ADVERSE DRUG REACTION

Acute hepatocellular and cholestatic injury in a patient taking celecoxib

S Nachimuthu, L Volfinzon, L Gopal

Abstract

A case of acute hepatocellular and cholestatic liver injury that may have been associated with the use of celecoxib is described. This case was reported to US Food and Drug Administration and the manufacturer of celecoxib.

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Department of Internal Medicine, Lutheran Medical Center, State University of New York Health Science Center, Brooklyn, NY 11220, USA
S Nachimuthu
L Volfinzon

Department of Internal Medicine, Brookdale University Hospital and Medical Center, Brooklyn, NY
L Gopal

Correspondence to:
Dr Nachimuthu
nsen1@hotmail.com

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Celecoxib (Celebrex, G D Searle & Co, Chicago, Illinois) is a newer non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities with minimal gastrointestinal, platelet, and renal side effects.[1] It has been widely used to alleviate pain and inflammation in osteoarthritis and rheumatoid arthritis. It acts by inhibiting the specific cyclo-oxygenase-2 (COX-2) enzyme. In controlled clinical trials of celecoxib, the incidence of borderline increases in liver test results was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable increases of alanine aminotransferase and aspartate aminotransferase.[1] To our knowledge, acute mixed liver injury induced by celecoxib has not been reported in the literature so far.

Case report

A 67 year old white woman presented to the hospital for severe right upper abdominal pain of two days' duration. She was in her usual state of health until two days before admission when she started to feel mild pain in the right upper abdomen. Since then the pain had progressively worsened. It was radiating to her back and was associated with nausea, vomiting, icterus, and loss of appetite. She denied any associated diarrhoea. On the day of admission, she had a high grade temperature (38.8°C/102°F) at home. She denied any history of recent transfusion or travel and any history of gallstones. She denied any recent intake of alcohol or intravenous drugs. She had no history of allergy to any medication.

She had multiple medical problems, which included hypertension, type II diabetes mellitus, New York Heart Association class II congestive heart failure, myocardial infarction, anaemia, gastrointestinal bleeding secondary to peptic ulcer disease, osteoarthritis, and bilateral knee joint replacement.

She was on the following drugs at the time of admission: enalapril, 5 mg twice a day; metoprolol, 50 mg twice a day; isosorbide mononitrate, 60 mg once a day; frusemide (furosemide), 40 mg once a day; NPH insulin, 20 units in the morning; iron sulphate, 325 mg/three times a day; vitamin C, 500 mg once a day. The patient was started on celecoxib 100 mg twice a day, a week before admission for severe osteoarthritis.

Physical examination revealed low grade fever (37.5°C/99°F), blood pressure 129/68 mm Hg, pulse rate 82 beats/min, respiratory rate 20 breaths/min, and oxygen saturation 95% in room air. Icterus was present and the abdomen was soft. Tenderness was present in the right upper quadrant without any guarding. A smooth, tender liver border was felt 2 cm below the costal margin. No other palpable mass was present. Bowel sounds were normal. Other systemic examinations were within normal limits.

Laboratory values at presentation were as follows: total leucocyte count 13.5 × 10^9/l, haemoglobin 112 g/l, glucose 8.21 mmol/l, blood urea nitrogen 13.7 mmol/l, creatinine 168 μmol/l, sodium 137 mmol/l, potassium 4.7 mmol/l, chloride 105 mmol/l, bicarbonate 25 mmol/l, cholesterol 4.39 mmol/l, protein 71 g/l, albumin 34 g/l, prothrombin time 12.6, international normalised ratio 1.02, and partial thromboplastin time 22.4. The serum amylase level was normal. Results of the liver function tests are shown in table 1.

Celecoxib was discontinued upon admission. In the following days the liver function tests considerably improved and in two weeks returned to normal (table 1).

The hepatic viral titres for A, B, and C were negative for acute hepatic infection. Abdominal sonography was negative for any gallstone,

Table 1 Liver test values in progressive days and weeks

Liver tests	*Baseline*	*Admission*	*Day 1*	*Week 1*	*Week 2*
Total bilirubin (μmol/l)	11.9	83.7	128.2	32.5	15.4
Direct bilirubin (μmol/l)	6.8	51.3	99.2	20.5	6.9
Alkaline phosphatase (U/l)	76	150	161	146	100
Aspartate aminotransferase (U/l)	20	753	279	34	24
Alanine aminotransferase (U/l)	14	603	305	23	27
Lactic dehydrogenase (U/l)	159	702	279	140	142
R value*		4.02			

*R is the ratio of serum activity of alanine aminotransferase to serum activity of alkaline phosphatase.
Normal liver values in SI units: total bilurubin 5.1–17 μmol/l, direct bilirubin 1.7–5.1 μmol/l, alkaline phosphatase 30–120 U/l, aspartate aminotransferase 0–35 U/l, alanine aminotransferase 0–35 U/l, lactic dehydrogenase 100–190 U/l.

gallbladder pathology, or biliary duct dilatation. The pancreas was unremarkable.

A liver biopsy was not done. The patient refused a rechallenge with the same medication.

Discussion

Our patient developed signs and symptoms of acute liver injury within a week of starting celecoxib. The signs and symptoms disappeared within a few days of discontinuing celecoxib. The liver function tests returned to baseline after two weeks of stopping the drug. These finding were consistent with drug induced hepatotoxicity. Though the temporal relationship in our case was very suggestive of celecoxib induced acute hepatic injury, many reports are needed for causality. There were no reports of acute mixed hepatic injury with the use of celecoxib at the time when this adverse reaction was notified to the manufacturer. The cumulative post-marketing data are pending. Recently, a case of acute pancreatitis and hepatitis with the use of celecoxib was reported.[2] The patient described in that report did not have any cholestatic injury. There was also one reported case of acute fulminant hepatic failure associated with the use of an another COX-2 inhibitor (nimulside).[3]

Most of the non-drug related causes of acute liver injury like viral hepatitis A, B and C, biliary pathologies, and shock liver have been excluded in our patient. We did not check for other viral, autoimmune, or metabolic causes of acute liver injury. They do not have to be excluded to diagnose a patient as having drug induced liver injury.[4]

Since histological data are not often available, an international consensus panel has agreed on certain laboratory and clinical criteria, to define a drug induced liver disorder.[4] Based on the definition, our patient had a mixed pattern of acute liver injury (both hepatocellular and cholestatic; see box 1).

Celecoxib administration did not produce any clinically relevant changes from baseline in bilirubin, aspartate aminotransferase, alanine aminotransferase, and creatine clearance in either hepatically impaired or normal subject groups.[1] Since celecoxib is metabolised predominately in the liver, it should be introduced at a reduced dose in patients with moderate hepatic dysfunction.[1] Celecoxib is not recommended for use in patients with severe hepatic impairment.[1]

The incidence of acute liver injury induced by NSAIDs was found to have no relationship to age and sex.[5 6] It is also not dependent on dose. The risk was found to be higher during first NSAID prescription.[5] Concomitant use of other hepatotoxic agents resulted in increased rate of liver injury.[5 6]

The exact underlying molecular mechanisms for NSAIDs induced liver injury are poorly understood. The adverse effects are due to either host dependent idiosyncratic reactions or dose dependent intrinsic reactions.[7 8] Idiosyncratic reaction, which is the most common type, is mediated by either an immunological mechanism or abnormalities in drug metabolism.[8] While most of the NSAIDs cause idiosyncratic reactions, a few NSAIDs like salicylates and sulindac exhibit intrinsic reactions.

NSAIDs produce different types of liver pathologies. Examples are granulomatous hepatitis (phenylbutazone), hepatonecrotic lesions (phenylbutazone, sulindac, diclofenac, pirprofen, piroxicam), cholestasis and cholestatic hepatitis (sulindac, benoxprofen, ibuprofen, phenylbutazone, piroxicam).

Recently it was found out that COX-2 enzymes were highly expressed in many gastrointestinal and skin cancers. They were also found to have a role in the pathogenesis of Alzheimer's disease.[9] In future, COX-2 inhibitors may have a role in the chemoprophylaxis of many cancers.[10] Physicians should be aware of the possibility of serious liver injuries with the use COX-2 inhibitors, and caution used if they are taken in combination with other hepatotoxic agents or in patients with underlying liver disorders.

Box 1: Criteria for drug induced liver disorder[4]

Abnormalities of liver tests
It is defined as rise in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or bilirubin between the upper limit of normal and twice of its value.

Acute liver injury
It is defined as an increase of more than twice of upper limit of normal range of alanine aminotransferase or a combined increase in aspartate aminotransferase, alkaline phosphatase, and total bilirubin, provided one of them was twice the upper limit.

Acute
Duration is less than three months.

Chronic
Duration is greater than three months.

Hepatocellular injury
An increase of more than twice of the upper limit of normal range in alanine aminotransferase or R>5 (R is the ratio of serum activity of alanine aminotransferase over serum activity of alkaline phosphatase).

Cholestatic injury
An increase of more than twice of the upper limit of normal range in alkaline phosphatase alone or R<5.

Mixed
Both alanine aminotransferase and alkaline phosphatase were increased and R is in between 2 and 5.

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