Published in final edited form as:
Clin Gastroenterol Hepatol. 2010 July ; 8(7): 635–637. doi:10.1016/j.cgh.2010.03.020.

Detective Work in Drug-induced Liver Injury: Sometimes It's All about Interviewing the Right Witness

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Abstract

Background—Diagnosing drug-induced liver injury (DILI) relies on history as there are no definitive diagnostic tests. We report four cases where DILI was missed or the drug misidentified when physicians relied solely on patient history.

Methods—We reviewed 27 cases referred with possible DILI from August 1, 2009 to February 1, 2010.

Results—Four patients seemed to be reliable historians, but their cases were clarified by a call to their pharmacist. One subject had an unfruitful evaluation including surgery. Another patient had acetaminophen toxicity that was missed, as she grossly under-reported her pain medication use. The third and fourth patients forgot taking amoxicillin/clavulanate, so another agent had been mistakenly implicated. Roussel UCLAF Causality Assessment Method (RUCAM) DILI scores were 8 (probable) or 9 (highly probable) for all four cases. Without pharmacy input, DILI was missed in two cases and the wrong agent implicated twice.

Conclusion—Pharmacy information carries important ramifications for patients and DILI research. We recommend calling the pharmacist directly for elevated liver enzymes of unclear source or suspected DILI regardless of patient history.

Keywords

Drug-induced liver Injury; DILI; hepatotoxicity; alfuzosin; acetaminophen; amoxicillin/clavulanate

Introduction

History taking is central to the diagnosis of drug-induced liver injury (DILI). The most cited DILI causality assessment tools are the Roussel UCLAF Causality Assessment Method (RUCAM), the Maria and Victorino scale, and expert opinion. Each relies on accurate information regarding agents taken and timing[1-3]. Health care providers are taught to trust patient histories when the patients appear to be reliable historians. As polypharmacy becomes more common, patient recall of medications can deteriorate within the time frames

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Disclosures: The authors have no conflicts of interest to disclose.

of delayed hepatoxicity seen in DILI. Getting outpatient pharmacy records is not often taught in training, but doing so can prove critical when investigating DILI.

Methods

We reviewed 27 patients referred for possible DILI, between August 1, 2009 and February 2, 2010. Twenty-four were ultimately diagnosed as DILI and enrolled in the Drug-induced Liver Injury Network (DILIN) registry.[3, 4] Four misdiagnosed patients (15%) are reported here. RUCAM scores were determined by the authors for all 4 cases.

Cases

Case 1

An 83 year old man went to the emergency room with upper abdominal pain. His bilirubin was 3.4 mg/dL, but his liver enzymes were normal. Four days later, his bilirubin was 14.2 mg/dL, with trivial elevations in his transaminases and alkaline phosphatase (AP). He admitted to taking only fexofenidine, omeprazole, restoril, and atenolol all for more than 2 years. Over the next two weeks the bilirubin climbed to 18mg/dl without a clear etiology in spite of a thorough investigation[i]. An abdominal ultrasound suggested cholelithiasis, followed by a failed ERCP. Cholecystectomy with open liver biopsy was done. Intra-operative cholangiogram was normal. The liver biopsy showed moderate cholestasis with non-alcoholic fatty liver disease. He was referred to our center, where a missed DILI was considered. A phone call to his pharmacist revealed a new medication, alfuzosin (Uroxatral®), for benign prostatic hypertrophy started 4-5 weeks prior to his elevated liver enzymes. When confronted with his pharmacy records, he and his wife embarrassingly admitted this oversight. He had stopped the medication on his own a few weeks prior to presentation because he noted abdominal discomfort. RUCAM score for this case was 8 or “probable” for DILI.

Case 2

A 70 year old woman with multiple medical problems, including chronic abdominal pain, anxiety, depression and idiopathic seizures, went to her physician for increased fatigue. Her ALT was 1170 U/L, AST 3150 U/L, AP 217 U/L, bilirubin 0.6 mg/dL and INR 1.0. When her INR climbed to 1.5, she was admitted. A thorough investigation was unrevealing. She was on 12 medications including enalapril, sertraline, cyclobenzaprine, atenolol, clonazepam, phenergan and phenytoin. She was on all her other medications for at least two years, the phenytoin at a stable dose for over 20 years. She admitted to taking acetaminophen + codeine (Tylenol #3®: 300mg acetaminophen + 30mg codeine) for migraines but *only 1-2 per month maximum*. She denied over-the-counter analgesics. With this history given to the admitting physicians, no acetaminophen level was checked and her liver enzymes improved quickly over 3-4 days. She was seen at our center 10 days later with normal LFTs. She gave the same medication history, but we suspected a missed DILI. A phone call to her pharmacist revealed numerous prescriptions for acetaminophen + codeine for at least the past five months from different providers. In the five weeks prior to her illness, a total of 128 tablets were dispensed. Assuming she took a relative overdose of acetaminophen in the setting of chronic phenytoin use, her RUCAM score would be 9 or “highly probable.”

[i]A “thorough investigation” for this and subsequent cases includes viral hepatitis serologies, autoimmune markers, serologies for primary sclerosing cholangitis and primary biliary cirrhosis as well as normal imaging unless otherwise stated.

Case 3

A 78 year old woman developed pruritus followed by elevated liver enzymes and jaundice over a week. Initial ALT was 312 U/L, AST 243 U/L, AP 371 U/L and bilirubin 2.2 mg/dL. Viral serologies, autoimmune markers and imaging were unremarkable. A liver biopsy showed lobular and portal inflammation of mixed cellular type with cholestasis but no fibrosis. Her liver enzymes steadily fell while holding all 13 of her medications, and 45 days later her liver enzymes and bilirubin were normal. All her medications were gradually re-introduced without difficulty except losartan and simvastatin which were discontinued permanently. Her admitting hospitalist and consulting gastroenterologist implicated these two agents as causing DILI. Upon evaluation at our center, her pharmacist was called. Records indicated that she picked up a prescription for amoxicillin/clavulanate 31 days prior to her illness. When confronted with this information, she then recalled taking this antibiotic for 10 days for an upper respiratory infection. She had not taken this medication before. RUCAM score was 9 or “highly probable” for amoxicillin/clavulanate.

Case 4

A 52 year old woman took 10 days of amoxicillin for cellulitis. She was adamant that only amoxicillin was given. Two weeks after starting the antibiotic she had nausea, dark urine and pruritus. Three days later, her ALT was 211 U/L, AST 118 U/L, AP 145 U/L and bilirubin 9 mg/dL. Viral hepatitis serologies were all negative. ANA was positive at 1:160, but ASMA and AMA were negative. Immunoglobulin levels were normal. A liver biopsy showed cholestasis with minimal inflammation and no plasma cell infiltrate, piecemeal necrosis or fibrosis. Her consulting gastroenterologist referred her to our center regarding possible rare amoxicillin DILI. On evaluation at our center, the patient was quite clear and adamant that there was no other medication except amoxicillin listed on the bottle dispensed to her. A phone call to the pharmacist confirmed that the patient was given amoxicillin/clavulanate. She recovered fully with her liver enzymes falling to normal 9 weeks after presentation. RUCAM score was 9 or “highly probable”.

Discussion

Complete identification of all medications is a fundamental element in determining DILI causality.[1-3] With increasing polypharmcy via multiple providers, obtaining a high level of accuracy can be difficult if one relies solely on patient recall. We present four remarkable cases where both primary care physicians and gastroenterologists were lead astray based on patient history alone. In each case, a phone call to the patient's pharmacist greatly clarified the diagnosis of DILI (Table 1).

In Case #1, the patient and his wife repeatedly told their physicians that no new medications had been taken. The evaluation prior to referral to our center was extensive and invasive, including an attempted ERCP, cholecystectomy and intraoperative cholangioram. A phone call to the patient's pharmacist confirmed alfuzosin as a new medication taken a few weeks prior. There are three reports of DILI in the literature, two hepatocellular injuries and one mixed, cholestasis and hepatocellular.[5-7]

For Case #2, the patient grossly under-reported her acetaminophen + codeine use. The discrepancy between her report and the amount dispensed was so large, that willful misreporting is highly suspected. This patient's threshold for acetaminophen toxicity is likely lower than normal due to her concomitant phenytoin use. Acetaminophen is metabolized by cytochrome (CYP) P4502E1 and CYP3A4. Phenytoin is a potent inducer of CYP3A4 and activation of this enzyme enhances acetominophen hepatotoxicity at doses as low as 2g per day [8]. Acetaminophen remains the leading cause of acute liver failure in the

United States and approximately half are due to medicinal over use without suicidal intent[9-11]. The patient recovered without use of N-acetylecysteine. We advised ‘unbundling’ her pain medications so that acetaminophen is not prescribed and she has done well without recurrence of liver injury.

Cases #3 and #4 involve amoxicillin/clavulanate, a combination medication well described to cause DILI.[12] In Case #3, the patient forgot taking the antibiotic, so a statin was implicated. In case 4, the patient identified only amoxicillin on her medication bottle. Since amoxicillin/clavulanate became generic, the well-known brand of Augmentin® is less often prescribed. “Amoxicillin/clavulanate” often does not fit on one line on a small prescription bottle. Many patients only remember the familiar “amoxicillin” portion of the first line.

The implications of missing pharmacy records in cases of DILI are vast. Unnecessary medical testing and invasive procedures may be done with increased cost and morbidity. Identifying the wrong medication leads to inappropriate avoidance of the wrongly implicated drug and risk of re-challenge with the culprit agent. Our cases illustrate how these mishaps may be avoided by interviewing a star witness to the incident: the pharmacist.

Recently, attention has been drawn to the quality of reporting DILI cases in the literature.[13] For growing registries in DILI research, drug misidentification changes a rather rare DILI case, amoxicillin, to one of the most common in the registry, amoxicillin/clavulonate [4]. As we move toward genome wide analysis of DILI populations, such misclassification could undermine downstream genetic analyses. Without pharmacy records, two of the cases would have been misclassified in the registry and the third would not have been enrolled.

For our center, calling a patient's pharmacist is routine in the evaluation of elevated liver enzymes of unknown etiology or DILI. While most times this endeavor corroborates the history obtained, important clarification is obtained in 15% of suspected DILI cases. For these patients, the implications are large and their cases can often be ‘closed’ with a single phone call. For DILI research, such accuracy increases the chances that genetic studies will bear useful information.

Acknowledgments

This research was supported, in part, by grants from the National Institutes of Health U01 DK065201, T32 DK07634 and P30 DK034987.

Abbreviations

DILI	Drug-induced Liver Injury
DILIN	Drug-induced Liver Injury Network
APAP	Acetaminophen
RUCAM	Roussel UCLAF Causality Assessment Method
NIH	National Institutes of Health
AST	aspartate aminotransferase
ALT	alanine aminotransferase
AP	Alkaline phosphatase
ANA	Anti-nuclear antibody
AMA	Anti-mitochondrial antibody

ASMA	anti-smooth muscle antibody
LFTs	Liver Function Tests

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Table 1

Summary of diagnoses and RUCAM scores before and after phone call to pharmacist

Case	Diagnosis before call to pharmacist	Diagnosis after call to pharmacist	RUCAM score	RUCAM category for likelihood of DILI
1	cholecystitis + cholangitis	alfuzosin DILI	8	probable
2	acute liver injury of unknown cause	acetaminophen DILI	9	highly probable
3	simvistatin DILI	amoxicillin/clavulanate DILI	8	probable
4	amoxicillin DILI	amoxicillin/clavulanate DILI	9	highly probable

DILI = drug-induced liver injury

RUCAM = Roussel UCLAF Causality Assessment Method. The RUCAM generates a score of attribution to a particular medication based on clinical information. Scores are then grouped into categories of “highly probable” (score > 8), “probable” (score 6-8), “possible” (score 3-5), “unlikely” (score 1-2) or “excluded” (score ≤ 0).[1]