HHS Public Access

Author manuscript

Drug Saf. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Drug Saf. 2017 September ; 40(9): 783–787. doi:10.1007/s40264-017-0547-9.

The incidence of drug- and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware

Maricruz Vega, MPH[1], **Manisha Verma, MD, MPH**[2], **David Beswick, MD**[3], **Stephanie Bey, PA-C**[4], **Jared Hossack, MD**[5], **Nathan Merriman, MD**[6], **Ashish Shah, MD**[4], **Victor Navarro**, and **MD (DILIN)**[8] **for the Drug Induced Liver Injury Network**

[1]Einstein Medical Center, 5501 Old York Road, Philadelphia, Pennsylvania, 19141, Telephone: (609) 364-2828

[2]Einstein Medical Center, 5501 Old York Road, Philadelphia, Pennsylvania, 19141

[3]Gastroenterology Associates, 4745 Ogletown Stanton Road, Medical Arts Building, Suite 134 Newark, Delaware, 19713

[4]Gastroenterology Associates, 4745 Ogletown Stanton Road, Medical Arts Building, Suite 134 Newark, Delaware, 19713

[5]Mid-Atlantic GI Consultants, 537 Stanton Christiana Rd Ste 203, Newark, Delaware 19713

[6]Gastroenterology Associates, 4745 Ogletown Stanton Road, Medical Arts Building, Suite 134 Newark, Delaware, 19713

[7]First State Gastroenterology, 644 South Queen St, Suite 106 Dover, Delaware, 19904

[8]Einstein Medical Center, 5501 Old York Road, Philadelphia, Pennsylvania

Abstract

Background and Aim—The population based incidence rate of drug induced liver injury (DILI) in the United States is not known. The Drug Induced Liver Injury Network (DILIN) accrues cases of hepatotoxicity due to medications and herbal and dietary supplements (HDS) from limited geographical areas. The current analysis was an ancillary study of DILIN aimed at determining the annual incidence of DILI in the US on a population basis, through surveillance in the state of Delaware.

Correspondence to: Maricruz Vega.

Conflicts Of Interest: Maricruz Vega, Manisha Verma, David Beswick, Stephanie Bey, Jared Hossack, Nathan Merriman, Ashish Shah and Victor Navarro have no conflicts of interest that are directly relevant to the content of this study.

Ethical Approval: This study was approved by the Einstein Medical Center Institutional Review Board. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient Consent: Informed consent was obtained from all patients who participated in this study.

Methods—At the outset of the study, there were 41 gastroenterologists in the state of Delaware and all agreed to participate in surveillance for DILI, which comprised active reporting of suspected cases to the DILIN. The gastroenterologists underwent training in the diagnosis of DILI and were provided with DILIN inclusion criteria. Only cases that met the DILIN laboratory inclusion criteria in 2014 were included in the incidence calculation, and these patients were invited to participate in the DILIN Prospective Study. The number of suspected cases that met inclusion criteria served as the numerator and the 2014 Delaware adult population as the denominator.

Results—During 2014, 23 patients were identified by the surveillance network, 20 of whom met DILIN laboratory inclusion criteria, leading to a incidence of 2.7 cases of DILI per 100,000 adult residents (95% CI: 1.5 to 3.9 per 100,000). Fourteen subjects agreed to participate in the DILIN; 6 declined. Among enrolled cases, the mean age was 51 years, 57% were women, and 71% were white. Eight cases were attributed to antibiotics (36%) and other drugs (21%) and 6 to HDS (43%). The pattern of injury was hepatocellular in all HDS cases but in only 50% of conventional drug cases (p=0.05) which more commonly presented with eosinophilia (p=0.47) and higher alkaline phosphatase levels (p=0.05). Half of patients were jaundiced, none developed liver failure and all recovered without the need for transplantation.

Conclusion—Prospective gastroenterologist-based surveillance for suspected DILI in Delaware yielded an incidence of 2.7 cases per 100,000 adults in 2014; this is the first prospective estimate of DILI for the US. Because surveillance was limited to subspecialists, the actual incidence of DILI is likely to be higher. These findings provide a benchmark statistic for the epidemiology of DILI in the United States, to be refined with expansion of the surveillance period.

Keywords

Drug induced liver injury; incidence; epidemiology of drug induced liver injury; Delaware; population based incidence

1. Introduction

For most drugs, the risk of drug-induced liver injury (DILI), which can be associated with impairment of liver function, disability, or death, is a rare event. It has been estimated to occur with a frequency of between 1 in 10,000 and 1 in 100,000 patients exposed. [1] The actual frequency of DILI in the population may be much higher than these estimates, as underreporting of drug reactions of any kind by practitioners is common. [2] A 2002 study gave insight into the extent of underreporting of DILI; when a trained cohort of physicians in France performed surveillance for DILI, an incidence rate of 14 cases per 100,000 inhabitants per year was found, which was 16 times the spontaneous reporting rate. [3]

Studies using retrospective approaches have been performed to give insight into DILI epidemiology. A group of investigators in Sweden identified DILI incidence of 2.3 per 100,000 inhabitants per year with antibiotics being the most common class of agents implicated. [4] This was similar to an incidence of 2.4 per 100,000 from a study in the United Kingdom. [5] A 2015 retrospective cohort study of drug induced acute liver failure in an integrated health care system in the United States, found an incidence of 1.61 events per

million person-years.[6] In a single center, non-population based experience in the United States, 0.8% of 4,039 patients referred to a hepatology clinic for acute or chronic liver dysfunction had DILI. [7] Finally, of 732 patients with jaundice presenting to a U.S. hospital, 29 (4%) had DILI, but only 5 (0.7%) had non-acetaminophen (idiosyncratic) injury. [8] In the only published prospective cohort population based study, Bjőrnsson et al found a DILI incidence of 19.1 cases per 100,000 in Iceland. [9] No such population based data exist in the United States. The disparate findings between the retrospective and prospective cohort studies, as well as the lack of U.S. epidemiological data for DILI, highlight the need to better understand its epidemiology. Population based estimates can clarify the scope of the problem and help to determine the need for research and, in the case of herbal and dietary supplement (HDS) induced injury, regulation.

The Drug Induced Liver Injury Network (DILIN) is a multi-center research network charged with improving the understanding of the etiologies, risk factors and outcomes of DILI in the United States.[10] As part of the DILIN Study, we aimed to determine the annual incidence of DILI in Delaware (DE), chosen because of its representative demography and established relationship with DILIN, by using active surveillance through gastroenterology practices in the State.

2. Methods

The DILIN sponsored the current study to ascertain the epidemiology of DILI in the state of Delaware for several reasons. First, there was no large referral liver center in the state. As a result, patients and referring primary care providers caring for patients with symptoms of DILI were likely to refer to in-state gastroenterologists. Second, the relatively small number of gastroenterologists within DE made frequent contact between the investigator team and the providers' offices for case identification feasible. Third, a DILIN clinical site maintained two offices in DE (Wilmington and Dover) which provided rapid access for patients entering the study for enrollment procedures. Finally, the population of DE closely matched the demography of the U.S. general population. Table 1 shows the comparative demographics between DE and the U.S. population.

At the outset of the study, there were 41 gastroenterologists in the state, as identified through google searches and proprietary provider databases; when approached, all agreed to participate in surveillance for DILI. Surveillance comprised active reporting of suspected cases by the gastroenterologists to DILIN between and including January 2014 and December 2014. Gastroenterologists underwent training in the recognition and diagnosis of DILI through a face-to-face session with a DILIN investigator (VN), and were provided with DILIN inclusion criteria which included: 1) aspartate or alanine aminotransferase (ALT or AST) levels above 5 times or alkaline phosphatase (AP) levels above 2 times the upper limit of the normal range (ULN) on two consecutive occasions, 2) any elevation in ALT, AST or AP with a total bilirubin (TB) ≥ 2.5 mg/dL or coagulopathy with an international normative ratio (INR) >1.5 in the absence of other diagnosis. Regular electronic and fax reminders of the study and entry criteria were provided. Only cases that met the DILIN laboratory inclusion criteria during 2014 were included in the calculation of incidence and all patients were invited to enroll in the DILIN Prospective Study. Those who enrolled into the DILIN

study were interviewed and examined by a DILIN investigator (VN); all potential causes of liver injury were excluded. Through the DILIN adjudication process, the likelihood of DILI was assessed, as was the specific drug cause for liver injury.[10] The number of suspected cases that met inclusion criteria served as the numerator and the 2014 DE adult (>18 years) population (729,779) as the denominator, with the corresponding 95% confidence intervals also computed. Gastroenterologists were offered nominal practice management fees to offset the clerical work of referring suspect cases to the research team.

For those enrolled in the DILIN study, comparisons of characteristics were made between those attributed to conventional medications and those due to herbal and dietary supplements (HDS). For continuous variables, Wilcoxon test was used for comparison of groups, while chi-square test (or Fisher exact test for situations with small frequencies) was used for comparison of categorical variables. A p-value of 0.05 or less is considered statistically significant. Informed consent was obtained from all individual participants included in the study.

3. Results

A total of 23 patients were identified by the surveillance network during the 12 month study period; 20 of 23 patients met DILIN laboratory inclusion criteria, leading to a yearly DILI incidence of 2.7 cases per 100,000 adult residents (95% CI: 1.5 to 3.9 per 100,000). Fourteen of the 20 individuals who met entry criteria signed consent to enroll in the DILIN study; 6 declined. More detailed information was available from the enrolled cases, the mean age was 51 years, 57% were women, and 71% white.

Liver injury for 8 of the 14 cases enrolled in the DILIN were attributed to conventional medications (antibiotics 36% and other drugs 21%) and 6 to HDS (43%). All HDS cases and 50% of conventional drug cases exhibited a hepatocellular pattern of liver injury (p=0.05) as defined by an R ratio of > 5 (R ratio = [ALT value/ALT ULN] ÷ [AP value/AP ULN])Both initial and peak ALT and AST values were higher in the HDS induced injury cases, whereas AP levels were higher in the conventional medication induced injury cases (p=0.05) (Table 2). Medication-associated DILI cases presented more commonly with eosinophilia than the HDS cases (p=0.47) and elevated alkaline phosphatase (p=0.05). Time from onset of DILI to a 50% reduction in total bilirubin was more rapid in the conventional drug associated injury (12 days) than with HDS injury (25 days) (p=0.05). Fifty percent of patients with HDS injury were symptomatic for more than 4 weeks, as compared to 25% due to drugs, although this finding was not statistically significant. Sixty-four percent of patients were hospitalized, 50% were jaundiced, none developed acute liver failure, all patients recovered and none required liver transplantation.

4. Discussion

This study is the first to report a population-based estimate of the frequency of DILI in an American cohort. We found an incidence of 2.7 cases per 100,000 adults in during the year 2014. From the subset of cases enrolled into the DILIN, we found that the majority of DILI cases were attributed to conventional medications, but liver injury induced by HDS

accounted for almost half of cases and antibiotics were the most frequent class of implicated medications. These findings are in keeping with our previous report, that HDS comprise the second most common culprit responsible for liver injury in the DILIN cohort. [13] The clinical patterns of injury, either hepatocellular, cholestatic, or mixed, is indicative of the typical pattern of injury associated with the implicated antibiotics, rather than a reflection of all conventional medications.

An accurate statistic for DILI epidemiology is important for several reasons. It defines the scope of the problem, and thus its impact on the population. This allows for comparison to other preventable and non-preventable negative health occurrences, such as disease specific attributable morbidity and mortality, overdose, poisonings, and motor vehicle accidents. The chasm between the epidemiologic estimates reported in retrospective studies, which were similar to our study, and the prospective studies in France and Iceland, begs further understanding to determine the impact of underreporting and to develop means of more complete DILI reporting. Finally, having credible population based data gives researchers, pharmaceutical companies, and regulators stronger rationale to allocate resources to drug and HDS injury prevention and treatment. This is particularly important in the case of injury due to HDS, as current regulations are not based upon proof of safety to the consumer. Arguably, that liver injury resulting from HDS is more common than some conventional pharmaceuticals should be reason enough to revisit the adequacy of current regulations.

Using Delaware for this epidemiological study was a matter of convenience; its demographic similarity to the US population made it a relevant population based cohort. Still, our findings represent a much lower incidence rate than was seen in Iceland and France. Because many cases might be identified and cared for by primary care or nongastroenterology providers without having been referred to a gastroenterologist participating in the surveillance network, the true incidence of DILI in the U.S. population is likely to be higher. Further, our surveillance network did not include hospitals and so patients with severe liver injury or acute liver failure were not detected. Therefore, our statistic must be viewed as the lower limit of reality. As such, our findings provide a benchmark statistic for the epidemiology of DILI in the United States, to be refined with expansion of the surveillance period.

5. Conclusions

Based on preliminary findings of a prospective surveillance network limited to gastroenterologists in the State of Delaware, the incidence of liver injury due to conventional medications or HDS is at least 2.7 cases per 100,000. The true incidence is likely higher and can only be determined by expansion and continuation of surveillance. Herbal and Dietary supplements continue to be a common cause of injury among those affected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. Jay Hoofnagle for advice on the analysis and careful review of the manuscript and Dr. Raghu Kottam, Dr. Carol Morris, Dr. Guatamy Dhadham, Dr. Harry Anagnostakos, Dr. Robert Deckmann, Dr. Armin Marefat, Dr. Paolo Peghini, Dr. Jon Wiggins, Dr. Mark Wilkenson, Dr. William Kaplan, Dr. Parag Lodhavia, Dr. Joel Chodos, Dr. Warren Butt, Dr. Dinu Cherian, Dr. Mark Corso, Dr. Fedele DePalma, Dr. Marciana Filippone, Dr. Joseph Hacker III, Dr. Irfan Hisamuddin, Dr. Vandana Long, Dr. Ashesh Modi, Dr. George Benes, Dr. Michael Brooks, Dr. Natwaral Ramani, Dr. Bhavin Dave, Dr. Donald Girard, Dr. Hasan Ali, Dr. Grace Goracci, Dr. Christine Herdman, Dr. Gaurav Jain, Dr. T. Prasad Kanchana, Dr. Scott Meyerson, Dr. Amy Patrick, Dr. Christopher Ruffini, Dr. Bradley Mackler, Dr. Khaled Elraie, Dr. Ziyad Wadi, Dr. Pedro Dayrit, and Dr. Richard Caruso for assisting with patient recruitment.

Funding: Financial assistance from by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health (NIH) was used to conduct the study described in the manuscript. See DILIN website https://dilin.dcri.duke.edu/publications-1 for a complete listing of funding sources, sites, investigators, co-investigators, coordinators, and staff.

References

1. Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis. 2002; 22(2):145–56. [PubMed: 12016546]
2. Moride Y, Haramburu F, Requejo AA, Bégaud B. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol. 1997 Feb; 43(2):177–81. [PubMed: 9131950]
3. Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology. 2002 Aug; 36(2):451–5. [PubMed: 12143055]
4. De Valle MB, Av Klinteberg V, Alem N, Olsson R, Björnsson E. Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. Aliment Pharmacol Ther. 2006 Oct; 24(8):1187–95. [PubMed: 17014577]
5. de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol. 2004 Jul; 58(1): 71–80. [PubMed: 15206996]
6. Goldberg DS, Forde KA, Carbonari DM, Lewis JD, Leidi KB, Reddy KR, et al. Population-representative incidence of drug-induced acute liver failure based on an analysis of integrated healthcare system. Gastroenterology. 2015 Jun; 148(7):1353–61. [PubMed: 25733099]
7. Galan MV, Potts JA, Silverman AL, Gordon SC. The burden of acute nonfulminant drug-induced hepatitis in a United States tertiary referral center. J Clin Gastroenterol. 2005 Jan; 39(1):64–7. [PubMed: 15599214]
8. Vuppalanchi R, Liangpunsakul S, Chalasani N. Etiology of new-onset jaundice: how often is it caused by idiosyncratic drug-induced liver injury in the United States? Am J Gastroenterol. 2007 Mar; 102(3):558–62. [PubMed: 17156142]
9. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013 Jun; 144(7):1419–25. [PubMed: 23419359]
10. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009; 32(1):55–68. [PubMed: 19132805]
11. United States Census Bureau, Population Division [Internet]. Table 1. Annual Estimates of the Resident Population for the United States, Regions, States, and Puerto Rico: April 1, 2010 to July 1, 2016 (NST-EST2016-01). 2016. [cited 2016 Sep 19]. Available from: https://www.census.gov/data/tables/2016/demo/popest/state-detail.html
12. United States Census Bureau [Internet]. American Fact Finder. 2014. [cited 2016 Sep 19]. Available from: https://factfinder.census.gov/faces/nav/jsf/pages/community_facts.xhtml
13. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014 Oct; 60(4):1399–408. [PubMed: 25043597]

Key Points

1) Prospective gastroenterologist-based surveillance for suspected DILI in Delaware yielded an incidence of 2.7 cases per 100,000 adults in 2014; this is the first prospective estimate of DILI for the United States. These findings provide a benchmark statistic for the epidemiology of DILI in the United States, to be refined with expansion of the surveillance period.

Table 1
Comparative Demographics between Delaware and the Total U.S. Population

	DELAWARE	UNITED STATES
Population, Census, 2014	934948	314107084
Persons under 18 years, percent, 2014	22.3	23.5
Female persons, percent, 2014	51.6	50.8
White alone, percent, 2014	69.7	73.8
Black/African American alone, percent, 2014	21.6	12.6
American Indian and Alaska Native alone, percent, 2014	0.3	0.8
Asian alone, percent, 2014	3.5	5
Native Hawaiian and Other Pacific Islander alone, percent, 2014	0.1	0.2
Two or More Races, percent, 2014	2.6	2.9
Hispanic or Latino, percent, 2014	8.6	16.9
High school graduate or higher, percent of persons age 25 years+, 2014	58.5	57.1
Bachelor's degree or higher, percent of persons age 25 years+, 2014	29.4	29.3
Median household income (in dollars), 2014	60231	Not Available
Mean household income (in dollars), 2014	74596	59521

Table 2

Selected Clinical Characteristics of Drug vs HDS Induced Liver Injury in Delaware Population

Characteristics	Drugs (n=8)	HDS (n=6)	P-value
Age in Years, Mean (Range)	47 (21-72)	55 (33-80)	0.44
Sex, Percent Male -- n (%)	4 (50%)	2 (33%)	0.63
Abdominal Pain -- n (%)	3 (38%)	0 (0%)	0.21
Jaundice at Onset -- n (%)	3 (38%)	4 (68%)	0.59
Rash at Onset -- n (%)	0 (0%)	1 (17%)	0.43
Fever at Onset -- n (%)	2 (25%)	1 (17%)	1.00
Eosinophilia at Onset (>5%) -- n (%)	2 (25%)	0 (0%)	0.47
Initial TB mg/dL, Median (25th, 75th)	5.9 (0.5,9.3)	4.6 (0.8,9.4)	0.80
Initial ALT U/L, Median (25th, 75th)	588 (379,1070)	1110 (548,1317)	0.31
Initial AST U/L, Median (25th, 75th)	317 (202, 719)	827 (662, 953)	0.12
Initial AP U/L, Median (25th, 75th)	363 (195, 527)	172 (147, 198)	0.05
Initial R-Ratio, Median (25th, 75th)*	4 (1.3, 35.1)	16 (14, 21)	0.30
Hepatocellular Pattern -- n (%)	4 (50%)	6 (100%)	0.05
Peak TB mg/dL, Median (25th, 75th)	8.2 (3.5,16.3)	5.3 (4.7,9.4)	0.37
Peak ALT U/L, Median (25th, 75th)	681 (558, 2172)	1205 (548, 1738)	0.69
Peak AST U/L, Median (25th, 75th)	545 (306, 1431)	1013 (662, 1086)	0.37
Peak AP U/L, Median (25th, 75th)	411 (199, 662)	172 (147, 228)	0.05
Median Days from Onset to Peak TB	15 Days	5 Days	0.65
Days from Peak to 50% Reduction in TB	12 Days	25 Days	0.05
Liver Injury Lasting >4 Weeks -- n (%)	2 (25%)	3 (50%)	0.09
Hospitalization -- n (%)	7 (88%)	2 (33%)	0.09
Death -- n (%)	0 (0%)	0 (0%)	----

TB-Total Bilirubin
ALT-Alanine Aminotransferase
AST-Aspartate Aminotransferase
AP-Alkaline Phosphatase