

A 53-year-old woman with a suspected drug overdose

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A 53-year-old woman was brought to the emergency department after being found unresponsive at home, surrounded by empty pill bottles. Her partner had spoken to her on the phone 5 hours earlier, when she was reportedly well. Her medical history included bipolar I disorder and 2 previous suicide attempts.

History from her partner raised concern that she may have ingested about ninety 0.5-mg tabs of lorazepam, seventy 1-mg tabs of alprazolam, forty-eight 1-mg tabs of clonazepam, twenty-four 50-mg tabs of quetiapine, ten 7.5-mg tabs of zopiclone and 1 bottle of NyQuil, which contains acetaminophen, dextromethorphan and doxylamine.

Before arrival at the emergency department the patient had been intubated by paramedics to protect her airway. On arrival, her temperature was 35.7°C, blood pressure 74/33 mm Hg, heart rate 115 beats/min, respiratory rate 8 breaths/min and oxygen saturation 98% on 100% FiO₂. She had a decreased level of consciousness, with a Glasgow Coma Scale score of 3T, and no agitation or excited delirium. Her capillary blood glucose was 14.6 (normal 3.8–7.0) mmol/L. Her pupils were 3 mm bilaterally and reactive to light. She had normal tone with no rigidity, hyperreflexia or clonus.

Which toxidrome best describes this patient?

- a. Serotonin syndrome
- b. Neuroleptic malignant syndrome
- c. Opioid toxicity
- d. Sedative or hypnotic toxicity
- e. Anticholinergic toxicity

The answer is (d). This patient presented with a decreased level of consciousness, without characteristic features to suggest another toxidrome (Table 1). Her physical examination suggested a sedative or hypnotic overdose, compatible with the collateral history of benzodiazepine, zopiclone and doxylamine ingestion. Although several features of opioid toxicity overlap with sedative or hypnotic toxicity, the former typically causes pinpoint pupils, which we did not see in this patient.¹ Serotonin syndrome and neuroleptic malignant syndrome (NMS) can both present with altered mental status and autonomic instability.¹ Serotonin syndrome is characterized by acute onset, hyperreflexia and myoclonus, while NMS occurs over days, classically with lead-pipe rigidity.¹ Anticholinergic toxicity presents with agitated delirium, hyperthermia, mydriasis, dry skin and mucous membranes, and urinary retention.¹

Which of the following decontamination strategies would be appropriate at this time?

- a. Activated charcoal
- b. Gastric lavage
- c. Whole bowel irrigation
- d. No gastrointestinal decontamination

The answer is (d). Although gastrointestinal decontamination is a critical component of managing some toxicologic emergencies, our patient presented hours after suspected ingestion, which would reduce the utility of activated charcoal.² There is no indication for

Table 1: Common toxidromes

Toxidrome	Temp	BP	HR	RR	Pupils	Mental status	Other
Opioids	↓	↓	↓	↓	↓	Depressed	Hyporeflexia
Sedative-hypnotic	−/↓	↓	↓	↓	−/↓	Depressed	Hyporeflexia
Anticholinergic	↑	−/↑	↑	−	↑	Agitated delirium	Dry mucous membranes and skin, urinary retention
Sympathomimetic	↑	↑	↑	↑	↑	Agitated delirium	Tremor, seizures, diaphoresis
Serotonin toxicity	−/↑	↑	↑	−/↑	−/↑	Agitated delirium	Hyperreflexia, clonus, tremor, seizures
Neuroleptic malignant syndrome	↑	↑/↓	↑	−/↑	−	Agitated delirium	Rigidity

Note: BP = blood pressure, HR = heart rate, RR = respiratory rate, temp = temperature.

whole bowel irrigation, which is considered in toxic ingestions of drugs in sustained-release preparations, for drugs not adsorbed by activated charcoal, or for removal of packets of illicit drugs.³ Gastric lavage should be considered only in patients presenting within 1–2 hours of a potentially lethal ingestion with no available antidote.⁴

Which of the following is the most important initial investigation for this patient with a depressed level of consciousness due to a suspected overdose?

- Abdominal radiograph to identify radio-opaque toxins
- Blood work to identify acid–base disturbances and calculate anion and osmole gaps (blood gas, electrolytes, glucose, urea, osmolality, ethanol level)
- Lumbar puncture to rule out a central nervous system infection
- Urine immunoassay drug screen to identify culprit toxins
- Electrocardiogram and high-sensitivity troponin to rule out myocardial ischemia

The answer is (b). First-line investigations in assessing a patient with a suspected overdose should include an arterial or venous blood gas, lactate, electrolytes, blood glucose, serum osmolality, urea, urine or serum ketones, and creatinine; the anion gap and osmole gap should be calculated.⁵ Serum drug levels can be helpful, including acetaminophen, salicylate, ethanol, toxic alcohols and any medications that have validated therapeutic drug monitoring levels.⁵ Urine immunoassay drug screens are less helpful in the acute setting, as technical factors and cross-reactivity can lead to false positives and false negatives, including for benzodiazepines, cannabinoids, opioids and anticholinergic medications.⁶ Central nervous system infections and acute coronary syndrome can present with some of the findings of this patient; however, the collateral history and presence of empty pill bottles made it highly likely that our patient's presentation was due to an overdose.

The results of initial investigations are shown in Table 2. The patient's anion gap was 19 (normal 5–11) mmol/L and osmole gap was 57 (normal < 10) mOsm/kg. Her acetaminophen level was 903 (therapeutic 65–130) µmol/L in the context of an

Table 2: Results of initial investigations of 53-year-old patient with a suspected drug overdose

Test	Result	Normal range
Arterial blood gas		
pH	7.12	7.35–7.45
pCO ₂ (mm Hg)	42	35–45
pO ₂ (mm Hg)	275	80–100
Bicarbonate (mmol/L)	13	23–28
Sodium (mmol/L)	140	135–145
Potassium (mmol/L)	2.7	3.2–5.0
Chloride (mmol/L)	108	100–110
Creatinine (µmol/L)	164	50–98
Albumin (g/L)	32	38–50
Lactate (mmol/L)	10.6	0.5–2.0
Serum ketones	Negative	Negative
Serum ethanol (mmol/L)	< 1	< 1
Random glucose (mmol/L)	13	3.8–7.0
Urea (mmol/L)	7.2	3.0–7.0
Serum osmolality (mmol/kg)	357	275–295
Acetaminophen (µmol/L)	903	65–130 (therapeutic level)
Aspartate aminotransferase (U/L)	17	5–34
Alanine aminotransferase (U/L)	15	7–40
Alkaline phosphatase (U/L)	58	40–150
Bilirubin (µmol/L)	< 3	≤ 22
International normalized ratio	1.1	0.9–1.2
Anion gap (mmol/L)*	19	5–11
Osmole gap (mOsm/kg)†	57	< 10

*Anion gap calculated by $[Na^+] - ([Cl^-] + [HCO_3^-])$
†Osmole gap calculated by subtracting serum osmolality ($2[Na^+] + [glucose] + [urea]$) from measured serum osmolality.

unknown time of ingestion. A 12-lead electrocardiogram showed sinus tachycardia with normal QRS and QTc intervals, suggesting the absence of substantial toxicant-induced sodium channel blockade (e.g., tricyclic antidepressant overdose), or potassium channel blockade (e.g., methadone, typical antipsychotics).¹

Which of the following toxins will not cause an elevated anion and osmole gap?

- Ethylene glycol
- Propylene glycol
- Methanol
- Isopropanol

The answer is (d). The finding of a simultaneously elevated anion gap and osmole gap should raise suspicion for the presence of toxic alcohols. The osmole gap is calculated in poisoned patients to screen for toxic alcohol ingestion. If the osmole gap is elevated, clinicians should determine if this can be accounted for solely by ethanol, which contributes about 1.21–1.25 mOsm for every 1 mmol.⁷ If there is a substantial osmole gap after correcting for ethanol, toxic alcohol ingestion should be suspected and serum levels ordered; however, these tests take time and treatment should be initiated before the results become available.⁸

In toxic alcohol ingestion, the parent alcohol contributes to the osmole gap, and is metabolized by alcohol dehydrogenase, producing acid metabolite(s) that contribute to the anion gap (Figure 1).⁸ Importantly, depending on the timing of ingestion, patients may present with any combination of elevations in osmole gap only, both osmole and anion gap, or anion gap only.⁸

Patients who present shortly after ingestion are expected to have an elevated osmole gap and a normal or near-normal anion gap, especially if they have co-ingested ethanol, which will temporarily block the metabolism of toxic alcohols.⁸ Patients who present later after ingestion may have a substantially elevated anion gap and a normal or near-normal osmole gap, as they have already metabolized the parent alcohol compound to its acid metabolites.⁸ Isopropanol is a tertiary alcohol that can cause an elevated osmole gap; however, it is metabolized to acetone, which does not cause an elevated anion gap.⁸

Our patient ingested NyQuil, which contains propylene glycol. As this alcohol is metabolized to lactaldehyde and subsequently oxidized to lactic acid, propylene glycol ingestion can result in high lactate levels, metabolic acidosis and an elevated osmole gap.⁸

Which of the following treatments is most appropriate at this time?

- Fomepizole
- Flumazenil
- Intravenous ethanol
- Hemodialysis

The answer is (a). The immediate priority in the management of suspected toxic alcohol exposure is the administration of an antidote. Although propylene glycol may explain the biochemical abnormalities, until levels are confirmed, there is no way to be certain the patient did not also co-ingest methanol or ethylene glycol. Fomepizole (4-methylpyrazole) is a competitive inhibitor of alcohol dehydrogenase with more than 1000 times greater

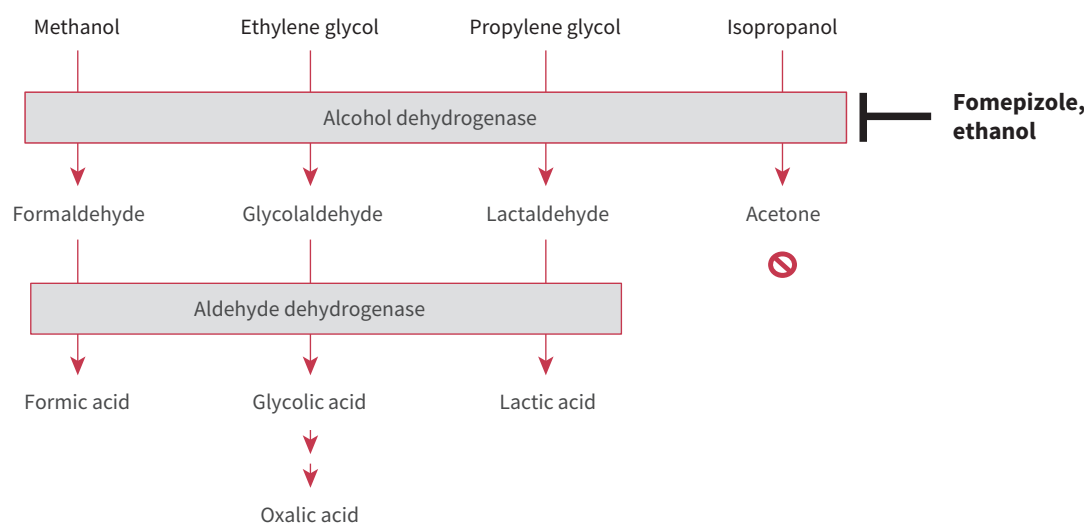


Figure 1: Metabolism of toxic alcohols. The parent alcohol contributes to the osmole gap and is metabolized by alcohol dehydrogenase (ADH) and then aldehyde dehydrogenase to produce acid metabolites that contribute to the anion gap. Isopropanol is the exception, as it is metabolized by ADH to acetone only, with no acid metabolite production. Ethanol is also metabolized by ADH but has a far greater affinity than other alcohols, thus competitively inhibiting this enzyme, and acting as a blocking agent. Fomepizole (4-methylpyrazole) also blocks ADH through competitive inhibition, with more than 1000 times affinity than toxic alcohols. Fomepizole is preferred to ethanol, given its better safety profile and ease of administration.^{8,9}

affinity than methanol or ethylene glycol (Figure 1).⁸ If available, fomepizole has replaced ethanol for the management of toxic alcohol poisoning because it is simpler to administer and safer.⁸ Hemodialysis is not indicated in the absence of confirmed toxic alcohol poisoning.

Flumazenil, a benzodiazepine antagonist, is potentially harmful in this patient, as administration can cause seizures and block therapeutic benzodiazepine use.¹⁰ In the setting of unknown polysubstance overdoses, co-ingestion of a benzodiazepine is often inadvertently protective against other stimulant ingestions.¹⁰

We gave our patient 1 dose of fomepizole and also started *N*-acetylcysteine, given the elevated acetaminophen level with an unknown ingestion time.¹¹ Although acetaminophen poisoning can also cause lactic acidosis, it would not explain the osmole gap, and this is typically associated with massive ingestions over 500 mg/kg, which was not suggested by the collateral history in our patient.¹¹ Intravenous fluids were administered while we waited for the results of toxicologic investigations. Methanol, ethylene glycol and isopropanol levels were undetectable, so fomepizole was discontinued. The patient's propylene glycol level was elevated at 31.5 mmol/L, explaining her elevated lactate, anion gap and osmole gap.

Discussion

Poisoning in patients is common and poses diagnostic and management challenges. Given the unpredictable nature of drug overdoses and poisonings, conducting randomized controlled trials is seldom practical; therefore, much of the evidence in toxicology relies on case series, animal models and expert opinion. Taking a careful history to detect all sources of drug exposure, along with a targeted examination for toxidromes (Table 1), is key in identifying the likely culprit poisoning(s) and guiding management until the results of definitive tests are available.^{1,5}

Propylene glycol is a diluent alcohol in many pharmaceuticals, foods and cosmetics.¹² The presentation of propylene glycol toxicity includes altered level of consciousness and can, rarely, lead to seizures and coma.⁹ Propylene glycol is rapidly absorbed and about 45% is excreted renally.¹² It has a half-life of 2–4 hours and is metabolized to lactic acid.¹² The lactic acidosis is typically well tolerated, as it reflects the metabolism of the parent compound, rather than underlying anaerobic metabolism due to severe illness.⁹ Propylene glycol intoxication can typically be managed with supportive care alone.

Case revisited

We consulted the regional poison centre and managed the propylene glycol and benzodiazepine poisonings with supportive care. The patient's hemodynamics improved with intravenous fluids, she recovered a normal level of consciousness, and she was extubated within 12 hours of presentation. Her anion gap, osmole gap and lactate level normalized. As this poisoning was intentional, she was assessed by the psychiatry service and was ultimately discharged with outpatient follow-up.

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