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CASE REPORT

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Once was not enough: A case report of the concomitant intoxication of amlodipine (calcium channel blocker) and clonazepam (benzodiazepine)

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Abstract

We report a case of concurrent ingestion of Clonazepam and Amlodipine in a 25-year-old man, in a second attempt to take his life, which resulted in unconsciousness, hypotension, and hypokalemia. The clinical and/or biochemical presentation varied from the individual pattern when ingested. In the scarcity of consensus recommendations, supportive treatment helped.

KEYWORDS

benzodiazepines, calcium channel blockers, overdose, poisoning

1 | INTRODUCTION

Amlodipine besylate is a dihydropyridine (DHP) calcium channel blocker (CCB), which blocks the L-type voltage-gated calcium channels in smooth muscle of peripheral vessels.[1,2] Clonazepam is a long-acting and highly potent benzodiazepine (BZD), which acts by increasing the frequency of opening of ligand-gated chloride channel by binding to gamma-amino-butyric acid type A (GABA-A) receptor.[3,4] The clonazepam like other benzodiazepines is used as adjuvant to substance abuse, and commonly coingested with alcohol, ketamine, amphetamine, and gamma-hydroxybutyrate (GHB).[5] To the best of our knowledge, till date, the reported case of clonazepam coingestion with amlodipine is nil.

Here, we report a case of concomitant ingestion of amlodipine and clonazepam resulting in hypotension and hypokalemia without noncardiogenic pulmonary edema, which was managed with fluids, insulin, and inotropes.

2 | CASE PRESENTATION

A 25-year-old man was brought to the Emergency Department (ED) after his family members found him unconscious in his bed at 9:00 AM in the morning.

Approximately 12 hours prior to presentation, he had ingested 60 tablets of clonazepam (0.5 mg/tablet, total 30 mg) with suicidal intent and had gone to sleep. The family members noted him unresponsive the very next day, and brought him to the ED with the empty strips of ingested medications, and dissolved liquid found remained in his room. On examination in the ED, he was drowsy with a decreased response. His Glasgow coma scale (GCS) score was 11/15 (E3V3M5). The pupils were bilaterally symmetrical, normal-sized, and reactive to light. The gag reflex and other reflexes were normal. The respiratory rate was 12 breaths per minute and regular, and oxygen saturation was 86% in room air. The pulse rate was 112 beats per minute and regular. The blood pressure was within the normal range. He was then immediately shifted to the Intensive Care Unit (ICU) in anticipation of further deterioration, and initial assessments and treatments were started in the line of benzodiazepine poisoning. Oxygen supplementation via nasal cannula was done. The plan to start Flumazenil, a nonspecific competitive antagonist of the BZD receptor, was in consideration. We opted not to use flumazenil (specific benzodiazepine receptor) as the drug may cause more harm than good.[6]

Regarding his past history, he was admitted 1 month back with similar incident of ingestion of 30 tablets of clonazepam (0.5 mg/tablet, total 15 mg), and was discharged after 5 days of hospital admission. After discharge from ICU, psychiatry consultation was done. The patient was advised for admission in psychiatry ward in view of suicidal attempt. The patient resisted with the admission and was discharged to oral medication with Sertraline (Selective Serotonin Receptor Inhibitor [SSRI]) and Clonazepam and warned of another possible suicidal attempt. He did not have any other comorbidities.

The patient was stable hemodynamically until he experienced a sudden drop in his blood pressure (Systolic: 75; Diastolic: 45 mm of Hg) after few hours of admission in the ICU. The causative agents for decrease in blood pressure were sought after. In the meantime, injection phenylephrine was given immediately (@500 mcg q1-2minutes) for hypotension, and injection noradrenaline was started as continuous IV infusion (@4 mcg/min as maintenance) via peripheral line. After multiple probing and discussion with the family members, they shared finding an empty strip of Amlodipine under the bed. He had taken 10 tablets of Amlodipine (10 mg/tablet, total 100 mg). Therefore, treatment was planned for coingestion of Clonazepam and Amlodipine. Gastrointestinal decontamination with charcoal was avoided due to delay in presentation, and in anticipation of aspiration due to depressed consciousness. Intravenous infusion of high dose insulin (1 IU/kg bolus followed by 1 IU/kg/h regular insulin), and dextrose (@25 g glucose as 50% dextrose in 50 ml; titrated to maintain euglycemia) with added potassium (KCl @40 mmol/L/day) was started. Arterial line and Central Venous Catheter (CVC) were inserted for invasive BP monitoring and inotropic support, and other supportive managements like input–output monitoring and random glucose monitoring were also initiated. ECG showed sinus tachycardia with normal QRS complexes with T-wave abnormalities and prolonged QTc interval to 472 milliseconds. Intravenous calcium gluconate (@40 ml of 10% calcium gluconate over 10–20 min) was administered.

Laboratory analysis showed hemoglobin of 12.3 g/dL (reference range: 12–16 g/dL) with normal cells counts and red blood cell indices. [TLC: 7500/mm^3 (4000–11 000/mm^3) N75L20M03E02B00, Platelets 145 000/mm^3 PCV 43.4% (40–50%), RBC: 4.41 (4–5.5 million/mm^3) MCV: 98.4 fl (80–100), MCH 31.3 pg (27–33), MCHC: 31.8% (32–36)]. The arterial blood gas analysis revealed respiratory alkalosis (pH 7.44, HCO3 20.4 mmol/L, PCO2 30.8 mm Hg). The serum lactate was 1.7 mmol/L (reference range: 0.7–2.5 mmol/L). The random blood sugar was 83 mg/dL (reference range: 60–140 mg/dL). The serum sodium was 135 mmol/L (135–145 mmol/L), and serum potassium was 3.2 mmol/L (reference range: 3.5–5.50 mmol/L). The serum urea and creatinine were 24 mg/dL and 0.9 mg/dL, respectively. His urinalysis findings were normal. The liver function tests were normal. Chest X ray and USG findings revealed no abnormality (Table 1).

On the second day of admission, the consciousness was improving. Infusion insulin-dextrose was stopped

TABLE 1 Arterial blood gas analysis and electrolytes levels of patient

	Arterial blood gas (ABG) analysis					Serum				
Day of admission	**pH**	**PCO2**	**HCO3**	**AG**	**Cl^-**	**Lactate**	**Na^+**	**K^+**	**Ca^{++}**	**Mg^{++}**
D1	7.44	30.8	20.4	16.3	110	1.7	135	3.2		
D2	7.43	37.4	24.4	15.4	101	0.3	135	3.4	10.2	2.1
D3	7.46	33.7	23.5	14.7	103	1.1	138	3.9	10.0	2.0

Note: Reference range: ABG (pH: 7.40 mmol/L, PCO2: 40 mmHg, HCO3: 24 mmol/L, Cl^-: 88–106 mmol/L, AG: 8–12 mmol/L) and serum (Na^+: 135–145 mmol/L, K^+: 3.5–5.5 mmol/L, Ca^{++}: 8.5–10.5 mg/dL, Mg^{++}: 1.8–2.6 mg/dL, lactate: 0.7–2.5 mmol/L).

Abbreviation: AG, Anion gap.

but potassium was continued as injection. Nasogastric (NG) feeding was started. Glucose monitoring was done 6 hourly, serum sodium and potassium were measured 12 hourly, and serum calcium and magnesium were measured once a day. Blood and urine culture, and serum procalcitonin were ordered for the new-onset fever.

On the third day of admission, GCS improved to 15/15. Fever subsided. Pro-calcitonin was 0.4 ng/mL (reference range: <0.5). NG feeding was stopped once oral feeding was tolerated. Arterial line and CVC were taken out. Injection potassium and other supportive measures were continued. Mobilization was done. ECG tracing was normal.

On the fourth day of admission, Foley's catheter was taken out. He remained anxious and had low mood. He was discharged on tablet pantoprazole [Proton-Pump Inhibitor (PPI)] and syrup lactulose. Neuropsychiatric workup was done, and discharged on (SSRI) Sertraline 50 mg OD for depression. Risk behaviors were explained to his family members.

3 | DISCUSSION

Our patient presented with clonazepam toxicity with amlodipine coingestion. To our knowledge, there has been no literature depicting the presentations of combined benzodiazepines and calcium channel blockers coingestion, and their management.

Our patient did not develop noncardiogenic pulmonary edema, which may be evident with amlodipine poisoning.[7,8]

Although hyperglycemia is seen in poisoning with CCBs, our patient had normal blood sugar level at the time of presentation. CCBs block the L-type voltage-gated calcium channel in pancreatic B cells, and inhibits insulin release resulting in hyperglycemia and hypoinsulinemia.[9] Meanwhile, BZDs, especially Clonazepam, have been found to be altering insulin sensitivity and/or insulin secretion in one clinical trial.[10] So, the normal blood glucose level in our patient could be due to effect of Amlodipine in raising blood glucose level and counter effect of Clonazepam in causing hypoglycemia.[10–12]

Our patient had acute compensated respiratory alkalosis instead of respiratory acidosis, which may be usually apparent with BZDs toxicity due to respiratory depression.[13] The possible pattern of respiratory alkalosis could be due to predominant effect of amlodipine over clonazepam.[8]

There is no existing guidelines for management of amlodipine intoxication.[7,8,14–16] The main stay of therapy for amlodipine intoxication is supportive care. The possible antidotes of CCBs are intravenous calcium and glucagon[9] but unfortunately glucagon is not available and not used routinely in our part of the world.

Hyperinsulinemic euglycemia in CCBs overdose has been recommended as an appropriate strategy for its management, and had been beneficial in some case reports.[17,18] The insulin effect is by increasing ionized calcium level, exerting independent ionotropic effect, improving myocardial utilization of carbohydrates, and improving hyperglycemic acidotic state.[19]

Flumazenil is a benzodiazepine analog, which antagonizes benzodiazepines by binding to the same GABA-A receptor.[20] However, it is contraindicated in patients with mixed or unknown overdose and risk of precipitating seizure. Therefore, the treatment of benzodiazepine overdose is also supportive care. There is also no role of activated charcoal, hemodialysis or whole bowel irrigation in BZDs poisoning.[21,22]

The pattern of clinical and/or laboratory presentation of both BZDs and CCBs toxicity could be different from each of individual toxicity. There are no consensus recommendations for their management, and it's definitely supportive with focus on appropriate assessments and abnormalities.

AUTHOR CONTRIBUTIONS

SG, MC, and SA diagnosed and managed the patient. GKY wrote initial draft of the manuscript. SG, MC, GKY, and SA revised the final draft. All authors have read and approved the final manuscript.

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None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written and understood consent was taken from the patient for the publication purpose.

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