Telmisartan/hydrochlorothiazide-induced hepatotoxicity

Marco Lorena[1], Aldo Autolitano[1], Giovanni Natale[1], Federica Uberti[1], Fabrizio Vitali[1], Camillo Schiantarelli[1], Nicola Lucio Liberato[2]

[1]Internal Medicine, Azienda Ospedaliera della Provincia di Pavia, Ospedale Civile "Asilo Vittoria", Mortara (PV), Italy
[2]Internal Medicine, Azienda Ospedaliera della Provincia di Pavia, Ospedale Civile "Carlo Mira", Casorate Primo (PV), Italy

Submitted: 27 May 2014
Accepted: 4 July 2014

Arch Med Sci 2015; 11, 4: 893–894
DOI: 10.5114/aoms.2015.53311

Corresponding author:
Nicola Lucio Liberato MD
Internal Medicine
Ospedale C. Mira
Piazzale Volontari del Sangue
27022 Casorate Primo (PV), Italy
Phone: +390290040224
Fax: +390290040304
E-mail: lucio_liberato@ospedali.pavia.it

Drug-induced liver injury (DILI) is a relatively infrequent form of adverse drug reaction, its incidence being between 1 : 1000 and 1 : 100 000; however, it accounts for approximately 10% of all cases of acute hepatitis, is the leading cause of acute liver failure, mainly due to acetaminophen overdose, and is the main reason for approved drug withdrawal from the market [1]. It is rarely predictable, in the majority of cases resulting from an idiosyncratic reaction, and some risk factors have been recognized (alcohol, diabetes, advanced age and female sex). Herein we describe a patient who developed DILI while taking telmisartan-hydrochlorothiazide.

A 72-year-old woman was referred to our department with a 7-day history of weakness, anorexia, nausea, progressive jaundice, dark-coloured urine and pruritus. The patient had a past medical history of arterial hypertension, and had been taking lercanidipine for about 5 years; 4 weeks before admission she was prescribed telmisartan/hydrochlorothiazide because of uncontrolled blood pressure values. She denied blood transfusion, recent surgery, alcohol abuse and relevant family history. Physical examination showed a 2 cm hepatomegaly, other than jaundice. Laboratory testing on admission showed total serum bilirubin to be 15.6 mg/dl (range: 0–1), direct bilirubin 14.8 mg/dl, aspartate (AST) and alanine (ALT) transaminases 33 IU/l and 87 IU/l, respectively (range: 0–32), alkaline phosphatase (AP) 183 IU/l (range: 35–105), γ-glutamyl transpeptidase 552 IU/l (range: 5–36); complete blood count, serum albumin level and coagulation profile, serum iron and ferritin, amylase, copper and ceruloplasmin were normal. Anti-nuclear, anti-smooth muscle, anti-mitochondrial and anti-liver/kidney microsome antibodies as well as viral serologic markers (anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV and HCV-RNA, anti-CMV and anti-EBV IgM and IgG) were all negative. An upper abdominal ultrasound and computed tomography revealed a scleroatrophic gallbladder with normal liver structure and intrahepatic bile ducts. A percutaneous liver biopsy was performed eight days after admission; liver histopathology showed mild mononuclear inflammatory infiltrates in portal tracts without hepatocyte necrosis. Drug-induced liver injury (DILI) was suspected and telmisartan/hydrochlorothiazide was stopped seven days after admission. Serum bilirubin remained substantially unchanged for the first ten days after discontinuation, then gradually began to decrease (Figure 1). Direct bilirubin at discharge (20 days after admission) was 10.3 mg/dl

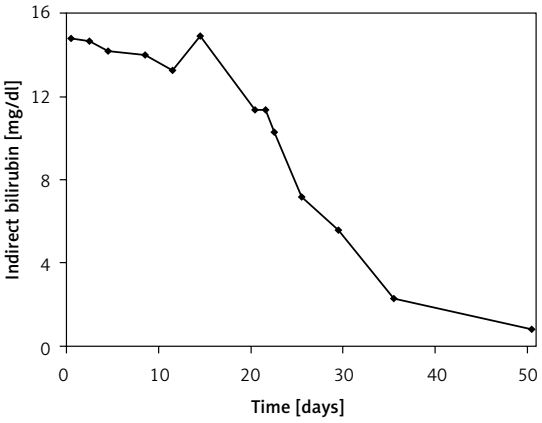

Figure 1. Evolution of indirect bilirubin levels

and returned to normal levels within the next 15 days.

Telmisartan is the angiotensin II receptor antagonist (ARB) with the highest affinity for the angiotensin II type 1 receptor and with the longest half-life. Furthermore, telmisartan acts as an agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ): the consequent expression modulation of genes involved in carbohydrate and lipid metabolism could be the basis for possible metabolic effects of the drug [2]. A marketed combination, frequently used to enhance the antihypertensive effect of ARBs, is telmisartan plus hydrochlorothiazide, a diuretic drug which belongs to the thiazidic class.

This patient was diagnosed with DILI on the basis of 1990 Consensus Meeting criteria [3]: the time to onset of jaundice from the beginning of drugs (25 days) was suggestive, the patient was female and more than 55 years old, alternative causes had been ruled out and the course of the reaction was highly suggestive (although rechallenge has not been performed for either drug). Acute DILI can have a varying pattern of expression [4]: hepatocellular, which mainly affects parenchymal cells; cholestatic, mainly affecting canalicular and/or ductular cells; and mixed cytotoxic/cholestatic. Our case fulfils the diagnostic criteria of cholestatic DILI [3]: although serum AP activity was not significantly increased, the ratio between serum ALT and serum AP activities was below 2. The patient did not report fever, chills or abdominal pain and liver histology showed only minimal inflammatory portal infiltrates: we can therefore more properly define our case as pure cholestasis, in contrast to the more common form of acute cholestatic hepatitis [5].

ARB-induced cholestatic hepatitis has been reported only during treatment with irbesartan [6], while other forms of hepatotoxicity (hepatocellular, mixed) have been reported also with valsartan [7] and losartan [8, 9]. On the other hand, two cases of hydrochlorothiazide-related cholestatic injury have been reported in the literature [10, 11]. Although rare, an acute DILI should therefore be taken into account in the presence of acute hepatotoxicity with negative anamnestic and serological data in hypertensive patients treated with ARB and/or hydrochlorothiazide.

Conflict of interest

The authors declare no conflict of interest.

References

1. Lee WM, Senior JR. Recognizing drug-induced liver injury: current problems, possible solutions. Toxicol Pathol 2005; 33: 155-64.
2. Kurtz TW. Beyond the classic angiotensin-receptor-blocker profile. Nat Clin Pract Cardiovasc Med 2008; 5 (Suppl 1): S19-26.
3. Benichou C. Criteria of drug-induced liver disorders. Report of an International Consensus Meeting. J Hepatol 1990; 11: 272-6.
4. Kaplowitz N. Drug-induced liver injury. Clin Infect Dis 2004; 38 (Suppl 2): S44-8.
5. Larrey D. Drug-induced liver diseases. J Hepatol 2000; 32 (Suppl 1): 77-88.
6. Andrade RJ, Lucena MI, Fernández MC, et al. Cholestatic hepatitis related to use of irbesartan: a case report and a literature review of angiotensin II antagonist-associated hepatotoxicity. Eur J Gastroenterol Hepatol 2002; 14: 887-90.
7. Kiykim A, Altintas E, Sezgin O, et al. Valsartan-induced hepatotoxicity in a HBs-Ag-positive patient. Am J Gastroenterol 2003; 98: 507.
8. Nygaard B, Strandgaard S. Marked hepatotoxicity associated with losartan treatment. Blood Press 1996; 5: 190-1.
9. Bosch X. Losartan-induced hepatotoxicity. JAMA 1997; 278: 1572.
10. Arinzon Z, Alexander P, Berner Y. Hydrochlorothiazide induced hepato-cholestatic liver injury. Age Ageing 2004; 33: 509-10.
11. Taglietti F, Del Nonno F, Baiocchini A, et al. Acute hepatocellular and cholestatic injury during therapy with hydrochloorothiazide – clinicohistopathologic findings: a case report. J Med Case Rep 2010; 4: 332.