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Important Elements for the Diagnosis of Drug-Induced Liver Injury

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Abstract

Background & Aims—Drug-induced liver disease is the leading cause of acute liver failure in the United States. Accurate reporting of drug-induced liver injury is essential for early detection of hepatotoxicity and for developing reliable, interpretable literature. We assessed the extent to which published case reports of drug-induced liver disease include sufficient clinical data for interpreting the cause of toxicity.

Methods—We developed a list of 42 pre-determined, specific minimal elements necessary in evaluating causality of drug-induced liver injury. We then analyzed 97 published case reports or series studies of hepatotoxicity from 6 drugs (from 3 classes): amoxicillin/clavulanic acid (n=35), troglitazone (n=32), rosiglitazone (n=10), pioglitazone (n=8), zafirlukast (n=8), and montelukast (n=4).

Results—Patient age, sex, primary disease, and drug name were reported in most, if not all, published case reports. However, many elements were under-reported; some publications did not mention initial bilirubin levels (12%), many did not provide initial alkaline phosphatase levels (58%), and others provided vague descriptions of how certain diagnoses were excluded, such as “tests for hepatitis A, B, and C were negative.” Data on abnormal results from serial liver tests were frequently absent. Exclusions of competing viral etiologies were reported in less than 50% of the studies.

Conclusion—Reports of drug-induced liver diseases often do not provide the data needed to determine the causes of the adverse effects. Efforts to promote and include a list of essential diagnostic elements in research articles could increase the quality and clinical utility of published case reports of drug toxicity.

Keywords

acute liver failure; adverse drug reaction reporting systems; case reports; hepatotoxicity; standards

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Drug-induced hepatotoxicity represents a significant proportion of acute liver disease cases (1) and is the single leading cause of acute liver failure in the United States (2). Drug-induced liver injury can be caused by an array of prescription medications, as well as herbal and dietary supplements (3). Accurate reporting of drug-induced liver disease is important for the early detection and awareness of drug-induced hepatotoxicity as well as for developing a prospective body of reliable, interpretable literature for agents that cause idiosyncratic hepatic injury. Published case reports that describe adverse events can provide significant clinical insight, especially for rare events that might not be detected in clinical trials. These reports can also increase awareness of issues possibly associated with a drug early in its development and use, which can thereby prompt further investigation. However, many publications or reports of drug-induced liver disease lack important or essential details for interpreting whether such episodes can be causally assigned to a specific drug or combination of drugs.

In 1984, professionals interested in adverse drug events and editors of major medical journals met under the auspices of the Council for International Organizations of Medical Sciences and proposed guidelines for editors to adopt when reviewing adverse event reports submitted for publication (4). However, a descriptive analysis published in 2003 suggested that many major medical journals still have only minimal requirements for publishing adverse event reports, and some have none at all (5). To explore the extent to which published case reports include clinically relevant data, we created a list of predetermined, specific minimal elements that should be detailed in case reports of drug-induced liver injury. Then we examined individual case reports involving 6 specific drugs from 3 different classes to determine the frequency with which such elements are described.

Experimental Procedures

Minimal Elements

As a part of the ongoing development and design of the Drug Induced Liver Injury Network (DILIN) (6), we developed a listing of elements that should be included in published cases of drug-induced liver injury (Table 1). These elements were considered necessary for diagnosis, and many are required to complete the RUCAM causality assessment form (6–8). The elements included details of patient's age and sex, time of starting and stopping the implicated medication, the time of onset of symptoms and jaundice, and results of laboratory tests at the onset of injury through the time to recovery. Other important elements related to exclusion of other causes of acute liver injury, such as viral hepatitis, other medications, autoimmune liver disease, biliary obstruction, alcohol, sepsis, and ischemia, were also considered.

Review of Case Reports

A list of 42 components of the “minimal” elements was used to assess 97 published case reports or case series of drug-induced liver disease related to one of 6 specific drugs: amoxicillin/clavulanic acid (n = 35, 1992–2007) (9–17), troglitazone (n = 32, 1998–2008) (18–35), rosiglitazone (n = 10, 2000–2008) (36–45), pioglitazone (n = 8, 2001–2007) (46–53), zafirlukast (n = 8, 2000–2002) (54–59), or montelukast (n = 4, 2003–2007) (60–63). Two of these drugs (amoxicillin/clavulanic acid and troglitazone) were chosen as examples of well-known causes of clinically apparent drug-induced liver disease. The other four were chosen as examples of agents that rarely cause liver injury but for which case reports have been important in documenting their potential for hepatotoxicity. Articles published before 1992 were not included because they predated availability of hepatitis C tests and advanced imaging techniques. Each publication was assessed by two of the authors independently for

whether the 42 components were accurately recorded and included for each case in each publication (if there were multiple cases described). Elements were only recorded if they were described in the actual case report. Vague terminology such as “viral screen negative” was not considered sufficient.

Type of publication

Each publication was also categorized by whether it was a single case report (n=23), a brief communication (n =7), a small case series (n= 46), or a letter to the editor (n=21). Finally, each publication was categorized by type of journal in which it was published: major internal medicine journal (n =20), gastroenterology and liver subspecialty journal (n=49) and other (n = 28). The rates of including the minimal elements were assessed by these categories of type of article and journal.

Statistics

Individual and aggregate drug data were summarized using simple descriptive statistics including medians and percents. Two-group comparisons were performed using the Wilcoxon-Mann-Whitney test; the Kruskal-Wallis test was applied for multi-group comparisons. All statistical analyses were performed using SAS version 9.1.

Results

While some elements, such as patient age, sex, primary disease, and drug name, were reported in most if not all published reports, many elements were under-reported. The rates of reporting each of the 42 elements by implicated drug are shown in Table 2, and the 10 most- and least-reported elements are shown in Table 3. No case report included all 42 elements. The percent missing elements in individual publications ranged from 9% to 81%, with a median of 48%. Twelve percent of publications did not mention initial bilirubin levels; many did not provide initial alkaline phosphatase levels (58%), and others provided vague descriptions of how other diagnoses were excluded (“tests for hepatitis A, B, and C were negative”). Data regarding serial liver test abnormalities were often absent. In the aggregate of cases, exclusion of other competing viral etiology was recorded less than half the time (Figure 1).

Overall, the trend of reporting was different for different classes of drugs (Figures 2–4). Serial blood tests were reported more frequently for events associated with the thiazolidinediones (ALT, 44%; alkaline phosphatase, 32%; bilirubin, 52%) than with leukotriene receptor antagonists (ALT, 25%; alkaline phosphatase, 17%; bilirubin, 25%), or with amoxicillin/clavulanic acid (ALT, 9%; alkaline phosphatase, 17%; bilirubin, 17%). Testing for viral hepatitis and liver imaging was done more often in toxicity cases reported with thiazolidinediones than leukotriene receptor antagonists. For cases involving amoxicillin/clavulanic acid, the frequency of performing individual hepatitis tests varied greatly, with IgM anti-HAV reported in 71% of cases and HBsAg reported in 26% of cases. Concomitant diseases were infrequently reported with amoxicillin/clavulanic acid (11%) and leukotriene receptor antagonists (33%) but more commonly for thiazolidinediones (82%).

The median percent of missing elements varied from 44% for the thiazolidinediones to 48% for amoxicillin/clavulanic acid and 49% for the leukotriene receptor antagonists ($p = 0.34$). No significant difference was observed by journal types, with median percent missing elements of 50% for major internal medicine journals, 48% for gastroenterology and liver subspecialty journals, and 45% in other types ($p = 0.23$). However, there were significant differences by publication type ($p < 0.001$), with significantly fewer missing elements in single case reports (median = 33%) than in letters to the editor (median = 50%, $p < 0.001$).

and small case series (median = 48%, $p < 0.001$); the comparison against brief communications reports (median = 43%) just failed to reach statistical significance ($p = 0.07$). No other pairwise comparisons by type of publication were statistically significant.

Discussion

In this analysis of 97 published case reports that attributed liver injury to a specific drug, all were lacking in at least some information important in determining the cause of the injury. Several publications did not contain information regarding important laboratory data, such as bilirubin or alkaline phosphatase levels. Even more common was a lack of specific information on testing for excluding viral hepatitis.

The list of elements assessed in this study was considered the minimal required for an accurate assessment of causality in drug-induced liver disease. Thus, knowledge of the latency between the starting of the medication and onset of injury is essential in assessing the likelihood that the liver injury is due to the specific drug (8). Furthermore, the onset of injury needs to be defined as either date of onset of first symptoms, appearance of jaundice (or dark urine), or first abnormal laboratory tests found (which may occur days or weeks after actual onset). Identification of the pattern of liver injury (whether hepatocellular, cholestatic, or mixed) requires knowledge of serum ALT and alkaline phosphatase levels (and the upper limits of their normal range) at the onset of injury. Assessment of the severity of the injury requires knowledge of the peak serum bilirubin and prothrombin time or INR (6). Finally, assessment of causality in drug-induced liver injury requires information about “dechallenge” and the time to resolution after the medication is stopped, usually based upon serial laboratory tests for ALT, alkaline phosphatase, or bilirubin (4–8). Yet, these results were provided in less than half of published case reports.

Drug-induced liver injury is a diagnosis of exclusion, and important conditions to exclude are hepatitis A, B, and C, alcoholic liver disease, biliary obstruction, and liver injury due to ischemia or other medications. Thus, minimal elements in presenting cases of drug-induced liver injury should carefully define tests or elements in the clinical history for excluding these diagnoses. Indeed, in some situations other laboratory tests beyond what was considered minimal would be helpful, such as results of assays for anti-HEV to exclude hepatitis E, tests for lactate dehydrogenase and creatine kinase to exclude ischemic hepatitis, or ERCP (endoscopic retrograde cholangiopancreatography) or MRCP (magnetic resonance cholangio-pancreatography) to fully exclude biliary obstruction. Other factors that may be helpful are patient BMI and levels of autoantibodies and immunoglobulins. Of course, an important other cause of liver injury is another medication or herbal being taken, which may have not been considered or mentioned. In this regard, testing for acetaminophen levels or adducts may be important to document the absence of a contribution by unintentional overdose of acetaminophen, particularly in patients with severe hepatocellular injury of sudden onset.

The percentage of missing elements did not appear to vary by drug class or journal type but was less for single case studies as compared with letters to the editor and small case series. These differences are not unexpected, as single case reports are more focused and likely to report more relevant elements than case series or letters to the editor.

In some instances the lack of reporting of critical elements in publications may have been due to the fact that the results were normal and therefore just not mentioned. Yet negative results can be important. Features that are sometimes absent but are important in diagnosis include absence of fever, rash, or eosinophilia. More commonly, a lack of elements may be due to the fact that they were not done or not available. This lack should also be mentioned

in reporting instances of drug-induced liver injury, as the information can be important in assessing the likelihood that the injury was due to the medication. Thus, the lack of pre-treatment levels of laboratory tests, the fact that some diagnostic tests were not done (such as HCV RNA, imaging of the biliary tree or liver biopsy), or the absence of follow-up laboratory tests are important in considering causality.

These results support the need for a more standardized approach to the reporting of drug-induced liver injury. Perhaps most helpful would be a checklist of minimal elements that are considered essential for diagnosis and causality assessment of any cases of drug-induced liver injury. Also useful would be a secondary list of elements that are helpful in many situations, but are not always essential. Although similar standards were suggested by medical professionals and journal editors in 1985 (4), the suggestions were not adopted for widespread use (5). Yet, in the more than 20 years since then, the proliferation of the World Wide Web has made sharing of such guidelines potentially much easier. Publishing guidelines that have been adopted for widespread use include those developed by the CONSORT Group (<http://www.consort-statement.org/>) for reporting results of randomized clinical trials. The CONSORT Statement comprises a 22-item checklist, which is used for detailing design and conduct of a trial, and a flow diagram, which is used to display the progress of participants through a trial. The CONSORT Statement is easily accessible online, and adherence to it is currently required by many peer-reviewed journals. The minimal elements for case reports of hepatotoxicity could be posted on a publicly funded Web site, such as the National Library of Medicine (<http://www.nlm.nih.gov/>), with the goal that they would ultimately be adopted by journal editors and posted on journal Web sites.

Similar lists of minimal elements might be developed for other types of adverse drug reactions, such as cardiovascular events or renal toxicity. Many of the items on our list, such as dates of starting and stopping therapy and whether a re-challenge was performed, would be relevant for other suspected drug-associated reactions.

In conclusion, reports of drug-induced liver injury are generally lacking in data needed for determining the cause of adverse effects. Efforts to promote and include a listing of essential elements in journal articles could significantly enhance the quality and clinical utility of published case reports of drug toxicity.

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Abbreviations

ALT	alanine aminotransferase
ANA	antinuclear antibody
AP	alkaline phosphatase
CT	computerized tomography
DILI	drug-induced liver injury
ERCP	endoscopic retrograde cholangiopancreatography

HAV	hepatitis A virus
HBc	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
INR	international normalized ratio
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
PT	prothrombin time

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Figure 1. Exclusion of a Competing Viral Etiology

Among 97 published case reports of drug-induced liver disease related to specific drugs, fewer than half specified whether competing viral etiologies were excluded. “Viral Screen Negative” represents percent of cases for which results of tests for competing etiology were vaguely reported (for example, “tests for hepatitis A, B, and C were negative”). ALT, alanine aminotransferase; ANA, antinuclear antibody; AP, alkaline phosphatase; HAV, hepatitis A virus; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Figure 2. Minimal Elements Reported in Published Case Reports of Hepatotoxicity with Thiazolidinediones

Reports were regarding troglitazone (n= 32), rosiglitazone (n= 10), and pioglitazone (n= 8). “Re-challenge” refers to whether a re-challenge with the same medication was reported as being done or not. ALT, alanine aminotransferase; ANA, antinuclear antibody; AP, alkaline phosphatase; HAV, hepatitis A virus; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Figure 3. Minimal Elements Reported in Published Case Reports of Hepatotoxicity with Leukotriene Receptor Antagonists

Reports were regarding zafirlukast (n=8) and montelukast (n= 4). “Re-challenge” refers to whether a re-challenge with the same medication was reported as being done or not.

Figure 4. Minimal Elements Reported in Published Case Reports of Hepatotoxicity with Amoxicillin/Clavulanic Acid (n = 35)
 “Re-challenge” refers to whether a re-challenge with the same medication was reported as being done or not.

Table 1**Minimal Elements for Reporting Drug-Induced Liver Injury.**

Minimal Elements
Patient's sex and age
Drug and its dose
Primary disease (for which drug was prescribed)
Concomitant diseases (with special mention of heart failure or episodes of hypotension, sepsis, or receipt of parenteral nutrition)
Pertinent past medical history (including previous exposure to drug, previous reaction to drug or other drugs, history of liver disease, and risk factors for liver disease)
History of alcohol use
Dates of start and discontinuation of therapy (or time from onset of event)
Symptoms
Date of onset
List of pertinent symptoms (fatigue, weakness, nausea, anorexia, abdominal pain, dark urine, jaundice, pruritus, rash, and fever)
Pertinent physical findings at the time of presentation (with special mention of whether or not there is fever, rash, jaundice, hepatic tenderness, or signs of chronic liver disease)
Medication history (other meds taken in the 3 months before onset of liver injury with dose, generic name, and duration)
Laboratory tests
Date or time of first abnormal laboratory test
Laboratory test results from before drug exposure (specifically liver tests)
Initial laboratory results at presentation (bilirubin, ALT, AP, INR or PT, and eosinophil count or percentage)
Laboratory results needed to exclude other causes (IgM anti-HAV, IgM anti-HBc, HBsAg, anti-HCV, HCV RNA, and ANA)
Course of serum bilirubin, ALT, AP, and INR levels (preferably in a table with entries dated from time of starting and stopping the drug and until resolution)
Imaging studies (abdominal ultrasound, CT, or MR)
Liver histology results (if obtained and date of procedure in relation to episode of DILI)
Whether re-challenge with the same medication was done and, if so, results of the challenge.

ALT, alanine aminotransferase; ANA, antinuclear antibody; AP, alkaline phosphatase; DILI, drug-induced liver injury; HAV, hepatitis A virus; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; PT, prothrombin time; CT, computerized tomography; MR, magnetic resonance.

Table 2

Elements Included in Case Reports of Drug-Induced Liver Disease.

Element	Amoxicillin/ Clavulanic Acid (n = 35)	Troglitazone (n = 32)	Rosiglitazone (n = 10)	Pioglitazone (n = 8)	Zafirlukast (n = 8)	Montelukast (n = 4)
Age of patient (y)	100	100	100	100	100	100
Sex of patient	100	100	100	100	100	100
Primary disease	100	100	100	100	75	75
Other diseases	11	81	90	75	13	75
Drug						
Name	100	100	100	100	100	100
Dose (/day)	91	81	80	100	100	75
Date start	9	50	20	38	25	0
Date stop	3	31	10	25	25	0
Duration Rx	100	81	40	63	88	50
Previous exposure	69	3	10	0	0	0
Other meds (timing)	94	84	80	100	100	100
Date (or latency) of Symptoms	91	72	30	25	75	25
Jaundice	91	44	10	25	38	0
Abnormal blood tests	17	9	10	13	25	0
Symptoms	100	97	100	100	100	100
Patient history						
Alcohol use	53	69	60	25	75	75
Liver disease	71	47	20	38	38	25
Risk factors	94	28	40	38	75	50
Drug reaction	20	13	30	0	0	0
Blood tests pre drug	6	66	70	75	50	50
Initial blood tests						
ALT	11	72	100	88	100	75
AP	26	47	60	88	25	50
Bilirubin	97	75	100	100	63	100
PT or INR	23	66	90	38	50	50

Element	Amoxicillin/ Clavulanic Acid (n = 35)	Trogilazone (n = 32)	Rosiglitazone (n = 10)	Pioglitazone (n = 8)	Zafirlukast (n = 8)	Montelukast (n = 4)
Eosinophils	94	13	10	13	38	75
Serial blood tests						
ALT	9	31	80	50	25	25
AP	17	28	50	25	25	0
Bilirubin	17	47	70	50	25	25
Final blood tests						
ALT	15	61	86	75	88	67
AP	15	35	57	63	50	67
Bilirubin	15	57	57	63	75	67
Time or date of final blood tests	15	57	71	88	75	67
Relevant physical exam (liver)	31	38	70	25	50	25
Viral hepatitis testing						
IgM anti-HAV	71	41	30	0	0	0
HBsAg	26	44	30	12	38	0
IgM anti-HBc	50	41	30	12	38	0
Anti-HCV	42	44	30	12	38	0
HCV RNA	6	9	10	12	0	0
ANA	69	72	70	50	50	25
Imaging of liver	100	53	90	75	25	38
Liver histology results	71	81	40	50	75	75
Re-challenge ^a	88	17	50	25	25	33

Values are percentages.

^aWhether re-challenge with the same medication was reported as being done or not.

ALT, alanine aminotransferase; ANA, antinuclear antibody; AP, alkaline phosphatase; HAV, hepatitis A virus; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; PT, prothrombin time.

Table 3

Most- and Least-Commonly Reported Elements Included in Case Reports of Drug-Induced Liver Disease Among 3 Classes of Drugs.

Element	Percent Cases (n = 97)
Most commonly reported	
Age of patient (y)	100
Sex of patient	100
Drug name	100
Symptoms (fever nausea, pain, anorexia, fatigue, rash, dark urine, jaundice)	99
Primary disease	96
Other meds (and timing)	91
Drug dose (/day)	88
Initial bilirubin	88
Duration Rx	81
Least commonly reported	
HCV RNA	7
Date (or latency) of abnormal blood tests	13
Patient history of drug reactions	14
Date stop drug	16
Serial AP	25
Date start drug	27
Previous exposure to drug	27
Serial ALT	29
HBsAg	31
Final AP	35
Re-challenge ^a	41

^aWhether re-challenge with the same medication was reported as being done or not.

ALT, alanine aminotransferase; AP, alkaline phosphatase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.