



Drug- and herb-induced liver injury: A case series from a single center

LIVER

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ABSTRACT

Background/Aims: Drug-induced liver injury (DILI) is common worldwide and has a potentially fatal outcome. It accounts for more than half of the cases of acute liver failure in the United States. Herb-induced liver injury (HILI) is a less documented condition but a growing problem. We present here the clinical characteristics and outcome of patients with drug- and herb-induced liver injury from our center.

Materials and Methods: In this 4-year retrospective study, 82 patients in whom there was a causal or highly probable relationship between herbal medicine or drug use and liver disease are presented.

Results: The mean age of patients was 43.1±14.8 years; sexual distribution was 53 females and 29 males. The major cause of hepatotoxicity was drugs (87.8%), with herbal medicine accounting for 12.2%. The leading causative agents were nonsteroidal anti-inflammatory drugs (NSAIDs) (23.1%), followed by antibiotics (19.5%). The pattern of hepatotoxicity was hepatocellular in 35 patients (42.6%), mixed in 28 (34.1%), and cholestatic in 19 patients (23.1%). *Teucrium polium* (known popularly as felty germander), which is a traditionally used herbal medicine of the Labiatae family in our region, was the most common cause of herb-induced liver injury and responsible in 7 of 10 herbal hepatotoxic cases. Acute liver failure developed in 3 patients (two patients related with flurbiprofen and diclofenac and one patient due to an isoniazid-rifampicin combination).

Conclusion: Antibiotics and NSAIDs were the most common etiologic agents for drug-induced liver injury. Surprisingly, herbs follow these groups of drugs and must be questioned more carefully.

Keywords: Drug, herbal preparation, toxicity, hepatitis

INTRODUCTION

Almost all drugs or compounds, including herbal medicines, have potential hepatotoxicity. It is not a rare diagnosis and potentially has fatal outcomes. Although many studies have been performed, the exact incidence of drug-induced liver injury (DILI) is poorly documented. The annual incidence rate of DILI has varied from 1.27 to 14 cases per 10⁵ inhabitants in reported studies from Europe (1,2). Hepatotoxicity accounts for up to 10% of all adverse drug reactions (3,4). DILI is the most common reason for withdrawal of an approved drug from the market. It is seen in 10% to 30% of patients presenting with acute hepatitis (5,6). In the U.S.

and Scandinavian countries, DILI is the number one cause of acute liver failure (7).

The incidence and etiology of herb-induced liver injury (HILI) are more difficult to document than DILI because of the use of a variety of non-commercial and non-prescribed medicines or dietary supplements. In addition, the incidence of HILI is underestimated due to the low frequency with which patients report their use. Although there are conflicting data about its incidence, HILI is also a threat to be taken seriously. According to United States (U.S.) data, the use of herbal and dietary medicine has risen dramatically over the past two de-

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cases; in 2004, 18.9% of U.S. adults reported using these medicines (8,9). In a prospective study from the U.S., herbal and dietary supplements were found to be implicated in 10% of DILI cases (10). In another U.S. study, in 7 of 20 (35%) cases of acute liver failure (ALF) referred for liver transplant surgery in 2001 and 2002, herbal and dietary supplements were the only identifiable cause of liver disease (11). The incidence of HILI seems to be high in the Far East. It accounts for 40% of the 30 patients reported in data from one center in China (12). In a prospective study from Singapore, herbal medicines were implicated in 15 of 22 (68%) patients with DILI (13). On the other hand, in a Spanish registry of DILI, only 2% of 531 cases of DILI were attributed to herbal remedies or dietary supplements (14).

The causality assessment of drug or herbal medicine for hepatotoxicity has varying degrees of uncertainty. A reliable diagnosis must have certain key features: compatible chronology of onset and use of medication, exclusion of any other etiologies, and response to suspension and reintroduction of the suspected medication. But, it may be impossible to prove causality because of several factors related with both the drug and the people using it. Thus, after clinical suspicion, the diagnosis is usually reached according to the history, findings, and all available biochemical data and imaging studies upon drug discontinuation. International criteria have been defined for this purpose and seem to be the best method for assessing causality (15). The anti-infective and nonsteroidal anti-inflammatory drugs (NSAID) groups of drugs were the most frequently incriminated in DILI in two recent studies (10,16).

Available data from Turkey about DILI are limited. Published data about DILI from our country consist of case reports and experimental studies. Moreover, data concerning HILI from Turkey are almost unavailable. In a large retrospective analysis from Ankara, antibiotics were the most common causative agents in 84 of 170 patients with DILI (17). Our country is located in the cradle of civilization, and the use of traditional herbal medicine is very common. Our center, located in southeastern Turkey, has a large community hepatology outpatient clinic. With this in mind, we designed a retrospective analysis of patients with drug- and herb-induced liver injury in order to contribute to decreasing the unknowns about this topic.

MATERIALS AND METHODS

We retrospectively studied all patients diagnosed with DILI and HILI in the Hepatology Outpatient Unit of Gaziantep University Medical School from June 2008 to June 2012. The data were collected from outpatient visit charts and inpatient records. A clinical investigation was completed for all patients, including a detailed history and physical examination, biochemical and serological tests, and radiologic imaging. The inclusion criteria were as follows: 1) age above 15 years, 2) alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or conjugated bilirubin greater than twice the upper normal limit, 3) history of drug or herbal medicine use within the past

6 weeks, and 4) elimination of any other causes of liver injury. The exclusion criteria were as follows: 1) history of any pre-existing liver disease, 2) alcohol consumption or receipt of blood products over the last 6 months, 3) suspicious or proven viral, metabolic, or any other etiology, 4) any radiological findings indicating other causes of liver injury, including significant hepatosteatosis, and 5) severe cardiopulmonary or renal disease.

Biochemical tests, including serum alanine aminotransferase (ALT), aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase (ALP), bilirubin, fasting glucose, cholesterol, triglyceride levels, complete blood cell counts, and prothrombin time, were recorded for all patients. Serological markers were studied, including for viral hepatitis: anti-hepatitis A virus IgM and IgG, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgM and IgG, anti-hepatitis C virus, anti-cytomegalovirus, anti-herpes simplex virus, and anti-Epstein-Barr virus; for autoimmune hepatitis, including anti-nuclear, anti-smooth muscle, anti-mitochondrial, and anti-LKM-1 antibodies; and for metabolic liver disease, including serum iron, total iron binding capacity, ceruloplasmin, urinary copper excretion, and alpha-1 antitrypsin levels.

Hepatobiliary imaging study was performed via abdominal ultrasonography. Portal Doppler ultrasonography for patients with suspected vascular liver disease and computed tomography and/or magnetic resonance imaging for suspicious space-occupying liver lesions were also performed. In patients with cholestatic liver disease, biliary tract abnormalities were ruled out through magnetic resonance and/or endoscopic retrograde cholangiography.

The diagnosis of DILI was established on the basis of a patient's history, clinical condition, biochemical and serological markers, and imaging studies. Standard definitions and criteria for assessing the causality of adverse drug reactions were characterized and adopted in accordance with the International Consensus Meeting. The pattern of DILI was defined according to the ratio of ALT to ALP (as a multiple of their upper normal limits): >5 hepatocellular, 2-5 mixed, and <2 cholestatic pattern (15,18,19).

RESULTS

In total, 82 patients with drug- or herb-induced liver injury (mean age 43.1 ± 14.8 years; 53 females, 29 males) were assigned. Females were predominant (64.6%). Liver injury was associated with a single agent in 73 of 82 (89%) patients, and two drugs were associated in the remaining 9 (10.9%) patients.

The major cause of hepatotoxicity was drugs (87.8%), with herbal medicine accounting for 12.2%. The leading causative agents were NSAIDs (23.1%), followed by antibiotics (19.5%). The most common NSAID was diclofenac (8 cases, 9.7%), followed by flurbiprofen and amoxicillin-clavulanate (7 cases, 8.5%). Diclofenac and flurbiprofen were responsible in 15 of

19 (78.9%) NSAID-related hepatotoxicities. Amoxicillin-clavulanate was the most common antibiotic and responsible in 7 of 16 (43.7%) cases of antibiotic-related hepatotoxicity. Surprisingly, *Teucrium polium* shares second place with flurbiprofen and amoxicillin-clavulanate. It was the most common cause of HILI and responsible in 7 of 10 cases.

Other common drug groups were immunosuppressives (8.5%), anti-convulsants (6.1%), anti-hyperlipidemics (4.9%), antithyroids (2.4%), antifungals (2.4%), oral contraceptives (2.4%), and drugs other than these groups in 6 patients (8.5%). Amiodarone, sulfasalazine, colchicine, rosiglitazone, ramipril, and albendazole were responsible for DILI in one patient each. The demographic, etiologically featured, and laboratory data are summarized in Table 1.

A sex-correlated etiological difference was noticed in our patients. The female sex was seemingly dominant in NSAID-related DILI (84.2%) and HILI (80%) cases. However, female and male cases were equal in antibiotic-related hepatotoxicity.

The pattern of hepatotoxicity was hepatocellular in 35 patients (42.6%), mixed in 28 (34.1%), and cholestatic in 19 patients (23.1%). A mixed pattern of hepatotoxicity was slightly predominant (47.3%) in NSAID-related cases, followed by hepatocellular (31.5%) and cholestatic (21%). But, the hepatocellular pattern is predominant (62.5%) in antibiotic-related cases, followed by cholestatic (25%) and mixed (12.5%). A hepatocellular and mixed pattern was seen in 50% of the HILI group without the cholestatic pattern.

Acute liver failure with encephalopathy developed in 3 patients (in two patients, this was related to flurbiprofen and diclofenac

and in one patient due to isoniazide with rifampicin). Two of three patients were not suitable for liver transplantation because of their infections and co-morbidities. Another patient (one of three) was referred to a living donor transplantation center, and he died while waiting for a liver donation. Except for these three patients, all patients fully recovered without chronicity in the follow-up after cessation of the suspected drug.

DISCUSSION

Liver injury of uncertain origin demands consideration of hepatotoxicity as a cause, which requires evaluation not only for the receipt of conventionally prescribed drugs but also for herbal products, nutritional supplements, and over-the-counter medications.

The incidence of DILI and HILI in Turkey is uncertain. Many difficulties confront studies, such as registry problems, a lack of exact consumption data on hepatotoxic drugs, and asymptomatic or lost cases, etc. The only data from Turkey are a retrospective analysis of Idilman et al. (17), who reported 170 cases from a tertiary referral center (3.1% of 5471 cases between 2001 and 2007). There are no data about herbal medicine in that report. Our study has many limitations, firstly in its retrospective design. Secondly, our center is a tertiary referral center; our data are not population- or registry-based. Additionally, our study provides only a small contribution about DILI due to insufficient data. Our center is located in southeastern Turkey, and the use of herbal medicine is common. The cases of HILI were published separately in some previous studies. These results were added to our study because of a lack of data about HILI from our country.

The most common cause of acute DILI in the United States is acetaminophen, followed by antibiotics (7,16). Although the

Table 1. Demographic, etiological, and laboratory features of cases (F/M: female/male, H/C/M: hepatocellular /cholestatic /mixed)

Drug Group	n	%	Age	Sex F/M	AST	ALT	ALP	GGT	TBIL	DBIL	INR	Pattern H/C/M
NSAIDs	19	23.2	40.9±16.9	16 / 3	377±386	534±608	400±236	217±228	5.31±7.87	4.03±6.59	1.62±1.76	6/4/9
Antibiotics	16	19.5	47.1±12.6	8 / 8	582±404	789±578	483±334	303±510	9.09±9.28	6.35±6.46	1.48±0.90	10/4/2
Herbal Medicine	10	12.1	41.6±15.1	8 / 2	624±682	788±790	304±205	148±145	6.96±6.24	5.08±7.25	1.18±0.31	5/0/5
Immunosuppressive	7	8.5	50.2±14.3	5 / 2	571±820	641±782	326±266	102±94	1.17±1.01	0.52±0.69	1.20±0.42	3/1/3
Anti-convulsant	5	6.1	40.0±14.8	3 / 2	251±140	487±321	473±267	280±239	4.00±4.87	2.29±3.13	1.02±0.16	1/2/2
Anti-hyperlipidemic	4	4.9	35.5±15.2	2 / 2	220±196	257±165	684±368	367±300	1.27±0.94	0.87±0.97	0.95±0.17	1/3/0
Antithyroid	2	2.4	31.5±0.7	1 / 1	220±188	378±359	420±177	78±63	0.65±0.35	0.32±0.38	1.10±0.28	1/1/0
Antifungal	2	2.4	46.0±18.3	0 / 2	76±37	157±70	435±478	60±18	0.90±0.0	0.20±0.14	1.10±0.14	0/2/0
Oral Contraceptive	2	2.4	31.0±1.4	2 / 0	1783±1932	2501±2544	157±101	540±33	3.60±2.68	2.85±2.75	1.63±0.32	2/0/0
Other	6	7.3	53.1±19.2	3 / 3	529±282	680±373	276±99	163±80	4.86±4.0	3.06±2.56	1.25±0.24	4/0/2
Multi-drug	9	10.9	38.4±11.4	5 / 4	465±705	444±487	200±135	138±164	4.84±7.2	3.13±5.20	1.26±0.95	2/2/5
Total	82	100	43.1±14.8	53/29	492±574	643±703	381±267	215±285	5.27±7.31	3.67±5.53	1.34±1.00	35/19/28

NSAIDs: non-steroidal anti-inflammatory drugs; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; TBIL: total bilirubin; DBIL: direct bilirubin; INR: international normalized ratio

first- and second-ranked causes may switch places, antibiotics and NSAIDs are the top two on the DILI list. Also worth noting is that in our study, the drugs that were the most frequent causes of DILI were NSAIDs and antibiotics, similar to the results of reported earlier studies (17,20-22). These two groups of drugs are commonly used worldwide. According to a survey from the United States, NSAIDs were the most commonly used drugs, including both prescribed and non-prescribed drugs (23). But, there are no data about antibiotics as to whether or not they are more commonly used than NSAIDs worldwide. Diclofenac-related DILI was diagnosed in 8 patients; flurbiprofen-related DILI was diagnosed in 7 patients. Fatal acute liver failure developed in each of the 15 patients using diclofenac and flurbiprofen. There was a significant female predominance of NSAID-related DILI in our cases (16 patients vs. 3). This is in line with the results of another study (24) but conflicts with others (25,26). All three cases of acute liver failure and mortality were female as well.

It is uncertain why antibiotics are associated with a high frequency of DILI, independent of the consumption rate. However, increased susceptibility of the liver to drug hepatotoxicity in the presence of infection and inflammation has been postulated (27). Whereas the study reported by Idilman et al. (17) found that the most common group was antibiotics, in our study, the first-ranked drug group was NSAIDs. In our country, almost the entire population has social insurance covered by the government, and as such, there is no difference in drug supply. Perhaps this is related to the more widespread use of NSAIDs in our region. The most common drug from the antibiotics group was amoxicillin-clavulanate (7 cases) in our study, which is similar to the results of the study mentioned (17). Clavulanate, rather than amoxicillin, was suggested to be responsible in most of the patients (28). All our cases with DILI that was related to antibiotics were resolved, except for one patient who developed fatal acute liver failure.

The third-largest group in toxic liver injury was herbal medicine. Ten patients suffered from herb-induced liver injury. Traditional therapeutic preparations and herbal medicine comprise a major group of DILI causes in the Far East (12). There are no data about herb-induced liver injury in Turkey. *Teucrium polium* was responsible in 7 of 10 patients, and the other ones in our study were related to green tea, *Chondrus crispus*, and *Momordica charantia*. *Teucrium polium* is known popularly as felty germander, which is a traditionally used herbal medicine of the Labiatae family. The plant is a commonly used local herb in the Middle East and the Mediterranean region for dyspepsia, abdominal colic, hemorrhoids, and diabetes. Its flowers are small and range from pink to white; its leaves are used in cooking and for medicinal purposes. Hepatotoxicity due to this herb has been reported previously, but the exact mechanism of liver damage is unknown (29). One case of *T. polium* toxicity requiring a liver transplantation has been reported (30). In traditional Persian medicine, *T. polium* (locally called "kalpooreh") is used as an anti-hypertensive, anti-bac-

terial, carminative, anti-nociceptive, anti-inflammatory, anti-diarrhea, anti-diabetes, and anti-convulsant agent. Caution should be applied with use of this herb due to its known liver and kidney toxicity. All patients with HILI recovered without chronicity in our study.

There is a significant female predominance in our study (62.5%) over the result of Idilman et al. (55.8%). The most common pattern of DILI in our patients is hepatocellular as well but at a rate lower than in the study mentioned above (42.6% vs. 50%).

Whatever the cause of liver injury, drug- or herbal-related, it has a very important diagnosis. Idilman et al. (17) reported that 7 of 14 patients with ALF died. Although our study is not large-scale or population-based, 3 mortalities due to fatal acute liver failure in 81 patients form sufficient evidence for the significance of hepatotoxicity.

Although NSAIDs and antibiotics were the most common causes of DILI, herbal medicine must be carefully questioned. Fortunately, most of the patients enjoyed a full recovery, but the risk of acute liver failure due to drugs or herbs must not be forgotten in patients with liver injury. It is important to emphasize that in the case of herbal treatments, "natural" or "alternative" does not equate to "safe." Herbal side effects, toxicities, and drug-herb interactions can occur. We must be cognizant and vigilant regarding herbal product use in patients with liver toxicities.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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