Herbal Drugs: Friend or Foe?

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We herein report a rather peculiar case of acute liver injury. A 78-year-old woman developed asthenia and weakness. Her previous medical history was irrelevant, except for having received etoricoxib 60 mg/24 h for osteoarthritis 1 month before. Liver biochemistry indicated hepatic failure; all tests for viral, bacterial, or parasitic infections were negative, as were the autoimmunity tests. As the patient's status gradually declined, a transjugular hepatic biopsy was obtained and confirmed hepatocyte necrosis with severe inflammation and presence of numerous eosinophils. Suspecting a potential toxic cause of the disorder, the patient was questioned and admitted curcuma consumption for a long time. She was asked to discontinue it and her status gradually improved, with normalization of all the analytical parameters. On the long-term follow-up, she remains well. We consider that this case of acute liver injury can be explained with the combination of the acute toxic effect of a drug, etoricoxib, and the herbal remedy curcuma. This case is illustrative of the risk of interactions between drugs and natural remedies, and to the best of our knowledge, it is the first case of severe hepatotoxicity related to etoricoxib, probably potentiated by long-term curcumin intake. Besides, it illustrates the fact that patients do not generally consider natural remedies as potential source of toxicity, and this can lead to a delay in diagnosis. (J CLIN EXP HEPATOL 2019;9:409–411)

It is a well-known fact that many drugs are potential sources of hepatotoxicity. The coxibs are a family of drugs that selectively inhibit cyclooxygenase 2¹ and have been used for the last decades as a therapeutic alternative for several severe inflammatory disorders because of their potent anti-inflammatory effect. In recent times, concerns have arisen regarding the increased risk of cardiovascular events, and some of them have even been withdrawn from the market.² Gastrointestinal adverse effects seem to be less with the coxibs than with the conventional nonselective anti-inflammatory drugs, but information regarding hepatic adverse effects is scarce. Hepatotoxicity is described in the fact sheet of all these drugs, mainly cholestatic, as stated by Bessone et al and has been reported, mainly with the newer agents rofecoxib and lumiracoxib,³ but to date no case of hepatic toxicity due to etoricoxib has been published, although this drug usually leads to asymptomatic increases of transaminases up to 3 times the upper normal limit of the normal.⁴ We herein report a rare case of hepatotoxicity in which possible coxib (Curcuma longa) consumption.

CASE REPORT

A 78-year-old woman complained of asthenia and epigastric pain 1 month after completion of prescribed etoricoxib (60 mg per day for 2 months) for osteoarthritis. She referred no weight loss, but physical examination revealed mild conjunctival icterus. Laboratory examinations were undertaken that revealed abnormalities in liver biochemistry. The patient had no prior analytical data for comparison. Her general practitioner referred the patient to the gastrointestinal unit at Hospital Clínico San Carlos for further testing. The biochemical abnormalities were confirmed in subsequent analysis, with transaminase values always more than 5 times the upper limit of the normal, and they also revealed a progressive platelet number decrease with prolongation of international normalized ratio (INR) values (Table 1). Abdominal ultrasonography revealed features suggestive of cirrhosis and portal hypertension. All tests performed to detect viral, bacterial, or parasitic infections were negative, as were also all the tests to discard autoimmune disorders, including celiac disease, for one of the patient's son is a celiac. Endoscopy revealed mild esophageal varices. Although she never developed hepatic encephalopathy, the patient's clinical situation did not improve, and a transjugular liver biopsy was performed to identify the cause and severity of liver injury.

At low-power view, the liver seemed to be completely replaced by fibrosis and inflammation. On high-power view, a prominent ductular proliferation was found with almost complete loss of hepatocytes (Figure 1), which persisted in small islands surrounded by fibrotic bands. The inflammatory infiltrate was mainly mononuclear with lymphocytes and prominent presence of eosinophils (Figure 2).

Keywords: coxibs, herbal remedies, toxicity, etoricoxib, *Curcuma longa*

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Table 1 Analytical Evolution of the Patient.

Date	GOT	GPT	Albumin	DB/IB	LDH	GGT	AP	INR	Platelet count
9/18/2015	856	442	3.2	3.8/6.7		202	230	2.3	72,000
10/9/2015	556	350	2.8	2/4.2	498	195	181	2.2	70,000
10/28/2015	458	237	2.6	1.2/3	483	167	185	2	67,500
11/17/2015	437	216	2.6	1.2/2.8	527	149	206	1.8	64,000
12/4/2015	400	212	2.8	1.7/4.1	438	135	207	1.8	60,000
4/21/2016 ^a	28	36	2.8	NA/1.3	526	27	98	1.5	62,000
9/9/2016	31	20	3.6	NA/1	430	19	87	1.3	64,000
6/7/2017	25	17	4.1	NA/0.9	332	16	77	1.3	67,000

GOT = alanine aminotransferase; GPT = aspartate aminotransferase; DB/IB = direct bilirubin/indirect bilirubin; LDH = lactate dehydrogenase; GGT = gammaglutamyl-transpeptidase; AP = alkaline phosphatase.

^aFirst analytical data after turmeric discontinuation.

Figure 1 Small islands of hepatocytes with loss of hepatic architecture and regenerative changes (hematoxylin-eosin, ×100).

Figure 2 High-power view of the inflammatory infiltrate with a prominent presence of eosinophils (hematoxylin-eosin, ×200).

On this information, the patient was asked again about potential toxic substance consumption and she denied any drug consumption since August, when she finished her etoricoxib course. However, when specifically questioned

about other kind of substances she might use, she acknowledged long-term use of turmeric for her osteoarthritis. She had never referred this use before, for she considered this substance healthy and secure. She was asked to completely withdraw curcuma, and she was started on steroids with an initial dose of 60 mg/day of prednisone. Her clinical situation gradually improved, and in April 2016, her biochemical data had completely returned to normal.

She was discharged with low doses of steroids (10 mg/24 h). At the time of writing, she remains well and disease free.

This case was considered because of the possible interaction between etoricoxib and curcuma, for both inhibit cyclooxygenase (COX)-2 and suffer hepatic metabolism, which could have increased toxicity and lead to the acute worsening of chronic liver disease.

DISCUSSION

Drug toxicity is well described, and many drugs have the potential to cause idiosyncratic, toxic, or allergic reactions. The coxibs are a group of selective inhibitors of COX-2 enzyme with a potent anti-inflammatory action, widely used for severe pain management, mainly in osteoarthritis or rheumatoid arthritis. Recently, concerns have arisen regarding potential cardiovascular adverse effects of this family of drugs, but most recent reports seem to blame rofecoxib, which has even been withdrawn in several countries, with significantly less risk for the other members of this drug family. A review of the potential hepatotoxicity of coxibs revealed a higher risk for rofecoxib and lumiracoxib, and even for these, the risk is less than 1 per 100,000 users. A review of coxibs toxicity indicated that there have been no reports on toxicity of etoricoxib, although this drug was usually associated with asymptomatic increases in the transaminase levels, even to 3 times the upper limit of the normal.

On the other hand, turmeric is a well-known spice with medicinal and cuisine uses. It is obtained from the

rhizomes of *Curcuma longa*, a plant growing in the far Eastern countries and has long been claimed to be a good remedy for joint health and also to protect against the toxic effects of hepatotoxic drugs, such as acetaminophen or alcohol. Lots of reports seem to confirm this protective action,⁵ which has also been described for other herbal products.^{6,7} However, little research has been made on the potential toxic effects of this substance. In a review by Balaji and Chempakan,⁸ it was noted that turmeric contains 184 toxic, 136 mutagenic, 153 carcinogenic, and 64 hepatotoxic components. These authors conclude that long-term consumption of this product can be dangerous. This suggestion is further supported by a recent report by Qiu et al.⁹ These authors have analyzed the effects of curcumin, the main component of turmeric, on the liver function. They have shown that curcumin induces overexpression of reactive oxygen expression and initiates a proinflammatory state mediated by interleukins and a decrease of antioxidant and detoxifying enzymes, such as superoxide-dismutase (SOD) and glutathione S-transferase (GST) in rats. These findings were associated with long-term use of this compound. The authors conclude that excessive doses of turmeric or long-term intake can induce oxidative stress, inflammation, and risk of liver injury through metabolic disarrangements and recommend periods of discontinuation of consumption.

We feel that etoricoxib induced hepatic toxic damage in our patient which was potentiated by the large doses of curcumin she had consumed for a long time. Before the coxib, she had had no adverse effects with the herbal remedy she took for her osteoarthritis, and the development of symptoms was coincident with the use of the coxib, so we feel it was this latter drug that initiated the toxic event. However, after coxib discontinuation, her situation gradually deteriorated, probably because of the continued consumption of curcuma, which she did not suspend, despite her situation. Moreover, curcumin can target many genes and molecules, including COX2, which could enhance the toxic effect of the coxib.⁹ We feel our conclusion is sound for all other causes of hepatic damage which were exhaustively discarded, and the biopsy showed prominent eosinophil infiltration; moreover, the withdrawal of these two products led to an improvement of the clinical situation of the patient with normalization of biochemical parameters of hepatic function.

We consider that this case is interesting and illustrative in another sense. The patient referred from the start the consumption of the anti-inflammatory drug and always denied other kind of consumption. Most patients still consider herbal remedies as healthy and secure, which cannot be true, mainly when combined with other drugs that can interact with them. When questioning patients with adverse reactions, it is always essential to specifically ask them about the consumption of this kind of herbal remedies and also vitamins or other supplements, which are not completely devoid of risks but can be falsely perceived as good by the patients.

In summary, we herein report the first case of acute liver injury due to the interaction of etoricoxib and turmeric. It also illustrates the potential risks of herbal remedies, mainly in patients receiving other kind of drugs.

CONFLICTS OF INTEREST

The authors have none to declare.

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