

• LETTERS TO THE EDITOR •

Acute cholestasis related to desloratidine

Ramón Pérez, Luis Rodrigo, Rosa Pérez, Ruth de Francisco

Ramón Pérez, Luis Rodrigo, Rosa Pérez, Ruth de Francisco,
Gastroenterology Service, Hospital Universitario Central de Asturias,
School of Medicine, Oviedo, Spain

Correspondence to: Dr. Luis Rodrigo, Gastroenterology Service.
Hospital Universitario Central de Asturias, c/ Celestino Villamil s/n.
33006. Oviedo. Spain. lrodrigos@terra.es

Telephone: +34-985-108058 Fax: +34-985-273614

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TO THE EDITOR

Desloratidine (Clarinet, Neoclaritin, Aerius, Azomyr, Opulis, Alex), the principal active metabolite of loratadine is itself a new oral antihistamine drug. Its main indications are for the treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU). The pharmacologic profile of desloratidine offers particular benefits, in terms of histamine H₁-receptor binding potency and H₁ selectivity. It has a half-life of 21-27 h, permitting a once-daily dose. No specific precautions are required with respect to its administration in renal or hepatic failure. No clinically relevant racial or gender variations in the disposition of desloratidine have been noted.

We present here a clinical case of acute reversible idiosyncratic liver toxicity, related to its administration.

CLINICAL CASE

A 41 year old Peruvian female, with antecedents of acute hepatitis A, hysterectomy for myoma 10 years ago, asthma, recurrent nasal polyposis and chronic rhinitis. The patient also reported having a drug-allergy to aspirin and other NSAIDs. She had been taking desloratidine-5 mg on a daily basis for the last month, for her recurrent rhinitis, when she presented with an episode of acute abdominal pain in the right upper quadrant, associated with abdominal distension, nausea and vomiting.

The patient was admitted to the hospital with a clinical diagnosis of biliary cholic. The hemogram, eosinophil count, coagulation study and serum levels of lipids, glucose, creatinin, amylase and lipase were normal. The liver enzymes were slightly

increased with values of AST = 54 IU/L ($n < 31$) (1.5 x), ALT = 170 IU/L ($n < 31$) (5.5 x), Alkaline Phosphatase = 169 IU/L ($n < 104$) (1.5 x) and Gamma-glutamyl-transferase (GGT) = 209 IU/L ($n < 39$) (5 x). Total bilirubin, was normal (0.8 mg/dL). Serologic markers of IgM Hepatitis A, B, C, EB virus, CMV, measles and simple herpes virus were negative. Anti-HAV IgG was positive, as a consequence of the past hepatitis. Auto-antibodies were negative, immunoglobulins, ferritin, ceruloplasmin and alpha-1 antitrypsin were also within normal range. Desloratidine was withdrawn on the first day of hospitalization. An ultrasonography was normal. No biliary stones or signs of pancreatitis were noted. A magnetic resonance cholangiography, an upper gastroduodenal endoscopy and a total colonoscopy were also completely normal. The patient received only analgesics on demand, as symptomatic treatment and her clinical evolution was excellent, and the patient was discharged 10 days after admission. She remained asymptomatic and the liver function tests returned to normal one month later. No liver biopsy was performed. She had taken no other drug but desloratidine, and referred to only sporadically taking inhaled salbutamol or corticosteroids.

COMMENTS

Desloratidine, is the biologically active metabolite of the second-generation antihistamine loratadine. It is a highly selective peripheral H₁ receptor antagonist that is significantly more potent than loratadine. This drug also has a higher affinity for histamine receptors, 25 to 100 times greater than those of the usual antihistamines, coupled with a capacity to inhibit the production of pro-inflammatory drugs. Desloratidine also inhibits the expression of cell adhesion molecules and the generation and release of inflammatory mediators and cytokines, and decreases eosinophil chemotaxis and superoxide generation^[1].

In combination with the cytochrome P450 inhibitors, ketoconazole and erythromycin, the AUC and C_{max} of desloratidine were increased to a small extent, but no clinically relevant drug accumulation occurred. The therapeutic recommended dose is 5 mg/o.d., and with the use of high-dose treatment (45 mg/d for 10 d), no significant adverse events were observed, despite the sustained elevation of plasma desloratidine levels. Desloratidine is non-sedating and free of antimuscarinic/anticholinergic effects in preclinical and clinical studies. Novel antiallergic and anti-inflammatory effects have also been noted with desloratidine, a fact which may be relevant in relation to its clinical efficacy^[2].

Studies in animals indicate that desloratidine does not cross the blood-brain barrier and therefore does not cause

sedation or impair cognition or psychomotor performance. It has an excellent overall safety profile. It has no effect on QRS and QTc intervals and does not cause arrhythmias. In clinical studies, oral desloratidine is rapidly absorbed and bioavailability is not affected by ingestion with food or grapefruit juice. This drug is not a substrate for P-glycoprotein or organic anion transport polypeptide and does not appear to be metabolized to any significant extent by the cytochrome P450-CYP3A4 pathway^[3].

Once daily administration of 5 mg of desloratidine, rapidly reduces the nasal and non-nasal symptoms of SAR, including congestion. In patients with concomitant asthma, desloratidine treatment is also associated with significant reductions in the total asthma symptom score and use of inhaled beta-2-agonists. Use of desloratidine in patients with CIU, is associated with significant reduction in pruritus, number and size of hives and interference with sleep and daily activities. Due to its powerful action, coupled with an excellent tolerance profile, desloratidine represents a real therapeutic advance for allergic patients. Clinical experience in over 2 300 patients has shown that the adverse effect profile of desloratidine is similar to that of placebo^[4,5].

The case presented here can be considered as a picture of acute cholestasis and is similar to that produced by certain antibiotics, such as amoxyciline/clavulanic or macrolides, NSAIDs and phenotiacines (clorpromazine) amongst others. The pain or sensation of discomfort in the upper right quadrant of the abdomen, the presence of fever and shivering are not rare and this form of presentation can be easily confused with a picture of cholangitis secondary to a biliary obstruction. In around 1% of the cases, the cholestasis persists in spite of the removal of the causal agent, due to a progressive destruction of the cholangiocytes resulting in a ductopenia.

The underlying mechanism of this particular form of hepatocanicular lesion is unknown, although it suggests a phenomenon of autoimmunity directed against the cells of the biliary epithelium after the initial episode of immuno-allergy, and it has been suggested recently that it could be related with a prolonged depletion of the intracellular levels

of adenosine triphosphatase (ATP)^[6].

The incidence of hepatotoxicity due to the new antihistaminics is low, but we should bear in mind that it is necessary to establish a narrow surveillance with all cases and bear in mind the recent report by our group of a similar case of acute hepatitis and skin eruptions related to cetirizine, another drug belonging to this pharmacologic group^[7].

There has been reported a case of severe hepatotoxicity after application of desloratidine and fluconazol in a female 38-year-old, and the authors suggest that all H1 blockers of the second generation should be avoided in patients treated with azole antimycotic agents^[8].

Additionally, three cases of severe liver damage have been described in patients taking loratidine. Two patients treated with loratidine and 1 patient, receiving loratidine and ketoconazole, developed liver injury. Two of the patients received a liver transplant^[9].

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