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CLOMETHIAZOLE-INDUCED HEPATOTOXICITY - A CASE REPORT

Matej Štuhec[1], Vesna Švab[1,2] & Ivan Malešič[1,3]

[1]Psychiatric Hospital Ormož, Ormož, Slovenia
[2]Department of Psychiatry, Faculty of Medicine Ljubljana, University of Ljubljana, Ljubljana, Slovenia
[3]Department of Clinical Chemistry, Faculty of Medicine Maribor, University of Maribor, Maribor, Slovenia

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Introduction

Clomethiazole is structurally related to thiamine, has been predominantly used for management of agitation, alcohol delirium and withdrawal and in rare cases for restlessness (Simi et al. 1999). Clomethiazole is generally a well-tolerated and safe drug. It is considered as safe drug because of its lack of hepatotoxicity, tolerability, short plasma half-life, a lack of any long-acting intermediate metabolites and adverse effects on the neuro-endocrine system (Majumdar 1986). Clomethiazole is an effective inhibitor of CYP2E1.

A number of phytochemicals can also potently inhibit CYP2E1-most notably certain isothiocyanates found in crucifera, such as sulforaphane and phenethylisothiocyanate, some interactions of which had already been described (McCarty 2011).

Chronic exposure to alcohol leads to a compensatory reduction in GABA receptor function. Clomethiazole acts as activator of the GABA receptor resulting in membrane hyperpolarization. Clomethiazole has high addictive potential in long-term treatment, and therefore is not recommended for use of more than 10 days (Hales et. al 1992). This is probably the most important problem of clomethiazole use in clinical practice and the reason why it is only used for short-term treatment.

Many medications are associated with hepatic toxicity as well. Drug-drug and drug-phytochemical interaction may lead to hepatic injury. The severity of drug-induced hepatic injury can range from transient asymptomatic liver enzyme elevation to fulminant hepatic failure (FHF). The exact incidence of FHF remains uncertain, but studies suggest that leading causes in North America are drug overdose and idiosyncratic drug reactions (Ostapowicz et al. 2002). There have been very few reports of acute clomethiazole-induced hepatotoxicity.

The present article describes a case of psycho-organic delirium treated with clomethiazole with drug induced hepatotoxicity. Upon discontinuation of clomethiazole levels of serum aspartate, amino transferase (S-AST), serum alanine amino transferase (S-ALT) and gamma glutamyl transpeptidase (S-GGT) declined progressively.

Case report

A 71-year-old Slovenian male P. M. was admitted in February 2012 to a psychiatric department, because of psycho-organic delirium. In his medical history, he denied alcohol, herbal products and/or other drug use. He was diagnosed with organic personality disorder and organic delusional disorder, while suffering from chronic respiratory insufficiency. His medications previous to hospitalization included pantoprazol 20 mg daily, perindopril 8 mg daily and salbutamol 6 mg daily. He had no known history of liver disease. Baseline laboratory results collected on admission included a normal platelet count, normal liver enzymes and liver function tests. Laboratory tests results before introducing clomethiazole and clozapine were as follows: S-ALT: 0.58 µkat/L (normal <0.74 µkat/L), S-AST: 0.65 µkat/L (normal <0.58 µkat/L), and S-GGT: 0.78 µkat/L (normal <0.92 µkat/L). Alkaline phosphatase (ALP), bilirubin, albumin, and prothrombin time were within the normal range. Autoimmune hepatitis markers, thyroid tests, ferritin, and ceruloplasmin were normal as well. Viral markers for A, B, and C were negative.

Treatment with intruduced clozapine 12.5 mg daily and clomethiazole titrated from 192 mg daily to 1152 mg daily was introduced by his psychiatrist in the hospital. After 8 days of treatment laboratory tests results were as follows: S-ALT 1.17 µkat/L, S-AST 1.00 µkat/L, S-GGT 0.78 µkat/L, the De-Ritis quotient (S-AST/S-ALT) was 1.17. After 11 days of treatment laboratory tests results were as follows: S-ALT 2.41 µkat/L, S-AST 2.75 µkat/L, S-GGT 3.42 µkat/L (Figure 1), the De-Ritis quotient was 0.85. ALP, bilirubin and albumin were within the normal range.

These findings were attributed to hepatocellular type liver damage associated with clomethiazole use. After a one-week withdrawal of clomethiazole, serum transaminase levels S-ALT and S-AST returned to normal range: S-ALT 0.72 µkat/L, S-AST 0.35 µkat/L, S-GGT 1.47 µkat/L. Clozapine was discontinued a week later. The patient did not undergo percutaneous liver biopsy as serum enzyme levels S-ALT and S-AST returned to normal range, and she did not consent to the biopsy procedure. Symptoms of delirium were treated

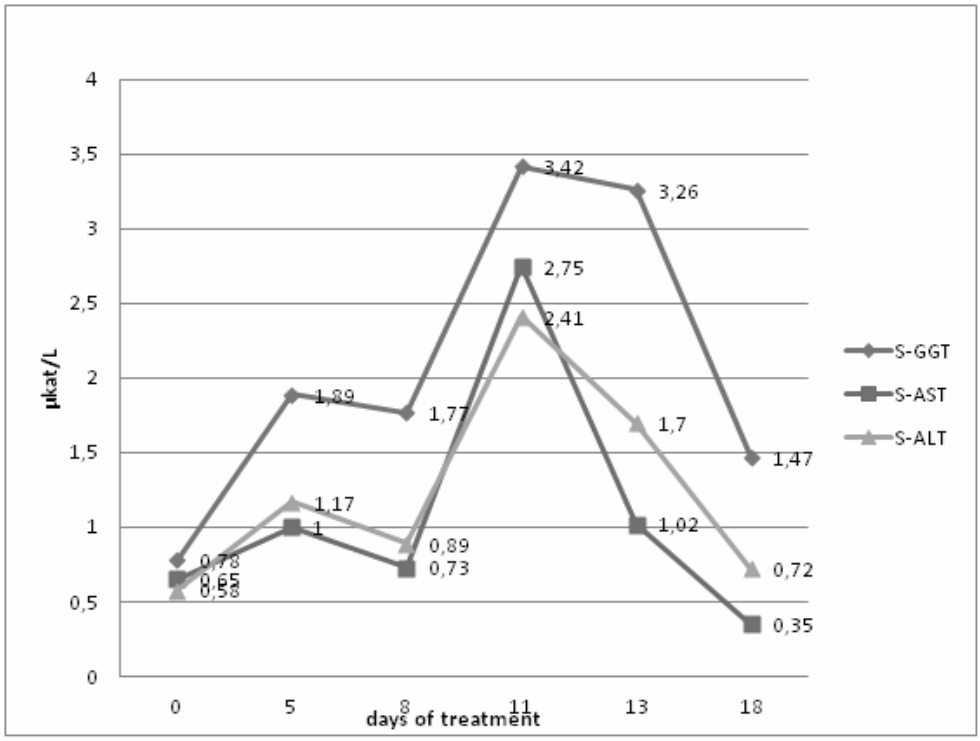

Figure 1. Time course of liver function tests

successfully with 20 mg zuclopenthixol daily, which was introduced immediately after clomethiazole discontinuation. S-AST, S-ALT and S-GGT were assessed in blood. According to the recommendations of the International Federation of Clinical Chemistry (IFCC), S-AST, S-ALT and S-GGT were ascertained by means of reference procedures at 37°C (Committee on Reference Systems for Enzymes 2002a, 2002b).

Discussion

Clomethiazole is predominantly metabolized in the liver through the cytochrome P450 system, by the enzyme P450 2E1. Concurrent administration of the strong CYP2E1 inhibitor increases the clomethiazole area under the curve and prolongs the plasma half-life. For this reason, strong inhibitors of CYP2E1 should be avoided, as they may increase plasma concentrations of clomethiazole (Dey et al. 2007).

Furthermore, it can be assumed that polymorphisms of the CYP2E1 gene may affect clomethiazole disposition. However, pharmacogenomical studies on the same gene did not show any correlation between gene polymorphisms and commonly observed toxicities such as hepatotoxicity (Eap et al. 1998). There are few reports of hepatotoxic adverse effects of clomethiazole. Developed hyperbilirubinemia without hepatocytes damage in patient with a history of alcoholism was reported. After discontinuation of clomethiazole symptoms of cholestasis improved (Heinemann et al. 1996).

The patient described in this case developed severe hepatic enzyme disturbances during clomethiazole treatment. All enzymes were three fold higher than normal. Treatment with clomethiazole was stopped abruptly. Treatment with clozapine was discontinued a week later after clomethiazole discontinuation. There was no evidence of viral or autoimmune hepatitis or any other cause of hepatitis before clomethiazole was introduced. The majority of the interactions with clozapine are reported to be mediated by cytochrome P450 (CYP) enzymes. CYP1A2 has a major role in the oxidative metabolism of clozapine, with a minor contribution from CYP3A4, and possibly CYP2D6, CYP2C9 and CYP2C19, so we don't believe that any interaction with clomethiazole and clozapine occurred (Chetty et al. 2007). There are some reports of clozapine-induced hepatotoxicity. Elevated hepatic enzymes, while patient was treated with clozapine were reported (Macfarlane et al. 1997). In our case, clozapine was withdrawn one week later when hepatic enzymes were normal. Our patient was also treated in clozapine in small doses, so we do not believe that clozapine induced-hepatotoxicity had occurred. The patient recovered in one-week after discontinuation of clomethiazole. Hepatic enzymes S-ALT and S-AST normalized rapidly after discontinuation of clomethiazole. From the ratio S-AST/S-ALT it is possible to conclude that hepatocytes damage already occurred and recovered soon after clomethiazole discontinuation. Clomethiazole seems to be the cause of hepatic injury. The laboratory test abnormalities appeared after its introduction. The hepatic function recovered after discontinuation of clomethiazole. No other medication was changed regarding dosage regime in this time.

To control symptoms of delirium rapid switching from clomethiazole to zuclopenthixol was necessary,

therefore zuclopenthixol in small doses could be used in treating patients with clomethiazole hepatotoxicity. Particular attention needs to be paid when prescribing clomethiazole to patients with alcohol dependence, because they can have elevated transaminases before treatment with clomethiazole. Our case demonstrates the potential risk of developing toxic hepatotoxicity during treatment with clomethiazole.

In addition, clomethiazole has protective effects in several cases. A liver protection from injury in vivo by inhibiting CYP2E1 was described (Goullion et al. 2000). Reduction of acetaminophen-induced liver injury in mice was also noted (Lee et al. 1999). Clomethiazole may be a useful adjunct to the development of neuro-protective drugs in the future (Hutchinson et al. 2002). More research is needed on neuroprotective effects of clomethiazole for clinical use as a neuroprotective agent.

Conclusion

In conclusion, even though clomethiazole is generally known to be a well-tolerated and safe drug, physicians should be aware of the risk of hepatotoxicity associated with clomethiazole use. Therefore caution is advised for patients with elevated liver enzymes who are receiving clomethiazole since elevated S-AST and S-ALT transaminases may be the earliest manifestation of hepatotoxicity. Unfortunately, it is not possible to reliably predict which patients will progress to hepatic failure. Nevertheless, carefully monitoring biochemical liver tests in patients receiving clomethiazole is indispensable to early evidence of the development of hepatotoxicity and possibly liver failure.

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Conflict of interest : None to declare.

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Correspondence:
Matej Štuhec, Pharm.D.
Psychiatric Hospital Ormož
Ptujska Cesta 33, Ormož, Slovenia
E-mail: matejstuhec@gmail.com