Eur J Med Res (2001) 6: 139-149

Review

Amoxicillin-clavulanic Acid Therapy May Be Associated with Severe Side Effects – Review of the Literature

U. Gresser

University of Munich, München, Germany

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 associated 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 suggestive 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				
Chopra [85]	1992	Saudi-Arabia	1	Permal [101]	1992	France	1
Cleau [86]	1990	France	1	Peroux [102]	1992	France	1
Corbalan [87]	2000	Espania	1	Postema [103]	1998	Netherlands	1
Desgrandchamps [88]	1987	Switzerland	1	Reddy [10]	1989	USA	18
Dowsett [13]	1989	UK	1	Richardet [104]	1999	France	1
Escallier [89]	1990	France	1	Rodriguez [105]	1991	Spain	1
Frieß [90]	1995	Germany	1	Ryley [106]	1995	UK	5
Galindo [91]	1995	Spain	1	Schippers [107]	1998	Netherlands	1
Habior [92]	1994	Poland	2	Schneider [11]	1989	USA	1
Hanssens [93]	1994	Belgium	4	Silvain [20]	1992	France	1
Hartleb [94]	1997	Poland	2	Smith [108]	1991	UK	2
Hautekeete [18]	1995	Belgium	8	Soza [109]	1999	Chile	1
Hautekeete [31]	1999	Belgium	27 (other patients are included in other reports)	Stricker [14]	1989	Netherlands	5
				Van den Broek [110]	1988	Netherlands	1
				Verhamme [12]	1989	Belgium	2
				Watteeuw [111]	1995	Belgium	1
				Wong [16]	1991	Australia	8
Hebbard [19]	1992	Australia	1	Yang [112]	1995	Taiwan	1
Horsmans [59]	1994	Belgium	1	Yap [113]	1993	Singapore	1

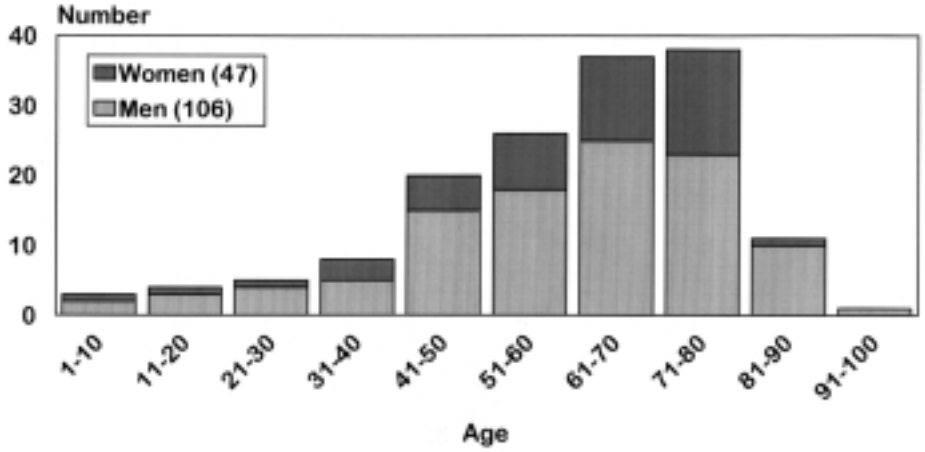

Fig. 1. Age distribution (n = 153) in men and women.

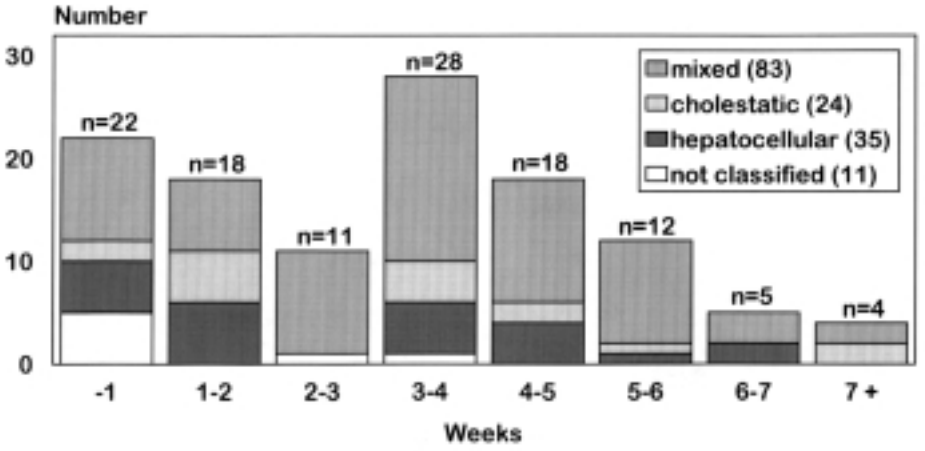

Fig. 2. Time of hepatic injury from onset of amoxicillin-clavulanic acid therapy to jaundice (n = 118).

(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 availabe 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, nicardipin, 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 occured 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 cholestic 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 $\pm$ 13.1) and France (63.7 $\pm$ 4.2) were older than the average patient (60 $\pm$ 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
Niflumin 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

signifiantly 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 patient (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 occured 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 medline 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 establishement 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 availabe 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 centrolobular 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 eleminated 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 hepatoxicity. 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 gluthatione 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 anomalia [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 inherient 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 occurence of hepatotoxocity 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:clavulante 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, di-cloxacillin, 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 cytolysis 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 occassions. 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 occassions, 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 multidrug 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-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.

REFERENCES

1. Rang HP, Dale MM, Ritter JM (1995) Harmful effects of drugs. In: Pharmacology (3rd ed), Churchill Livingstone, Edinburgh London, pp 797-816
2. D'Arcy PF (1993) Drug reactions and interactions. Int Pharm J 7: 140-142
3. Consensus (1990) Criteria of drug-induced liver disorders. J Hepatol 11: 272-276
4. Larrey D (2000) Drug-induced liver diseases. J Hepatol 32 suppl 1: 77-88
5. 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
6. Hautekeete ML (1995) Hepatotoxicity of antibiotics. Acta Gastroenterol Belg 58: 290-296
7. Thomson JA, Fairley CK, Ugoni AM, Forbes AB, Purcell PM, Desmond PV, Smallwood RA, McNeil JJ (1995) Risk factors for the development of amoxcycillin-clavulanic acid associated jaundice. Med J Aust 162: 638-640
8. Australian Adverse Drug Reactions Bulletin Vol 15, No. 2; May 1996 1-4
9. ADRS Report 9
10. Reddy KR, Brillant P, Schiff ER (1989) Amoxycillin-clavulanate potassium-associated cholestasis. Gastroenterology 96: 1135-1141
11. Schneider JE, Kleinman MS, Kupiec JW (1989) Cholestatic hepatitis after therapy with amoxicillin/clavulanate potassium. N Y State J Med 89: 355-356
12. Verhamme M, Ramboer C, Vandebruaene P, Inderadjaja N (1989) Cholestatic hepatitis due to an amoxycillin/clavulanic acid preparation. J Hepatol 9: 260-264
13. Dowsett JF, Gillow T, Heagerty A, Radcliffe M, Toadi R, Isle I, Russel RCG (1989) Amoxycillin/clavulanic acid (Augmentin)-induced intrahepatic cholestasis. Dig Dis Sci 34: 1290-1293
14. Stricker BHCh, Vandenbroek JWG, Keuning J, Eberhardt W, Houben HGJ, Johnson M, Blok APR (1989) Cholestatic hepatitis due to antibacterial combination of amoxycillin and clavulanic acid (Augmentin). Dig Dis Sci 34: 1576-1580
15. Michielsen PP, Vanoutryve MJ, Vanmarck EA, Demaeyer MH, Pelckmans PA, Vanmaercke YM (1990) Amoxycillin/clavulanic acid induced cholestasis. J Hepatol 11: 392
16. Wong FS, Ryan J, Dabkowski P, Dudley FJ, Sewell RB, Smallwood RA (1991) Augmentin-induced jaundice. Med J Aust 154: 698-701
17. Alexander P, Roskams T, Vansteenbergen W, Petermans W, desmet V, Yap SH (1991) Intrahepatic cholestasis induced by amoxicillin/clavulanic acid (Augmentin R): a report of two cases. Acta Clin Belg 46: 327-332
18. Hautekeete ML, Brenard R, Horsmans Y, Henrion J, Verbist L, Derue G, Druez P, Omar M, Kockx M, Hubens H, Haber I, Rahier J, Geubel AP (1995) Liver injury related to amoxycillin-clavulanic acid: interlobular bile duct lesions and extrahepatic manifestations. J Hepatol 22: 71-77
19. Hebbard GS, Smith KGC, Gibson PR, Bathal PS (1992) Augmentin-induced jaundice with a fatal outcome. Med J Aust 156: 285-286
20. Silvain C, Fort E, Levillain P, Labat-Labourdette J, Beauchant M (1992) Granulomatous hepatitis due to combination of amoxycillin and clavulanic acid. Dig Dis Sci 37: 150-152
21. Grange JD, Gouyette A, Gutmann L, Amiot X, Kitzis MD, Islam S, Acar JF, Jaillon P (1989) Pharmacokinetics of amoxycillin/clavulanic acid in serum and ascitic fluid in cirrhotic patients. J Antimicrob Chemother 123: 605-611
22. Ricart E, Soriano G, Novella MT, Ortiz J, Sabat M, Kolle L, Sola-Vera J, Minana J, Dedeu JM, Gomez C, Barrio JL, Guarner C (2000) Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. J hepatol 32: 596-602
23. O'Donohue JW, Oien K, Brown RC, Bramley P, Cochran KM, Crofton RW, Hislop WS, Park R, MacSween RNM, Mills PR (1997) Jaundice associated with Augmentin: the tip of the iceberg? Gut 40 (Suppl 1): W49
24. de Haan F, Stricker BH (1997) Liver damage associated with the combination drug amoxicillin-clavulanic acid. Ned Tijdschr Geneeskd 141: 1298-301
25. Larrey D (1995) Hépatites médicamenteuses: aspects épidémiologiques, cliniques, diagnostiques, et physiopathologiques en 1995. Rev Med Int 16: 752-758
26. Brogden RN, Carmine A, Heel RC, Morley PA, Speight TM, Avery GS (1981) Amoxycillin/clavulanic acid: a review of its antibacterial activity, pharmacokinetics and therapeutic use. Drugs 22: 337-362
27. Farrell GC (1994) Drug-induced liver disease. Churchill Livingstone, London
28. Pessayre D, Larrey D, Biour M (1999) Drug-induced liver injury. In: Bircher J, Benhamou JP, McIntyre N, Rizzeto M, Rodés J (eds) Oxford Textbook of Clinical Hepatology (2nd ed,. Vol 2), Oxford University Press, Oxford, pp 1261-1315
29. Larrey D, Pageaux GP (1997) Genetic predisposition to drug-induced hepatotoxocity. J Hepatol 26: 12-21
30. Hautekeete ML, Horsmans Y, van Waeyenberge C, Demanet C, Henrion J, Verbist L, Brenard R, Sempoux C, Michielsen PP, Yap PSH, Rahier J, Geubel AP (1999) HLA association of amoxicillin-clavulanate-induced hepatitis. Gastroenterology 117: 1181-1186
31. Trevisani F, Panicone L, Bernardi M, Mazzatti M, Gasbarrini G (1988) Beta-lactam antibiotic-induced cholestasis: synergistic of phenobarbitone plus corticosteroid treatment. Ital J Gastroenterol 20: 134-136
32. Van der Auwera P, Legrand JC (1985) Ticarcillin-clavulanic acid therapy in severe infections. Drugs Exp Clin Res Suppl 11: 805-813
33. Maggini M, Raschietti R, Agostinis L, Cattaruzzi C, Troncon MG, Simon G (1999) Use of amoxicillin and amoxicillin-clavulanic acid and hospitalization for acute liver injury. Ann Ist Super Sanita 35: 429-433
34. Todd PA, Benfield P (1990) Amoxicillin/clavulanic

acid. An update of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 39: 264-307
35. Reed MD (1989) The clinical pharmacology of amoxicillin and clavulanic acid. Pediatr Infect Dis J 17: 957-962
36. Severin A, Severina E, Tomasz A (1997) Abnormal physiological properties and altered cell wall composition in Streptococcus pneumoniae grown in the presence of clavulanic acid. Antimicrob Agents Chemother 41: 504-510
37. Seikel K, Shelton S, McCracken GH (1997) Middle ear fluid concentrations of amoxicillin after large dosages in children with acute otitis media. Pediatr Infect Dis J 16: 710-711
38. Dinis PB, Monteiro MC, Martins ML, Silva N, Gomes A (2000) Sinus tissue pharmacokinetics after oral administration of amoxicillin/clavulanate acid. Laryngoscope 110: 1050-1056
39. Nathani MG, Mutchnick MG, Tynes DJ, Ehrinpreis MN (1998) An unusual case of amoxicillin/clavulanic acid-related hepatotoxicity. Am J Gastroenterol 93: 1363-1365
40. Perez Gutthann S, Garcia Rodriguez LA (1993) The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 4: 496-501
41. Cavanzo FJ, Garcia CF, Botero RC (1990) Chronic cholestasis, paucity of bile ducts, red cell aplasia and the Stevens-Johnson syndrome. Gastroenterology 99: 854-856
42. Davies MH, Harrison RF, Elias E, Hubscher SG (1994) Antibiotic-associated acute vanishing bile duct syndrome: a pattern associated with severe, prolonged, intrahepatic cholestatis. J Hepatol 20: 112-116
43. Stricker BHCh (1992) Drug-induced hepatic injury (2nd ed), Elsevier, Amsterdam
44. Onoratu IM, Axelrod JL (1978) Hepatitis from intravenous high-dose oxacillin therapy findings in an adult inpatient population. Ann Int Med 89: 497-500
45. Tauris P, Jorgensen NF, Petersen CM, Albertsen K (1985) prolonged severe cholestasis induced by oxacillin derivatives: a report on two cases. Acta Med Scand 217: 567-569
46. ten Pas A, Quinn EL (1965) Cholestatic hepatitis following the administration of sodium oxacillin. JAMA 191: 674-675
47. Enat R, Pollack S, ben-Arieh Y, Livni E, Barzilai D (1980) Cholestatic jaundice caused by cloxacillin: macrophage inhibition factor test in preventing rechallenge with hepatotoxic drugs. Br Med J 280: 982-983
48. Olsson R, Wiholm BE, Sand C, Zettergren L, Hultcranz R, Myrhed M (1992) Liver damage from flucloxacillin, cloxacillin and dicloxacillin. J Hepatol 15: 154-161
49. Bosio M (1983) Cholestatic jaundice and hematuria due to hypersensitivity to cefaclor in a child. J Toxicol Clin Toxicol 20: 79-84
50. Eggleston SM, Belandres MM (1985) Jaundice associated with cephalosporin therapy. Drug Intell Clin Pharm 19: 553-555
51. Schaefer UW, Hackenberg K, Reinwein D (1975) Cholestatische Hepatitis als ungewöhnliche allergische Reaktion bei Cephalothin-Behandlung. MMW 117: 251-252
52. Ammann R, Neftel K, Hardmeier H, Reinhardt M (1982) Cephalosporin-induced cholestatic jaundice (lett.) Lancet II: 336-337
53. Konikoff F, Alcalay J, Halevy J (1986) Cloxacillin-induced cholestatic jaundice. Am J Gastroenterol 181: 1082-1083
54. Viteri AL, Greene JF, Dyck WP (1979) Erythromycin ethylsuccinate-induced cholestasis. Gastroenterology 75: 1007-1008
55. Inman WH, Rawson NS (1983) Erythromycin estolate and jaundice. Br Med J 286: 1954-1955
56. Zafrani ES, Ishak KG, Rudzki C (1979) Cholestatic and hepatocellular injury associated with erythromycin esters: report of nine cases. Dig Dis Sci 24: 385-396
57. Anonymous (1979) FDA begins proceedings to remove erythromycin estolate from market. FDA Drug Bull 9: 26-27
58. Funck-Brentano C, Pessayre D, Benhamou JP (1983) Hépatites dues à divers dérivés de l'erythromycine. Gastroenterol Clin Biol 17: 362-369
59. Horsmans Y, Geubel AP (1994) Amoxycillin-clavulanic acid-erythromycin cross-liver toxicity: a case report. J Hepatol 21: 911-912
60. Dubois A, Nakache N, Raffanel C, Balmes JL (1989) Hépatite aigué cholestatique après prise de roxithromycine. Gastroenterol Clin Biol 13: 317-318
61. Delcourt A, Lambert M, Brenard R, Geubel A (1990) Reversible liver injury possibly due to roxithromycin therapy. Acta Clin Belg 45: 206
62. Nair SS, Kaplan JM, Levine LH, Geraci K (1980) Trimethoprim-sulfamethoxazole induced intrahepatic cholestasis. Ann Intern Med 92: 511-512
63. Thies PW, Dull WL (1984) Trimethoprim-sulfamethoxazole-induced cholestatic hepatitis: inadvertent rechallenge. Arch Intern Med 144: 1691-1692
64. Munoz SJ, Martinez-Hernandez A, Maddrey WC (1990) Intrahepatic cholestasis and phospholipidosis associated with the use of trimethoprim-sulfamethoxazole. Hepatology 12: 342-347
65. Colucci CF, Cicero ML (1975) Hepatic necrosis and trimethoprim-sulfamethoxazole. J Am Med Assoc 233: 952-953
66. Bröckner J, Boisen E (1978) Fatal multisystem toxicity after cotrimoxazole. Lancet I: 831
67. Ransohoff DF, Jacobs G (1981) Terminal hepatic failure following a small dose of sulfamethoxazole-trimethoprim. Gastroenterology 80: 816-819
68. Ockner RK, Davidson CS (1967) Hepatic effects of oral contraceptives. N Engl J Med 276: 331-334
69. Schreiber AJ, Simon FR (1983) Estrogen-induced cholestasis: clues to pathogenesis and treatment. Hepatology 3: 607-613
70. Konturi M, Sotaniemi E, Ahlqvist J (1972) Liver damage and estrogen therapy of prostatic cancer. Scand J Urol Nephrol 6: 289-294
71. Swank LA, Cheijfec G, Nemchausky BA (1978) Allopurinol-induced granulomatous hepatitis with cholangitis and a sarcoid-like reaction. Arch Intern Med 1138: 997-998
72. Garcia Rodriguez LA, Ruigomez A, Jick H (1997) A review of epidemiologic research on drug-induced acute liver injury using the General Practice Research Database in the United Kingdom. Pharmacotherapy 17(4): 721-728
73. Perez Gutthann S, Garcia Rodriguez LA (1993) The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 4: 496-501
74. Finegold SM (1999) In vitro efficacy of beta-lactam/beta-lactamase inhibitor combinations against bacteria involved in mixed infections. Int J Antimicrob Agents 12 Suppl 1: S9-S14
75. Ballester Fayos J, Rodriguez Gil FJ, Paredes Arquiola JM, Garcia del Castillo G, Anton-Conejero MD, Anon Rodriguez R, Moreno-Osset E (1998) Amoxicillin-clavulanic acid hepatotoxicity. Gastroenterol Hepatol 21:

114-115
76. Barrio J, Castiella A, Lobo C, Indart A, Lopez P, Garcia-Bengoechea M, Cosme A, y Arenas JI (1998) Hepatitis colestasica agda secundaria a amoxicilina-acido clavulanico. Papel del acido ursodesoxicolico en la colestasis inducida por drogas. Rev Esp Enferm Dig 90: 523-526
77. Belknap MK, McClelland KJ (1993) Cholestatic hepatitis associated with amoxicillin-clavulanate. Wis Med J 92: 241-242
78. Benjamin S, Mueller BA (1999) Erythema multiforme secondary to amoxicillin/clavulanic acid exposure. Ann Pharmacother 33: 109-110
79. Beurton I, Germanese JC, Becker MC, Koch S, Carbillet JP, Miguet JP, Bresson-Hadni S (1999) Acute hepatitis and destructive cholangitis probably induced by amoxicillin-clavulanic acid combination. Gastroenterol Clin Biol 23: 1097-1098
80. Boucher E, Kerlirzin A, Turlin B, Brissot P, Deugnier Y (1995) Acute cholangitis caused by an amoxicillin-clavulanic acid combination. Gastroenterol Clin Biol 19: 957-958
81. Bralet MP, Zafrani ES (1996) Hepatitis caused by the amoxicillin-clavulanic acid combination. An example of drug-induced biliary hepatotoxicity. Ann Pathol 116: 425-429
82. Bustamente Balen M, Perez Aguilar F, Rayon Martin M, Garcia Herola A, Berenguer Lapuerta J (1997) Cholestatic hepatitis by amoxycillin-clavulanic acid. Presentation of a new case. Gastroenterol Hepatol 20: 187-189
83. Cabelleria Rovira E, Masso Ubeda RM, Arago Lopez JV, Sanchis Closa A (1992) Hepatitis colestasica por amoxicilina-acido clavulanico. An Med Intern 9: 360-361
84. Chawla A, Kahn E, Yunis EJ, Daum F (2000) Rapidly progressive cholestasis: An unusual reaction to amoxicillin/clavulanic acid therapy in a child. J Pediatr 136: 121-123
85. Chopra S, Al Najjar MJ (1992) Hepatitis associated with Co-amoxiclav (Clavulanate potentiated Amoxycillin) therapy. Saudi Med J 13: 448-450
86. Cleau D, Jobard JM, Alves T, Gury S, Rey B, Vuillemard M, Noirot A, Floriot C, Wagschal G, Vieille J, Daoudal P, Ory JP (1990) Hépatite cholestatique due à l'association amoxicilline-acide clavulanique. Un cas et revue de la littérature. Gastroenterol Clin Biol 14: 1007-1009
87. Corbalan-Vélez R, Péon G, Ara M, Carapeto FJ (2000) Localized toxic follicular pustuloderma. Int J Dermatol 39: 205-217
88. Desgrandchamps D, Schnyder C (1987) Severe neutropenia in prolonged treatment with orally administered Augmentin. Infection 115: 260-261
89. Escallier F, Dalac S, Caillot D, Boulitrop C, Collet E, Lambert D (1990) Erythème polymorphe, aplasie hépatite cholestatique au cours d'un traitement par Augmentin. Rev Med Interne 11: 73-75
90. Frieß G, Wienbeck M (1995) Cholestatic jaundice after taking amoxicillin and clavulanic acid. DMW 1120: 1356-1360
91. Galindo C, Buenestado J, René JM, Pinol MC (1995) Pancreatitis aguda asociada a hepatotoxicidad por amoxicilina-clavulanico. Rev Esp Enf Digst 87: 597-600
92. Habior A, Walewska-Zielecka B, Butruk E (1994) Hepatocellular-cholestatic liver injury due to amoxycillin-clavulanic acid combination. Clin Invest 72: 616-618
93. Hanssens M, Mast A, van Maele V, Pauwels W (1994) Cholestatische icterus door amoxicilline-clavulaanzuur bij 4 patienten. Ned Tijdschr Geneeskd 138: 1481-1483
94. Hartleb M, Bodys H, Januszewski K, Blaszcynska M, Nowak A (1997) Vanishing bile duct syndrome after amoxicillin/clavulanic acid (A/CA) J Hepatol 26(Supp1):160
95. Julve R, Garcia A, Gomez A, Primo J, Moles JR, Hinojosa J (1998) Acute hepatocellular injury induced by amoxicillin-clavulanic acid. Gastroenterol Hepatol 21: 92-94
96. Limauro DL, Chan-Tompkins NH, Carter RW, Brodmerkel GJ, Agrawal RM (1999) Amoxicillin/clavulanate-associated hepatic failure with progression to Stevens-Johnson syndrome. Ann Pharmacother 33: 560-564
97. Ma C, Bayliff CD, Ponich T (1997) Amoxicillin/clavulanic acid-induced hepatotoxicity. Can J Hosp Pharm 50: 90
98. Pedro-Botet J, Supervia A, Barranco C, Sola R, Bruguera M (1996) Intrahepatic cholestasis without hepatitis induced by amoxycillin/clavulanic acid. J Clin Gastroenterol 123: 137-138
99. Pelletier G, Ink O, Fabre M, Hagege H (1990) Hépatite cholestatique probablement due à làssociation d'amoxicilline et d'acide clavulanique. Gastroenterol Clin Biol 14: 601-607
100. Pérez-Castrillon JL, Duenas A, Goyeneche MA, Martin-Escudero JC, Herreros V (1997) Hemorrhagic colitis due to amoxicillin/clavulanate and nasal decongestants? J Clin Gastroenterol 25: 701
101. Permal S, Cadranel JF, Lebrun P, Grimaldi A (1992) Un cas d'hépatite cholestatique secondaire à prise de l'association acide clavulanique-amoxicilline. Ann Med Interne (Paris) 143: 348-349
102. Peroux JL, Peroux E, Jais F, Philit F, Chichmanian RM (1992) Hépatotoxicité de l'Augmentin: responsabilité de l'acide clavulanique? A propos d'un cas. Gastroenterol Clin Biol 16: 102-103
103. Postema RR, Ong GL, Bruining HA (19989 Fever in intensive care: keep medications in mind all times. Ned Tijdschr Geneeskd 142: 2177-2179
104. Richardet JP, Mallat A, Zafrani ES, Blazquez M, Bognel JC, Campillo B (1999) Prolonged cholestasis with ductopenia after administration of amoxicillin/clavulanic acid. Dig Dis Sci 44: 1997-2000
105. Rodriguez M, Sleiman H, Suarez A, Rodrigo L (1991) Hepatitis colestatica por amoxicillina-acido clavulanico. Medicina Clinica 96: 78
106. Ryley NG, Fleming KA, Chapman RWG (1995) Focal destructive cholangiopathy associated with amoxycillin/clavulanic acid (Augmentin). J Hepatol 23: 278-282
107. Schippers EF, de Meijer PHEM, Meinders AE (1998) Klinisch denken en beslissen in de praktijk. Een patient met icterus. Ned Tijdschr Geneeskd 142: 2622-2626
108. Smith PM, Wilton A, Routledge PA (1991) Case report. Jaundice associated with amoxycillin-clavulanate potassium therapy. Eur J Gastroenterol Hepatol 13: 95-96
109. Soza A, Riquelme F, Alvarez M, Duarte I, Glasinovic JC, Arrese M (1999) Hepatotoxicity by amoxicillin/clavulanic acid: case report. Rev Med Chil 127: 1487-191
110. van den Broek JWG, Buennemeyer BLM, Stricker BHCh (1988) Cholestatische hepatitis door de combinatie amoxicilline en clavulaanzuur (Augmentin). Ned Tijdschr Geneeskd 132: 1495-1497
111. Watteeuw G, Vasilevski D, Hautekeete M, Taton G, Lambilliotte JP, Francois E, Adler M (1995) Cholestatic hepatitis and amoxicillin-clavulanic acid combination. Personnel case report and literature review. Rev Med Brux 16: 391-393
112. Yang WG, Chan CY, Lu CL, Tsay SH, Lee SD (1995) Amoxicillin/clavulanic acid associated cholestasis in a

patient with chronic hepatitis B: A case report. Chin Med J (Taipei) 55: 64-68
113. Yap I, Gwee KA, Wee A (1993) Augmentin-induced cholestatic jaundice - A case report. Singapore Med J 34: 464-465

Received: March 5, 2001 / Accepted: March 16, 2001

Address for correspondence:
Prof. Dr.med. Ursula Gresser
University of Munich
c/o Medizinische Poliklinik
Pettenkoferstr. 8a
D-80336 München, Germany
Phone +49 8104/88 78 22
Fax +49 8104/88 78 24
e-mail: info@praxisklinik-sauerlach.de