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LETTER TO THE EDITOR

From tinnitus to acute hepatitis: Drug-induced injury caused by use of naftidrofuryl for one year

KEYWORDS
Naftidrofuryl;
Acute hepatitis;
Drug-induced liver injury

Naftidrofuryl is a vasodilator marketed in Europe for the treatment of intermittent claudication in chronic arteriopathy, but is also used for the treatment of tinnitus.

We report a case of acute cytolytic hepatitis induced by naftidrofuryl.

A 61-year-old woman was seen in consultation for elevated liver enzymes in a blood sample performed for asthenia. Her medical history included hepatitis A, endometriosis and appendectomy.

She had not travelled or eaten risk foods (pork products, mushrooms). She drank alcohol occasionally, and smoked three cigarettes per day.

She had been taking naftidrofuryl oxalate (400 milligrams per day) for one year to treat tinnitus. She occasionally took esomeprazole for epigastralgia, and had taken two grams of paracetamol one month earlier for a headache.

On clinical examination, there was no hepatomegaly, no signs of hepatocellular insufficiency or portal hypertension. She had nausea and moderate abdominal pain.

Liver enzymes were normal one year before when a blood test was performed by the Occupational Medicine service.

Laboratory examination revealed cytolysis with a predominantly high alanine aminotransferase level associated with icteric cholestasis (Table 1).

Blood tests for the most common causes, including hepatitis A, B, C and E, Epstein Barr virus, cytomegalovirus, autoimmune hepatitis and Wilson's disease were negative. An abdominal ultrasound was normal. Cholangio magnetic resonance imaging showed no cholelithiasis.

A liver biopsy showed lesions consistent with drug-induced involvement, with many eosinophilic cells. The other abnormalities included an inflammatory infiltrate in the portal spaces attacking the border blade and lesions of cholangitis (Fig. 1).

One month after stopping naftidrofuryl, cytolysis regressed and asthenia decreased (Table 1). Due to the strong likelihood of drug toxicity we filed a statement with pharmacovigilance.

The diagnosis of drug-induced liver injury relies on clinical and chronological criteria [1]. Using these criteria and the Roussel Uclaf Causality Assessment Method (RUCAM) [2], drug causality assessment was ''probable''.

Naftidrofuryl is used for treatment of chronic arteriopathy and for tinnitus. Three cases of acute cytolytic hepatitis induced by this drug have been reported in the literature [3—5].

We report a new case of cytolysis hepatitis in a patient who took naftidrofuryl for one year. The mechanism of liver injury may concern a delayed immunoallergic reaction.

Table 1 Evolution of liver tests.

	2014	11/2015	12/2015	01/2016	2017
AST (U/L) [*n*: 10—35]	N	640	164	55	23
ALT (U/L) [*n*: 10—35]	N	1174	253	71	18
GGT (U/L) [*n*: 5—36]	N	420	325	153	17
PAL (U/L) [*n*: 35—105]	N	164	124	98	60
Total bilirubin (μmol/L) [*n* < 21]	N	39	25	16	8
Conjugated bilirubin (μmol/L) [*n* < 4]	N	30	15	7	4
Prothrombin ratio (%) [*n* > 75]	N	81	81	100	100

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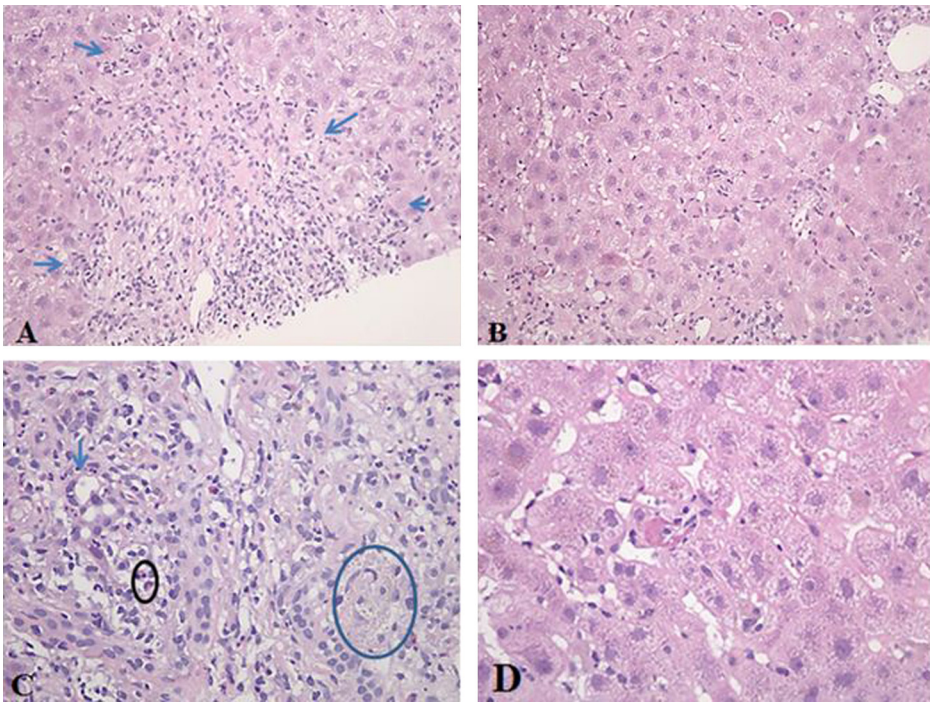

Figure 1 Pathology of the liver, HE staining. Panel A: Aggression of the hepatocyte limiting plate; Panel B: Foci of inflammatory cells with eosinophilic polynuclear cells, lymphocytic cells and histiocytic cells with brownish cytoplasm; Panel C: Cholangitis and polynuclear neutrophil cholangiolitis; Arrow: polynuclear neutrophil; Black circle: eosinophilic polynuclear; Blue circle: histiocytes with brownish cytoplasm; Panel D: Apoptotic body.

Due to an exclusively marketing in Europe, naftidrofuryl is not referenced on the NIH LiverTox website [6]. So we reported this case to remind European clinicians that naftidrofuryl is a potential cause of acute liver injury, even in case of prolonged use.

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None.

Disclosure of interest

The authors declare that they have no competing interests.

References

[1] Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990;11:272—6.
[2] Danan G, Teschke R. Drug-induced liver injury: why is the roussel uclaf causality assessment method (RUCAM) still used 25 years after its launch? Drug Saf 2018;41:735—43, http://dx.doi.org/10.1007/s40264-018-0654-2.
[3] De Caestecker JS, Heading RC. Naftidrofuryl-induced acute hepatic necrosis. Postgrad Med J 1986;62:309—10.
[4] Hebuterne X, Laugery A, Chichmanian RM, Tran A, Rampal P. Acute cytolytic hepatitis probably caused by naftidrofuryl. Gastroenterol Clin Biol 1990;14:514—5.
[5] Cholongitas E, Papatheodoridis GV, Mavrogiannaki A, Manesis E. Naftidrofuryl-induced liver injury. Am J Gastroenterol 2003;98:1448—50, http://dx.doi.org/10.1111/j.1572-0241.2003.07506.x.
[6] NIH LiverTox website, https://livertox.nih.gov/; 2018 [accessed 17 December 2018].

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