Acute Bromide Intoxication in a Patient with Preserved Renal Function

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Conflict of interest: None declared

Patient: Female, 70-year-old

Final Diagnosis: Bromide intoxication

Symptoms: Fatigue

Medication: Naron Ace

Clinical Procedure: —

Specialty: Toxicology

Objective: Unexpected drug reaction

Background: Electrolyte imbalance is frequent in many situations, but severe hyperchloremia is markedly rare in the absence of renal impairment. We report a patient with preserved renal function who exhibited severe hyperchloremia and negative anion gap.

Case Report: A 70-year-old female with preserved renal function presented with fatigue and impaired consciousness. Venous blood gas analysis was notable for a chloride level of 137 mEq/L and anion gap of –18.2 mEq/L. Careful history taking revealed that she had taken bromide-containing over-the-counter painkillers. Her symptoms and laboratory tests gradually improved after intravenous hydration and painkiller withdrawal. The serum level of bromide ions on admission was later found to be 4-times higher than that considered toxic.

Conclusions: It is important to recognize that hyperchloremia with a negative anion gap strongly suggests bromide intoxication, and that bromide intoxication can develop even in patients with preserved renal function. Careful history taking is essential to the diagnosis because some over-the-counter drugs that are widely available and a few prescription drugs contain bromides.

MeSH Keywords: Acid-Base Equilibrium • Bromides • Chlorides

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/922019
**Background**

Electrolyte imbalance is frequent in many situations, but severe hyperchloremia is markedly rare without specific conditions such as renal impairment [1] or sepsis [2]. We report a patient who had no signs suggestive of these specific conditions but exhibited severe hyperchloremia and negative anion gap. A diagnosis of bromide intoxication due to over-the-counter painkillers was made by careful history taking.

**Case Report**

A 70-year-old female was admitted to our hospital because of fatigue and impaired consciousness. The patient had been in her normal state of health until approximately a week before admission, when fatigue and appetite loss developed. During the period of a week before admission, she had moved more slowly and talked less frequently. The patient was transferred to the emergency department of our hospital. She denied any antecedent trauma, but stated that she had often had nausea, vomiting, chest pains, back pains, and dizziness. Review of systems was negative for night sweats, body weight loss, and loss of conscience.

The patient had migraines, depression, and a previous history of pneumonia. Her medications included paroxetine hydrochloride at 20 mg, flunitrazepam at 2 mg, brotizolam at 0.25 mg, sumatriptan succinate at 50 mg as needed, and clotiazepam at 5 mg as needed. She did not smoke, drink, or use illicit drugs, and had pollen allergy. Her family history was unremarkable except that her brother had gastric cancer.

On examination, she was lethargic, disoriented (Japan Coma Scale 1), and appeared anorexic. Her height was 158 cm, weight was approximately 34 kg, and body-mass index was 13.6, which had not changed for years. Her blood pressure was 126/78 mmHg, pulse was 150 beats per minute, body temperature was 36.6°C, respiratory rate was 30 breaths per minute, and oxygen saturation was 97% while breathing ambient air. The mucous membrane of the oral cavity was dry, but the remainder of the examination, including cranial nerves, was normal.

On admission, venous blood gases obtained without supplemental oxygen flow had a pH of 7.589, partial pressure of carbon dioxide of 15.6 mmHg, lactate of 28 mg/dL, and bicarbonate of 15.0 mEq/L. Of note, the chloride level was increased up to 137 mEq/L (reference 100 to 110 mEq/L) and the anion gap was markedly low at ~18.2 mEq/L (reference 10 to 14 mEq/L), although the laboratory tests indicated a chloride level of 94 mEq/L (reference 26 to 70 μmol/L).

Urinalysis revealed a pH of 5.5, glucose −, protein +/−, ketone 3+, urobilinogen +/−, and a specific gravity of 1.016. Electrocardiography demonstrated sinus tachycardia with a heart rate of 146 beats per minute, and neither ST-T segment changes nor abnormal Q waves. Bedside echocardiography revealed normal ventricular function, in addition to a collapsed inferior vena cava. A cardiothoracic ratio of 35% without pulmonary congestion or pleural effusion was noted on chest radiography.

A tentative diagnosis of malnutrition and dehydration with electrolyte imbalance was made, and intravenous hydration was initiated, accompanied by potassium supplement. Careful history taking after admission revealed that she had taken the over-the-counter painkillers NARON ACE (Taisho Pharmaceutical Co., Ltd., Tokyo, Japan) at 2 tablets 3 times per day for almost 1 month due to frequent headaches. The dose that she took at one time included 144 mg of ibuprofen, 84 mg of ethenzamide, 200 mg of bromovalerylurea, and 50 mg of anhydrous caffeine. The patient reported that her appetite had decreased but that she did not stop taking the painkillers, which were discontinued after admission. Her calorie intake was increased slowly to avoid the development of refeeding syndrome. Her condition and laboratory tests gradually improved within a week, as shown in Table 1, and she was discharged home with advice not to take any painkillers without consulting her physician. It was later confirmed that the serum level of bromide ions, the metabolites of bromovalerylurea, was 93.6 mg/dL on admission (a serum level >20 mg/dL considered toxic [3]).

**Discussion**

The patient presented with a 1-week history of fatigue and appetite loss. The physical examination was unremarkable except for the low body-mass index, but laboratory tests demonstrated an uncommon electrolyte imbalance – a markedly high level of chloride and low anion gap. A diagnosis of bromide intoxication as a result of continuous use of over-the-counter painkillers was finally confirmed by careful history taking and concentration measurement.
Table 1. Laboratory data.

| Variable                      | Reference range | On admission | Next day after admission | One week after admission |
|-------------------------------|-----------------|--------------|--------------------------|--------------------------|
| White blood cell count (μL)   | 4,000–9,000     | 7,100        | 7,200                    | 3,300                    |
| Hemoglobin (g/dL)             | 11.5–16.5       | 13.4         | 10.3                     | 9.6                      |
| Platelet count (μL)           | 150,000–420,000 | 323,000      | 241,000                  | 326,000                  |
| Total bilirubin (mg/dL)       | ≤1.2            | 0.8          | 0.6                      | 0.2                      |
| Aspartate aminotransferase (U/L) | ≤30          | 45           | 38                       | 20                       |
| Alanine aminotransferase (U/L) | ≤30            | 29           | 25                       | 17                       |
| Lactate dehydrogenase (U/L)   | 110–120         | 290          | 241                      | 194                      |
| Total protein (g/dL)          | 6.7–8.8         | 7.4          | 5.7                      |                           |
| Albumin (g/dL)                | ≥4.0            | 4.2          | 3.3                      |                           |
| Sodium (mEq/L)                | 135–147         | 131          | 138                      | 142                      |
| Potassium (mEq/L)             | 3.6–5.0         | 2.4          | 2.5                      | 4.5                      |
| Chloride (mEq/L)              | 100–110         | 94           | 103                      | 109                      |
| Calcium (mg/dL)               | 8.2–9.8         | 9.3          | 7.6                      |                           |
| Phosphorus (mg/dL)            | 2.3–4.3         | 0.9          | 3.1                      |                           |
| Magnesium (mg/dL)             | 1.8–2.4         | 1.9          | 1.7                      |                           |
| Urea nitrogen (mg/dL)         | 8–20            | 10           | 3                        | 8                        |
| Creatinine (mg/dL)            | 0.45–0.81       | 0.62         | 0.53                     | 0.54                     |
| Amylase (U/L)                 | 37–125          | 186          | 138                      |                           |
| Creatine kinase (U/L)         | ≤175            | 192          | 163                      |                           |
| C-reactive protein (mg/dL)    | ≤0.25           | 0.05         | 0.45                     | 0.51                     |
| Blood sugar (mg/dL)           | 70–108          | 140          | 74                       |                           |
| eGFR (mL/min/1.73 m²)         | ≥60             | 71.5         | 84.8                     | 83.1                     |
| Glycated hemoglobin (%)       | 4.6–6.2         | 5.0          |                           |                           |

Arterial blood gases

| Variable                  |                |              |                          |                          |
|---------------------------|----------------|--------------|--------------------------|--------------------------|
| pH                        | 7.35–7.45      | 7.531        |                          |                          |
| PaCO₂ (mmHg)              | 32–48          | 13.7         |                          |                          |
| PaO₂ (mmHg)               | 83–108         | 122          |                          |                          |
| Bicarbonate (mEq/L)       | 22–31          | 11.4         |                          |                          |
| Chloride (mEq/L)          | 100–110        | 138          |                          |                          |
| Anion gap (mEq/L)         | –17.9          |              |                          |                          |
| Lactate (mg/dL)           | 4.5–14.4       | 10           |                          |                          |

Venous blood gases

| Variable                  |                |              |                          |                          |
|---------------------------|----------------|--------------|--------------------------|--------------------------|
| Chloride (mEq/L)          | 137            | 132          | 121                      |                          |
| Anion gap (mEq/L)         | –18.2          | –11.9        | –2.2                     |                          |

eGFR – estimated glomerular filtration rate; PaCO₂ – partial pressure of arterial carbon dioxide; PaO₂ – partial pressure of arterial oxygen.
The most notable finding in the current case was the combination of hyperchloremia and negative anion gap. This unusual coexistence can help diagnose bromide intoxication [4–6]. Although rarely acknowledged, bromide ions are usually mistaken as chloride ions by automated analysis using an ion-selective electrode [7], as observed in the gas analyses at our institute. Thus, the excessive intake of bromovalerylurea, a non-benzodiazepine sedative and hypnotic of the bromoureide class that contains bromide, is known to lead to spurious hyperchloremia, although salicylate is also reported to be associated with an increased level of chloride ions [8]. Of note, direct measurement of the ion level in the serum should be considered when spurious hyperchloremia is suspected by automated analysis.

Bromide intoxication can develop as a result of bromide-containing product use, especially in a non-prescription setting. Symptoms associated with bromide intoxication include neurological manifestations, which may be dose-related but the effects of its blood level on toxicity remain unclear [4]. Although bromide ions are excreted from the kidneys with a long half-life of 10 to 14 days [9], the half-life can be reduced to one-quarter by saline diuresis alone [10] and to a few hours by hemodialysis therapy [11]. In the current case, hemodialysis was not introduced because the symptoms smoothly improved by hydration.

Renal function was considered to be preserved in the current case based on the estimated glomerular filtration rates of greater than 60 mL/min/1.73 m² with a creatinine level of around 0.6 mg/dL during the clinical course. Furthermore, considering the common dosage of the over-the-counter drug (although at the maximum dosage for a relatively prolonged period), the reason why bromide intoxication developed in this patient remains unclear. One possible explanation is the aforementioned long half-life of bromide ions and dehydration, suggested by the serial change in the data, including the hemoglobin, albumin, and echocardiography. Other underlying factors, such as the low body-mass index observed in the current case, may have affected the development of bromide intoxication although the effects of such conditions on pharmacokinetics is not fully understood.

Conclusions

It is important to recognize that hyperchloremia with a negative anion gap strongly suggests bromide intoxication, and that bromide intoxication can develop even in patients with preserved renal function taking the common dosage because of its long half-life. Additionally, careful history taking is essential to the diagnosis because some over-the-counter drugs, which are widely available, and a few prescription drugs contain bromides.

Conflicts of interest

None.

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