Continuous intravenous flumazenil infusion in a patient with chlordiazepoxide toxicity and hepatic encephalopathy

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ABSTRACT

Flumazenil, a benzodiazepine receptor antagonist, is the drug of choice for the diagnosis and treatment of benzodiazepine overdose. We are presenting a patient with chronic alcoholism and alcoholic liver disease, who came with alcohol withdrawal symptoms and treated chlordiazepoxide. Subsequently he developed a prolonged change in mental status that required treatment for benzodiazepine overdose and hepatic encephalopathy with flumazenil infusion for 28 days.

Key Words: Chlordiazepoxide, flumazenil, hepatic encephalopathy

INTRODUCTION

Alcoholism is a major cause of morbidity and mortality. Alcoholic liver disease and liver cirrhosis are common complications of alcoholism. Hepatic encephalopathy is a serious complication of liver cirrhosis. Precipitating factors could be related to infection, gastrointestinal bleeding (GIB), dehydration, constipation, or medication effect including benzodiazepines. Chlordiazepoxide is a long acting benzodiazepine that is widely used in the treatment of patients with alcohol withdrawal symptoms. Most benzodiazepines are metabolized in the liver and can have elevated levels of the drug metabolites in the system for an extended amount of time in patients with chronic liver disease. Flumazenil, a benzodiazepine receptor antagonist, is the drug of choice for the diagnosis and treatment of benzodiazepine overdose. We are presenting a patient with chronic alcoholism and alcoholic liver disease, who came with alcohol withdrawal symptoms and treated chlordiazepoxide, subsequently developing a prolonged change in mental status that required treatment for benzodiazepine overdose and hepatic encephalopathy with flumazenil infusion for 28 days.

CASE REPORT

A 55-year-old African American male patient with a past medical history significant for chronic pulmonary obstructive disease and alcohol dependence for the last 20 years presented with alcohol withdrawal symptoms characterized by headache, tremors, and sweating. He denied any history of liver disease. He also denied any sleep disturbances, memory changes, or seizures in the past. On examination, the vital signs were stable. The patient appeared anxious, tremulous, had a slow and delayed response to questions, and an unsteady gait. He had scleral and skin icterus. Examination of the chest showed gynecomastia and bibasilar crackles on auscultation, and the liver edge was palpable 3cm below costal margin. Examination of extremities revealed asterixis, nail clubbing, and non-pitting edema of the legs. Initial diagnostics revealed a macrocytic anemia with a hemoglobin of 11.3 g/dl and Mean Corpuscular Volume (MCV) 101.8 fL as well as a platelet count of 83,000/μL. Liver function tests revealed a total protein 8.2 g/dL, albumin 2.8 g/dL, total Bilirubin 3.9 mg/dL, Aspartate Aminotransferase (AST) 69 U/L, Alanine Aminotransferase (ALT) 36 U/L, and ammonia level 124 mcg/dl. The patient also had an International Normalized Ratio (INR) of 1.6.
Computed tomography of the abdomen showed evidence of early cirrhosis.

The patient was admitted to the hospital with the diagnosis of alcohol withdrawal and possible hepatic encephalopathy. A chlordiazepoxide-based alcohol withdrawal protocol with tapering doses was started together with lactulose for hepatic encephalopathy. A total of 300 mg of chlordiazepoxide was given over the next 9 days in tapering dose with good control of the patient’s withdrawal symptoms. On the tenth day of his hospital stay, the patient’s mental status deteriorated and he was upgraded to the intensive care unit. Further work-up was done which included a urine drug screen which was positive for benzodiazepines. The repeat ammonia level was 121 mcg/dl. Septic work-up was otherwise unremarkable. The patient was given the diagnosis of benzodiazepine-induced hepatic encephalopathy. A single dose of flumazenil 1mg intravenously was given followed by a significant improvement of mental status where the patient was fully awake, responsive, and obeying commands. The effect was short-lived, lasting no more than 20 minutes, after which the patient’s mental status deteriorated again. Repeated single doses of flumazenil on the subsequent days failed to maintain arousal. Therefore, the decision was made to start the patient on a flumazenil drip at a rate of 0.25 mg/hour which was enough to keep the patient aroused. The patient complained of persistent nausea, which is a known side effect of flumazenil. He was treated with ondansetron. Flumazenil was otherwise well tolerated. Attempts to decrease the rate of infusion resulted in the deterioration of the patient’s mental status. Of note, repeated urine benzodiazepine testing came back positive on three separate occasions. The patient was maintained on flumazenil drip for 28 days until it was tapered off successfully.

The patient’s mental status returned to normal, a repeat urine benzodiazepine test was negative, and the patient was discharged home in a stable condition.

**DISCUSSION**

Acute encephalopathy is a commonly encountered clinical scenario by physicians. There is a multitude of causes ranging from structural to metabolic. Drugs such as benzodiazepines are a major cause of acute encephalopathy as they are readily used for situations like sedation, alcohol withdrawal, and seizures in an in-patient setting.

Chlordiazepoxide is a benzodiazepine that is widely used in hospitals to control alcohol withdrawal symptoms. It possesses a greater threat than most benzodiazepines due to the prolonged half life of its metabolites. A minor metabolite desmethyldiazepam has a half life as long as 200 hours. This situation is further complicated in patients with obesity or with an underlying hepatic dysfunction. Drugs like benzodiazepines show an increased volume of distribution and elimination half life in the obese population when compared to normal weight individuals. In chronic liver disease, most benzodiazepines demonstrate an increased half life; the underlying mechanism could be impaired hepatic metabolism and clearance coupled with hypoalbuminemic states which raise the free drug concentration of benzodiazepines. In comparison, lorazepam and oxazepam, due to lack of any major active metabolites, with similar efficacy, appear to be a safer option in such patients.

Flumazenil is a competitive inhibitor of the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. It has a dose dependant action with doses of approximately 0.1 mg to 0.2 ml producing partial antagonism, whereas higher doses of 0.4-1 mg usually produce complete antagonism in patients. The onset of reversal is usually evident within 1-2 minutes after the injection is completed as was observed with the trial dose in our patient. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6-10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of flumazenil.

Though flumazenil is approved in the USA for use as bolus injections, there are instances of continuous flumazenil infusion being used to reverse benzodiazepines overdose mostly in other countries. In a controlled trial by Hojer et al., 0.5mg/h infusion of flumazenil used empirically prevented relapse into coma in severe benzodiazepine overdose. The required duration of infusion in these cases had ranged from 3-16 days. Flumazenil infusion was seen to be helpful in maintaining higher level of consciousness in severe benzodiazepine intoxication, but it was not shown to reduce the rate of complications such as airway compromise, pneumonia, death, etc.

An issue of concern with the use of flumazenil, especially for prolonged duration, has been its safety profile. Few of the known side effects of flumazenil are seizures, nausea, vomiting, etc. However, in studies with flumazenil infusion, the incidence of serious side effects has been non-significant. Flumazenil was also found to be quite safe when used in pediatric population. Another point of consideration while administering flumazenil bolus or infusion is its decreased clearance in hepatic dysfunction. In patients with moderate liver dysfunction, the clearance of flumazenil is decreased to 40% to 60%; and in severe liver dysfunction, it is decreased to 25% of normal value, compared with age-matched healthy subjects.

The reported case demonstrates the successful use of flumazenil infusion for a very prolonged period to reverse sedation from chlordiazepoxide, without significant side effects. This should bring into limelight the option of using flumazenil as an infusion with more clinical trials being pursued to determine guidelines and safety for its effective use.

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