CASE REPORTS

Hepatotoxicity by Bosentan in a Patient with Portopulmonary Hypertension: a Case-Report and Review of the Literature

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Abstract

Bosentan is an endothelin receptor antagonist approved for treatment of pulmonary arterial hypertension. Mild liver reactions occur in about 10% of treated patients but severe hepatotoxicity is rare. We present clinical data and treatment outcome of a severe drug induced liver injury due to bosentan in a patient with non-cirrhotic portopulmonary hypertension.

After 18 months of uncomplicated therapy with bosentan 125 mg b.i.d., the patient developed a severe mixed hepatic injury. Serum levels of bilirubin were 316 µmol/l (ref. value <20 µmol/l), AST 14 µkat/l (ref. value < 0.9 µkat/l), ALT 10 µkat/l (ref. value < 0.9 µkat/l), ALP 8 µkat/l (ref. value <1.8 µkat/l) and INR 1.8 (ref. value 0.9-1.1). Complete diagnostic work-up disclosed no other cause of hepatotoxicity. Treatment with prednisolone 40 mg/day in tapering doses was ultimately added and the patient made a full recovery. Subsequent treatment with sildenafil and ambrisentan for pulmonary arterial hypertension was well tolerated and liver function tests have remained normal during 12 months' follow-up. A review of the literature revealed three other women with severe hepatotoxicity due to bosentan.

Bosentan may cause severe liver injury, even after long uneventful therapy, and current recommendations on regular monitoring of liver function tests are reinforced. Ambrisentan may be a therapeutic alternative in patients with pulmonary arterial hypertension and hepatotoxicity by bosentan.

Key words

Portopulmonary hypertension – bosentan – adverse effects – hepatotoxicity.

Received: 13.05.2010 Accepted: 26.05.2010
J Gastrointestin Liver Dis
March 2011 Vol. 20 No 1, 77-80
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Introduction

Portopulmonary hypertension (PPHTN) is a rare condition characterized by pulmonary arterial hypertension (PAH) in association with portal hypertension [1, 2]. The latter may be caused by liver cirrhosis or extrahepatic conditions such as portal vein thrombosis. Pulmonary arterial hypertension is defined according to right heart catheterisation showing increased mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exercise [3]. Various studies report occurrence of PPHTN in 2-5% of patients with portal hypertension [1]. However, the frequency may be higher in patients with end stage liver cirrhosis undergoing evaluation for transplantation [4]. Females with liver disease have a higher risk than males of developing PPHTN. Furthermore, autoimmune hepatitis is associated with higher risk and chronic hepatitis C with a lower risk of PPHTN compared to other liver diseases [5]. The presence of PAH in cirrhosis is a serious prognostic factor and may complicate or preclude liver transplantation.

Bosentan is a dual endothelin receptor antagonist approved for treatment of PAH. It produces pulmonary vasodilatation and improves exercise capacity, cardiopulmonary haemodynamics and delays the time to clinical worsening compared to placebo [6,7]. The most significant adverse effects are liver damage and major birth defects. Mild liver side effects in the form of elevated aminotransferases occur in about 10% of patients and regular monitoring of liver function tests is therefore recommended during treatment. A severe or permanent liver damage has rarely been reported. We therefore report clinical data and treatment outcome of a patient with severe drug-induced liver injury due to bosentan.

Case report

The patient was a 29-year-old woman, who underwent splenectomy in 2001 due to idiopathic thrombocytopenic purpura unresponsive to corticosteroid therapy. In 2007 she suffered from increasing fatigue, severe dyspnoea and right-sided pleural effusion. A diagnosis of PPHTN was made after cardiovascular and hepatologic investigation.

Pulmonary artery pressure was increased to 107/40 mmHg, mean 65 mmHg, and systolic function of the right ventricle was impaired. An abdominal CT scan revealed findings of a previous portal vein thrombosis with an occluded portal vein, multiple collaterals and oesophageal varices were diagnosed at gastroscopy. Liver function tests were normal apart from International Normalized Ratio (INR) 1.3 (ref value 0.9-1.1). A liver biopsy revealed only hepatic steatosis. No underlying myeloproliferative or coagulation disorder was found and the portal vein thrombosis was considered as postoperative after previous splenectomy.

Treatment of pulmonary hypertension with furosemide, spironolactone and bosentan in increasing dose up to 125 mg twice daily was introduced. Oesophageal varices were treated with primary endoscopic ligation, as beta-blockers were considered inappropriate with respect to her cardiovascular disease due to their negative inotropic and chronotropic effects. The patient improved and liver function tests remained normal during regular follow-up.

After 18 months of uncomplicated treatment with bosentan 125 mg twice daily and diuretics, the patient became ill and was admitted to hospital due to jaundice associated with 2-3 weeks history of fatigue, nausea, and poor appetite resulting in weight loss of 6 kg. Laboratory tests showed a mixed hepatic injury pattern. Serum levels of bilirubin were 170 µmol/l (ref. value <20 µmol/l), AST 14 µkat/l (ref. value < 0.9 µkat/l), ALT 10 µkat/l (ref. value < 0.9 µkat/l), ALP 8 µkat/l (ref. value <1.8 µkat/l), INR 1.52 (ref. value 0.9-1.1). Analyses of antibodies against hepatitis A, B, C, Epstein Barr, cytomegalovirus, and autoantibodies (anti-nuclear antibody, smooth muscle antibody, anti-mitochondrial antibody) were all negative. No other medications or herbal products had been used. Drug-induced liver injury was suspected and bosentan was withdrawn on admission.

During the following week, the patient's condition deteriorated both clinically and with respect to liver function tests. Bilirubin increased to 316 µmol/l and INR to 1.8 and aminotransferases remained elevated on the same level. There was no rash, fever, itching, ascites or encephalopathy. Abdominal ultrasound and CT scan were normal except for findings of past portal vein thrombosis. Treatment with prednisolone 40mg/day in tapering doses was ultimately added which turned the course of the condition (Fig. 1). The patient improved and was able to be discharged one week later. The liver tests normalized during the following weeks and corticosteroids were gradually reduced and withdrawn after 8 weeks. As symptoms of PAH worsened after withdrawal of bosentan, sildenafil 20 mg t.i.d. was added to diuretics and presently is combined with ambrisentan 5mg once daily. This therapy has been well tolerated during 12 months treatment and liver function tests have remained normal (Fig. 1).

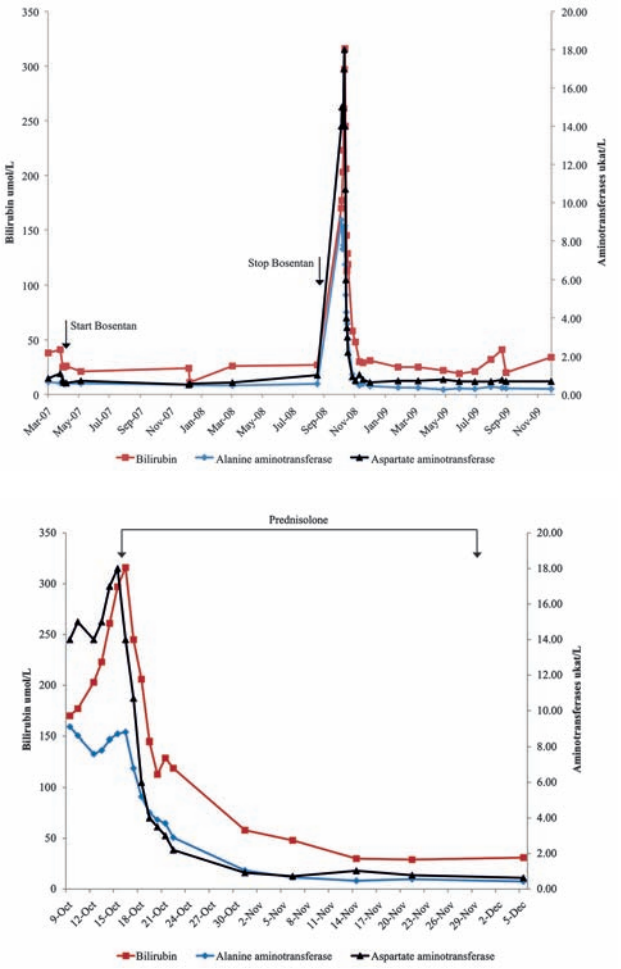

Fig 1. Liver function tests A) during treatment with bosentan and follow-up period after liver damage; and B) magnification of period of liver damage and relation to treatment with prednisolone during the period October-December 2008.

Discussion

Mild hepatotoxicity is a well-recognized side effect of bosentan and elevated aminotransferase levels may occur in about 10% of treated patients. In a European post-marketing surveillance of bosentan in PAH, 352 (7.6%) out of 4,623 treated patients had elevated aminotransferases resulting in withdrawal of therapy in 150 (3.2%) patients [8]. In 10 patients, the liver reaction was reported as serious but other clinical data were not given. Aminotransferase levels of 3-5 times the upper limit of normal (ULN) were most frequent. Abnormal liver function tests occurred mainly during the first 6 months of bosentan therapy and less often after one year [8]. In most cases, liver function tests (LFTs) returned to pre-treatment levels in a few days up to 9 weeks after dose reduction, withdrawal of therapy or even despite continued therapy.

Monthly monitoring of LFT is therefore recommended throughout bosentan treatment. Permanent discontinuation of therapy is advised if aminotransferase levels are greater than 8 times ULN. In levels between 3 to 5 times ULN, the dose of bosentan should be reduced or treatment interrupted. If aminotransferases return to pre-treatment values, bosentan therapy may be continued or reintroduced. In case of aminotransferase levels between 5 to 8 times ULN,

withdrawal of therapy is recommended and if LFTs return to pre-treatment values, reintroduction of treatment may be considered with careful monitoring of LFT [8].

Small variations in occurrence of liver toxicity between different subpopulations have been observed. A higher incidence was reported in patients with PAH secondary to mixed connective tissue disease and a lower incidence in children and in patients with PAH associated with congenital heart disease [8, 9].

Patients with PAH and underlying liver disease with well-preserved liver function may safely be treated with bosentan [8]. This is supported by a small report on 11 patients with cirrhosis (Child-Pugh class A) and PPHTN, who tolerated bosentan well during one year without signs of hepatotoxicity [10]. However, it is recommended that bosentan should be avoided in patients with moderately or severely impaired liver function (Child-Pugh class B or C) [8]. Our patient had non-cirrhotic portal hypertension due to extrahepatic portal vein thrombosis and we considered that her underlying condition did not predispose to liver toxicity.

The liver reaction in our patient differed from clinical trials and postmarketing surveillance data, as the reaction occurred after 18 months of uncomplicated treatment. Furthermore, the liver damage was severe, according to Hy´s rule [11], with distinct clinical symptoms and pronounced jaundice due to a mixed hepatic injury. To the best of our knowledge, there are three other case-reports of severe hepatotoxicity by bosentan [12-14]. A lethal liver injury was seen in a female with mixed connective tissue disease who was treated with bosentan owing to recurrent digital ulcers and progressive gangrene [13]. After two months of treatment with bosentan 125 mg/day, a severe hepatocellular injury occurred and the patient deceased one month later. Dwyer et al reported on a female with PAH and scleroderma, who had an uncomplicated treatment with bosentan for 15 months [12]. Methotrexate was then added, first orally and later on subcutaneously, and after three injections of methotrexate a mixed liver reaction occurred that resolved with supportive therapy only. Oral methotrexate, without concomitant bosentan, was later resumed without further liver complications. The third case was a female with chronic thromboembolic pulmonary hypertension treated with atorvastatin 80mg/day for many years [14]. She presented with vomiting, malaise and jaundice 19 weeks after introduction of bosentan up to 125 mg twice daily. Hepatocellular damage was diagnosed with bilirubin 342 µmol/l and significant elevations of aminotransferases more than 15 times ULN. The abnormal liver function tests were normal within 4-5 weeks without further treatment than withdrawal of bosentan and atorvastatin. Bosentan alone was reintroduced and after only two doses of 62.5 mg the liver damage recurred. Our patient recovered, with respect to both clinical condition and liver function tests, only after corticosteroids were introduced. However, it is hard to state with certainty whether the improvement was because of the steroid treatment or in fact the natural course of the liver damage.

The selective endothelin receptor antagonists sitaxentan and ambrisentan are in general associated with less risk of adverse liver reactions [15, 16]. However, Lavelle et al reported on two patients with severe hepatotoxicity, one of them fatal, occurring 4 months after start of sitaxentan therapy [17]. Hoeper et al presented another female with PAH, who owing to mild bosentan liver reaction was treated with sitaxentan [18]. Four months later she developed severe hepatocellular injury. Treatment with prednisolone was given and LFTs normalised and the patient recovered. Two additional cases of sitaxentan - induced liver damage, one of them lethal, was reported by Barst et al [15]. In an editorial, a 40-yr-old female was described, who after treatment with sitaxentan for 1.5 years developed liver failure that ultimately required urgent transplantation of liver, heart and lungs [19]. It was not determined whether that case was causally related to sitaxentan, as the patient was also treated with other potentially hepatotoxic drugs.

Of interest is that our patient tolerated ambrisentan well during 12 months follow-up. This is consistent with a report of 31 patients, who in spite of earlier abnormal LFT owing to bosentan tolerated ambrisentan well for a median treatment period of 102 weeks [20]. The authors conclude that ambrisentan may be a viable treatment option for patients with PAH who previously have had abnormal LFTs during bosentan therapy. The three existing endothelin receptor antagonists differ in several aspects, including pharmacokinetics, receptor affinity and chemical structure. Bosentan and sitaxentan are sulphonamide analogues, whereas ambrisentan is a non-sulphonamide, propanoic acid derivative. This difference may account for variations in their hepatotoxic effect [21].

The proposed mechanism for bosentan hepatotoxicity is, at least in part, mediated by inhibition by bosentan and its metabolites of the hepatocanalicular bile salt export pump causing intracellular accumulation of cytotoxic bile salts resulting in liver cell damage [22]. In the present case, however, an idiosyncratic drug reaction probably caused the liver damage as liver injury worsened for several weeks after drug discontinuation and responded to corticosteroid treatment. The clinical course of our patient resembled another case with severe sitaxentan liver injury and may support that idiosyncratic mechanisms might occasionally be involved in liver injury caused by endothelin receptor antagonists [19].

Other causes of liver damage in our patient such as viral hepatitis, autoimmune liver disease or other drug or herbal toxicity were ruled out. The long uneventful follow-up furthermore supports that bosentan was the cause of liver injury. Reintroduction of drug will give the ultimate proof of drug-induced liver toxicity but was contraindicated in the present case.

In **conclusion**, the present case and review of the literature emphasize that endothelin receptor antagonists, even after long uncomplicated therapy, may cause severe hepatotoxicity. This is a rare complication but may be lethal in exceptional cases. Current recommendations on

continuous monitoring of liver function tests during such treatment are reinforced by the present data. Ambrisentan may be an alternative in patients with PAH having liver damage by bosentan.

Conflicts of interest

None to declare.

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