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SHORT COMMUNICATION

Drug-induced toxic hepatitis associated with the combination of quetiapine and fluphenazine: A case report

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Abstract Toxic hepatitis is an inflammation of the liver that occurs in response to various substances, such as alcohol, drugs and various chemicals. It may develop either within hours or days, or after several months or years of exposure to a toxic agent. Schizophrenia is a chronic and progressive disease with a high risk for the development of various somatic diseases. Previous studies have shown that all generations of antipsychotics can cause a variety of somatic disturbances, visible in laboratory parameters, which can lead to serious physical disorders. Therefore, during long-term treatment with antipsychotics we must pay attention to the impact of drugs on the development of certain physical disturbances. In our case, the long-term treatment of schizophrenia with quetiapine and fluphenazine led to the development of mild toxic hepatitis. Our goal was to pay attention to the risks of prescribing a combination of antipsychotics in order to prevent the development of physical disease in psychiatric patients.

Introduction

Toxic hepatitis is an inflammation of the liver that occurs in response to various substances. It is most commonly caused by alcohol and drugs, particularly painkillers and various industrial chemicals. In some cases, toxic hepatitis develops within a few hours or days of exposure to the toxin. In other cases it can take months before the signs and symptoms of toxic hepatitis become visible. The symptoms often subside when exposure to the toxin stops. Toxic hepatitis can permanently damage the liver, and in some cases can lead to liver failure. Mild forms of toxic hepatitis may not cause any symptoms and will be detected only by laboratory tests. Common signs and symptoms of toxic hepatitis include jaundice, itching, pain in the upper right abdomen, fatigue, loss of appetite, nausea and vomiting, rash, weight loss, and dark or tea-colored urine. The liver performs myriad vital functions, including the metabolism and removal of most chemicals from the blood stream and body. Though the liver has a great potential to repair, constant exposure to toxic substances can cause serious and sometimes irreversible damage. More than 1000 drugs have showed toxic effects on

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the liver, of which 16% are neuropsychiatric drugs. Antidepressants (TCA or SSRI), mood stabilizers and antipsychotics imply certain biological and/or clinical hepatotoxicity.[1] In the literature, among the drugs that can cause toxic hepatitis are also antipsychotics; in our case quetiapine and fluphenazine. Drugs act on the liver to influence the production of cytokines, the major mediators of inflammation.[2] Toxic hepatitis caused by drugs is rarely encountered, constituting 1–3% of all patients with hepatitis; while as much as 30% of all cases of fulminant hepatitis is due to the effects of drugs.[3] In the literature only a few cases of the acute toxic hepatitis were caused by quetiapine. The clinical picture developed after the introduction of quetiapine in the treatment; after the discontinuation of quetiapine and the introduction of steroids, improvement and recovery of the liver was observed.[1] Two cases have been described, in first one where quetiapine caused fulminant hepatic failure in a very short period of time,[4] and in second, where in elderly mortality occurred after introduction of small doses of quetiapine.[5] The toxicity of fluphenazine on the liver in humans has been rarely described. In one study of 1, 248 people with side effects from fluphenazine, 1 had hepatic lesion.[6]

Schizophrenia is a chronic progressive disease, where the long duration and nature of symptoms poses a risk of developing various physical illnesses.[7] The prolonged use of antipsychotic drugs in the treatment of schizophrenia increases the incidence of physical comorbidity. It has been shown that psychiatric patients have a 15–20 year reduced life-expectancy. Possible reasons for this include sedentary lifestyle, inadequate medical care, stressful events such as rehospitalization and psychotic symptoms, lack of awareness about diet, smoking and the use of addictive substances.[8]

Here we described a patient, who after 12 years of partial remission with quetiapine, and three years treatment with the combination of quetiapine and fluphenazine developed toxic hepatitis.

Case report

A 53-year-old unmarried male, retired, without children and living with his mother, with schizophrenia diagnosed in his early youth presented to our clinic for treatment. In early youth was marked by repeated hospital admissions. Upon presentation, the patient had been in partial remission for the last 13 years, and had been regularly taking prescribed medications and going for check-ups. He does not drink alcohol or smoke cigarettes. A family history of liver disease was negative. For the last 12 years he has been treated with quetiapine, the last three of which with quetiapine in combination with fluphenzine due to progression of disease. In August of 2016, during a regular psychiatric check-up, he complained of pain under his right rib cage. Laboratory tests revealed elevated liver enzymes: AST 55 IU/L, ALT 112 IU/L, GGT 189 IU/L, bilirubin was within normal values (see Table 1). First diet food was proposed, that the patient adhered to. A hepatoprotective diet was prescribed, to which the patient adhered. His psychotropic medication was then adjusted. 200 mg of quetiapine 1/2, 1/2, 1 tbl. was gradually discontinued, he remained on 2 mg of clonazepam parenterally daily, and 2.5 mg tablets of fluphenazine 3x1 tablets were removed from therapy. We introduced sulpiride 200 mg 1, 1, 0 tbl., clozapine and 25 mg of 0, 0, 1 tbl. and diazepam 5 mg 3 × 1 tablets. Following the removal of the offending agents and the introduction of a hepatoprotective diet, liver enzymes began to decrease: 124 GGT, ALT 45 IU/L, triglycerides 2.26 mmol/L, HDL was reduced 0.73, while the cholesterol and LDL were within normal values. However, his clinical state began to deteriorate and he was consequently admitted for workup and further modification of pharmacotherapy in a hospital setting. Blood tests revealed a normal blood count and renal function, while liver transaminases remained elevate. The patients blood alcohol level was 0. Abdominal ultrasound revealed normal findings. The patient was examined multiple times by a gastroenterologist, and differential diagnoses of liver lesions including viral hepatitis, autoimmune hepatitis, Wilson's disease, Gilbert's syndrome, and Budd–Chiari's syndrome were excluded (anti-HCV negative, the anti HBsAg 0.18 mIU/ml, anti HBC overall negative, bilirubin 13 μmol/L, Cu 18.5 pmol/L, ceruloplasmin 0.27 g/L, Fe 15 μmol/L, UIBC 43 μmol/L, TIBC 58 μmol/L, 60 g protein/L). During hospitalization sulpiride was discontinued and fluphenazine was gradually reintroduced at a dose of 2.5 mg twice daily with clozapine and diazepam. This again resulted in elevations of hepatic transaminases (GGT 184, 199 IU/L, ALT 148, 99 IU/L.). Consequently, fluphenazine was discontinued, and 50 mg of clozapine and 20 mg of diazepam remained in therapy. Following these modifications a drop in liver transaminase levels and improvement in the patient's condition was observed. 2 months after discharge from hospital on clozapine and diazepam, the patients liver enzymes are still regressing and the patient is in stable remission (Table 1).

Table 1 Values of liver enzymes.

Day	ALT	GGT
23.08.2016	112	189
27.09.2016	45	124
04.10.2016	148	184
10.10.2016	99	199
17.10.2016	95	176
06.12.2016	72	168

Discussion

Quetiapine is an atypical antipsychotic used in the treatment of psychosis for both positive and negative symptoms of disease. It has a low side effect profile and is well tolerated in therapeutic ranges from150 to 750 mg. Quetiapine's mechanism of action is antagonism of dopamine (D2) and 5-hydroxytryptamine-2 (5HT2) receptors, while its metabolite, N-desalkilquetiapin blocks the noradrenergic transporter. Quetiapine also has affinity for other receptors such as serotonin 5HT2C, 5HT3, 5HT7 receptors. It is metabolized by the cytochrome P450 3A4 isoenzyme. Quetiapine is considered as weak hepatotoxic drug and causes only mild asymptomatic increases of liver transaminases.

Fluphenazine is an old antipsychotic with a high affinity for D2 receptors and antagonistic effects on the 5HT6 and 5HT 7 receptors. Because of weak antihistaminic and anticholinergic effects, therapeutic doses are not sedating

and do not cause significant orthostatic hypotension. Higher doses may cause extrapyramidal symptoms. It is metabolized by CYP2D6, and is also an inhibitor of the same isoenzyme.

Hepatic toxicity in our patient probably was caused by the combination of quetiapine and fluphenazine. Other etiologies including alcoholic liver lesions, hepatitis A, B, and C, metabolic causes such as Wilson's disease, and vascular patterns such as Budd–Chiari syndrome were excluded following work-up. After the discontinuation of quetiapine and fluphenazine a mild decrease in liver transaminases was observed. Following the reintroduction of fluphenazine mild increases in liver transaminases were seen. Side effects of quetiapine include mild asymptomatic liver disease like increased liver enzymes, with leukopenia, pancytopenia, and thrombotic trombocytopenic purpura seen only rarely. In rare cases, quetiapine can cause neuroleptic malignant syndrome, hyperprolactinemia, myoclonus, cardiac arrhythmia, and toxic hepatitis. Previous studies have shown that the toxic effects on the liver are typical for clozapine, olanzapine and risperidone.

In one study, comparing liver tolerance of clozapine ($n = 167$) to haloperidol ($n = 71$), 37.3% of patients treated with clozapine showed a relevant increase in liver enzymes compared to 16.6% of patients treated with haloperidol.[9] In reviewing the literature, significant liver damaged linked to treatment with quetiapine has only been reported in three cases. The first case was a bipolar patient, where liver damage developed after one month of treatment with quetiapine.[1] The second case involved a patient with rapid increases in liver transaminases after three days of treatment with quetiapine.[9] The third case involved an elderly female patient suffering from Parkinson's disease, where quetiapine prescribed at low doses for insomnia led to fulminant liver damage and death.[4] One study with mice demonstrating fluphenazine toxicity in liver and kidney tissue, caused by oxidative stress, found that the same can be prevented by parallely taking diphenyl diselenide, which is not in human use.[10] Liver damage usually occurs within the first few weeks of the introduction of any drug, while liver damage from clozapine can be seen anywhere between 1 and 8 weeks, 12 days to 5 months for olanzapine, and 1 day to 15 months for risperidone. All described cases of acute liver damage are generally reversible after the removal of the offending agent. The mechanism of hepatic damage remains not fully understood. The presence of other risks factors, such as high plasma concentrations of the drug, age, harmful alcohol use, obesity and eating habits must also be taken into account. Special attention before prescribing the drug must be given to the above mentioned risk factors. The usage of several drugs increases the likelihood of developing liver damage. Monotherapy has an advantage in that identifying the offending agent is straightforward harmful and it is easier to remove the drug from treatment. One study has shown that liver damage caused by medications in previously healthy patients, carries a lower risk of mortality than in patients who already had diagnosed liver cirrhosis, in older patients and in patients who have many somatic comorbidities.[11] Diagnosing toxic hepatitis is mainly based on the coincidence of treatment initiation and symptom development, and the exclusion of other possible causes. In our case, we think that quetiapine was the agent that caused liver damage, while fluphenazine only contributed to further damage, although we cannot exclude the effects of other risk factors. We therefore advocate regularly monitoring laboratory values in order to prevent toxic liver damage.

Conclusion

There is no doubt that various medications can damage the liver, usually causing toxic hepatitis soon after the drug introduction. Fortunately, in most cases, the damage is reversible. We described a patient who developed a liver lesion after 3 years of taking combination treatment with quetiapine and fluphenazine. We consider that it is important to monitor patients for liver damage due to the cumulative toxic effects of combination drug treatment.

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Conflicts of interest

The author has no conflict of interest to declare.

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