# Pseudohyperchloremia caused by the long-term use of phenobarbital and sodium bromide compound tablets: a case report

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**Background:** Serum chloride ($Cl^-$), which is an important analyte that reflects the electrolyte and acid-base balance in humans, is affected by several specific agents or substances. It has been reported that the abuse of bromine-containing drugs, such as bromvalerylurea may lead to pseudohyperchloremia, which is very rare yet, caused by the treatment dose of bromine-containing drugs. In this case report, we describe an epilepsy patient whose serum $Cl^-$ was falsely elevated due to the long-term use of phenobarbital and sodium bromide compound tablets. We also discuss the anti-interference capacity of different analyzers and the disturbance of bromide-containing drugs in $Cl^-$ determination.

**Case Description:** A 34-year-old woman diagnosed with epilepsy for 11 years was admitted to our hospital for further treatment. She had increasingly frequent loss of consciousness and seizures. Her medication history included carbamazepine, levetiracetam, phenobarbital and sodium bromide compound tablets. The video electroencephalogram (VEEG) was moderately abnormal. No obvious abnormality was found in blood routine test, liver and kidney function, except an aberrantly elevated serum $Cl^-$ level of 130 mmol/L; however, the patient did not present with the relevant signs and symptoms of hyperchloremia, such as thirst, fatigue, nausea and vomiting. Subsequently, we used three different analyzers to determine her $Cl^-$ level and obtained the following results: an arterial blood $Cl^-$ level of 107 mmol/L; a serum $Cl^-$ level of 112 mmol/L; and no result. Reviewing her medical history, we discovered that the patient had been taking phenobarbital and sodium bromide compound tablets for 6 months to treat her seizures. Her serum bromide was 4.89 mmol/L, which may cause pseudohyperchloremia. After changing her treatment to phenobarbital tablets, her serum $Cl^-$ returned to the normal range (106 mmol/L).

**Conclusions:** Bromide-containing drugs can cause a falsely elevated $Cl^-$ level. When pseudohyperchloremia is suspected, different methods or instruments should be used to measure $Cl^-$ levels.

**Keywords:** Pseudohyperchloremia; bromide-containing-drugs; analyzer; interference; case report

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## Introduction

Chloride ($Cl^-$), which is the most abundant anion in extracellular fluid, plays an important role in regulating acid-base balance, osmotic pressure, and water distribution in the human body. Hyperchloremia refers to elevated plasma chlorine levels (≥110 mmol/L), which usually occurs with hypernatremia, impaired renal function, hypertonic dehydration, nephritis, or respiratory alkalosis (1). If misdiagnosed as hyperchloremia, unnecessary chloride reduction treatment will further lead to electrolyte disorders, low chloride, and even life risks. Thus, the accuracy of $Cl^-$ detection is critical in clinical testing, especially in critically ill patients.

The $Cl^-$ level can be measured by numerous methods (2), such as the inductively coupled plasma mass spectrometry method, the ion chromatography (IC) method, the ion selective electrode (ISE) method, and the enzyme coupling method. IC is recommended as a candidate reference method because it is a simple, rapid, accurate, and sensitive technique (2). In relation to cost and convenience, the ISE method is the most common method used to determine the serum $Cl^-$ level in many hospitals.

The electrodes are very selective; however, they are not free from interference. Numerous substances, such as salicylate (3), bromide, iodide, nitrate, thiocyanate, can affect the accurate detection of the $Cl^-$ level (4). As bromide has gradually been removed from prescription drugs, its interference with the detection of $Cl^-$ has largely been ignored. In this article, we report the case of an epileptic patient with an extremely elevated level of $Cl^-$ but with no relevant symptoms related to hyperchloremia. By using three different analyzers, we suspected that the long-term use of phenobarbital and sodium bromide compound tablets may have resulted in pseudohyperchloraemia, avoiding misdiagnosis of hyperchloride and unnecessary hypochloride therapy. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3419/rc).

## Case presentation

### *Chief complaints*

A 34-year-old woman suffering from recurrent seizures was admitted to the Department of Neurology at our hospital in February 2019.

### *History of past illness*

The patient had been diagnosed with epilepsy 11 years ago and did not present with any other chronic diseases, such as diabetes, hypertension, or nephritis. She had increasingly frequent loss of consciousness and seizures. Her medication history included carbamazepine, levetiracetam, phenobarbital and sodium bromide compound tablets.

### *Physical examination*

The patient's blood pressure was 123/89 mmHg, her pulse rate was 84 beats per minute, and the body temperature was 36.5 ℃ at admission. Her general conditions were well with no dizziness, fatigue, nausea, vomiting and other complaints of hyperchloremia. No other obvious abnormalities were found during her physical examination.

### *Laboratory examinations*

The video electroencephalogram (VEEG) was moderately abnormal: during the interictal period, synchronous single-shot 14–15 Hz high-amplitude spikes in bifrontal pole, right frontal, right anterior temporal, and right middle temporal leads are frequently seen during wakefulness and sleep, especially during sleep; during the attack period, low-amplitude fast rhythm onset in the right middle temporal leads and rapid spread to all leads. Her initial laboratory assessment revealed that her hemogram, electrolyte levels (including sodium and potassium levels), and liver and renal function tests were almost within the normal range, except for a finding of aberrant hyperchloremia (130 mmol/L, VITROS 5600, USA, using the direct ISE method). *Table 1* sets out the complete results of the patient's laboratory assessments. To validate the test results, we carefully checked the quality control and reagents of the $Cl^-$ assay and conducted the assay again on the VITROS 5600 analyzer. The result remained the same (i.e., 130 mmol/L). In the clinic, it is uncommon that $Cl^-$ elevated alone while other ions are normal. After consulting other clinicians, we confirmed that no sign of dehydration or over-dosage of $Cl^-$ infusion was evident from her clinical history or physical examination. Additionally, neither acidosis nor alkalosis was suspected from the results of other blood tests or clinical symptoms. Thus, we suspected

 

**Table 1** Results of the laboratory assessments

| Test | Results on admission (reference range) |
|---|---|
| Leukocyte count ($10^9$/L) | 4.27 (3.50–9.50) |
| Absolute neutrophil count ($10^9$/L) | 1.87 (1.80–6.30) |
| Erythrocyte count ($10^{12}$/L) | 3.9 (3.8–5.1) |
| Hemoglobin (g/L) | 127 (115–150) |
| Platelets ($10^9$/L) | 208 (125–350) |
| Sodium (mmol/L) | 138 (137–147) |
| Potassium (mmol/L) | 3.89 (3.50–5.30) |
| Chloride (mmol/L) | 130 (99–110) |
| Carbone dioxide (mmol/L) | 19 (20–30) |
| Total protein (g/L) | 64.5 (65.0–85.0) |
| Total bilirubin (μmol/L) | 6.94 (0.00–23.00) |
| Alanine aminotransferase (U/L) | 9 (7–45) |
| Aspartate aminotransferase (U/L) | 13 (13–35) |
| Urea (mmol/L) | 4.1 (2.6–7.5) |
| Uric acid (μmol/L) | 256.2 (150.0–350.0) |
| Creatinine (μmol/L) | 53 (41–73) |

that the patient may have pseudohyperchloremia.

### *Further investigations of the Cl concentration*

To confirm our hypothesis, we attempted to detect the patient's $Cl^-$ level using different testing platforms. Another automatic biochemical analyzer (Abbott C16000, USA, indirect ISE method) was used to examine the patient's $Cl^-$ concentration. Surprisingly, the Abbott C16000 analyzer displayed no result because of an interference warning. We also measured the patient's arterial blood $Cl^-$ using the GEM 4000 blood gas analyzer (USA), which uses the direct ISE method, and obtained a result of 107 mmol/L, which differed noticeably to the result of 130 mmol/L of the VITROS 5600 analyzer. It has been reported that the $Cl^-$ level of whole blood is slightly lower than that of serum (5); however, we were of the view that the great discrepancy between the 2 results was not related to the different sample types and that other substances were interfering with the results.

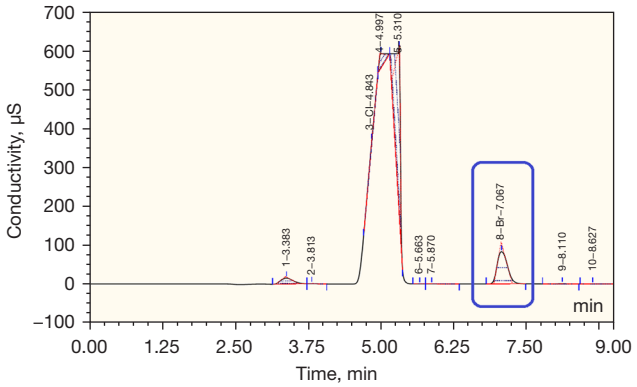


**Figure 1** Ion chromatography of bromide in the patient. The sample was diluted 20 times before testing. The bromide retention time was 7.067 min. The peak area was 17.055 μS×min. The diluted sample concentration was 19.5393 ppm as calculated by the bromide standard curve (y=0.922x–0.961, $r^2$=0.997). x: bromide concentration (ppm); y: peak area (μS×min). The original sample concentration was 390.7855 ppm (4.89 mmol/L).

When a detailed clinical history was elicited, we found that the patient was suffering from epilepsy, and had been taking phenobarbital and sodium bromide compound tablets, an antiepileptic compound drug, 3 times a day for 6 months. This drug contains phenobarbital (30 mg) and sodium bromide (100 mg). The bromide ion ($Br^-$), like $Cl^-$, is also a halide and has been reported to be an interfering substance in $Cl^-$ detection with ISEs. There were no records indicating that the patient had been prescribed salicylate, iodide, nitrate, or the thiocyanate component. Consequently, we then determined the concentration of $Br^-$ in the patient's serum using the Thermo Fisher ICS 600 analyzer (USA) based on the IC method, and the patient's serum $Br^-$ and $Cl^-$ levels were 4.89 and 112 mmol/L, respectively. A study has shown that 1 mmol/L of bromide might cause 4–5 mmol/L raise of chloride, generating pseudohyperchloremia (6). That means 4.89 mmol/L bromide could cause about 20 mmol/L raise of chloride with ISE. This appeared to be consistent with our case. *Figure 1* shows the $Br^-$ results, and *Table 2* shows the comparison of $Cl^-$ concentrations for the 4 platforms.

Thus, we believed that the serum $Cl^-$ level obtained from the VITROS 5600 was falsely elevated due to the interference of bromide, which was generated by the phenobarbital and sodium bromide compound tablets. Thus, we explained the results to the patient's physician,

**Table 2** Comparison of the 4 platforms

| Machine | Method | Sample type | Result (mmol/L) |
|---|---|---|---|
| VITROS 5600 | Direct ISE | Serum | 130 |
| Abbott C16000 | Indirect ISE | Serum | NA |
| GEM 4000 | Direct ISE | Whole blood | 107 |
| ICS 600 | Ion chromatography | Serum | 112 |

ISE, ion selective electrode.

and suggested that the patient's medication be adjusted.

### *Final diagnosis*

The patient did not have electrolyte disturbances. The final diagnosis of the patient in this case was pseudohyperchloremia.

### *Treatment*

Based on the patient's condition, the phenobarbital and sodium bromide compound tablets were replaced with phenobarbital tablets to treat her epilepsy from March 2019 onwards.

### *Outcome and follow-up*

After substituting phenobarbital and sodium bromide compounds with phenobarbital to treat her epilepsy, her serum $Cl^-$ level returned to normal (106 mmol/L, Abbott C16000 instrument).

### *Ethical statement*

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

Hyperchloremia is a common electrolyte disorder in the clinic. Hyperchloremia can occur in the following conditions: (I) metabolic acidosis, such as renal tubular acidosis, certain cases of chronic kidney disease, and the use of carbonic anhydrase inhibitors; (II) respiratory alkalosis; (III) loss of water in excessive electrolytes, such as certain forms of diarrhea, osmotic diuresis; (IV) net water losses, such as fever, perspiration, diabetes insipidus; (V) excessive chloride administration, such as large volume administration of 0.9% sodium chloride solution, administration of hypertonic saline. The identification of hyperchloremia and pseudohyperchloremia should mainly rely on the patient's clinical symptoms, underlying diseases, and medication history. When it is suspected that the high chloride is caused by drugs, other testing indicators should be combined to judge, and different testing methods should be used for testing. In this case report, we measured a patient's $Cl^-$ level using 4 platforms based on 3 different methods. Because of their different capabilities in resisting interference, the 4 instruments provided extremely disparate results (see *Table 2*).

Using a Thermo Fisher ICS 600 analyzer and the IC method, the patient's $Cl^-$ concentration was 112 mmol/L. IC is a method that uses the principle of ion exchange to continuously separate multiple co-existing anions or cations. The ions being tested have different affinities to the ion exchange resin, which causes different retention times in the separation column. Using the peak area and the standard curve, the concentration of the target ion is calculated. Many studies have shown that IC accurately determines $Cl^-$ ions in serum and sweat samples (2,7), and it has been recommended as a candidate reference method for the determination of $Cl^-$ in human serum (2). In this case, we assumed that the 112 mmol/L $Cl^-$ concentration was more accurate than the 130 mmol/L concentration.

The other 2 methods of indirect ISE and direct ISE were also used (see *Table 2*). The VITROS 5600 and the GEM 4000 both employ the direct ISE method, while the Abbott C16000 employs the indirect ISE method. Both methods are based on the principle of ISEs, in which an electrical potential is established across a membrane resulting from

 

**Table 3** Partial interference data of $Cl^-$ on Abbott C16000*

| Interfering Substance | Interferent concentration (mmol/L) | N | Target (mmol/L) | Observed (mmol/L) | Observed (% of Target) |
|---|---|---|---|---|---|
| Lithium | 2.5 | 4 | 83.0 | 85.7 | 103.3 |
| bromide | 5.0 | 4 | 83.0 | 91.5 | 110.2 |
| Lithium | 2.0 | 4 | 83.1 | 86.1 | 103.6 |
| Iodide | 4.0 | 4 | 83.1 | 89.3 | 107.5 |

*, the information is quoted from Abbott's original ICT ($Na^+$, $K^+$, and $Cl^-$) sample diluent instructions.

**Table 4** Partial interference data of $Cl^-$ on GEM 4000*

| Substance | Affected analyte (s) | Concentration producing interference |
|---|---|---|
| Bromide | $Cl^-$ | 10 mmol/L |
| Fluoride | $Cl^-$, lactate | 500 mg/dL |
| Iodide | $Cl^-$ | 3 mmol/L |

*, the information is quoted from the GEM 4000 reference guide. The substances above may cause falsely elevated results.

the chemical selectivity of the membrane to a specific ion, and the concentration of ions is calculated using the Nernst equation. Thus, the selectivity and specificity of the membrane is key for accurate results. The main difference between the 2 methods is that the sample needs to be diluted with diluent at a ratio of 1:20 to 1:34 in the indirect ISE method. Membranes of the most currently used $Cl^-$ electrodes contain a quaternary ammonium $Cl^-$ as an ion-exchanger (4). The selectivity of the membrane is governed by the ion hydration energy. Thus, the ions, such as bromide, iodide, thiocyanate, and salicylate, with higher hydration energies than $Cl^-$ are considered potentially interfering ions (4). In this case report, the patient took an antiepileptic compound drug that contained bromide.

Bromide, as an active ingredient, is commonly used in a variety of tranquilizers, sedatives, and anticonvulsants, and its long-term use can cause chronic bromine toxicity and pseudohyperchloremia (8). Some case reports previously published in PubMed have described spurious hyperchloremia due to bromvalerylurea abuse (8-11) and the use of other bromide-containing compounds, such as dextromethorphan bromide (12) and pyridostigmine bromide (13). However, the interference of the antiepileptic compound drug, phenobarbital and sodium bromide compound tablets on hyperchloremia has rarely been reported. Since bromides have been removed from most prescription and over-the-counter drugs in the United states, pseudohyperchloremia caused by brominated drugs has become very uncommon (6). However, bromide-containing drugs are still used in some areas or to treat certain conditions. This case report highlights the risk of pseudohyperchloremia caused by the use of bromide-containing drugs. The limitation of the case is that the $Cl^-$ concentration was not determined by a reference method. In addition, it is incomplete that the $Cl^-$ and $Br^-$ levels were not continuously monitored after changing the medication.

Another important point of this case is that the interference of the patient's $Br^-$ concentration (4.89 mmol/L, Thermo Fisher ICS 600 analyzer) caused disparate results in different analyzers. We found some clues about the $Br^-$ interference by checking the users' guides for the machines (see *Tables 3*,*4*). Notably, 5 mmol/L of lithium bromide can increase the $Cl^-$ level by 10.2 percent when its value is 83.1 mmol/L on the Abbott C16000 analyzer. On the GEM 4000 analyzer, the interference concentration of bromide can have an effect when it reaches 10 mmol/L. On the VITROS 5600 instrument, 1 millimole of bromide from therapeutic drugs and ointments may cause 5 mmol/L positive bias of $Cl^-$ level, which is consistent with previous literature reports (6). Importantly, normal physiological levels of bromide do not cause interference. The patient's bromide level of 4.89 mmol/L was much higher than the normal concentration of 0.06 mmol/L (14). Based on the above information, we hypothesized that 4.89 mmol/L of $Br^-$ concentration affects $Cl^-$ detection on the Abbott C16000 and VITROS 5600 analyzers, but not on the GEM 4000 analyzer. The effect of the addition of $Br^-$ on $Cl^-$ assays vary significantly among different ion detection instruments (9).

Therefore, the interference varies widely and was caused by the high concentration of $Br^-$ on the 4 instruments. This difference was not only due to the different methodologies, it was also influenced by the performance of the ISEs, the specificity of its membranes, and the manufacturing

 

techniques of the reagents, which all need to be further explored. In addition, laboratory technicians and clinicians need to be able to recognize the characteristics of the specific instruments used in their hospitals to avoid misdiagnosis. Hyperchloremia is a common electrolyte disorder that is associated with a diverse group of clinical conditions. To a large extent, the diagnosis of hyperchloremia relies heavily on laboratory electrolyte assessments. Thus, it is important that laboratory technicians to report clinical results in an accurate and timely manner. In this case report, we detected the $Cl^-$ level on 4 platforms and speculated that the patient's pseudohyperchloraemia was due to the long-term use of phenobarbital and sodium bromide compound tablets, avoiding a clinical misdiagnosis. This case report brings pseudohyperchloremia caused by bromide-containing drugs back to the forefront and is a reminder of the importance of using different methods and instruments to verify suspicious results.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3419/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3419/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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