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Case Report

Agomelatine-induced liver injury in a patient with choledocholithiasis

Eder P, Permoda-Osip A, Majewski P, Linke K, Rybakowski J K. Agomelatine-induced liver injury in a patient with choledocholithiasis.

Objective: A case of agomelatine-induced hepatotoxicity is described in a 47-year female patient who has received the drug, 25 mg/day, for 4 months, for the treatment of depression.
Methods: The patient was admitted to the Department of Gastroenterology because of fatigue and nausea, with concomitant elevation of alanine aminotransferase (ALT), 550 U/L, and asparagine aminotransferase (AST), 300 U/L.
Results: Liver biopsy showed diffuse lymphocyte infiltration in the dilated portal spaces without lesion of hepatic lobules. Several weeks after stopping agomelatine, the liver enzymes returned to normal. Subsequently, small gallstones in common bile duct were detected and removed by the endoscopic sphincterotomy.
Conclusions: It is hypothesized that choledocholithiasis could theoretically increase a risk of developing agomelatine-induced hepatotoxicity in this patient. Any pre-existing liver disease should be a contraindication for treatment with agomelatine.

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Introduction

Drug-induced liver injury (DILI) is one of the leading causes of acute liver failure with an annual incidence rate worldwide of 14–24/100 000 (1). Among patients treated with antidepressants, 0.5–3% may develop asymptomatic or clinically unspecific elevation of serum alanine aminotransferase (ALT) and asparagine aminotransferase (AST). Antidepressants associated with a greater risk of hepatotoxicity include iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine and agomelatine (2). Agomelatine is a new antidepressant, being a melatonin receptor agonist (MT1 and MT2) and a subtype 5-HT2C serotonin antagonist. Despite the relatively mild profile of the side effects of this drug, its impact on the liver has aroused special concern. According to the Drug Safety Update (3) the elevation of liver enzymes can occur in 1–10/100 patients treated with agomelatine. Gahr et al. (4) analyzed the database of the German Medical Regulatory Body and found 58 cases of DILI caused by agomelatine. They estimated that age >50 years, female sex and polypharmacy may be risk factors for the development of agomelatine-induced hepatotoxicity and also suggested that pre-existing liver disease may be a contraindication for treatment with agomelatine. On the other hand, Karakus et al. (5) published an interesting study showing a potent hepatoprotective effect of agomelatine on paracetamol-induced liver damage, in rats, via antioxidant activity and reduction of proinflammatory cytokines.

In this paper, we report on a female patient with a reversible agomelatine-induced liver injury.

Case report

A female patient, aged 47, with a personal and familial history of gall bladder stones has also suffered short periods of depression for >20 years. In 2001, the first

depressive episode occurred, and she began psychiatric treatment. Since then she has been treated with paroxetine, with fluctuating periods of mild depression and insomnia, and in 2011, the drug was changed to mianserin. Like her mother and older brother who had previously undergone cholecystectomy due to gallstones, she underwent the same operation in 2008, due to symptomatic cholelithiasis. In summer 2013, an exacerbation of depression appeared, with low mood, anxiety and sleep disturbances for which she received trazodone, 75–150 mg/night, with some improvement. In December 2013, owing to another exacerbation of depression, agomelatine, 25 mg/night, was instituted, resulting in significant sleep improvement. In January 2014, the patient began to complain of abdominal pain, lack of appetite and loss of weight (3 kg within 3 months). However, the liver enzymes were normal and she has continued to take agomelatine. During this period the patient did not take other medications except for agomelatine.

In April 2014, the patient was admitted to the Department of Gastroenterology because of fatigue and nausea with concomitant elevation of liver enzymes with ALT and AST levels rising to above 550 U/l (~14 times the upper limit of normal – ULN) and 300 U/l (~8 times ULN), respectively. At the time of admission, there were no signs of liver encephalopathy or jaundice. The physical examination did not reveal any abnormalities and the body mass index was 18.6 kg/m^2 (height 165 cm, weight 50.5 kg). During a thorough interview by an experienced psychiatrist, the patient denied any alcohol consumption within the previous 4 months. Other laboratory tests performed at the time of admission showed elevated concentrations of alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP) (303 and 423 U/l, respectively). Total bilirubin was not elevated. Blood coagulation tests were within the normal ranges and the tests for viral hepatitis (hepatitis A virus – HAV, HBV, HCV, cytomegalovirus) were negative. Wilson's disease and hemochromatosis were also excluded. In an autoimmune assay, an elevated level of anti-nuclear antibodies (ANA, 1 : 5120, with a speckled pattern of staining) was found. Other autoimmune antibodies (including anti-mitochondrial antibodies) were negative. We performed a differential diagnosis, based on clinical and biochemical findings, and no possible causes of ANA elevation were found. Abdominal ultrasound examination was normal. Performed computed tomography (CT) revealed a slightly dilated and irregular common bile duct – CBD (diameter – 9 mm), without any signs of choledocholithiasis or narrowing. Liver biopsy was performed, and showed diffuse lymphocyte infiltration in the dilated portal spaces without any lesions in the hepatic lobules (Fig. 1). The histopathological

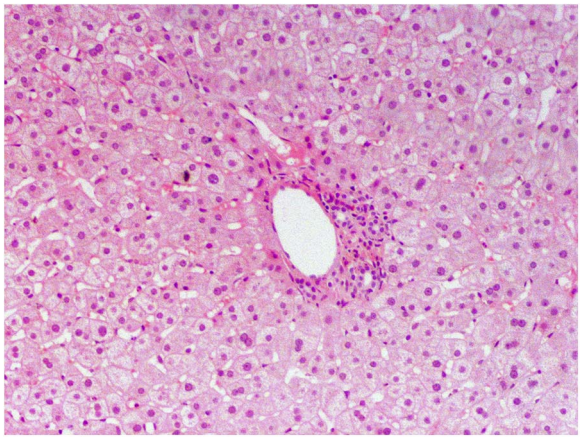

Fig. 1. Liver biopsy. Diffuse lymphocyte infiltration is seen in the dilated portal spaces without lesion of hepatic lobules (H + E, original magnification 100 ×).

examination was suggestive of DILI. Thus, agomelatine, as a potential cause of DILI, was discontinued. Control liver tests within the following weeks revealed a slow normalisation of the ALT and AST levels, associated with a clinical improvement.

In June 2014, the patient was admitted to the Department of Gastroenterology for the second time, in order to conduct control tests. The patient was symptomless, with the ALT and AST within normal ranges. As the concentration of GGTP was slightly elevated, magnetic resonance cholangiopancreatography (MRCP) was performed. This showed the presence of small gallstones in the CBD. Endoscopic retrograde cholangiopancreatography was performed and endoscopic sphincterotomy with balloon-assisted removal of gallstones was undertaken. The post-procedure course was uneventful. Liver tests performed 4 weeks later remained normal.

Discussion

The DILI after agomelatine is predominantly hepatotoxic, however, according to an European Medicines Agency (EMA) report (6), there are also some rare cholestatic cases (0.01–0.1% of adverse effects). In our patient, we found a mixed-type DILI with a predominance of the hepatotoxic component. Probably this is a result of a 'hidden' disease of the bile duct, with some additional cholestatic features which increased the probability of developing hepatic complications after starting agomelatine. It is a matter of debate whether the small gallstones, which were present in the CBD, could have contributed to the acute liver injury in our patient. Most of the data are suggestive of DILI as a main cause. First, the liver enzymes were normal before the introduction of agomelatine and became elevated sometime in the course of treatment with the drug. Second, there was a significant improvement after

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stopping agomelatine, with normalisation of the ALT and the AST, which occurred before endoscopic gallstone removal was performed.

Although a high level of ANA was observed in our patient, there were no other biochemical or clinical signs of autoimmune hepatitis or other ANA-related autoimmune diseases that might suggest that the ANA were drug induced. The clinical presentation as well as the other laboratory investigations and the biopsy result were not characteristic for autoimmune hepatitis. Thus, besides the elevated ANA level, none of the other diagnostic criteria of the International Autoimmune Hepatitis Group were found (7). Up to 20% of healthy individuals have an elevated ANA and this is also observed in some autoimmune diseases, such as lupus erythematosus and rheumatic disease (8). However, no signs or symptoms of these diseases were seen in our patient. Therefore, the coincidence of liver injury and ANA elevation allows us to hypothesise that this was a case of immune-mediated DILI.

Most importantly, the histopathological examination revealed features of DILI and excluded other possible causes of the observed abnormalities (i.e. autoimmune hepatitis). Using the Roussel Uclaf Causality Assessment Method scale, which is believed to be the most sensitive tool to diagnose DILI, our patient obtained 9 points, providing a definite diagnosis of DILI (1).

The choledocholithiasis occurring in the presented case appears to be a concomitant finding and its relationship to developing DILI after the introduction of a potentially hepatotoxic drug seems weak. First of all, this was a case of microcholedocholithiasis, as the abdominal ultrasound examination, as well the CT scan, did not reveal any stones in the bile duct. Only MRCP was helpful in detecting the small gallstones. This is a characteristic feature of microcholedocholithiasis (9). As the process of gallstone formation takes several months (in the vast majority of cases at least 5–6 months) (10), it is highly probable that the microcholedocholithiasis was present in our patient long before agomelatine was started, that is when all the liver tests were normal. Second, there was a significant clinical improvement with normalisation of the ALT and AST after stopping agomelatine, but before the endoscopic gallstone removal. It should also be added that the removal of the small gallstones in our patient was performed as a protection from a possible acute pancreatitis in the future, as micro calsoli in the CBD are believed to be one of the main causes of so called 'idiopathic' acute pancreatitis. Moreover, if choledocholithiasis (stones in the CBD) was the reason for the significant elevation of liver enzymes, it ought to be rather accompanied by hyperbilirubinemia, which did not occur in our patient. However, it could be hypothesised that any structural and/or functional abnormalities of the liver can increase the risk of this complication in patients receiving agomelatine.

Stuhes (11) recently reported on hepatotoxicity in a 44-year-old female patient, with no known history of liver disease, which occurred after 3 weeks of treatment with agomelatine. Our patient had both a family and a personal history of cholecystectomy owing to gallstones. However, the detection of the small gallstones in the CBD, which may theoretically increase the risk of DILI, was only possible by MRCP.

According to the EMA report (6), liver enzymes levels should be strictly monitored before the start of agomelatine and during the therapy. Our case shows that it is also essential to search for any factors increasing the risk of agomelatine-induced liver injury before introducing this drug and that in patients with a pre-existing liver disease, agomelatine is contraindicated.

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None.

Conflicts of Interest

During last 3 years Janusz K. Rybakowski has acted as a consultant or as a speaker for the following companies: AstraZeneca, Bristol-Myers-Squibb, Janssen-Cilag, Lundbeck and Servier. For the remaining authors none were declared.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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