

Continuous Intravenous Flumazenil Infusion Used in Iatrogenic Chlordiazepoxide Overdose in Setting of Alcoholic Withdrawal Syndrome Management

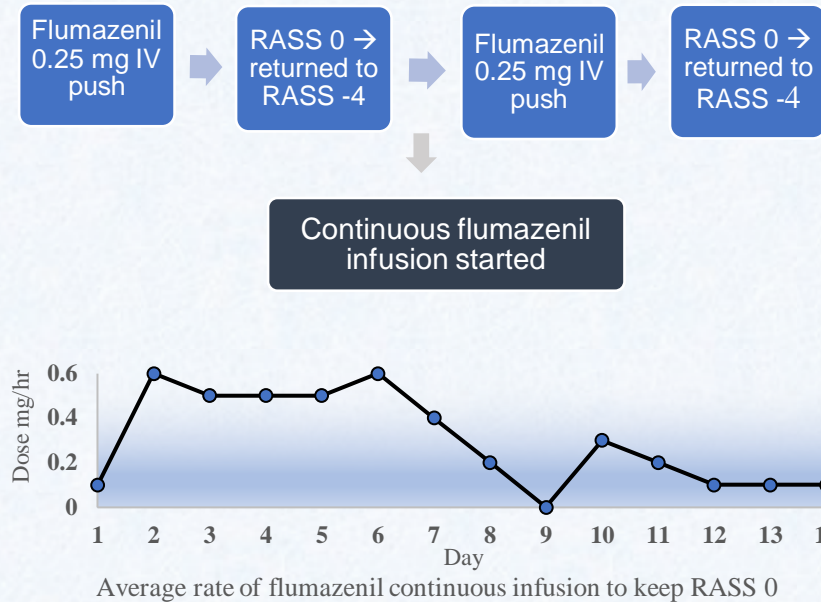
Introduction

- Benzodiazepines (BZO), including chlordiazepoxide, are the first line treatment for alcohol withdrawal syndrome (AWS).
- BZO overdose can be iatrogenic and can cause encephalopathy or respiratory depression.
- Flumazenil IV push is the first line treatment for BZO overdose. Rarely, a continuous infusion has been used.

Case Presentation

- A 63-year-old female with multiple hospital admissions for AWS, obesity & hepatitis C presented with acute alcohol intoxication (ethanol level 279 mg/dL) & bilateral pneumonia.
- She was treated for AWS with a chlordiazepoxide-based AWS protocol using fixed & symptom triggered therapy.
- 1375 mg of chlordiazepoxide was administered over 4 days.
- Concern for overdose when patient became lethargic.
- Physical exam: VS stable. Lethargic obese female. RASS -4.
- Albumin 2.5 g/dL, total bilirubin 0.8 mg/dL, ALT 34 U/L AST 13 U/L, ammonia 41 umol/L, INR 1.24, Cr 0.62 mg/dL, pH 7.23, pCO2 72.0 mmHg pO2 63 mmHg.
- ABG, EEG, CT of the brain, MRI of the brain, cultures & LP showed no explanation for patient's encephalopathy. CT abdomen: Liver was 24 cm with moderate hepatic steatosis.
- Admitted to ICU and required mechanical ventilation.

*Giselle Volney, MD & Robyn Scatena, MD
Norwalk Hospital, Norwalk, CT*



Outcome

- Patient extubated after day 3 of flumazenil continuous infusion.
- Blood chlordiazepoxide and nordiazepam level 21 days post final administration of chlordiazepoxide were 513 ng/mL and 324 ng/mL respectively.
- Repeat urine benzodiazepine testing was positive 35 & 55 days after last administration of chlordiazepoxide.
- No seizure activity or other adverse effects from continuous infusion.
- Patient is doing well 10 months after discharge.

Discussion

- Obesity, chronic liver disease and acute kidney disease are risk factors for prolonged excretion of BZO.¹
- Chlordiazepoxide has a long duration of action and converts to active metabolites in the liver.²
- Improvement in mental status after flumazenil injection is diagnostic for benzodiazepine overdose.³
- A single dose of flumazenil up to 1mg IV can show improvement in arousal but the effect may be short-lived due to the short elimination half-life and short duration of activity of flumazenil.³
- The reversible effect on mental status is dose-dependent.⁴
- **When repeated single doses of flumazenil fail to maintain alertness, a continuous infusion titratable to mental status can be used.³**
- Seizures, nausea and vomiting are side effects of flumazenil, however continuous infusion is generally well tolerated.³

References

1. Nelson A, Schiavo, Oeckler R: Continuous infusion flumazenil for prolonged benzodiazepine-induced sedation. Crit Care Med. 2013, 41:A323. 10.1097/01.ccm.0000440490.85099.53
2. Maxa JL, Ogu CC, Adeeko MA, Swaner TG: Continuous-infusion flumazenil in the management of chlordiazepoxide toxicity. Pharmacotherapy. 2003, 23:1513-1516. 10.1592/phco.23.14.1513.31941
3. Al-Halawani M, Sen P, Abdeen Y, et al.: Continuous intravenous flumazenil infusion in a patient with chlordiazepoxide toxicity and hepatic encephalopathy. J Emerg Trauma Shock. 2015, 8:58-60. 10.4103/0974-2700.145422
4. Karavokiros KAT, Tsipis GB: Flumazenil: a benzodiazepine antagonist. DICP. 1990, 24:976-981. 10.1177/106002809002401013