIDs, macrolides, beta-lactam antibiotics, carbamazepine and gold salts may induce acute cholestatic

hepatitis. Other forms of drug-induced liver injury are acute and chronic cholangitis, chronic and granulomatous hepatitis [4]. Antibiotics which were introduced into the market almost 20 years ago are in general not considered to be hepatotoxic, although there are case reports available that they may induce transient increase of liver enzymes. In case of amoxicillin-clavulanic acid, however, the frequency of antibiotic induced hepatitis can be estimated as between 1/10,000 and 1/100,000 prescriptions [5, 6]. However, in recent reports it has been suggested that the actual risk for jaundice may be even higher than suspected [7].

In May 1996 the Australian Adverse drug reactions bulletin announced that in 314 cases amoxicillin/potassium clavulanate has been associated with drug induced liver disease of which 9 were lethal [8]. From 1982 until 11/2000 1536 reports are on file for this compound in Australia. Of these bilirubinemia accounts for 2 cases. There are 13 cases of hepatic failure, 104 patients with abnormal hepatic function, 2 patients with hepatic necrosis, 83 cases of hepatitis, and 89 cases of cholestatic hepatitis. Hepatocellular damage has been reported in 10 instances, hepatomegaly in 12 patients. Jaundice occurred in 248 patients [9]. The interpretation of the data, however, does not allow the establishment of a firm causality as the data

Table 4. Distribution of age, daily dosage and treatment duration in Australia, Belgium, Spain, France, Netherlands, U.K., USA versus all patients.

Country	Patients (n)	Age (years)#	Daily Dosage (mg)*	Treatment duration (days)*
Australia	9	63.3 ± 14.6	1531.2 ± 468.2 1171.1 - 1890.9 p = 0.0222	29.7 ± 36.9 1.336 - 58.064
Belgium	46	66.4 ± 13.1 p = 0.0092	1569 ± 1195 1213.8 - 1924.2 p = 0.0343	13.3 ± 7.8 10.982 - 15.618
Spain	11	56 ± 24	1875 ± 118.6 1795.3 - 1954.7	10.7 ± 6.7 6.199 - 15.201
France	29	63.7 ± 4.2 p = 0.0253	2250 ± 1132.6 1819.2 - 2680.7	15 ± 11.4 10.665 - 19.335
Netherlands	8	54.6 ± 24.4	2062.5 ± 1091.9 1149.5 - 2975.5	7.5 ± 3.5 4.573 - 10.425 p = 0.0008
U.K.	8	61 ± 15.3	2362.5 ± 1750.1 899.15 - 3825.9	9.6 ± 5.8 4.750 - 14.450 p = 0.0901
USA	23	54.3 ± 17.7	1576.6 ± 834.4 1215.8 - 1937.4 p = 0.0397	13.8 ± 8.1 10.297 - 17.303
All	153	60 ± 17.9	1990 ± 1031.3 1827.1 - 2152.9	13.9 ± 12.7 11.894 - 15.906

* mean ±SD; 95% CI; # mean ±SD

were collected mainly by spontaneous drug surveillance programs. The selection process may be subject to biases. In 1990 in a consensus conference criteria for assessing the causality of adverse drug-induced liver disorders were established. For this study a med-line search of case reports on amoxicillin-clavulanate induced liver disorders was performed. Data from 55 reports were evaluated of which 44 were published after the establishment of standard criteria for reporting drug-induced liver disorder in 1990. In total 208 patients were reported to have amoxicillin-clavulanic acid induced hepatitis, sufficient clinical details were available in 153 patients for evaluation.

CHARACTERISTICS OF HEPATOTOXICITY OF AMOXICILLIN-CLAVULANIC ACID

The hepatotoxicity appears to be more frequent in older men who take a prolonged (mean 13.9 days) course of the drug. Larrey et al. reported a characteristic delay between drug intake and the appearance of jaundice [5]; this delay can range from several days up to 5 weeks which is supported by our findings. The pattern of liver injury is usually cholestatic, although mixed and hepatocellular patterns have been described. Histologic findings include centrilobular cholestasis, portal inflammation, steatosis, hepatocytic necrosis and lobular inflammation. Rarely granulomatous hepatitis is found [10-20]. Co-medication and co-morbidity have been indicated to be risk factors in the development of hepatotoxicity. However, Thomson et al. reported that history of serious medical illness, drug dose, route and duration of therapy, other medications, smoking and previous drug allergies or use of amoxicillin-clavulanic acid were not significantly associated with jaundice. The higher risk of jaundice with increasing age has been confirmed by Thomson et al. [7]. This result that preexisting liver disease as confounding factor in the amoxicillin-clavulanic acid-induced hepatitis may not be relevant is further substantiated by the findings in two studies in which amoxicillin-clavulanic acid was given to cirrhotic patients. No adverse events were observed in these clinical studies [21, 22].

In West of Scotland 19 cases of co-amoxiclav-induced jaundice were identified in the time period from 1992 to 1996 with full clinical details available in 15 patients. Median interval between onset of drug therapy and development of jaundice was 14.5 days (range 6-46 d). Cholestasis resolved after median 93d (range 35-186d) in all but one patient, in whom elevated transaminases persisted for four years. Duration of jaundice correlated with the length of interval between drug exposure and onset of jaundice, but not with age, sex, dose or duration of treatment. The implied frequency in the West of Scotland in 1996 was one case of cholestasis per 22,000 amoxicillin-clavulanic acid prescriptions [23]. These and our findings are supported by another report from the Netherlands. All reports (n = 40) of hepatic injury attributed to amoxicillin-clavulanic acid (causal relationship "possible", "probable" or "certain") received by the Drug Safety Unit in the time from 1982

until August 1996 (28 men and 12 women) with an average age of 61 years were evaluated. The main indication for treatment has been respiratory infection. The latency period between first in-take and onset of symptoms was 3 weeks on an average. The mean duration of hepatic injury was approximately six weeks. The pattern of hepatic injury was mostly cholestatic or mixed hepatocellular-cholestatic [24].

EPIDEMIOLOGY

The epidemiology of drug hepatotoxicity remains poorly documented despite the efforts of Drug Safety Departments. Despite a growing body of evidence in case reports and risk factor analysis amoxicillin-clavulanic acid continues to be one of the most frequently prescribed antibiotics. Not only missing epidemiologic studies but also a wide variability of hepatotoxicity prevalence from one drug to another adds to the difficulty to diagnose amoxicillin-clavulanic acid-induced liver injury. Drugs with a high prevalence (>1%) are quickly eliminated before marketing [4]. But for most drugs the risk of toxicity ranges from 1/1,000 to 1/100,000 which makes it very unlikely to detect toxicity during therapeutic trials done to obtain marketing authorization when most trials include only 1000 - 3000 patients [25]. Amoxicillin-clavulanate up to now has been considered to be a well tolerated antibiotic with nausea, diarrhea and skin rash being the most frequently reported adverse events [26].

RISK FACTORS MODULATING HEPATOTOXICITY

Several acquired and genetic factors may influence the risk of drug hepatotoxicity. Acquired factors are age above 40, female gender, quality of nutrition, pregnancy, chronic alcohol abuse, and drug interactions [27, 28]. Genetic factors listed are deficiency in cytochrome P-450 D6 (CYP 2D6), cytochrome P-450 2C19 (CYP 2C19), deficiency in acetylation capacity, in sulfoxidation, in glutathione synthetase [29]. There is only one study which investigates the genetic factors in the development of amoxicillin-clavulanic acid induced liver disorders. The presence of DRB1*1501 haplotype was associated with amoxicillin-clavulanate-induced hepatitis but not with clinical characteristics, severity of hepatitis, outcome or histological anomalies [30]. With the exception of minor differences in age, dosage and treatment duration, the evaluation of the data did not reveal any significant characteristics which may be inherent to either patients in Europe, North America or Australia.

Men are much more frequently affected by amoxicillin-clavulanic acid induced hepatitis than women (male/female ratio 4:1 in the study of Larrey 1992) [5]. The frequency of prescription according to data provided by Beecham Laboratories, cited in Larrey 1992 was almost equal among men and women: 58% in men and 42% in women (all ages) and 50% in men and women older than 65 years [5].

The occurrence of hepatotoxicity may correlate to the treatment duration. The usual length of treatment calculated for all patients who received the drug was

8.4 days according to Beecham Laboratories [5]. We and others found that patients with co-amoxiclav induced liver disorder were treated for 14 days on an average.

With regard to the time from treatment to the onset of hepatitis we discovered that there may be two time peaks, one with early predominant cholestatic liver injury (1-3 weeks) and another with mixed hepatic injury (3-6 weeks). This observation is supported by the suggestion that metabolic factors may play a greater role in the pathogenesis of hepatocellular liver injury, whereas immunologic factors may be more important in the pathogenesis of cholestatic cases [30].

Amoxicillin-clavulanate is a compound consisting of amoxicillin and clavulanic acid. It is unlikely that amoxicillin is the responsible part for the hepatotoxicity. For more than 15 years there was only one case of hepatitis caused by amoxicillin reported [31]. By several other reports an involvement of clavulanic acid in hepatotoxicity is suggested [32]. The ratio of amoxicillin and clavulanic acid has been different in amoxicillin-clavulanic acid in different countries. The ratio of amoxicillin to clavulanic acid was reported to be in Italy 875/125 mg (7/1) with a usual dosage of one tablet every 12 hours [33]. In other countries a formulation with a ratio of 4/1 or 2/1 are marketed [34]. Further evidence for the pathogenetic role of clavulanic acid for acute hepatic injury came from several reports on reformulation of amoxicillin-clavulanate changing the 4:1 amoxicillin:clavulanate ratio from 4:1 every 8h to 7:1 every 12h to 14:1 [35-37]. It is unclear, however, how clavulanic acid, especially in a reduced ratio, can provide enough anti-beta-lactamase activity capable to enhance the activity of amoxicillin [38]. Re-challenge with amoxicillin-clavulanic acid led to hepatic injury but not when amoxicillin alone was given. In a report by Nathani an inadvertent re-challenge with co-amoxiclav led to a re-induction of cholestatic hepatitis [39]. This observation is supported by similar observations in other antibiotics where the second part of a compound, e.g., estolate salt, may carry the highest risk of toxicity whereas other forms of erythromycin salts are less toxic [40].

HEPATOTOXICITY OF COCOMITANT MEDICATION

Alterations of liver enzymes are frequently observed during antimicrobial treatment. The co-medication of the patients in this study consisted of antibiotics. Ampicillin and amoxicillin seem to have very little hepatotoxicity; however a case of vanishing bile duct syndrome has been described for both [41, 42]. The penicillinase-resistant penicillins oxacillin, dicloxacillin, and flucloxacillin also have a hepatotoxic potential [43-47]. The frequency of hepatotoxicity of flucloxacillin is estimated at between 1/11,000 and 1/30,000 prescriptions [48]. Most cephalosporins have been associated with a mild, transient elevation of serum transaminase activity, but symptomatic liver injury related to cephalosporin use seems exceedingly rare. Very occasionally cholestatic jaundice has been observed after administration of some cephalosporins,

e.g., cefaclor, cephalexin [49-53]. Erythromycin hepatotoxicity has become a classic example of drug-induced hepatitis [54-58]. There may be a common metabolic pathway for both amoxicillin-clavulanic acid and erythromycin ethylsuccinate [59]. Other macrolides can cause similar reactions as erythromycin. Roxithromycin may cause cholestatic or mixed hepatic injury [60, 61]. Mild and mostly transient elevations of liver enzymes have been described during the use of fluoroquinolones. Cholestasis and/or cytotoxicity has been described after administration of ciprofloxacin, ofloxacin and norfloxacin, but cases are poorly documented. Hautekeete has observed a case of cholestatic hepatitis after 5 days of treatment with ciprofloxacin [6]. Several cases of symptomatic hepatic injury have been reported after the use of sulfamethoxazole/trimethoprim [62-67]. However, Nathani (1998) could rule out TMP-SMZ as etiology of hepatitis in view of the uneventful use of this medication on multiple occasions. Hepatic injury in relation with the use of aminoglycosides seems almost absent. Clindamycin causes mild and mostly transient elevation of liver enzymes. The hepatotoxicity of metronidazole is poorly documented; a few cases of cholestasis have been described [43]. Even if we assume that one of these antibiotics may have contributed to the liver injury, the concomitant use of amoxicillin-clavulanic acid in older patients seems to be the leading factor for the development of liver injury. The possibility of ethinylestradiol increased susceptibility to amoxicillin-clavulanate-induced cholestatic hepatitis was suggested by Hebbard et al. (1992) in a case of fatal outcome [19]. Oestrogens are known to cause a non-inflammatory cholestasis and alter the physical properties of liver cell membranes [68-70]. Other compounds, e.g., allopurinol, which are known to cause increase in liver enzymes or liver injury on very rare occasions, were given as co-medication to these patients [71]. In most instances these drugs were given as longterm medication which makes a causal relationship rather unlikely. But even in the case of the potential of hepatotoxicity the combination of these drugs with amoxicillin-clavulanic acid may increase the risk for hepatic injury, especially in older patients, several fold. With regard to the multi-drug prescriptions in older patients the presented data should alert the physician to consider amoxicillin-clavulanic acid as a risk factor for the development of liver failure.

In a review of epidemiologic research on drug-induced acute liver injury Garcia Rodriguez et al. found a group of important hepatotoxic drugs with an associated incidence rate of acute liver injury greater than 100/100,000 users, including chlorpromazine and isoniazid. Agents with greater than 10/100,000 users were amoxicillin-clavulanic acid and cimetidine. Their results provided evidence of relative safety for commonly administered agents such as NSAIDs, amoxicillin, omeprazole, and ranitidine [72]. The risk of hospitalization for acute noninfectious liver injury is different among users of various individual potential hepatotoxic drugs. Concomitant exposure to two or more drugs increases this risk above what would merely be expected from the sum of the individual

risks [73]. It is very likely that most of the patients exposed to treatment with amoxicillin-clavulanate were primed for hepatic injury by concomitant use of amoxicillin-clavulanate with other potential hepatotoxic drugs. However, given the fact, that other antibiotics, e.g., ampicillin-sulbactam, piperacillin-tazobactam, are available to treat respiratory infection or sinusitis which do not contain the risk of inducing hepatotoxicity either alone or in combination with other compounds there is no need to advocate the use of amoxicillin-clavulanate [74]. In case amoxicillin-clavulanate is prescribed, transaminase, alkaline phosphatase and bilirubin tests should be obtained within the first two weeks and after four to five weeks after beginning of treatment to recognize early enough undesired hepatic side effects.

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