Late Metabolic Acidosis Caused by Renal Tubular Acidosis in Acute Salicylate Poisoning

Norihiro Sakai¹, Yasuo Hirose¹, Nobuhiro Sato¹, Daisuke Kondo², Yuko Shimada³ and Yasushi Hori³

Abstract

A 16-year-old man was transferred to our emergency department seven hours after ingesting 486 aspirin tablets. His blood salicylate level was 83.7 mg/dL. He was treated with fluid resuscitation and sodium bicarbonate infusion, and his condition gradually improved, with a decline in the blood salicylate level. However, eight days after admission, he again reported nausea, a venous blood gas revealed metabolic acidosis with a normal anion gap. The blood salicylate level was undetectable, and a urinalysis showed glycosuria, proteinuria and elevated beta-2 microglobulin and n-acetyl glucosamine levels, with a normal urinary pH despite the acidosis. We diagnosed him with relapse of metabolic acidosis caused by renal tubular acidosis.

Key words: drug overdose, acid-base disturbance, renal tubular injury

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Introduction

Acute salicylate poisoning is common, and metabolic acidosis with an increased anion gap is a well-known feature of salicylate poisoning. We herein describe a case of acute salicylate poisoning that progressed to renal tubular acidosis (RTA) eight days after ingestion, presenting as relapse of metabolic acidosis without an increased anion gap.

Case Report

A 16-year-old man was transferred to a local hospital four hours after ingesting 486 aspirin tablets (330 mg tablets) in a suicide attempt. He did not have diabetes or renal failure. He complained of nausea and frequent vomiting and was tachypneic. The laboratory findings showed the following data: Na 141 mEq/L, K 3.3 mEq/L, Cl 101 mEq/L, pH 7.523, arterial pO₂ 108.5 mmHg, pCO₂ 21.6 mmHg, HCO₃ 17.4 mEq/L and base excess -2.9 mEq/L. Therefore, an acid base disturbance with respiratory alkalosis was diagnosed secondary to acute salicylate toxicity, and he was managed with intravenous fluids, sodium bicarbonate (NaHCO₃), gastric lavage and activated charcoal via a gastric tube.

The patient was subsequently referred to our emergency department for further treatment, where he was seen seven hours after ingestion, at which point he was sleepy and diaphoretic. His vital signs revealed a heart rate of 116 beats/min, blood pressure of 97/54 mmHg, respiratory rate of 23 breaths/min, body temperature of 37.2°C and oxygen saturation of 97% on room air. The initial laboratory values were as follows: white blood cell count 14.5×10⁹/L, hemoglobin 169 g/L, platelet count 770×10⁹/L, Na 144 mEq/L, K 3.5 mEq/L, Cl 95 mEq/L, blood urea nitrogen (BUN) 12.4 mg/dL, creatinine 1.05 mg/dL and random glucose 122 mg/dL. An arterial blood gas analysis showed respiratory alkalosis (pH 7.526, arterial pO₂ 111.4 mmHg, pCO₂ 31.8 mmHg, HCO₃ 25.7 mEq/L, base excess 3.8 mEq/L and an elevated anion gap at 23.3), and a urinalysis showed glycosuria, proteinuria and ketonuria. Upon arrival (7 hours after ingestion), the blood salicylate level was 83.7 mg/dL, and hemodialysis was not performed. He was treated with fluid resuscitation and NaHCO₃ infusion (approximately 300 mEq/day), and his condition gradually improved, with a decline in the blood salicylate level (Figure). On the fourth day of admission, he was asymptomatic and the bicarbonate ther-
On admission, his vital signs were as follows: heart rate 56 beats/min, blood pressure 122/60 mmHg, respiratory rate 18 breaths/min and body temperature 37.3°C. Cardiac, respiratory and abdominal examinations were normal. A venous blood gas analysis revealed metabolic acidosis (pH 7.245, pO₂ 35.1 mmHg, pCO₂ 44.4 mmHg, HCO₃ 18.8 mEq/L and base excess - 8.3 mEq/L), with a calculated anion gap of 7.2. The PCO₂ level seemed to be relatively high in the presence of the low bicarbonate level; therefore, we consider this finding to be a measurement error on the venous blood gas analysis, as he did not show respiratory failure at that time. Furthermore, the blood salicylate level was undetectable (<0.1 μg/mL), whereas the serum potassium and phosphate levels were within the normal limits (K 4.1 mEq/L, Cl 107 mEq/L). A urinalysis showed glycosuria, proteinuria, elevated beta-2 microglobulin (31.75 mg/L) and N-acetyl glucosamine (15.4 U/L) levels and a urinary pH of 6.5, despite the metabolic acidosis. These symptoms, together with the absence of further salicylate elevation, suggested renal tubular dysfunction (Table). We therefore considered that the relapse of metabolic acidosis was caused by RTA. The patient gradually recovered with intravenous bicarbonate therapy (approximately 300 mEq per day), which was discontinued 18 days after admission and replaced with oral bicarbonate therapy (3 g per day). He was discharged 26 days after admission. At the follow-up visit two weeks later, he was asymptomatic. Additionally, a urinalysis showed no glycosuria and minimal proteinuria, and his renal function had normalized (BUN 13.0 mg/dL and creatinine 0.98 mg/dL).

### Discussion

Salicylate overdoses are commonly encountered in the emergency department. Although the overall mortality rate of salicylate poisoning is low, metabolic acidosis, convulsions, coma, hyperpyrexia, pulmonary edema, renal failure and death occur in 5% of severe cases (1). Salicylate toxic-

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**Table.** Comparison of the Acid–base Status at the Initial Visit, on Admission and during Late-onset Metabolic Acidosis.

<table>
<thead>
<tr>
<th>Time after ingestion</th>
<th>Initial</th>
<th>On admission</th>
<th>Late-onset acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.523</td>
<td>7.526</td>
<td>7.245 (venous)</td>
</tr>
<tr>
<td>Anion gap</td>
<td>22.6</td>
<td>23.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.3</td>
<td>3.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Phosphate (mEq/L)</td>
<td>101</td>
<td>95</td>
<td>107</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.95</td>
<td>1.05</td>
<td>1.99</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>17.4</td>
<td>25.7</td>
<td>18.8 (venous)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>25</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Salicylate level (mg/dL)</td>
<td>NP</td>
<td>83.7</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Aceturia</td>
<td>NP</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>NP</td>
<td>1+</td>
<td>4+</td>
</tr>
<tr>
<td>β2MG (mg/L)</td>
<td>NP</td>
<td>NP</td>
<td>31.75</td>
</tr>
<tr>
<td>NAG (U/L)</td>
<td>NP</td>
<td>NP</td>
<td>15.4</td>
</tr>
<tr>
<td>Urine pH</td>
<td>NP</td>
<td>8.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Initially, the patient presented with metabolic acidosis with an elevated anion gap and respiratory alkalosis. However, during late-onset acidosis, the anion gap was not elevated, and there was evidence of proximal tubular injury.

NP: not performed
β2MG: Beta-2 Microglobulin, NAG: N-acetyl Glucosamine

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**Figure.** Blood salicylate level (mg/dL) by time after ingestion (hours). A gradual decline in the blood salicylate level was observed over time. Of note, the blood salicylate level was undetectable (<0.1 mg/mL) when late-onset metabolic acidosis occurred (201 hours after ingestion).
ity initially causes respiratory alkalosis because of a stimula-
tory effect on the respiratory center. Anion gap metabolic
acidosis then follows because of accumulation of lactic acid
and ketones (2). The course of the present case was consist-
tent with this description, initially presenting as an acid-base
disturbance with an elevated anion gap. Respiratory alkalosis
was also present based on the salicylate level. This type of
mixed acid-base disturbance is characteristic of acute severe
salicylate poisoning (2, 3).

Despite successfully treating the initial acid-base distur-
rance in this case, relapse occurred on the eighth day of ad-
mission. The late-onset acidosis had characteristics different
from the initial mixed acid-base disturbance, in that it pre-
vented with a normal anion gap without an elevated sali-
cylate level. Previous case reports have described delayed
presentations of metabolic acidosis in patients with acute
salicylate poisoning (4-6). However, the delayed toxicities in
these cases were explained by delayed absorption caused by
the enteric coating on the drug for sustained release (5) or
bezoar formation (6). In the current case, the delayed toxicity
could not be explained by delayed salicylate absorption
because the salicylate level remained undetectable.

At the time of recurrence of metabolic acidosis, a urinaly-
sis showed glycosuria, proteinuria and elevation of β-2 mi-
croglobulin and N-acetyl glucosamine, with a urinary pH of
6.5 despite metabolic acidosis. These findings strongly sug-
gested the presence of proximal tubular injury and impaired
acidification of the urine. RTA is characterized by a defect
in the ability of the renal tubules to maintain a normal acid-
base status and is accompanied by metabolic acidosis with a
normal anion gap (3). Therefore, we considered that the re-
lapse of metabolic acidosis in this patient was due to RTA.
Furthermore, glycosuria had already been reported seven
hours after ingestion, and there is a possibility that renal tu-
bular acidois may progress insidiously, as became apparent
following the discontinuation of bicarbonate therapy. Clinici-
al reports of RTA caused by acute salicylate poisoning are
rare. To our knowledge, only one such report has previously
been published, which concerned a 17-year-old patient pre-
senting with renal tubular dysfunction, similar to that seen
in Fanconi syndrome (7). However, RTA can be caused by
various drugs, including non-steroidal anti-inflammatory
drugs (3). Salicylate-induced proximal tubular dysfunction is
also reported to occur in animals and usually develops
within few hours after administration (8). Therefore, it is
possible that the occurrence of RTA in cases of acute sali-
cylate poisoning is under-reported. Clinicians should there-
fore consider the possibility of RTA in patients with sali-
cylate poisoning who display acid-base disturbances, espe-
cially in cases involving late-onset metabolic acidosis and a
normal anion gap.

We herein reported a case of successful treatment of
metabolic acidosis due to salicylate poisoning, which re-
lapsed with late-onset normal anion gap metabolic acidosis
and an undetectable serum salicylate level. Physicians
should consider the possibility of RTA when patients de-
velop late-onset metabolic acidosis following acute salicylate
poisoning.

The authors state that they have no Conflict of Interest (COI).

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