CASE REPORT

Celecoxib-induced cholestatic liver injury

Timothy J. Judson, Rachel M. Feldman, Kevin Wood, Carlos A. Pagan, David W Wan, Todd Cutler

Weill Cornell Medical College, New York, United States

Correspondence: Timothy J. Judson, MPH. Address: 420 East 70th St, Weill Cornell Medical College, New York, NY 10021, United States. E-mail: tij2004@med.cornell.edu

Received: February 28, 2014 **Accepted:** April 30, 2014 **Online Published:** May 13, 2014
DOI: 10.5430/crcp.v1n2p90 **URL:** http://dx.doi.org/10.5430/crcp.v1n2p90

Abstract

Although drug-induced liver injury is common, physician awareness of specific drug reactions is often limited. Celecoxib-induced drug injury has not been widely reported. We describe the case of a 28 year-old woman who presented to the emergency department with cholestatic liver injury following 13 days of celecoxib use. We searched the literature and reviewed existing case reports of celecoxib-induced liver injury to highlight similarities and offer a discussion of the associated pathology.

Key words

Cholestasis, Liver injury, Adverse drug reaction, Celecoxib, NSAIDs, Jaundice

1 Introduction

Although drug-induced liver injury is common, the mechanism of action is often unknown. Treatment primarily consists of withdrawal of the offending agent and supportive care. Therefore, it is vital that physicians be aware of adverse drug events so that, in cases where there is suspicion for underlying iatrogenic injury, the offending agent can be withdrawn rapidly. There is a need for documentation of specific drug-induced causes of liver injury to increase such awareness. In this article, we present the case of a woman with severe cholestasis after 13 days of use of the non-steroidal anti-inflammatory drug (NSAID), celecoxib, and we provide a review of the available literature on this cause of drug-induced liver injury.

2 Case report

In October 2013, a 28-year-old Caucasian woman presented to our hospital with worsening jaundice. She started taking celecoxib 200 mg once daily for knee pain following a sports injury. Ten days later, she noticed dark urine that did not improve with hydration. On day 13, she developed diffuse pruritus, light colored stools, and nausea without vomiting and stopped taking celecoxib. She then presented to an outside hospital where her total bilirubin (mg/dl)/alkaline phosphatase (IU/L)/aspartate aminotransferase (IU/L)/alanine aminotransferase (IU/L) were 3.9/194/107/246 (see Table 1). An abdominal ultrasound and CT imaging of the abdomen and pelvis were unremarkable.

Approximately 15 days after beginning celecoxib she presented to an outpatient gastroenterologist who noted that her liver function tests continued to increase (15.6/244/145/291). An infectious work-up for viral hepatitis and autoimmune

hepatitis was unrevealing. She was prescribed ursodiol, cholestyramine, and amitriptyline for symptom control. Her symptoms continued to worsen and approximately 31 days after starting the drug she presented to our emergency department for evaluation.

Table 1. Liver function tests over course of illness

Approximate Days after starting Celecoxib	13	15	31 (Admission to our hospital)	34 (Discharge from our hospital)	55	125	214
Total bilirubin (mg/dl)	3.9	15.6	18.8	15.7	10.9	1.0	0.5
Direct bilirubin (mg/dl)	-	-	12.5	9.7	-	-	-
Alkaline phosphatase (IU/L)	194	244	175	157	208	357	203
Aspartate aminotransferase (IU/L)	107	145	49	42	141	80	37
Alanine aminotransferase (IU/L)	246	291	107	72	157	98	37
INR	-	-	0.9	1.0	1.1	1.1	-

On presentation, she reported persistent pruritus, nausea, fatigue, night sweats, right upper quadrant tenderness and an 11-pound weight loss over three weeks. She had no recent travel or sick contacts. Her past medical history was significant for gastroesophageal reflux disease (GERD), migraines and Epstein-Barr Virus (EBV) infection approximately one and a half years prior to admission. She had no known drug allergies and endorsed minimal social alcohol use of one drink every two weeks. The only other drug she took prior to symptom onset was esomeprazole 20 mg daily, which she began taking for GERD several years prior to presentation.

Her vital signs on admission were 36.8°C, HR 77, BP 116/64, RR 18, and oxygen saturation 99%. Her exam was notable for diffuse jaundice and scleral icterus. Her abdomen was soft and tender to palpation in the right upper quadrant. The liver was not tender and was not enlarged. The physical exam was otherwise unremarkable, without asterixis or other evidence of hepatic encephalopathy.

Laboratory studies on admission confirmed the presence of hyperbilirubinemia with total bilirubin (mg/dl)/alkaline phosphatase (IU/L)/aspartate aminotransferase (IU/L)/alanine aminotransferase (IU/L)/INR of 18.8/175/49/107/0.9. Serologies were negative for viral hepatitis A, B and C, HSV, EBV, and CMV. Autoimmune workup (anti liver/kidney microsomal antibodies, antimitochondrial antibodies and antismooth muscle antibodies) was negative. Ceruloplasmin and iron studies were within normal limits.

Magnetic resonance cholangiopancreatography showed no evidence of biliary obstruction or pancreatic mass. An ultrasound-guided liver biopsy performed on day two of admission revealed extensive canalicular and hepatocyte cholestasis (see Figure 1) and hepatocyte regeneration (see Figure 2) consistent with drug-induced injury. There was no fibrosis (see Figure 3), making chronic liver injury unlikely, and no iron deposits (see Figure 4), ruling out hemochromatosis. In addition, there was no bile duct injury or loss, inflammation or steatosis.

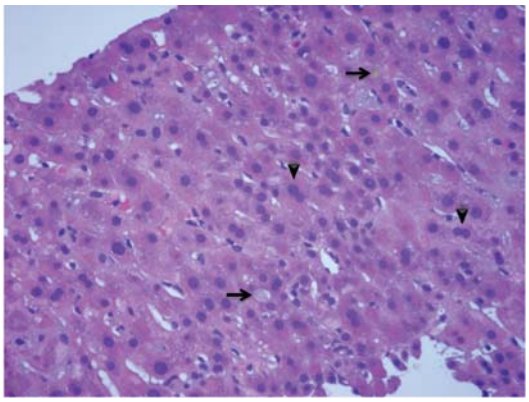

Figure 1. Liver biopsy (H&E 400×) showing cords of hepatocytes, extensive canalicular and hepatocellular cholestasis (arrows) and binucleation (arrow heads)

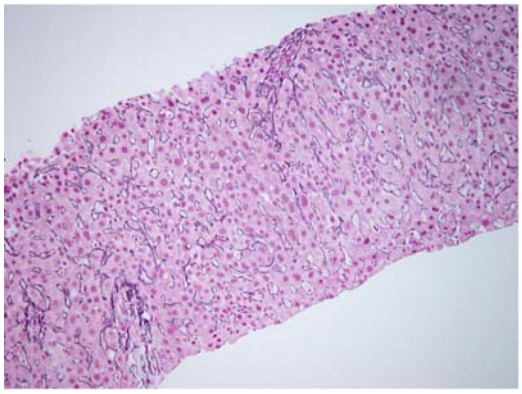

Figure 2. Liver biopsy (Silver/Reticulin stain 200×) outlines hepatocyte architecture showing regenerative features and parenchymal collapse

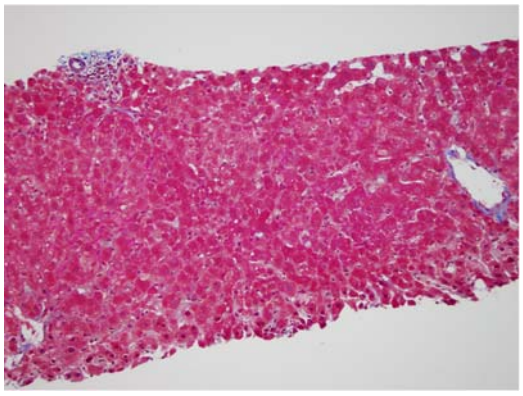

Figure 3. Liver biopsy (Trichrome stain 200×) with no evidence of perihepatic, portal or central fibrosis

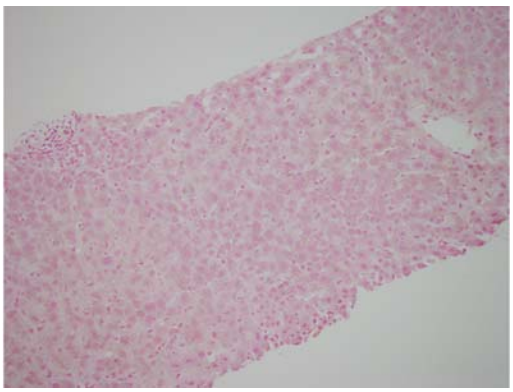

Figure 4. Liver biopsy (Iron stain 200×) showing no iron deposition

A diagnosis of drug-induced liver injury secondary to celecoxib use was made and the patient was discharged from the hospital 34 days after her initial exposure (on day 4 of hospitalization). Three weeks later (day 55) her LFTs were 10.9/208/157/141/1.1 showing a downtrending total bilirubin but increasing alkaline phosphatase, AST and ALT. She continued to have pruritus, nausea and weight loss. Pruritus was managed with doxepin and phototherapy.

Approximately four months after starting celecoxib the patient was asymptomatic without jaundice, nausea or pruritus. Her labs were improving (1.0/357/80/98/1.1), though her alkaline phosphatase remained elevated. About seven months after celecoxib use, the patient's labs improved further (0.5/203/37/37). With continued avoidance of celecoxib and other NSAIDs, a full recovery is expected.

3 Literature review

We identified nine cases of cholestatic injury in which celecoxib was believed to be the offending agent. We used the search engines PubMed, Scopus and Web of Science and the search terms: "celecoxib" and "cholestasis" or "hepatitis" or

 ISSN 2331-2726 E-ISSN 2331-2734

"jaundice" in title, abstract or key words. The nine cases were published between 2001 and 2013. Including the case described above, we have compiled data from the 10 suspected cases of celecoxib-induced liver injury.

4 Data analysis

Eight of the ten reported cases occurred in females with a median age of 50 years old. Most patients had no or noncontributory past medical history. There was a wide range of duration of celecoxib use and time to presentation. One patient took celecoxib for two years prior to presentation [1] while another took just three total doses [2]. Median time to presentation was approximately three weeks. The most common presenting symptoms were jaundice, dark urine and pruritus (see Table 2).

Table 2. Most common presenting symptoms

Symptom	(%, n = 10)
Jaundice/icterus	80
Choluria (dark urine)	60
Pruritis	60
RUQ/epigastric pain	40
Nausea	40
Fatigue/malaise	40
Anorexia	40
Pale stools	30
Weight loss	20

Total bilirubin on admission ranged from 3.4 mg/dl – 31.6 mg/dl, with a median of 23.3 mg/dl. Median alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase were 325 IU/L, 802 IU/L and 710 IU/L, respectively (see Table 3). Biopsies were performed in eight of the ten cases. In several cases, pathology showed bile plugs with varying degrees of inflammatory infiltrate suggestive of drug-induced liver cholestasis.

Table 3. Lab values on admission (included on separate document for easier viewing)

Case	Nachimuthu 2001 [9]	Grieco 2002 [2]	Zinsser 2004 [1]	Hajj 2009 [10]	Chamouard 2005 [11]	Nayudu 2013 [6]	Galan 2001 [12]	O'Beirne 2001 [13]	Alegria 2002 [14]	Cornell 2014	Range	Median
Duration of celecoxib use	7 days	3 days	2 years	10 days	12 days	3 weeks	16 days	6 days	15 days	13 days	3 days- 2 years	12.5 days
Total Bilirubin (mg/dl)	4.5	17.2	8.8	10.5	19.7	3.4	12.2	7.2	32	18.8	23.3	13.4
Alkaline Phosphatase (IU/L)	150	302	1101	700	613	231	283	232	205	175	325	399
AST (IU/L)	753	45	1032	104	83	244	193	1650	66	49	802	422
ALT (IU/L)	603	97	1058	255	69	458	261	-	49	107	710	329
Approx. time to resolution of lab values	2 weeks	3 weeks	1 year	liver transplant	3 months	1 month	4 months	1 month	3 months	7 months	2 weeks- no resolution	3 months

Treatment consisted of supportive care and withdrawal of celecoxib. Nine of ten cases resolved with cessation of celecoxib use; one patient required a liver transplant. Time to resolution of laboratory values and symptoms ranged from two weeks to 18 months with most resolving in 4 to 12 weeks.

5 Discussion

Although nearly all NSAIDS have been implicated in causing liver injury, selective cyclooxygenase 2 (COX-2) inhibitors like celecoxib are thought to have less potential for hepatotoxicity relative to nonselective NSAIDs [3]. Our case report and existing literature suggests that this risk persists with celecoxib. Celebrex, the Pfizer-owned brand name of celecoxib, was the 21st best-selling drug in the United States in Q4 of 2013 with over $580 million in sales [4]. As with any adverse drug effect, physicians who prescribe celecoxib should be aware of this risk.

The exact mechanisms of liver injury by celecoxib and other NSAIDs remains unclear but are likely due to host-dependent idiosyncratic reactions. Deleterious immunological mechanisms or abnormalities in drug metabolism have been implicated as possible causes [5]. For example, one proposed mechanism involves altering of hepatocellular proteins by acidic NSAIDs, resulting in an antigenic reaction in susceptible patients [5]. Genetic factors that affect hepatic drug metabolism may explain the susceptibility of some patients to drug reactions.

Liver injury can manifest with primary hepatocellular, primary cholestatic or mixed pictures. The degree of these findings can be variable and the differential diagnosis can be broad. In the setting of an acute cholestatic injury, an investigation for acute viral hepatitis, autoimmune and metabolic etiologies of liver injury should be performed. In our case both liver function tests and pathology showed a nearly pure cholestatic injury, which in the absence of a necroinflammatory pattern suggested drug-induced liver injury. Of interest, the pathology in one reported case of celecoxib drug-induced liver injury showed small biliary ducts and pathological features resembling small duct sclerosing cholangitis [6].

Patients who develop NSAID-induced hepatotoxicity must be advised to stop taking NSAIDs permanently. There does not appear to be a clear role for steroids in the management of these patients and we found no published studies addressing this issue. Paracetamol remains the analgesic drug of choice for these patients [7, 8]. Patients may use aspirin safely because aspirin does not contain the diphenylamine ring molecular structure that is believed to give NSAIDs and COX-2 inhibitors their toxicity [15].

To our knowledge, this is the youngest reported case of celecoxib-induced cholestatic liver injury. While celecoxib-induced cholestatic liver injury is a rare event, it is important for physicians to be aware of the risk of possibly fatal hepatoxicity when prescribing this and other NSAIDs, as timely recognition and discontinuation of the drug may prevent life-threatening complications.

References

[1] Zinsser P, Meyer-wyss B, Rich P. Hepatotoxicity induced by celecoxib and amlodipine. Swiss Med Wkly. 2004; 134(13-14): 201. PMid: 15106034.

[2] Grieco A, Miele L, Giorgi A, Civello IM, Gasbarrini G. Acute cholestatic hepatitis associated with celecoxib. Ann Pharmacother. 2002; 36(12): 1887-9. PMid: 12452750. http://dx.doi.org/10.1345/aph.1C110

[3] Maddrey WC, Maurath CJ, Verburg KM, Geis GS. The hepatic safety and tolerability of the novel cyclooxygenase-2 inhibitor celecoxib. Am J Ther. 2000; 7(3): 153-8. PMid: 11317164. http://dx.doi.org/10.1097/00045391-200007030-00003

[4] U.S. Pharmaceutical Sales Q4 2013. Available from: http://www.drugs.com/stats/top100/sales. Accessed February 3, 2014.

[5] Boelsterli UA, Zimmerman HJ, Kretz-rommel A. Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology. Crit Rev Toxicol. 1995; 25(3): 207-35. PMid: 7576152. http://dx.doi.org/10.3109/10408449509089888

[6] Nayudu SK, Badipatla S, Niazi M, Balar B. Cholestatic hepatitis with small duct injury associated with celecoxib. Case Rep Med. 2013; 315479.

[7] Prescott LF. Effect of non-narcotic analgesics on the liver. Drugs. 1986; 32(Suppl 4): 129-47. PMid: 3552580. http://dx.doi.org/10.2165/00003495-198600324-00010

[8] Jones AL. Recent advances in the management of late paracetamol poisoning. Emerg Med. 2000; 12: 14-21. http://dx.doi.org/10.1046/j.1442-2026.2000.00088.x

[9] Nachimuthu S, Volfinzon L, Gopal L. Acute hepatocellular and cholestatic injury in a patient taking celecoxib. Postgrad Med J. 2001; 77(910): 548-50. PMid: 11470953. http://dx.doi.org/10.1136/pmj.77.910.548

[10] El hajj II, Malik SM, Alwakeel HR, Shaikh OS, Sasatomi E, Kandil HM. Celecoxib-induced cholestatic liver failure requiring orthotopic liver transplantation. World J Gastroenterol. 2009; 15(31): 3937-9. PMid: 19701976. http://dx.doi.org/10.3748/wjg.15.3937

[11] Chamouard P, Walter P, Baumann R, Poupon R. Prolonged cholestasis associated with short-term use of celecoxib. Gastroenterol Clin Biol. 2005; 29(12): 1286-8. http://dx.doi.org/10.1016/S0399-8320(05)82223-7

[12] Galan MV, Gordon SC, Silverman AL. Celecoxib-induced cholestatic hepatitis. Ann Intern Med. 2001; 134(3): 254. PMid: 11177350. http://dx.doi.org/10.7326/0003-4819-134-3-200102060-00028

[13] O'beirne JP, Cairns SR. Drug Points: Cholestatic hepatitis in association with celecoxib. BMJ. 2001; 323(7303): 23. http://dx.doi.org/10.1136/bmj.323.7303.23

[14] Alegria P, Lebre L, Chagas C. Celecoxib-induced cholestatic hepatotoxicity in a patient with cirrhosis. Ann Intern Med. 2002; 137(1): 75. PMid: 12093262. http://dx.doi.org/10.7326/0003-4819-137-1-200207020-00030

[15] O'connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM. 2003; 96(11): 787-91. PMid: 14566034.