Presentation of drug-induced liver injury in Singapore

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ABSTRACT

Introduction: Drug-induced liver injury (DILI) is an important clinical problem. However, although traditional Chinese medicines (TCM) are widely consumed in Asia, most cases of TCM-DILI are reported as case reports or case series. We aimed to evaluate the clinical course of DILI at an Asian tertiary liver centre.

Methods: All patients with DILI seen by one hepatologist from July 2003 to June 2004 at a local liver centre were prospectively collected and reviewed.

Results: 29 cases of DILI were seen by the hepatologist over the 12-month period. Median age was 51 (range 18-76) years, 20 (69 percent) were female, and 24 (83 percent) were Chinese. TCM were the commonest group of drugs implicated as 15 (52 percent) of the patients had presumed DILI from TCM, while four (14 percent) were from anti-tuberculosis drugs. 18 (62 percent) presented as hepatitic picture, seven (24 percent) as cholestatic, and four (14 percent) as mixed picture. Extrahepatic manifestations were seen only in ten percent of patients. Three (ten percent) died and one (3 percent) underwent liver transplant for liver failure.

Conclusion: DILI is a common clinical problem with significant mortality. TCM is an important cause of DILI in Asia. Further studies on DILI from TCM or other complementary medicines are needed.

Keywords: drug-induced liver injury, drug toxicity, herbal medicine, liver failure, traditional Chinese medicine

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INTRODUCTION

Drug-induced liver injury (DILI) is an important clinical problem. In two recent prospective population surveys from France and Spain, the incidence of DILI in the general population was estimated to be between 7.4 and 13.9/100,000[1,2] which is almost half as common as hepatitis C (30 per 100,000) in the same region[3]. Excluding acetaminophen overdose, idiopathic DILI constitutes about 13% of acute liver failure in the United States[4]. DILI events occur suddenly, are iatrogenic, and generally affect healthy individuals, and thus are particularly tragic and may even involve the medical-legal aspects.

DILI is a heterogeneous group of disorder and is not well characterised, as most reports were in the form of case reports or case series. Hence, it is difficult to assess the clinical course and outcome of the disease as a whole. In the two recent surveys from Europe, mortality was reported to be 5.9% and 11.9%, respectively, with antibiotics, lipid-lowering drugs, antidepressants, and analgesics being the most common drugs implicated[1,2]. Although these surveys were well-performed, their results may not be applicable in regions outside Europe.

Although herbal medicines are widely consumed both in the United States and many parts of Asia, none of the reported cases of DILI in the French study and only 10% of the cases in the Spanish study were due to herbs[5-8]. This figure is likely to be much higher in the Asian population than in the European population. Consequent to that, the clinical features and outcomes in Asian patients with DILI may be vastly different from those from Europeans. To date, no prospective series on DILI among Asians has been performed, and the clinical significance of herbal medicine-induced liver injuries is uncertain. Hence, in this local pilot study, we aim to review the clinical course of DILI as a disease syndrome among Singaporean patients at a tertiary hospital.

METHODS

All cases of DILI seen by one hepatologist at the Division of Gastroenterology at the National University Hospital, Singapore, have been

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prospectively recorded since July 2003. Cases of DILI seen over a 12-month period from July 2003 to June 2004 were reviewed for this study.

Cases of hepatotoxicity were first ascertained by the clinical judgment of the hepatologist and were then evaluated according to the criteria of the International Consensus Meeting for causality assessment[9,10]. All cases of DILI in this study fulfilled all of the following criteria: an appropriate temporal sequence from administration of the drug to onset of event; an appropriate course of the reaction after cessation of the offending drug; and absence of alternative causes. Re-challenge was not performed. As chronic hepatitis B is prevalent in Singapore and many other parts of Asia, presence of hepatitis B surface antigen (HBsAg) did not exclude diagnosis of DILI, unless it was accompanied by elevated HBV DNA titer and/or appropriate histology[11]. Patients with liver injury caused by overdose of medications above therapeutic level, such as acute hepatitis from overdosing of paracetamol, or steatohepatitis from prolonged treatment of methotrexate, were not included in the study.

The pattern of liver injury was defined according to the criteria of the International Consensus Meeting[9]. Hepatocellular injury was defined by an increase above five-fold the upper limit of the normal (ULN) of alanine aminotransferase (ALT) alone or a serum ALT/alkaline phosphatase (ALP) ratio ≥5. Cholestatic injury was defined as an increase above two-fold the upper limit of the normal range of ALP or a serum ALT/ALP ratio ≤two. Mixed injury was defined as a ratio of serum ALT/ALP between two and five.

For cases of hepatocellular injury, minimal investigations included serological markers of acute hepatitis A, B, and serological markers for hepatitis C. For cases of cholestatic and mixed injuries, minimum investigations included imaging of the biliary tree by either ultrasound or computed tomography of the upper abdomen. Resolution was defined as a drop in either ALT or ALP by more than 50%. Time to resolution was defined as duration from onset of symptoms till resolution. Data were expressed in median (mean±S.E.M., range) unless otherwise stated, and were analysed by Statistical Package for Social Sciences (SPSS) version 10.0 (Chicago, IL, USA).

RESULTS

Over the 12-month period, 29 patients with DILI were seen by one hepatologist. During the same period, the average number of patients seen by the same hepatologist was 215 per month. Hence, DILI accounted for approximately 1.1% of patients attended to by the hepatologist. Mean age of patients was 52 (52±3, 18-76) years, and 20 (69%) were female. 24 patients (83%) were Chinese, four (14%) were Malay, and one (3%) was Indian by ethnicity. None of the patients consumed alcohol regularly.

Clinical features of each of the 29 patients were listed in Table I. 18 (62%) had hepatocellular injury, seven (24%) had cholestatic injury, and four (14%) had mixed injury. 17 patients (59%) were hospitalised for management while the other 12 (41%) were managed as outpatients. Eight (28%) underwent liver biopsy and one had explant liver for histological examination. Three had cholestatic hepatitis, two had pure cholestasis, two had macrosteatohepatitis, one had microsteatohepatitis, and the explant liver showed submassive necrosis with increased eosinophilic infiltration.

24 patients (83%) recovered, one (3%) had on-going cholestasis after two months, three (11%) died, and one (3%) underwent liver transplant for subacute liver failure. Rate of transplant-free survival was 16/18 (89%) in those with hepatocellular injury and 9/11 (82%) among those with cholestatic or mixed injury (p=0.49). Among the extrahepatic manifestations, none had eosinophilia or arthralgia, two (7%) had skin rash and three (10%) had fever.

30 drugs were implicated, as subject no. 11 took both TCM and ketoconazole. TCM was the commonest drug implicated, accounting for 15 (52%) of all study subjects. Anti-tuberculosis drugs, consisting of isoniazid, pyrazinamide, and rifampicin, were the second commonest, accounting for four (14%) cases, followed by all-trans retinoeic acid (ATRA) in two (7%). DILI from other drugs were rare.

Three patients died and one underwent liver transplant. Subject no. 13 was a 72-year-old woman who had non-ST elevation myocardial infarct in September 2003. She was given ticlopidine (Ticlid®) after her myocardial infarct and she became jaundiced in November 2003. Despite stopping ticlopidine immediately, her jaundice worsened gradually and she eventually died of subacute liver failure in February 2004, four months after onset of jaundice.

Subject no. 15 was a 68-year-old man who had lung cancer with pulmonary tuberculosis, developed anti-tuberculosis drug-related liver injury four weeks after taking isoniazid, rifampicin, and pyrazinamide. Although his transaminases improved within one week after stopping the anti-TB drugs,

Table 1. Clinical details and biochemical parameters of 29 patients with drug-induced hepatotoxicity.

Case	Gender/ age (years)	Drug	Presentation	Duration of therapy	Time to onset	Bilirubin (U/L)	ALT (U/L)	ALP	Pattern of hepatitis	Outcome	Time to recover	Comments
1	F/58	Indian herbs	Tea-coloured urine	6 months	6 months	53	486	198	Hepatocellular	Recovered	3 weeks	
2	F/46	TCM	Jaundice	4 days	4 days	44	325	224	Mixed	Recovered	6 weels	
3	M/53	TCM	Jaundice	2 weeks	2 weeks	53	2,389	201	Hepatocellular	Recovered	3 days	Biopsy: cholestatic hepatitis
4	M/40	ATRA	Abnormal LFT	7 weeks	7 weeks	6	1,350	389	Hepatocellular	Recovered	1 week	
5	M/46	Spirulina	Abnormal LFT	10 months	10 months	8	102	319	Cholestatic	Recovered	3 months	
6	F/57	Tamoxifen	Abnormal US	11 months	11 months	7	77	55	Mixed	Recovered	6 months	Biopsy: steatohepatitis
7	F/41	ATRA	Abnormal LFT	5 months	5 months	13	262	101	Mixed	Recovered	6 months	Biopsy: steatohepatitis
8	F/44	Norethis-terone	Jaundice	6 months	6 months	92	54	626	Cholestatic	Recovered	3 months	
9	F/35	Propyl-thiouracil	Jaundice	6 weeks	6 weeks	166	1,764	393	Hepatocellular	Recovered	5 days	Biopsy: cholestatic hepatitis
10	M/74	Anti-TB drugs (I/R/P)	Drowsiness	8 weeks	8 weeks	111	15	258	Cholestatic	Recovered	1 week	
11	F/51	TCM Ketoconazone	Jaundice	2 months	2 months	159	1,090	164	Hepatocellular	Transplanted 4 weeks later		Explant liver: submassive necrosis
12	M/29	Shin-Min	Jaundice	6 months	6 months	160	2,022	143	Hepatocellular	Recovered	2 weeks	
13	F/72	Ticlid(r)	Nausea	8 weeks	8 weeks	91	145	1,577	Cholestatic	Died of liver failure 8 weeks later		
14	F/28	TCM	Jaundice	3 weeks	3 weeks	59	389	229	Mixed	Recovered	3 weeks	Biopsy: cholestasis
15	M/68	Anti-TB drugs (I/R/P)	Abnormal LFT	4 weeks	4 weeks	7	358	195	Mixed	Died of lung cancer 9 weeks later		
16	F/18	Amoxycillin	Erythema multiforme	4 days	4 days	76	3,944	483	Hepatocellular	Recovered	2 days	
17	F/51	Faverin	Abnormal LFT	5 days	5 days	17	1,199	12	Hepatocellular	Recovered	1 week	
18	F/39	TCM	Abdominal pain	6 months	6 months	8	1,113	106	Hepatocellular	Recovered	3 weeks	Biopsy: microvesicular steatosis with lobular hepatitis
19	M/76	TCM	Jaundice	2 weeks	2 weeks	154	192	572	Cholestatic	Recovered	4 weeks	Biopsy: cholestatic hepatitis
20	F/53	TCM	Jaundice	1 year	1 year	79	1,323	244	Hepatocellular	Recovered	2 days	
21	M/53	Anti-TB drugs (I/R/P)	Jaundice	6 weeks	6 weeks	48	683	99	Hepatocellular	Recovered	10 days	
22	F/48	TCM	Jaundice	1 months	1 months	213	1,309	233	Hepatocellular	Died of liver failure 3 weeks later		
23	F/70	Phenytoin valproate	Abnormal LFT	10 weeks	10 weeks	10	97	322	Cholestatic	Recovered	3 weeks	
24	F/75	Lovastatin	Abnormal LFT	8 months	8 months	12	396	182	Hepatocellular	Recovered	4 weeks	
25	M/53	OTC supplements	Jaundice	3 months	3 months	98	29	445	Cholestatic	Ongoing after 2 months		Biopsy: cholestasis
26	F/64	TCM	Abnormal LFT	5 months	5 months	37	592	71	Hepatocellular	Recovered	6 weeks	
27	F/44	TCM	Jaundice	3 months	3 months	58	905	148	Hepatocellular	Recovered	8 weeks	
28	M/58	TCM	Abnormal LFT	2 weeks	2 weeks	12	783	93	Hepatocellular	Recovered	8 weeks	
29	M/48	Anti-TB drugs (I/R/P)	Abnormal LFT	4 weeks	4 weeks	15	285	288	Hepatocellular	Recovered	2 weeks	

ATRA: all-trans retinoeic acid; ALP: alkaline phosphatase; ALT: alanine transferase; F: female; I/R/P: isoniazid, rifampicin, pyrazinamide; LFT: liver functional test; M: male; TB: tuberculosis; TCM: traditional Chinese medicine.

he died of lung cancer nine weeks later. Subject no. 22 was a 48-year-old woman who developed acute hepatitis leading to acute liver failure one month after consuming traditional Chinese medicines. She died of liver failure three weeks after presentation.

One patient developed subacute liver failure requiring liver transplant. Subject no. 11 was a 51-year-old woman who had been taking TCM for two months, and intermittent ketoconazole for skin fungal infection for two months. She developed acute hepatitis, which progressed to subacute liver failure. Liver biopsy done three weeks after admission showed submassive hepatic necrosis with increased infiltration of eosinophils. She eventually underwent living-related right lobe liver transplant six weeks after admission. She remained well seven months post-transplant.

DISCUSSION

Idiopathic DILI is a serious condition, accounting for about 13% of all cases of acute liver failure in the USA. In another recent study from the United Network of Organ Sharing (UNOS) database, 137/2,291 (15%) of patients underwent emergency liver transplant for idiopathic DILI over a 13-year period[12]. Unfortunately, prospective studies on the clinical features and course of DILI are few, and were mainly performed among Caucasians. From our study, DILI is not an uncommon condition in Singapore, averaging more than two cases monthly from one hepatologist, or 1.1% of all cases seen by a hepatologist, and with a significant rate of liver transplant or mortality at 4/29 (14%).

Similar to prior reports and review, our patients with DILI were predominantly female (69%), and had more hepatocellular type of injury (62%) than cholestatic and mixed injury (38%). Similarly, anti-tuberculosis drugs (isoniazid, pyrazinamide, and ethambutol) were the commonest prescribed drugs implicated. Overall, 86% of patients had spontaneous recovery and most recover within two months after cessation of the implicated drugs. However, we noted that extrahepatic manifestations of allergy, such as fever, arthralgia, skin rash, and eosinophilia, were uncommon in our population. Although our small sample size makes it difficult to draw a firm conclusion, the relatively low incidence of extrahepatic manifestations (10%) may suggest that they are rare in Asians. Therefore, further prospective validation of the prevalence of extrahepatic manifestations among Asians with DILI is needed.

Another important finding from this study was that TCM was implicated in 15/29 (52%) of patients in our cohort. As the number of the people in the general population consuming TCM is not known, the rate of DILI by TCM cannot be ascertained. However, our findings did provide anecdotal data to suggest that, contrary to popular belief, use of TCM may be associated with liver toxicity. Although the regulatory authority in Singapore routinely tests TCM for adulterous, active contents, TCM are not subjected to clinical trials and many idiosyncratic reactions may not be discovered until a serious reaction occurs.

Finally, we found that the two most widely-used clinical diagnostic scoring systems, the Council for International Organizations of Medical Sciences (CIOMS) and Clinical Diagnostic Scores (CDS), may not be applicable in Asians[9,13]. Both systems were derived using Caucasians and took into account temporal relationships, exclusion of alternative causes, extrahepatic manifestations, re-challenge, and prior literature reports. Although TCM is the commonest implicated drug for DILI in our cohort, yet pharmacoanalysis is hardly performed in TCM. Many TCM also appear in different forms, different packaging, and may be contaminated with other active ingredients, making it difficult to identify any constituents responsible for the liver injury. We also found that extrahepatic manifestations are uncommon in our patient cohorts. As prior reports on DILI on a particular drug and extrahepatic manifestations are considered important diagnostic criteria in both the CIOMS and CDS systems, most of our patients, who have consumed TCM with no prior report of DILI and without extrahepatic manifestations, would not score well under either diagnostic systems. This discrepancy is associated with medical-legal implications. Further validation studies on both scoring systems in Asians and in patients taking TCM are urgently needed.

We acknowledge weaknesses and limitations of our study. To begin with, our sample size may be too small to make generalised conclusions. Although our cohort of 29 cases is considered a reasonable number, pooling of all cases of DILI seen by all hepatologists in our institution, or surveying all cases of DILI in Singapore through a nation-wide study, would have increased the sample size and added more weight to our conclusion. This pilot study only gathered data from one hepatologist in the institution and hence, reliability and generalisability of the results are limited. Unfortunately, we did not keep a registry of patients with DILI so we were unable to pool all cases of DILI at our institution. Nevertheless,

this pilot study showed that although DILI is an uncommon event, it is associated with significant morbidity and mortality, and TCM is the commonest drug implicated in DILI in Singapore. This warrants further prospective studies in evaluating incidence, aetiology, and clinical characteristics of DILI in Singapore. Lastly, pharmacoanalysis was not performed in any of the TCM that were consumed by our patients. Further studies are currently underway at our institution to identify active and adulterous substances in TCM that could be related to DILI. Eventually, a large-scale nation-wide study collecting data from all major hospitals, primary care physicians, and even TCM practitioners, with pharmacoanalysis to identify adulterous substances, would be needed to confirm our findings.

In conclusion, DILI is a common disorder in Singapore, with a good spontaneous recovery rate of 86%. TCM is implicated in approximately one-half of the cases of DILI. Current diagnostic scoring systems in diagnosing DILI may not be applicable in Asians or patients taking TCM. Further prospective studies on the prevalence and clinical characteristics of DILI, with pharmacoanalyses of the implicated TCM are needed to improve our understanding of DILI.

REFERENCES

1. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002; 36:451-5.
2. Ibanez L, Perez E, Vidal X, Laporte JR; Grup d'Estudi Multicenteric d'Hepatotoxicitat Aguda de Barcelona (GEMHAB). Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol 2002; 37:592-600.
3. Minello A, Boschi F, Harb M, et al. Creation of a viral hepatitis B and C in the Cote-d'Or department. Methodology and initial results. Gastroenterol Clin Biol 1998; 22:766-71.
4. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137:947-54.
5. Flora KD, Rosen HR, Benner KG. The use of naturopathic remedies for chronic liver disease. Am J Gastroenterol 1996; 91:2654-5.
6. Yoshida EM, McLean CA, Cheng ES, et al. Chinese herbal medicine, fulminant hepatitis, and liver transplantation. Am J Gastroenterol 1996; 91:1436-8.
7. Chitturi S, Farrell GC. Herbal hepatotoxicity: an expanding but poorly defined problem. J Gastroenterol Hepatol 2000; 15:1093-99.
8. Schuppan D, Jia JD, Brinkhaus B, Hahn EG. Herbal products for liver diseases: a therapeutic challenge for the new millennium. Hepatology 1999; 30:1099-104.
9. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990; 11:272-6.
10. Aithal GP, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. J Hepatol 2000; 33:949-52.
11. James L, Fong CW, Foong BH, et al. Hepatitis B seroprevalence study 1999. Singapore Med J 2001; 42:420-4.
12. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl 2004; 10:1018-23.
13. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology 1997; 26:664-9.