PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 January 28; 13(4): 628-632
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Evaluation of prognostic markers in severe drug-induced liver disease

Bo Li, Zhi Wang, Jian-Jiang Fang, Ci-Yi Xu,Wei-Xing Chen

Bo Li, Jian-jiang Fang, Department of Emergency, Lihuili Hospital of Ningbo Medical Center, Ningbo 315041, Zhejiang Province, China
Zhi Wang, Department of Pediatrics, Ningbo Women and Children's Hospital, Ningbo 315012, Zhejiang Province, China
Ci-Yi Xu, Department of ICU, Lihuili Hospital of Ningbo Medical Center, Ningbo 315041, Zhejiang Province, China
Wei-Xing Chen, Department of Gastroenterology, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China
Correspondence to: Bo Li, Department of Emergency, Lihuili Hospital of Ningbo Medical Center, Ningbo, 315041, Zhejiang Province, China. libo19810427@163.com
Telephone: +86-574-87018638 Fax: +86-574-87392232
Received: 2006-10-27 Accepted: 2006-11-14

Abstract

AIM: To analyze the outcome of patients with severe drug-induced liver disease (DILD) associated with jaundice classified as hepatocellular, cholestatic or mixed liver injury and to evaluate the validity of Hy's rule and the most important predictors for outcome.

METHODS: The Adverse Drug Reaction Advisory Committee was set up in 1997 in our hospital to identify all suspicions of DILD following a structured prospective report form. Liver damage was divided into hepatocellular, cholestatic, and mixed types according to laboratory and histologic criteria when available. Further evaluation of causality assessment was performed.

RESULTS: From January 1997 to December 2004, 265 patients were diagnosed with DILD, and 140 (52.8%) of them were female. hepatocellular damage was the most common (72.1%), the incidence of death was 9.9% in patients with hepatocellular damage and 9.5% in patients with cholestatic/mixed damage ($P < 0.05$). There was no difference in age of dead and recovered patients. The proportion of females and males was similar in recovered and dead patients, no difference was observed in duration of treatment between the two groups. The serum total bilirubin ($P < 0.001$), direct bilirubin ($P < 0.001$) and aspartate transaminase (AST) ($P = 0.013$) values were higher in dead patients than in recovered patients. Chinese herbal medicine was the most frequently prescribed, accounting for 24.2% of the whole series. However, antitubercular drugs (3.4%) were found to be the primary etiological factor for fetal DILD. Factors associated with the development of fulminant hepatic failure were hepatic encephalopathy (OR = 43.66, 95% CI = 8.47-224.95, $P < 0.0001$), ascite (OR = 28.48, 95% CI = 9.26-87.58, $P < 0.0001$), jaundice (OR = 11.43, 95% CI = 1.52-85.96, $P = 0.003$), alcohol abuse (OR = 3.83, 95% CI = 1.26-11.67, $P = 0.035$) and direct bilirubin (OR = 1.93, 95% CI = 1.25-2.58, $P = 0.012$).

CONCLUSION: Death occurs in 9.8% of patients with DILD. Chinese herbal medicine stands out as the most common drug for DILD. While antitubercular drugs are found to be the primary etiological factor for fetal DILD, hepatic encephalopathy, ascites, jaundice, alcohol abuse and direct bilirubin levels are associated with the death of DILD patients.

Key words: Drug-induced liver disease; Prognosis; Prognostic marker; Mortality

Li B, Wang Z, Fang JJ, Xu CY, Chen WX. Evaluation of prognostic markers in severe drug-induced liver disease. *World J Gastroenterol* 2007; 13(4): 628-632

http://www.wjgnet.com/1007-9327/13/628.asp

INTRODUCTION

Drug-induced liver disease (DILD) is an adverse drug reaction-induced disease. Almost all drugs can elevate liver enzyme level and cause DILD. However, the majority of drugs exhibit low incidences of hepatic adverse reactions. Therefore, DILD is mostly identified only after broad clinical drug application (phase Ⅳ). Well-established causes of DILD include non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antiepileptics, statins, tuberculostatics and herbal medicines[1,2].

High serum aminotransferase (hepatocellular injury) and jaundice levels induced by different drugs have been reported to result in a mortality of 10%-50%[3-5]. These observations have been named "Hy's rule" after Hyman Zimmerman, who first described them. The rule states that if both drug-induced hepatocellular injury and jaundice occur simultaneously without biliary obstruction, a mortality of at least 10% can be expected[3,5,6]. Hy's rule defined as DILD with serum alanine aminotransferase (ALT) levels 3 or more times the upper limit of normal

(ULN) + serum bilirubin levels 2 or more times the ULN level, has been advocated by the US Food and Drug Administration for use in the assessment of hepatotoxicity of newly developed drugs[5,7]. However, this rule has never been scientifically validated. The sensitivity and specificity of clinical jaundice for the outcome in patients with drug-induced hepatocellular (HC) injury are unknown. The most important predictors of outcome in DILD with HC injury have not been analyzed in a large number of patients. Furthermore, information about the prognosis in other forms of DILD (e.g., DILD with cholestatic or mixed damage) is limited.

In our hospital, a systematic monitoring system for DILD has been in use since 1997, with regular causality assessment offering the opportunity to evaluate a large number of patients with DILD. The aim of this study was to analyze the outcome of patients with severe DILD associated with jaundice classified as HC, cholestatic (CS), or mixed liver injury and to evaluate the validity of Hy's rule and the most important predictors for outcome.

MATERIALS AND METHODS

All reports of suspected drug-induced liver injury received by the Adverse Drug Reaction Advisory Committee (ADRAC) in our hospital between 1997 and 2004 have been computerized and are available for legally acceptable users with a password online. Our analysis was restricted to patients with serum bilirubin levels two-fold higher than the ULN level. Furthermore, in patients with HC injury, our analysis was restricted to those patients with ALT levels 3 or more times the ULN level as well as serum bilirubin levels 2 or more times the ULN level.

A total of 301 reports fulfilling these criteria were evaluated using international consensus criteria [RousselUclaf causality assessment method (RUCAM)][8,9] to assess the probability of a causal relationship between drug exposure and liver disease. Causality assessment was performed based on information about the onset time of reaction of the drug, the development of liver tests after cessation of the drug, the presence of risk factors, and known hepatotoxicity of the suspected drug and concomitant drug or drugs[8]. Furthermore, investigations were performed to exclude non-drug causes for the reaction. Thus, abnormal liver tests shortly after the use of a new drug, rapid decline of abnormal liver test values after stopping the drug, and exclusion of other causes gave high scores compatible with the drug as a possible, probable, or highly probable cause of the reaction[8]. If the report did not receive a high enough score to consider a causal relationship with the suspected drug, the reaction did not likely occur in accordance with the criteria or the relationship was excluded. Each author scored approximately one fifth of the cases. We all performed assessment of 100 cases independently and found very low intraobserver variability with no disagreement in the assessment of cases.

Because many patients had been exposed to several drugs at the time when liver injury occurred, it is not always possible to deduce which drug is most likely responsible for it. In such cases, the reaction was judged to bepotentially caused by more than one drug. On the other hand, if there was a close temporal relationship between the liver injury and treatment of patients with only one of many drugs, which was then considered to be the suspected drug.

The computerized reports include all relevant facts from medical records and the results of laboratory investigations. The following information was collected from the reports: duration of exposure, drug(s) suspected to be responsible, age and sex of the patients, duration of treatment, type of liver injury, results of AST and ALT as well as alkaline phosphatase (ALP) and bilirubin tests, nondrug causes, and outcome of the patients (recovery, death or liver transplantation).

The type of liver damage was classified according to the International Consensus Meeting criteria[8,9], using ALT and alkaline phosphatase activity, expressed as a multiple of the upper limit of normality, to determine the ratio (R) of ALT/AP. The type of liver damage was hepatocellular when $R > 5$, cholestatic when $R < 2$, and mixed when $R > 2$ but < 5. The liver tests used for the classification of liver damage were the first blood test available after liver injury.

Statistical analysis

For descriptive purposes, Fisher's exact test was used to test differences in dichotomous variables between groups. Mann-Whitney test was used for continuous variables. Stepwise logistic regression was performed for multivariate purposes to predict death. All tests were two-tailed and conducted at a 5% significance level.

RESULTS

During 1997-2004, ADRAC received 301 reports of suspected DILD. Of which 265 reports of DILD fulfilled the RUCAM criteria for at least a possible relationship. According to the RUCAM criteria, 22 reports (8.3%) had a possible relationship, 183 (69.1%) a probable relationship, and 60 (22.6%) a highly probable relationship. These 265 reports with a possible/probable/highly probable relationship to drug(s) included 191 with HC injury, 51 with CS injury, and 23 with mixed liver injury (Table 1).Table 1 shows the age and sex, duration of treatment, and peak liver test values in patients with different types of DILD.

There were no differences in the age of patients with HC or CS or mixed injury ($P = 0.127$). A higher proportion of females were observed in all different subgroups, in which females accounted for 53%. The total protein was different both in patients with HC and CS injury ($P = 0.003$) and in those with CS and mixed injury ($P = 0.041$).The difference in albumin between patients with HC and CS injury was significant ($P < 0.001$). Total and direct bilirubin levels were higher in patients with CS injury than in those with HC injury ($P = 0.043$ and $P < 0.001$ respectively) and mixed injury ($P < 0.001$ and $P = 0.01$ respectively). Obviously, the ALT, AST and ALP values were different in patients with mixed injury or with HC or CS injury.

Twenty-six (9.8%) of the 265 patients died of liver

Table 1 A age and sex, duration of treatment, and peak liver test values in patients with different types of DILD

	Total	Hepatocelluar	Cholestatic	Mixed
Number	265	191	51	23
Age ($\bar{x} \pm s$)	48.6 ± 13.7	47.8 ± 13.8	52.1 ± 13.0	47.3 ± 14.0
Sex (F/M)	140/125	100/91	27/24	13/10
Duration of	25.9	24.6	31.4	21.7
treatment (d)	(1-121)	(1-120)	(8-121)	(1-47)
Total bilirubin	95.7	67.5	236	105.5
(μmol/L)	(7-701)	(7-701)	(11-615)	(14-630)
Direct bilirubin	49.4	31.8	126.8	47.5
(μmol/L)	(2-461)	(2-338)	(3-461)	(3.3-281)
Total protein (g/L)	66.9 ± 9.4	67.7 ± 9.6	63.3 ± 8.8	68.1 ± 8.0
Albumin (g/L)	38.1 ± 7.3	39.1 ± 6.9	34.9 ± 8.3	36.4 ± 6.2
ALT (U/L)	351.5	313.8	123.4	557
	(13-2652)	(20-2652)	(13-1079)	(92-1600)
AST (U/L)	230.1	282.9	111.8	393
	(18-1925)	(19-1925)	(18-1165)	(48-1553)
ALP (U/L)	141.8	69.6	117.8	318.8
	(51-1165)	(51-370)	(70-1165)	(147-801)
GGT (U/L)	200.7	112.9	254	241
	(16-3102)	(17-788)	(16-3102)	(87-969)

The laboratory parameters are all peak values before treatment.

Table 2 Comparison between died and recovered patients with DILD

	Died	Recoverd	*P*
Age	52 ± 13.8	48 ± 13.7	0.187
Sex (F/M)	13/13	127/112	NS
Duration of treanment (d)	29 (1-79)	25.7 (1-121)	NS
Total bilirubin	333.3 (38-695)	82.7 (7-701)	< 0.001
Direct bilirubin	218.2 (11.5-330)	44.0 (2-461)	< 0.001
ALT	351 (78-1906)	341.8 (13-2652)	0.293
AST	339 (52-1700)	213.8 (18-1925)	0.013
ALP	139.1 (51-561)	144.4 (51-1165)	0.805
GGT	124.8 (44-1483)	203.8 (16-3102)	0.193

The laboratory parameters are all peak values. Results are expressed as mean ± SD or medians.

failure (Table 2).The following drugs were associated with death: antitubercular drugs (n = 9), medicinal herbs (n = 5), immunodepressants (n = 2), antimycotic drugs (n = 2), antiinfection drugs (n = 1), nonsteroidal anti-inflammatory drugs (n = 1), antidepressant drugs (n = 1), antithyroid drugs (n = 1), antigout preparation (n = 1), and other drugs (n = 3). There were no differences in age of the dead and recovered patients. The proportion of females and males was similar in recovered and dead patients, and no difference was observed in duration of treatment between them.

The levels of serum total bilirubin, direct bilirubin and AST were higher in dead patients than in recovered patients, whereas the levels of ALT, ALP and GGT were similar in the two groups.

A comparison between the dead and recovered patients in the HC group revealed no differences in age, sex, duration of treatment, ALT or ALP (Table 3). Total bilirubin and AST levels were higher in deceased patients with HC injury than in those with CS/mixed injury, while total bilirubin levels were significantly higher only in deceased patients (Table 3).

Table 3 Comparison between died and recovered patients with hepatocellular injury or with cholestatic/mixed liver injury

	Hepatocellular injury		Cholestatic/mixed injury	
	Died	Recovered	Died	Recovered
Number	19	172	7	67
Age	51.3 ± 13.4	47.5 ± 13.9	54.0 ± 15.7	50.3 ± 13.2
Sex, F/M (%)	11/8	89/83	2/5	38/29
Duration of	30.8	23.8	22	30
treatment	(1-79)	(1-120)	(13-40)	(1-121)
Total	330.5	67.6	169.6	83.8
bilirubin	(38-695)	(7-701)[b]	(50-630)	(11-615)[b]
ALT	488.5	414.5	230.5	192.5
	(106-2652)	(20-1906)	(78-692)	(13-1600)
AST	392.3	270.8	265.5	143.0
	(99-170)	(19-1925)[a]	(52-1272)	(18-1553)
ALP	133.7	130.1	268	310.1
	(51-370)	(51-266)	(70-561)	(72-1165)

The laboratory parameters are all peak values. Results are expressed as mean ± SD or medians. [a]$P < 0.05$, [b]$P < 0.001$ *vs* the control group.

Table 4 Factors associated with death of the patients with DILD

Independent variables	Coefficient	OR (95% CI)	*P*
HE	2.232	43.66 (8.47-224.95)	< 0.001
Ascite	2.883	28.48 (9.26-87.58)	< 0.001
Jaundice	1.124	11.43 (1.52-85.96)	0.003
Alcohol abuse	1.511	3.83 (1.26-11.67)	0.035
Direct bilirubin	-0.007	1.93 (1.25-2.58)	0.012

CI = confidence interval; OR = odds ratio, HE = hepatic encephalopathy, Constant = -15.37.

Logistic regression analysis showed that hepatic encephalopathy ($P < 0.001$), ascite ($P < 0.001$), jaundice ($P = 0.003$), alcohol abuse ($P = 0.035$) and direct bilirubin ($P = 0.012$) could independently predict death (Table 4).

The drugs associated with DILD are listed in Table 5. The largest number of reports on drug-induced fatal HC injury was related to antitubercular drugs (because only 2 DILDs were associated with antigout drug, we did not calculate the mortality induced by this drug). In this group, 7 out of the 20 patients died (35%).The second most commonly reported drug type associated with mortality was antifungal agents (33.3%). The mortality ranging from 35% of antitubercular drugs to 0% in reports is related to many other drugs. As in CS/mixed injury, the highest number of reports of death is related to immunosuppressive agent (28.6%). The mortality ranges from 0% with most of the drugs to 28.6%. Overall, antitubercular drugs (32.1%) are the primary etiological factor for fetal DILD.

DISCUSSION

Drug-induced hepatotoxicity remains a challenge to modern hepatology. Hepatotoxicity is typically detected when several thousands of patients are exposed to drugs, and regulatory authorities are often compelled to make dicisions based on scanty, fragmentary, and incomplete

Table 5 Patients with hepatocellular, cholestatic or mixed liver injury and their death due to different drugs

	Hepatocellular	Death	Cholestatic/mixed	Death	Total study group	Death
Antituberculous drugs	20	7	8	2	28	9
Immunodepressant	26	0	7	2	33	2
Antineoplastic agent	8	0	6	0	14	0
Antibiotics	17	1	8	0	25	4
Chinese herbal medicine	51	5	13	0	64	5
Antipyretic analgesic	8	1	2	0	10	1
Antidepressant drug	5	0	5	1	10	1
Cardiovascular drugs	10	0	1	0	11	0
Sedative hypnotics	1	0	0	0	1	0
Drugs for peptic ulcer	1	0	0	0	1	0
Antithyroid drugs	12	0	11	1	23	1
Antifungal agent	6	2	2	0	8	2
Hypoglycemic agent	5	0	2	0	7	0
Drugs for prostate	1	0	0	0	1	0
Antigout drug	2	1	0	0	2	1
Others	18	2	9	1	27	3

epidemiologic data. In addition, a major challenge is the ability to identify predisposed subjects before they receive drugs. The susceptibility of individuals to genetic and environmental factors is still poorly understood. In this study, we analyzed cases of toxic liver injury prospectively collected from our hospital during the past 8 years.

Hyman Zimmerman, the pioneer in the field of DILD, observed that combined HC injury (high aminotransferase) and jaundice induced by a drug is associated with the poor prognosis of patients, with a fatality rate of 10%-50% for different drugs involved (Hy's rule)[3-6]. It was reported that a new drug should be stopped in patients if their AST and ALT levels are 3-fold higher than ULN level, and bilirubin levels are 2-fold higher than ULN level[7]. Concomitant jaundice and hepatocellular injury observed in clinical trials of new drugs are considered to cause serious troubles concerning safety in the postmarketing phase, when a much larger number of patients are exposed to drugs[5].

Our analysis is unique because it was performed in a large cohort of patients with severe DILD, giving the opportunity to elucidate the most important predictors for outcome. Adverse drug reactions are significantly underreported. The true incidence of hepatic adverse drug reactions has been recently observed. However, a recent prospective survey of drug-induced liver injury in the general population in France suggests that at most, only 1 out of 16 cases of DILD in France is actually reported[10].

Heptatotoxicity was found in a higher proportion of females (53%) in our study, which is consistent with the reported epidemiologic data[10,11]. No difference was found in age of the deceased and recovered patients in our study. A recent study from Japan reported that there is also no difference in age of decreased and recovered patients with DILD[12]. The levels of serum total bilirubin and AST were higher in deceased patients than in recovered patients, whereas ALT, ALP and GGT levels were similar in the two groups in the current study, suggesting that hepatic encephalopathy, ascites, jaundice, alcohol abuse and direct bilirubin increase the risk of death in patients with DILD.

We found that the main causative drugs were Chinese herbal medicine (24.2%), followed by immunosuppressive agents (12.5%), antituberculous drugs (10.6%), antibiotics (9.4%), antithyroid drugs (8.7%). But antituberculous drugs (32.1%) were the leading cause of fatal DILD.

In summary, Chinese herbal medicine is the most common drug associated with liver injury, and the mortality rate is 9.8% in patients with DILD. Hepatic encephalopathy, ascites, jaundice, alcohol abuse and direct bilirubin are associated with the death of patients with DILD. Our ADRAC has proved to be an effective instrument in detecting cases of idiosyncratic liver disease and delineating a profile of risk factors for severity. Further efforts must be made to prevent hepatic adverse reactions to drugs.

REFERENCES

1 **Pratt DS**, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000; **342**: 1266-1271

2 **Lee WM**. Drug-induced hepatotoxicity. *N Engl J Med* 1995; **333**: 1118-1127

3 **Zimmerman HJ**. Drug-induced liver disease. *Clin Liver Dis* 2000; **4**: 73-96, vi

4 **Black M**, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. *Gastroenterology* 1975; **69**: 289-302

5 **Senior JR**. Regulatory perspectives. In: Kaplowitz N, DeLeve LD, editors. Drug-Induced Liver Disease. New York: Marcel Dekker, 2003: 739-754

6 **Zimmerman HJ**. Drug-induced liver disease. In: Sciff ER, Sorrell MF, Maddrey WC, editors. Sciff"s Diseases of the Liver. 8th ed. Philadelphia:Lippincott-Raven Publishers, 1999: 973-1064

7 **Davidson CS**, Leevy CM, Chamberlayne EC, editors. Guidelines for Detection of Hepatotoxicity Due to Drugs and Chemicals. Fogarthy Conference, 1978. NIH publication no. 79-313. Washington, DC: US Government Printing Office, 1979

8 **Danan G**, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; **46**: 1323-1330

9 **Bénichou C**. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990; **11**: 272-276

10 **Sgro C**, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, Lenoir C, Lemoine A, Hillon P. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology*

2002; **36**: 451-455

11 **Friis H**, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. *J Intern Med* 1992; **232**: 133-138

12 **Ohmori S**, Shiraki K, Inoue H, Okano H, Yamanaka T, Deguchi M, Sakai T, Takase K, Nakano T, Tameda Y. Clinical characteristics and prognostic indicators of drug-induced fulminant hepatic failure. *Hepatogastroenterology* 2003; **50**: 1531-1534

S- Editor Liu Y **L- Editor** Wang XL **E- Editor** Lu W