

TEACHING CASE REPORT

Negative anion gap and elevated osmolar gap due to lithium overdose

The case: A 65-year-old man was found in a state of clouded consciousness of unknown duration. At hospital his Glasgow Coma Scale score was 9. Naloxone and thiamine were administered. A CT head scan showed no acute injury. The serum anion gap was 1 mmol/L, and the osmolar gap 12.8 mOsmol/kg (Table 1). The patient was normoglycemic, and

results of urine and serum toxicology screens were positive for lithium; no other toxins were present. The lithium level was above 6 mmol/L, and the patient was subsequently transferred to our hospital for acute hemodialysis.

On arrival, the patient's blood pressure was 91/64 mm Hg, heart rate 111 beats/min, respiratory rate 22 and temperature 35.6°C; the jugular venous pressure was not visible. His urine output over 6 hours was 2.4 L and dilute in appearance. Repeat blood work revealed an anion gap of -2 mmol/L, an osmolar gap of 36 mOsmol/kg, a serum creatinine level of 89 µmol/L, a serum calcium level of 2.64 mmol/L

and a lithium level of 14.5 mmol/L. The patient had a history of suicidal ideation, bipolar affective disorder and hypertension. His medications included hydrochlorothiazide and long-term lithium therapy.

Aggressive rehydration was begun with 3 L of normal saline, as was conventional hemodialysis using a 1.8-m² high-flux dialyzer at a blood pump speed of 300 mL/min and a dialysate flow rate of 750 mL/min. A bicarbonate bath dialysate was used. The lithium level rapidly fell to 4.7 mmol/L over

Table 1: Results of laboratory tests

Test (normal range)	Results available from transferring hospital	Results at presentation
Sodium, mmol/L (135-145)	143	142
Potassium, mmol/L (3.2-5.0)	3.6	3.8
Chloride, mmol/L (100-110)	109	115
Bicarbonate, mmol/L (23-29)	36	26
Creatinine, µmol/L (< 99)	95	89
Calcium, mmol/L (2.20-2.62)	2.68	2.64
Albumin, g/L (35-45)	40	40
Anion gap, mmol/L (7-13)	-2	1
Lithium, mmol/L (0.6-1.2)	> 6*	14.5
Urea, mmol/L (2-8)	5.2	6.6
Plasma glucose, mmol/L (3.8-7)	4.0	4.9
Plasma osmolality, mOsm/kg (275-295)	308	324
Calculated osmolality, mOsm/kg (275-295)	295.2	295.5
Osmolar gap, mOsm/kg (< 20)	12.8	28.5
Phosphate, mmol/L (0.8-1.4)	—	< 0.5
Hemoglobin, g/L (110-145)	—	138
pH (7.35-7.45)	—	7.38
Partial pressure of carbon dioxide, mm Hg (35-45)	—	47
Partial pressure of oxygen, mm Hg (80-100)	—	80
Serum and urine toxicology screen	Positive for lithium only	Positive for lithium only

Note: The electrolytes were measured using the Badebehring Dimension (colorimetric). The osmolality was measured using the freezing point, and the plasma sample for lithium levels was collected using a nonheparinized tube. About 12 hours elapsed between values obtained at the referring hospital and those obtained at our institution. Toxicology tests performed included screening for toxic alcohols, acetylsalicylic acid, acetaminophen, theophylline, digoxin, opiates, benzodiazepines and cocaine.

*Exact value unavailable.

Box 1: Adverse effects of lithium

Central nervous system

- Altered level of consciousness
- Dysarthria
- Psychomotor retardation
- Vertigo
- Nystagmus
- Tremor
- Parkinsonian movements
- Seizures
- Pseudotumour cerebri

Dermatologic

- Folliculitis
- Alopecia

Cardiovascular

- Cardiac arrhythmia
- Hypotension
- Bradycardia
- Syncope

Endocrine

- Hypo- or hyperthyroidism
- Goiter
- Hyperglycemia
- Hypercalcemia
- Hyperparathyroidism

Gastrointestinal

- Anorexia
- Nausea or vomiting
- Diarrhea
- Metallic taste
- Excessive salivation

Renal

- Nephrogenic diabetes insipidus
- Glucosuria
- Chronic renal failure
- Proteinuria

4 hours. Hemodialysis was continued for a total of 24 hours, and the patient's level of consciousness improved. Forty-eight hours after discontinuing dialysis, the lithium levels rebounded to more than 4 mmol/L, and the patient's speech became slurred. Continuous venovenous hemodiafiltration was performed at a blood flow rate of 100 mL/min, a dialysate flow rate of 1500 mL/min and a replacement fluid (75 mmol/L saline) flow rate of 1000 mL/min. Dialysis was continued for 40 hours. During this period, the patient's urine output was more than 4 L/d, and his speech returned to normal. After discontinuation

Box 2: Principles of management of lithium intoxication

- Recognize clinical and biochemical features of intoxication
- Decrease gastric absorption by means of whole-bowel irrigation
- Stop all further use of lithium, diuretics and nonsteroidal anti-inflammatories
- Begin aggressive rehydration
- Begin hemodialysis
- Maintain water balance

Box 3: Anion gap

Calculation

Anion gap = Na – (chloride + bicarbonate)

The anion gap is the difference between measured cations and anions, with normal values falling between 7 and 13 mmol/L. This difference is due to charges on plasma proteins, particularly albumin, and must be adjusted downward in patients with hypoalbuminemia. For every decrease in albumin of 10 g/L, the anion gap decreases by about 2.5 mmol/L.

Differential diagnosis of a low anion gap

- Hypercalcemia
- Hypermagnesemia
- Hyperkalemia
- Cationic immunoglobulins (as in plasma cell dyscrasias)
- Bromide intoxication
- Nitrates
- Lithium

of dialysis, the patient rapidly recovered. He was discharged from hospital 2 weeks later with no detected neurologic deficits.

Lithium is highly effective in the treatment of bipolar disease, with success rates approaching 70%. However, because of the drug's narrow therapeutic window, toxic effects are common (Box 1). The most common manifestation of toxicity is altered mental status. Our patient also had a high urine output of 2.4 L in 6 hours, which suggests polyuria due to a concentrating defect. Depending on the length of lithium use, toxic effects can occur with levels as low as 2.5 mmol/L. Severe toxic effects have been reported in acute overdoses with levels of 5–9 mmol/L. Risk factors for lithium toxicity include the use of thiazide diuretics, renal insufficiency, congestive heart failure and volume depletion. The principles of management of lithium intoxication are outlined in Box 2. The mortality is as high as 25%, and 10% of survivors will have permanent neurologic deficits.¹

The anion gap is a key diagnostic clue when approaching the differential diagnosis of toxidromes and metabolic acidosis. The formula is given in Box 3.

Lithium is a positive charged ion with valence of 1 and electrochemical properties similar to those of sodium and potas-

sium. Large quantities of positive cations in the plasma are balanced by the anions bicarbonate and chloride and can cause a negative anion gap because sodium, but not lithium, is included in the calculation. Our patient had only a mildly elevated calcium level with a normal albumin level. Of note, the severe lithium intoxication in this case resulted in a negative anion gap that was corrected with dialysis (Fig. 1).

The osmolar gap is another useful diagnostic clue in cases of overdose. Common causes of an elevated osmolar gap and the formula are outlined in Box 4. In our patient, the osmolar gap was elevated at 36 mOsmol/kg. Other causes of elevation were excluded since the results of the toxicology screen were negative for alcohols, serum ketones and lactate and the patient had a normal lipid profile. We postulate that the high level of lithium with its anion, bicarbonate (from lithium carbonate), contributed to an increase in plasma osmolality. This is further supported by the patients' elevated bicarbonate level of 36 on presentation. The expected increase in osmolar gap would be 2 times the lithium level, or about 28 mOsmol/kg, which is similar to the level in our patient. Lithium has never been previously reported to lead to an elevation in the osmolar gap and should be included in the list of currently known causes. The combination

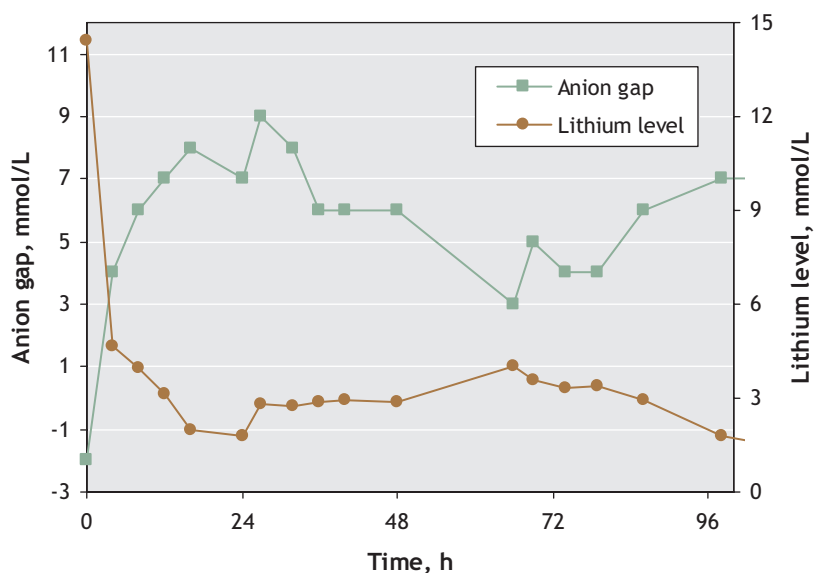


Fig. 1: Inverse correlation between lithium level and anion gap over time. Of note, the initial anion gap of -2 mmol/L corresponded to a lithium level of 14.5 mmol/L.

Box 4: Osmolar gap**Calculation**

Osmolar gap = measured osmolality
– calculated osmolality =
plasma osmolality – [(2 × Na) +
plasma glucose + urea]

Differential diagnosis of an elevated osmolar gap

- Isopropanolol
- N-propanolol
- Propylene glycol
- Ethylene glycol*
- Methanol*
- Formaldehyde*
- Paraldehyde*
- Mannitol
- Diethyl ether ingestion
- Lithium overdose

*Denotes causes associated with an elevated anion gap metabolic acidosis.

of an elevated osmolar gap and decreased anion gap without metabolic acidosis should be considered highly suggestive of severe lithium intoxication after exclusion of severe hyperproteinemia, hyperlipidemia and mannitol ingestion.

Lithium is absorbed through the gastrointestinal tract, with peak plasma levels occurring within 1–4 hours and steady state levels in 6 days. Lithium has a large volume of distribution of 0.6–0.9 L/kg, and its primary route of excretion is through the kidneys. Because of its large volume of distribution, lithium shifts into the intracellular compartment of cells. With long-term use, the intracellular concentration of lithium increases, which thereby results in an increased total body lithium load. The intracellular concentration is not reflected by the plasma level, which measures only the extracellular fluid concentration. In our case, assuming a volume of distribution close to 1 L/kg and complete gastric absorption, each 300-mg tablet will increase the plasma lithium level by 0.1 mmol/L. Therefore, a plasma lithium level of 14.5 mmol/L correlates with the ingestion of about 145 tablets.²

Intermittent hemodialysis is the treatment of choice for lithium intoxication in patients who are hemodynamically stable. In our case, hemodialysis was initiated at a high blood pump speed

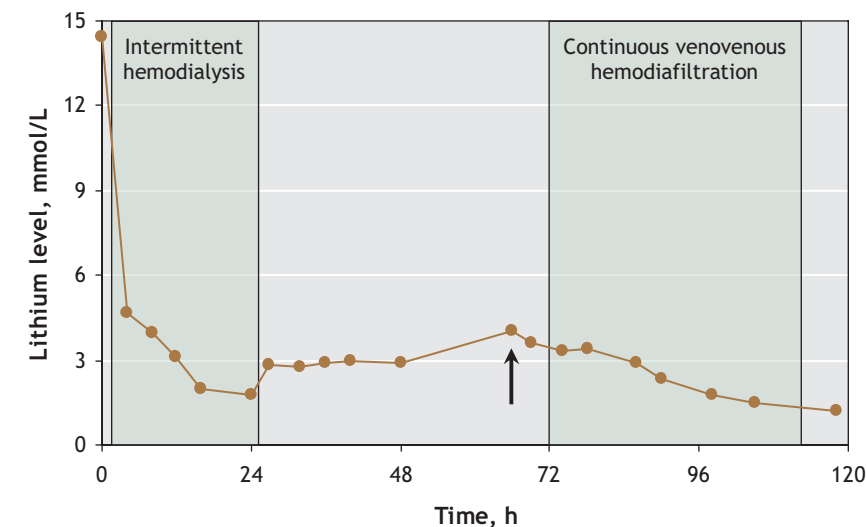


Fig. 2: Effects of intermittent hemodialysis and continuous venovenous hemodiafiltration on lithium levels. Time zero was arrival at our centre. Arrow indicates rebound in lithium levels that required initiation of continuous venovenous hemodiafiltration.

of 300 mL/min, which achieved a measured lithium clearance of 262 mL/min (lithium clearance = blood pump speed [Qb] × [(lithium level arterial side – lithium level venous side)/lithium level arterial side]). This high rate of clearance resulted in a dramatic decrease in the plasma lithium levels, from 14.5 to 4.7 mmol/L, in 4 hours (Fig. 2). Previous reports of intermittent hemodialysis for lithium removal achieved clearances of 94–170 mL/min with lower blood and dialysate flow rates.^{3,4} We stopped intermittent hemodialysis after 24 hours because our patient's cognitive status improved and his plasma lithium level fell to 1.8 mmol/L. Discontinuation of hemodialysis often results in a rebound of plasma lithium levels as intracellular lithium shifts to the extracellular space. Three days after the ingestion of lithium and 48 hours after hemodialysis was stopped, our patient's lithium level rebounded to more than 4 mmol/L. Continuous venovenous hemodiafiltration was then started, because of hemodynamic instability, and continued for 40 hours. Hazouard and associates previously demonstrated that lithium elimination with continuous renal replacement therapy linearly correlated with the volume of hemofiltration plus dialysate flow rate.⁵ Of note, lithium levels fell rapidly with the use of intermittent hemodialysis, whereas the use of continuous ven-

ovenous hemodiafiltration, with its slower blood flow rates, resulted in much slower lithium clearance. Unfortunately, our patient's hemodynamic status did not allow us to safely use intermittent hemodialysis, but it is much more effective at removing lithium from the blood in cases of intoxication.

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This article has been peer reviewed.

Competing interests: None declared.

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