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ISOLATED BENZODIAZEPINE TOXICITY AND THE USE OF FLUMAZENIL: AN EYE-OPENING ANTIDOTE CASE REPORT IN A TERTIARY CARE HOSPITAL

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ABSTRACT Since its debut in the 1960s, the broad use and availability of benzodiazepines has mirrored the increased incidence of overdose cases. Due to its non-specific presentation, there is often a delay in diagnosis. We report a case of Benzodiazepine toxicity in a 70-year-old man who presented to us in a comatose state. He was evaluated at another hospital initially and was intubated in view of his low Glasgow Coma scale. A CT brain plain study was done suspecting a basilar artery thrombus and he was referred to us for Neuro-Interventional procedures. As radiological, laboratory and electrophysiological investigations were unremarkable a provisional diagnosis of drug intoxication was made after patient medication review and a trial of Flumazenil was given, after which the patient had improved dramatically. Flumazenil is not routinely used due to fears of withdrawal seizures and its high cost. It also has no effect on reversing sedation caused by barbiturates, ethanol, or opioids. The antidote has a favorable risk-benefit ratio when dosed appropriately and can be a helpful diagnostic tool after ruling out the more common causes of acute sensorium loss as demonstrated by this case report.

KEYWORDS : Benzodiazepines, Flumazenil, Overdose

INTRODUCTION

Benzodiazepines are one of the most extensively utilized medication because of their broad spectrum of therapeutic actions. The use of this group of medication as an anxiolytic, anticonvulsant, sedative hypnotic and muscle relaxant as well as having a better safety profile than Barbiturates, has resulted in higher prescription rates and usage. In developed countries, there are strict rules in place to regulate its usage however this is not the case in lesser developed nations. This results in a high risk of benzodiazepine usage and abuse. The elderly are identified as being particularly vulnerable to the dangers connected with the use of benzodiazepines (1). Flumazenil has been explored for a range of purposes, including as an antidote to benzodiazepine overdose and for stimulating comatose patients, reversing sedation after surgery and in critically ill patients, and treating hepatic encephalopathy. This case report highlights a commonly overlooked condition and the obvious benefit of the use of Flumazenil.

CASE REPORT

A 70-year-old Indian man was taken to the emergency room after becoming unresponsive one morning. Apart from an occasional cough, he appeared to be symptom-free the night before. His relatives noticed him lying in bed, he was drowsy but arousable to repeated stimuli. Bedwetting was noted. His previous medical history included a recent SARS-CoV-2 infection, Ischemic Cardiomyopathy and Chronic Kidney disease for which he was on antiplatelets, diuretics and other supportive care. He was initially taken to a nearby hospital - where he was intubated in view of his low Glasgow Coma Scale score. He was given Midazolam and scoline pre intubation. A non-contrast CT scan of the brain was ordered which showed evidence of a hyperdense basilar artery [Fig 1].

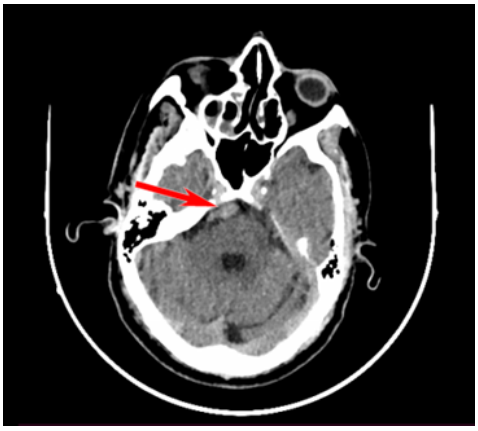

Fig 1: CT Brain study suspecting Basilar artery thrombus

A provisional diagnosis of Basilar artery thrombosis was made and was referred to our center for endovascular procedure. Upon arrival, as he was paralyzed and sedated, a full neurological exam was not possible. He was hemodynamically stable, with normal blood sugars. His ABG was unremarkable. A quick screening neurological examination revealed equal pupillary size (3.5mm) with a sluggish reaction to light. Oculo-Cephalic reflex was intact. Bilateral plantar reflex was mute. He was immediately scheduled for a CT Angiogram study. On discussion of the study with the Radiologist it was concluded that his basilar artery had no occlusion. A dilated dolichoectatic basilar artery had mimicked a basilar artery thrombus [Fig 2]

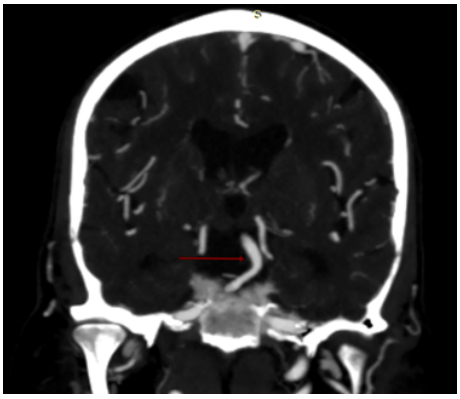

Fig 2: CT brain angiography study revealing dolichoectatic Basilar artery

In view of his recent SARS CoV-2 infection, possibility of post infectious demyelination and aseptic meningitis was considered. Routine laboratory investigations were sent which were unremarkable apart from elevated creatinine (2.1 mg/dL). He was scheduled for MRI Brain with contrast study, which was negative for both Demyelination and Meningoencephalitis. Cardiology evaluation revealed no evidence of acute MI, although a screening ECHO revealed a Left Ventricular Ejection Fraction of 25%. The cardiology team were of the opinion that a poor Ejection Fraction had led to decreased cerebral perfusion leading to Hypoxic Ischemic Encephalopathy. He had intermittent episodes of hypotension which was normalized with pressure supports, although there was no improvement in his sensorium. Electroencephalogram was done which demonstrated delta waves. There was no evidence of Non-Convulsive Status Epilepticus. Patient's relatives were called in again and upon further questioning, it was revealed that the patient had been suffering from insomnia for the past few years and was on Clonazepam 0.5mg for the same. Flumazenil was ordered, and with a single shot (0.2mg) he was up and awake asking for water. He had further episodes of unresponsiveness and required 3 more additional shots. On day 3 of admission, he was extubated and had a Glasgow coma score of 15.

DISCUSSION

Acute sensorium loss can be characterised as either neurologic (both structural and non-structural) or toxic metabolic. Trauma, tumours, vascular disease, infectious disease, and seizures are the most prevalent neurological causes. They can be ruled out with either brain imaging, electrophysiological studies or laboratory investigations. As the above-mentioned investigations were unremarkable, drug intoxication was suspected. Benzodiazepines attach to the GABA-A receptor's interface and lock it into a configuration that increases the receptor's affinity for GABA. Benzodiazepines do not affect GABA synthesis, release, or metabolism; instead, they enhance or amplify GABA's inhibitory effects through increasing receptor binding. This binding ultimately increases the flow of chloride ions through the GABA ion channel, causing postsynaptic hyperpolarization, which decreases the ability to generate an action potential. Patients with isolated benzodiazepine overdose will typically present with central nervous system (CNS) depression and normal or near-normal vital signs. Respiratory compromise is uncommon in solitary benzodiazepine ingestions, although can occur when combined with co-ingestants such as ethanol or other drugs/medications(2).Flumazenil is a competitive antagonist at the benzodiazepine binding site on the GABA-A receptor. It reverses the clinical effects of benzodiazepines but will not counteract other drugs which act on GABA receptors including barbiturates and ethanol. Flumazenil has a half-life of 50 minutes, which suggests that benzodiazepine intoxication symptoms can reoccur after initial reversal. The initial 0.2 mg IV dose should be given within 30 seconds. If the desired degree of consciousness is not achieved after 2 minutes, an additional 0.2 mg IV dose can be administered over 30 seconds to a maximum total cumulative dose of 3 mg [Fig 3].

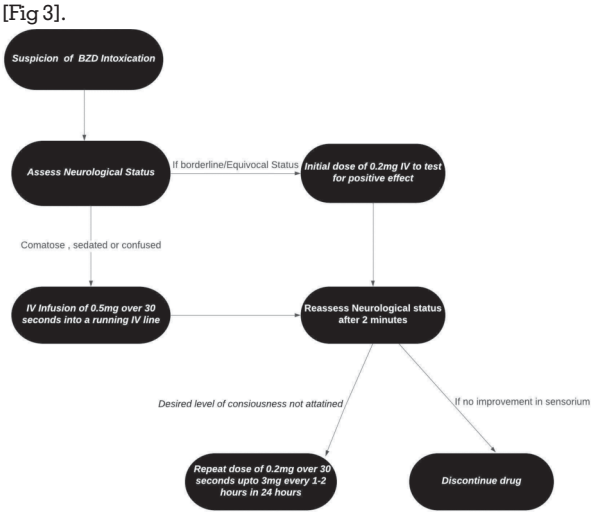

Fig 3: Flumazenil dosing flowchart

As it functions as a direct competitive antagonist, the dose is typically not adjusted based of weight or age of the patient. In unconscious or intoxicated patients who are unable to provide information about the type and amount of toxic agent consumed, Flumazenil administration can be a useful diagnostic tool. When correctly dosed, the antidote generates negligible negative effects even in the case of combination medication ingestions and in patients with a variety of medical comorbidities(3). Clinical examination of vital signs, cognition, and neuromuscular activity, followed by parallel infusion of antidote and reassessment of neurobehavioral condition, is key to its safe usage. The primary goal of this case report was to show how we used flumazenil to diagnose and treat benzodiazepine delirium. Flumazenil was found to have a good risk-benefit ratio when administered intermittently, as assessed by bedside evaluation(4). In situations of isolated ingestion of Benzodiazepines, gastrointestinal cleansing with activated charcoal is generally of little use and increases the risk of aspiration(5). We recommend that BZD toxicity patients not be treated with Activated charcoal unless a life-threatening co ingestant is detected and the airway of the patient is patent.(6)

CONCLUSION

Although benzodiazepine poisoning is a straightforward diagnosis, it is commonly overlooked. CNS depression with normal vital signs is the characteristic presentation of a patient with an isolated BZD overdose. A diagnosis of drug intoxication should only be considered after all other evident causes of acute sensorium loss have been eliminated, as stated above. Due to the patient's altered mental state, obtaining a reliable history may be challenging. Any respiratory or abnormal vital signs should be handled first in a patient presenting with altered mental status and suspected overdose or toxicity before any diagnostic tests are undertaken. Mechanical ventilation and intravenous fluids may be required to address respiratory compromise and hemodynamic instability. When no definite diagnosis has been made, flumazenil can be used as an effective diagnostic tool. If correctly dosed, the antidote has little adverse effects even in the case of combined medication ingestions and in individuals with a range of medical comorbidities(7). Flumazenil can be safely provided to non-habitual benzodiazepine users. This is a common occurrence in the juvenile population (8) due to inadvertent consumption or following procedural anaesthesia. This case study stresses the importance of patient medication reassessment and the

benefits of Flumazenil in cases of suspected benzodiazepine toxicity.

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