ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 10;4 http://apjmt.mums.ac.ir December 2021

CASE REPORT

Sequence of Unfortunate Events Leading to Persistent Acidosis Ending Fatally

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Abstract

Introduction: Methanol intoxication causes high anion gap metabolic acidosis in addition to Central Nervous System (CNS) depression. Benzodiazepines in co-ingestion with other CNS depressants as alcohol can cause significant respiratory depression. Liraglutide is a novel antidiabetic agent whose acute overdose is not well studied. This case report aimed to present a case with combined intake of the three above-mentioned chemicals.
Case Description: A case of 43-year-old male not diabetic, not an alcohol consumer, uses benzodiazepines regularly for sleep disorders. The patient unintentionally took 10 tablets of benzodiazepines over a period of 24 hours, aiming to sleep. He also consumed one glass of ethanol containing methanol (used for disinfection). The patient was on liraglutide subcutaneous injections for weight loss, with one injection 2 days before admission.
The night before admission, the patient first felt light headed and complained of blurring of vision. The condition progressed and the patient was taken to the emergency department where he presented with coma, apnea, and shock.
On the arrival of the patient, he was intubated and mechanically ventilated for having a disturbed conscious level and apnea.
Laboratory testing identified severe persistent mixed type acidosis, hypoglycemia, and urinary toxicology screen was positive for benzodiazepine. IV fluids, vasopressors, Dextrose, bicarbonate, flumazenil, vitamin B, and folinic acid were given. Although urgent haemodialysis was undertaken, acidosis continued. The patient passed away after 37 hours of intensive care unit admission.
Conclusion: Combined exposure to alcohol and benzodiazepines can cause significant mixed type acidosis. CNS depression can result from combined alcohol, benzodiazepines, and prolonged hypoglycemia.

Keywords: Methanol, benzodiazepines, liraglutide, hypoglycemia, acidosis.

How to cite this article: Fouad MM, Zawilla NH, Ashoush OA. Sequence of Unfortunate Events Leading to Persistent Acidosis Ending Fatally. *Asia Pac J Med Toxicol* 2021; 10(4):145-148.

INTRODUCTION

Methanol intoxication including the counterfeit alcoholic beverages is allied to substantial morbidity and mortality that needs eminent health policies to effectively control the increasing rates (1, 2). In Egypt, methanol toxicity is quite common (3). Although methanol itself is not very toxic, it is metabolized by alcohol dehydrogenase into formaldehyde and then into formic acid.

These metabolites cause anion gap metabolic acidosis, blindness, irreversible brain damage, and finally death (4). Methanol intoxication cases cannot be easily identified specially when history is not available and entails a high level of suspicion. Rapid recognition and early treatment with alcohol dehydrogenase inhibitors are decisive, as the irreversible effects caused by formic acid is time-sensitive.

Benzodiazepines are tranquilizing and anxiolytic drugs, known to be safer than barbiturates by causing less respiratory depression in overdose settings. Though cases of serious and fatal benzodiazepine overdoses such as alprazolam intoxication have been reported with significant respiratory depression, it usually occurs in co-ingestion with another central nervous system depressant such as alcohol (5).

Liraglutide is a novel long acting glucagon-like peptide-1 (GLP-1) receptor agonist that mimics incretin and helps to maintain glucose homeostasis through the stimulation of glucose-mediated insulin secretion and inhibition of glucagon release in a glucose-dependent manner. Additional therapeutic effects include increased satiety and weight loss (6). The GLP-1 agonists are not expected to cause hypoglycemia as monotherapy in therapeutic doses for diabetic patients and they are not well studied in overdose and therefore information regarding acute overdose is limited to case reports (7). Prolonged hypoglycemia can lead to unconsciousness, repeated episodes of severe hypoglycemia can cause long term cognitive dysfunction (8).

In the current study, we aimed at presenting a case of combined exposure to these 3 substances in a male patient that ended in persistent coma, metabolic acidosis, and death.

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CASE PRESENTATION

This research explored a case of 43-year-old male who was not diabetic, nor an alcohol consumer, but treated with benzodiazepines for sleep disorders and anxiety. The patient unintentionally took 10 tablets of diazepam 10 mg over a period of 24 hours, aiming to sleep. He also consumed one glass of denatured ethanol containing methanol that he bought from the pharmacy (used for disinfection) that he mixed with a can of soda as a traditional advise from a friend to treat renal stones. The patient was on liraglutide subcutaneous injections for weight loss, with one injection 2 days before the hospital admission.

The family repudiated any history of trauma or major psychiatric disorder as he was a well to do, educated man with a permanent stable job. His medical history is free from any chronic diseases apart from history of renal stones that he tried to ingest alcohol the day before the admission to dissolve it after he had taken its ordinary medications.

The patient was presented to the emergency department with coma, apnea, and shock, his Glasgow Coma Scale score was 3/15, with bilateral constricted pupil, he was hypotensive his blood pressure was 60/40, his heart rate was 112, he was apneic, his oxygen saturation in room air was 80 by pulse oximetry, and his temperature was 37.

The examination showed generalized hypotonia, diminished reflexes, and absent plantar response with no meningeal signs. The patient was immediately intubated and mechanically ventilated on volume control mode. Resuscitation was done to the patient by IV fluid challenge of 1000 ml normal saline 0.9% infused over 30 minute, vasopressors and inotropes (noradrenaline started by 0.01 mic/kg/ min and titrated to reach systolic pressure 90), ABG showed severe mixed metabolic and respiratory acidosis where PH was 6.75, PCO2: 34.8, HCO3: 4.8, PO2: 82.4 (table 1), bicarbonate 150 meq of 8.4 % diluted in 1 liter of dextrose 5% was given IV infusion over one hour.

Random blood sugar showed hypoglycemia (50 mg/dl). 100 ml dextrose 25% was given IV. Urinary toxicology screening was done revealing positive benzodiazepines only for which 5 ampoules of flumazenil 0.5 mg IV sequentially were together with vitamin B 100 mg IV slowly and folinic acid 50 mg IV every 6 hours (table 2) Once blood pressure was stabilized emergency hemodialysis for 2 hours was done.

After the dialysis session the patient's blood pressure was maintained on 90/60 by noradrenaline 3.3 mic/kg/min and adrenaline 2 mic/kg/min, HR: 110 b/min, GCS: 3/15, RR: 20 on ventilator volume control FiO2: 60%, temp: 37. The GCS did not improve above 3/15 and the pupils were dilated.

Laboratory follow up: repeated ABG showed metabolic acidosis, PH: 7-7.1, Hco3: 8-9 (table 1) and bicarbonate according to deficit was continued. Renal functions showed renal impairment with serum creatinine 2.6-2.8 mg/dl, BUN: 45mg/dl , liver functions were within normal , random blood sugar measurements were in a range of 70-75 mg/dl, Na and K range were (139-147 mmol/L) and (3.2-3.7 mmol/L), respectively, complete blood count with differential count was within normal. ECG showed inferior leads ischemia in a form of inverted T wave in II, III, aVf, and sinus tachycardia (figure 1). CT brain and CXR were done to the patient with no abnormality found.

Table 1. example serial ABG measurement along the patient hospital stay

On admission	One hour later	Serial ABG examples over remaining 36 hours hospital stay			
PH: 6.75	PH: 6.78	PH: 7.07	PH: 7.08	Ph: 7.11	Ph: 6.93
PCO2: 34.8	PCO2: 26.7	PCO2: 31.3	PCO2: 28.3	Pco2: 63.3	Pco2: 66
PO2: 82.4	PO2 : 131.1	PO2: 67.2	PO2: 52.8	Po2: 52.6	Po2: 18.7
HCO3: 4.8	HCO3: 5.1	HCO3: 9	HCO3: 9.7	Hco3: 19.6	Hco3 :13.8
		O2 sat: 80	O2 sat: 74.3	O2 sat: 70.5	O2 sat: 11.5 %

Table 2. Medication Summary

On Admission	Over the 37 Hours hospital Stay
1000 ml normal saline 0.9% infused over 30 minute	Continue IV fluid by rate 80 ml/H
Noradrenaline 0.01 mic/kg/ min IV infusion	Titrated Noradrenaline up to 3.3 mic/kg/ min IV infusion Adding adrenaline up to rate 2 mic/kg/ min IV infusion
Sodium bicarbonate 150 meq of 8.4 % diluted in 1 liter of dextrose 5% was given IV infusion over one hour	Continue bicarb same dose every 4 hours according to the ABG
100 ml dextrose 25% IV	
5 ampolues Flumazenil 0.5 mg IV sequentially	
Vitamin B 100 mg IV slowly	
Folinic acid 50 mg IV every 6 hours.	Continue Folinic acid same dose

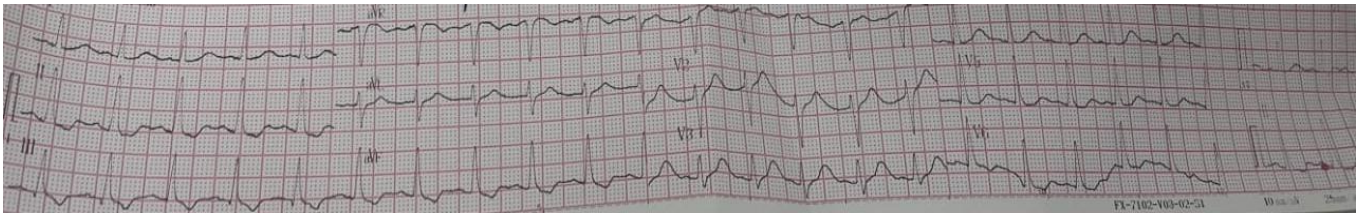

Figure 1. ECG showed inverted T wave in II, III , aVf and sinus tachycardia

severe acidosis persisted (table 1) along the 37 hours hospital stay, and inaudible blood pressure despite maximum vasopressors and inotropes, patient arrested for 18 minutes followed by return of spontaneous circulation (ROSC) for 5 minutes, with supraventricular tachycardia and 2 DC shock done then returned sinus. Patient arrested again with no ROSC for 40 minutes baseline ECG declared death after 2 hours on ventilator.

DISCUSSION

Methanol is a colorless, igneous, and poisonous fluid that is usually used as an industrial solvent (9). Methanol intoxication frequently happens from ingesting adulterated alcohol or denatured ethanol. Absorption of methanol is rapid after oral intake, with peak serum concentrations gotten within 1–2 h. Without treatment, methanol is eliminated via zero-order kinetics at a rate of 8.5 mg/dL/h following overdose, the time needed to accumulate methanol metabolites accounts for the latent period between methanol ingestion and clinical manifestations (10). The diagnosis of methanol poisoning necessitates a high degree of suspicion, as testing for methanol level is not broadly obtainable and frequently must be done at a reference laboratory besides hardly, if ever, reviewing results in proper time to support clinical management. In cases where history is not available or in severely obtunded patients, the presence of high anion gap metabolic acidosis and increased serum osmolar gap act as an important diagnostic evidence. However, either can be absent depending on time after exposure as well as simultaneous presence of ethanol (11). A latent period lasts approximately 12-24 hours when uncompensated metabolic acidosis develops with its consequences (12).

The clinical outcome correlates more with the severity of acidosis rather than the concentration of methanol (13). In our patient, the anion gap and osmolar gap were not calculated as the chloride level was not available for calculating the anion gap beside serum osmolality measurement cannot be done in our lab, also serum alcohol leveling is not available in our lab, so we depended on the history of methanol ingestion as he ingested the denatured alcohol used as a disinfectant from the pharmacy in addition to blurring of vision the patient complained of the night before admission. In disturbed conscious patients such as ours, neuroimaging can be assist in differentiating methanol intoxication from other causes of altered sensorium that is why CT brain was done. Management includes acidosis correction, with intravenous sodium bicarbonate, in cases of significant acidosis, as condition may far worse when systemic acidaemia is present (14**).** It also comprises fomepizole or ethanol administration as inhibitors of alcohol dehydrogenase, which is a crucial enzyme in the metabolism of methanol, in addition to the administration of intravenous folic acid that enhances the metabolism of formic acid (12). The best method for rapid removal of both the parent alcohol and toxic metabolites is hemodialysis. It has a vital role in managing severely intoxicated patients such as those with seizures, coma, new vision deficits, metabolic acidosis with blood pH $\leq$7.15, and a serum anion gap higher than 24 mmol/L (15). In our patient, hemodialysis was the best choice of management beside folinic acid as fomepizole and pure ethyl alcohol were not available.

Apparent renal injury seems relatively frequent following severe methanol poisoning. Isolated renal injury is less common than renal impairment accompanying other organs dysfunction. In our sampling, proximal tubular dysfunction, rather than glomerular, is preferentially noted. The mechanisms of nephrotoxicity are likely multifactorial. The role of direct factors remains highly speculative: possible injury to the tubular cells due to the osmotic effects of high blood methanol concentrations, and/or cytotoxic effects related to possible formate actions on proximal tubular cells. Among indirect factors, hemolysis and myoglobinuria were frequently observed. Acute renal injury may be associated with other signs of severity in methanol poisoning, but it is almost always reversible in survivors (16**).** Our patient had renal impairment and that may be related to either the methanol effect or as a complication of renal stones as renal stones itself is a risk for chronic kidney disease (17).

Benzodiazepines may actually depress respiratory drive in some individuals even at therapeutic doses. At higher doses or when combined with other medications, benzodiazepines depress the CNS in a dose-dependent fashion in most individuals. CNS depression is the most common cause of death in benzodiazepine overdose. Benzodiazepine can lead to acute respiratory failure and respiratory acidosis (18). Benzodiazepine antidote is flumazenil that reverses the effects of benzodiazepines by competitive inhibition at the benzodiazepine binding site on the GABA A receptor. Administered at the dose of 1.0 mg, it improved patient's consciousness for about 30 minutes. (19). But in our case the patient consciousness level did not improved at all after the administration of flumazenil owing to the combined effect of CNS depressant of benzodiazepines together with methanol in addition to the hypoglycemia of unknown period that

might all together have led to that depressed conscious level of our patient.

Liraglutide the GLP-1 agonist is associated with a low risk of hypoglycemia and modest weight loss, but may cause gastrointestinal disturbances, including nausea, vomiting, and diarrhea (20). Our patient had hypoglycemia on admission and this may be attributed to liraglutide administration.

CONCLUSION

The management of methanol poisoning included standard supportive care, the correction of metabolic acidosis, the administration of folinic acid, and selective hemodialysis to correct severe metabolic abnormalities and to enhance methanol and formate elimination. However, in this patient, combined exposure to alcohol and benzodiazepines as well as prolonged hypoglycemia had resulted in refractory metabolic acidosis and CNS depression. The series of unfortunate and unplanned events as well as lack of awareness about the combined effects of alcohol, benzodiazepines and hypoglycemic agents, had resulted in death of a fairly healthy young male patient.

ACKNOWLEDGMENT

The authors would like to acknowledge the patient's family for their honesty, cooperation, and patience in detailed history narration.

Funding and support: None.
Conflict of Interest: None to be declared.

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