CASE REPORT

Zinc-Induced Gastric Ulcer: Case Report on Two Patients with Wilson's Disease

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ABSTRACT

Zinc has been developed as an effective and nontoxic therapy in Wilson's disease. Zinc salts are generally well tolerated. Mild gastrointestinal discomfort is the major observed side effect and may be dependent on the zinc salt employed. Here, we report two Wilson's disease patients who presented with severe gastric ulceration few months after beginning treatment with zinc acetate 50 mg three times a day. Our patients were not taking any ulcerogenic drugs and had no evidence of Helicobacter pylori infection. In both patients, zinc acetate was replaced by penicillamine and proton pump inhibitor therapy was initiated with complete resolution of gastrointestinal symptoms. To our knowledge, this is the first report of zinc acetate-induced gastric ulceration, which should be looked for in Wilson's disease patients who develop abdominal discomfort while on this drug.

Keywords: Gastric ulcer, Wilson's disease, Zinc acetate

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism. Dysfunction of ATP7B protein, important copper transporter in hepatocytes that is responsible for Wilson's disease, can lead to copper accumulation in the liver and in extrahepatic organs, such as brain and cornea. This can lead to neurological symptoms and variable degrees of hepatic damage, and often to combination of these.[1]

The aim of treatment is reduction of tissue copper concentration either by enhancing its urinary excretion or by decreasing its intestinal absorption. Medical therapies include copper chelators (penicillamine, trientine, tetrahiomolibdate) and zinc salts.[2] Zinc is used mainly as a first line therapy in asymptomatic patients, as maintenance therapy and for patients with a mainly neuropsychiatric involvement.[3] It has very few side effects and is well tolerated. Gastric irritation is the only side effect ocurring in aproximately 10-15% of patients which usually decreases over time or can be overcome by replacing one zinc salt with another.[3]

We present, for the first time to the best of our knowledge, two cases of zinc acetate-induced gastric ulceration in patients with Wilson's disease.

CASE REPORTS

Case 1

In 2005, a 25-year-old Caucasian female with 2-months history of vertigo, tremor, dysarthria and ataxia of trunk and extremities was diagnosed as having Wilson's disease by clinical, laboratory and immaging assesments. Laboratory data indicated low ceruloplasmine (0,08 g/L, normal range 0,17-0,66 g/L), low serum copper (3,5 mmol/L, normal range 12,2-25,1 mmol/L), mildly increased 24-hours urinary copper (2,5 mmol/dU, normal range <1,5 mmol/dU). Brain magnetic resonance imaging revealed bilateral abnormal basal ganglia with increased intensity. Ophtalmologic examination confirmed Kayser-Fleisher rings and sunflower cataracts on both eyes. Molecular analyses of the ATP7B gene showed that the patient was compound heterozygous for A1003T and H1069Q mutations. She had a signs of concomitatnt liver involvement as, aminotransaminases were mildly elevated (aspartate aminotransferase 76 U/L, normal range 11-38 U/L; alanine aminotransferase 100 U/L, normal range 12-48 U/L), her platelet count was mildly decreased (116 × 10^9/L, normal range 158-424 × 10^9/L) and abdominal sonography disclosed hepatosplenomegaly. Her past medical history was significant for type I diabetes for fifteen years. She had no previous personal or family history of ulcer disease. She was nonsmoker and she denied using alcochol, aspirin or non-steroidal anti inflammatory drugs (NSAIDs).

The patient was placed on penicillamine 600 mg/day with stepwise dose increasing and low copper diet. Ten days after starting therapy severe thrombocytopenia occured (26 × 10^9/L, normal range 158-424 × 10^9/L). Penicillamine was stopped and trientine 250 mg three

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times per day was started. Soon problem occured with purchasing of drug and trientine therapy was therefore stopped.The patient was placed on zinc acetate (150 mg/day) with satisfactory compliance. Ten months after initiation of zinc therapy worsening of symptoms occured in the form of expressed tremor. In addition, she started complaining of severe epigastric pain occurring soon after meals. An upper endoscopy was performed and 20 mm large, oval ulcer was seen on the posterior wall of distal portion of stomach corpus. The edges of the ulcer were slightly elevated and its base was smooth and white in color. There were also several superficial erosions in the gastric antrum. Histologic examination of the biopsies were reported as acute erosive gastritis and no Helicobacter pylori was seen. Zinc was discontinued and the patient was started on esomeprazole 40 mg daily for a total of six weeks. The patient had queek relief from symptoms. Two months later, a second endoscopic examination showed complete healing of the ulcer.

As there were no further therapeutic options for patient andthrombocytopenia recovered to a normal values, we decided to reintroduce penicillamine in therapy. Penicillamine was started again, the dose being gradually increased to 900 mg/day with no side effects and good compliance. On regular follow-up thrombocytes were stable at 90 × 10^9/L to 110 × 10^9/L (normal range 158-424 × 10^9/L). After a year of penicillamine the tremor had greatly improved and the ataxia and dysarthria dissapeared. She has since returned to work and her manner appears normal.

Case 2

In 2009, a 20-year-old male patient was diagnosed as having asymptomatic Wilson's disease. The diagnosis of Wilson's disease was established by laboratory assessment during family screening as his sister had liver cirrhosis due to Wilson's disease. Biological tests revealed low ceruloplasmine (0,13 g/L, normal range 0,17-0,66 g/L), normal serum copper (15,2 mmol/L, normal range 12,2-25,1 mmol/L) and mildly increased 24-hours urinary copper (2,5 mmol/dU, normal range <1,5 mmol/dU). Molecular analyses of the ATP7B gene showed that the patient was homozygous for H1069Q mutation. His medical history was unremarkable for any other diseases and he was not taking any other medication. He had no previous personal or family history of ulcer disease.He had no history of tobacco smoking and denied alcochol intake.

The patient was placed on zinc acetate 150/day divided in three doses and low copper diet. He was taking zinc acetate in pulver form, three times per day, one hour before meal and reported no adverse effects. Six months after initiation of zinc therapy he started to complain of upper abdominal discomfort and loss of appetite. Esophagogastroduodenoscopy (EGD) revealed active, hematin covered ulcer in the antrum of the stomach (Figure 1). Microscopy and immunohistochemistry on gastric biopsy did not reveal infection with Helicobacter pylori. Treatment with esomeprazole was intiated at a single daily dose of 40 mg which resulted in partial resolution of symptoms. Follow-up EGD after 2 mo showed persistent gastric ulcer in gastric antrum despite proton pump inhibitor (PPI) treatment. Treatment with zinc-acetate, suspected as primary cause of gastric ulcer, was discontinued and the patient was started on penicillamine 900 mg/day. Follow-up endoscopy at another 2 and 4 mo showed complete restitution of gastric mucosa and the patient had no complaints.

DISCUSSION

The treatment of Wilson's disease is effective and has evolved dramatically in the last fifteen years. Treatment includes copper-chelators, such as penicillamine and trientine as well as zinc salts. Liver transplantation is a treatment of choice in case of acute liver failure or in patients with end-stage liver cirrhosis.

D-penicillamine is still the gold standard of therapy due to broad basis of clinical data and many years of experience.[1] However, it must be kept in mind that approximately 25% of patients treated with penicillamine experience adverse effects of sufficient severity to deem this therapy intolerable.[4] Amongst neurological patients, a significant number of patients may experience an initial worsening of symptoms before they get better.[2] As evidence grows for the effectiveness of trientine, with fewer side-effects arising than with penicillamine, trientine is now regarded as an accepted alernative to penicillamine for initial treatment of Wilson's disease.[1]

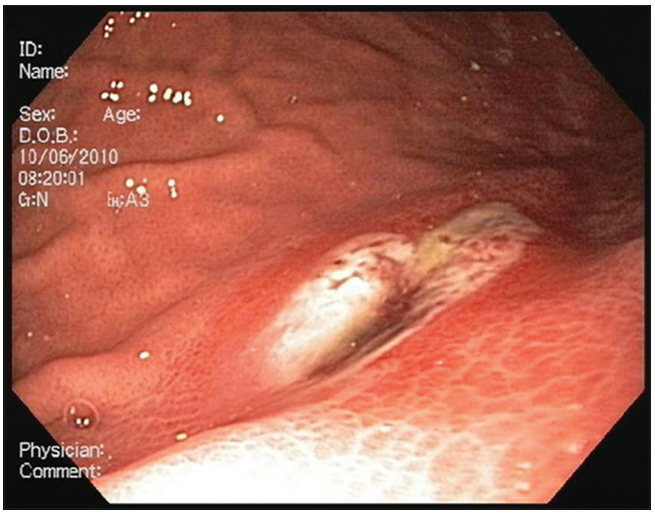

Figure 1: Zinc-induced gastric ulceration

Zinc has been developed as an effective and nontoxic therapy in this disease by two groups, one in Netherlands[5] and one in the United States[6] Zinc acts by blocking the carrier in the intestinal epithelial cells for copper transport.[7] In addition, it increases the levels of metallothionein in enterocytes, which acts as an intracellular ligand binding metals[8] According to the results of systematic review of mostly observational studies, it seems that zinc therapy is the best choice in presymptomatic patients, as it is effective and has negligible adverse side effects. Conversly, acutely ill hepatic patients and symptomatic neurological patients might do better on D-penicillamine, as zinc might act too slowly in this group of patients[3] Furthermore, it is important to identify patients who do not respond to zinc therapy and have increased activities of liver enzymes, indicating that a chelating agent should be added to the therapeutic regimen.[9]

Our first case report describes a young female who exhibited combined, hepatic and neurological clinical symptoms consistent with Wilson's disease. Ten days after starting penicillamine therapy the patient developed severe thrombocytopenia. Penicillamine was stopped and trientine was started. As problems with trientine supply ocurred the only available and applicable drug was zinc acetate. Second patient was asymptomatic as the diagnosis of Wilson's disease was established through family screening so he was treated with zinc-acetate from the begining. In both patients, zinc had been prepared in our own hospital pharmacy in tablet form.

Zinc's major advantage over the chelating agents is its extremely low level of toxicity. During zinc therapy, mild gastrointestinal discomfort is the major observed side effect and may be dependent on the zinc salt employed. The acetate and gluconate salts are reported to be better tolerated in terms of gastric irritation.[9]

Our patients developed severe symptoms during zinc therapy that were suggestive for gastric ulceration. Both endoscopy and histopathology confirmed significant mucosal damage. Other possible causes of gastric ulcerations were ruled out. There was no personal or family history of ulcer disease. Both patients had been taking zinc acetate for several months before the onset of gastric ulceration and they had not been taking any other medications. After excluding zinc-acetate from therapy and introduction of PPI both patients had complete relief of symptoms and mucosal healing according to follow-up upper endoscopy.

On the other hand, it must be emphasized that there are also few studies about protective role of zinc in gastric ulcer. Zinc compounds hasten the healing of gastric ulcers in humans and rats and prevent various kind of experimentally induced gastric lesions.[10] Bulbena et al. have provided evidence that zinc acexamate (ZnA) affords protection against gastric damage induced by nonsteroidal antiinflammatory drugs (NSAIDs) in the rats.[10] Lapenna et al. investigated gastroprotective-antioxidant properties of zinc on free radical-related models of gastric mucosal injury.[11] Watanabe et al. studied the effect of dietary zinc depletion on development and healing of gastric ulcer in rats. They concluded that zinc is crucial for healing of gastric ulcers, especially at the early stage.[12]

Our case reports serves to alert clinicians to consider the diagnosis of gastric ulcerations in Wilson's disease patients taking zinc salts. Gastric ulcer should be considered in the differential diagnosis of abdominal pain in Wilson's disease taking zinc salts and upper endoscopy should be performed. If gastric ulcer is found endoscopically the zinc salts should be stopped and replaced by another drug to reduce the possibility of further damage to the gastric mucosa and possible complications.To our knowledge, this is the first report about gastric ulcerations caused by zinc acetate.

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How to cite this article: Kalauz M, Telarovic S, Grgic D, Brkic T, Grubelic RK. Zinc-induced gastric ulcer: Case report on two patients with Wilson's disease. Acta Medica International. 2014;1(2):140-142.

Source of Support: Nil, **Conflict of Interest:** None declared.