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# Proximal Tubule Dysfunction Secondary to Salicylate Intoxication

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**Abstract**

Aspirin overdose is still a common cause of presentation to the emergency department and is commonly seen in the setting of one-time, accidental or intentional ingestion of large amounts of salicylate-containing compounds, though can occur with long-term ingestion of super-therapeutic doses of medications. Salicylate toxicity has a predictable progression from early respiratory alkalosis to late metabolic acidosis. We present the case of a 14-year-old girl who intentionally ingested a handful of Aspirin and despite appropriate therapy, developed transient proximal tubule dysfunction. This case highlights the need for a change in the short-term medical management of children presenting with salicylate toxicity.

**Keywords**

adolescent medicine, emergency medicine, general pediatrics, nephrology

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## Case report

A 14-year-old previously healthy, Caucasian female with a recent informal diagnosis of depression presented to our hospital for intentional aspirin overdose and suicidal ideation that required admission for bicarbonate infusion and close monitoring.

She presented to the ED about 90 minutes after intentional ingestion of a handful of 325 mg Aspirin tablets. She swallowed the pills with water and there was no concern for co-ingestion of other medications at the time. While in the ED, she appeared tearful with a flattened affect but otherwise well and noted only mildly muffled hearing. Physical exam and an EKG showed no abnormalities. Initial salicylate level approximately 2 hours after ingestion was 22 mg/dL (Table 1). She received 1L of normal saline as well as 50 g activated charcoal (1 g/kg with max of 50 g). Alkalization was not started as the salicylate level had not reached threshold for initiation of therapy per Poison Control. Initial VBG showed pH of 7.41, $pCO_2$ of 32, $pO_2$ of 38, $HCO_3$ of 20 and base excess of −3.4.

The girl was admitted to inpatient floor for close monitoring and treatment of an intentional aspirin overdose. Review of systems on the floor was normal except for muffled hearing without tinnitus and a short episode of right-sided chest pain that had occurred prior to ingestion. She was not in any pain and had 1 episode of nausea and emesis containing activated charcoal about 10 hours after time of ingestion. Her vitals were stable, although she was mildly tachycardic. Physical exam was without deficits or abnormalities. At admission, her salicylate level had risen to 36.4 mg/dL, so alkalization was initiated with D5W + 150 mEq $NaHCO_3$/L at 2× maintenance rate (180 mL/hours). These fluids ran for approximately 8 hours. Upon normalization of salicylate levels, fluids were switched to D5W + 20 mEq KCl for hyperhydration. The patient remained nothing by mouth for the first 19 hours to avoid confliction of diet and medical management. She was also kept off acetaminophen and ibuprofen to avoid compounding deleterious renal effects. Poison Control was consulted multiple times to ensure treatment plan alignment.

On day 2 of admission, the patient was feeling much better and noted that the muffled hearing had resolved. She was not in any pain and had tolerated food from the

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**Table 1.** Serial Salicylate Levels.

| | Hours after ingestion | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 4.5 | 7 | 9.5 | 13 | 15 | 17 | 19 | 21 | 25 | 30 | 33.5 |
| Salicylate level (mg/dL) | 22.2 | 27.6 | 31.4 | 36.4 | 38 | 29.3 | 21.1 | 16.3 | 10.6 | 5.3 | 3.3 | 1.7 |

**Table 2.** Serial Urinalysis Results.

| | Hours after ingestion | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 3 | 13.5 | 15.5 | 17.5 | 19 | 21 | 31.5 | 43 | 55.5 |
| Urine pH | 6.5 | 6 | 7 | 7 | 7 | 8 | 7 | 7 | 5 |
| Urine protein (mg/dL) | — | — | 30 | 100 | — | 30 | 100 | — | 30 |
| Urine glucose (mg/dL) | — | — | 50 | 50 | 50 | 50 | 50 | — | — |
| Urine ketones (mg/dL) | — | — | — | — | — | — | — | — | — |
| Urine RBCs (per hpf) | 1 | 1 | 2 | 1 | 1 | 1 | 5 | — | — |
| Urine WBCs (per hpf) | 1 | 1 | 2 | 4 | 1 | 3 | 12 | 2 | 7 |

previous night well. Review of systems was normal. The tachycardia that had been noted the day before had resolved. Her physical exam was normal. Serial labs were notable for glucosuria and proteinuria (Table 2) with normal serum glucose and albumin, suspicious for proximal tubule dysfunction, or Fanconi syndrome. These abnormalities developed approximately 15 hours post-ingestion and around the time the salicylate level was less than 30 mg/dL. These urinary abnormalities were transient and corrected before discharge about 60 hours post-ingestion.

IRB approval was not required for this case report per the head of research programs at our institution. No identifiable patient information was included, however verbal informed consent to publish was completed with the patient's guardian. There were two physicians present for completion of our institutional "Authorization Form for Publication of a Case Report" over the phone. Written consent was not obtained as the consent occurred after the patient was discharged home.

## Discussion

Salicylate overdose is common, with 8011 reports of single-drug ingestion of acetylsalicylic acid (ASA) to Poison Control in 2019 alone.[1] Of these, 4651 were cases reported in children less than 20 years old.[1] The annual Poison control report also states that 3929 (49%) of the total cases were due to unintentional ingestion while 3678 (46%) of the total cases were due to intentional ingestion.[1] One contributory factor to why there are so many salicylate/Aspirin overdoses is that there are many prescription and over-the-counter formulations containing salicylate. The most readily available of these is Aspirin. However, Pepto-Bismol is also a common over-the-counter medication used for indigestion and diarrhea that contains bismuth subsalicylate. And while it is more difficult to consume toxic levels of salicylate in Pepto-Bismol, it is not unheard of and is most often seen in elderly patients with chronic ingestion as opposed to large, single-time doses.[2,3] One of the most concentrated formulations is oil of wintergreen which is about 98% methyl salicylate per volume, where 1 mL of the oil contains 1.4 g of salicylate.[4] There have been multiple case reports published about children, adolescents and young adults dying or acquiring lifelong organ damage from accidental or intentional ingestion of oil of wintergreen, and these are summarized nicely in 2 reviews.[4,5] In the end of the 20th century, there was a combination of limited distribution of aspirin to young children due to the discovery of Reye's syndrome, development of child-resistant packaging, and improvement of hospital management of toxicity that all led to a rapid decline in the number of deaths from salicylate toxicity in the US.[4] However, we are again seeing an increase in the number of reported toxicities from salicylates, likely due to the wide availability of other salicylate-containing formulations.

Despite the number of cases of salicylate overdose every year, there is a paucity of data on proximal tubular dysfunction as a result of salicylate ingestion, especially in the pediatric population. There have been several case reports of transient proximal tubule dysfunction or Fanconi syndrome developing following salicylate intoxication in a total of 7 children and young adults.[6-9] Another study in 1997 showed that even with ASA doses slightly larger than the therapeutic range, some proximal

tubule dysfunction occurred in the form of increased proteinuria and urinary alkaline phosphatase.[10] In all cases, the tubule dysfunction was temporary and resolved within a few days. Here, we report another case of an adolescent with transient proximal tubule dysfunction secondary to intentional salicylate intoxication.

ASA has various physiologic effects on the body and can manifest as abnormalities to the CNS, metabolic and renal systems. Early toxicity has a stimulatory effect on the respiratory center of the medulla leading to hyperventilation and resultant respiratory alkalosis. Later, the buildup of ketoacid breakdown products of salicylate, along with the normal renal response to respiratory alkalosis, leads to a high anion gap metabolic acidosis. Uncoupling of the electron transport chain (ETC) within mitochondria leads to increased heat production and oxygen consumption and manifests as tachypnea, fever, diaphoresis, and dehydration. Over time, the fever, diaphoresis, and tachypnea can lead to insensible water loss, volume contraction and hypernatremia. The compensatory activation of the renin-angiotensin-aldosterone system (RAAS) can also lead to hypokalemia, which is commonly seen in patients presenting with salicylate overdose.

One of the curiosities of this case was that the patient never developed an anion gap metabolic acidosis, even prior to alkalization when her salicylate level was greater than 35 mg/dL. This has been described before, although not commonly, and is likely due to increased retention of chloride causing normalization of the anion gap.[11] The excretion of the acidic breakdown products of salicylate occurs in the form of sodium and potassium salts, and this can lead to a relative volume depletion which can actually increase reabsorption of sodium and chloride.[12,13] This results in the hyperchloremic normal anion gap metabolic acidosis that was observed in our patient prior to initiation of alkalization. The excretion of sodium salts with organic acid byproducts of salicylate also contributes to the appearance of a concurrent type II (proximal) renal tubular acidosis (RTA) as the organic acids ordinarily buffer similarly to bicarbonate in the body. Therefore, organic acid loss along with the body's compensatory response to a respiratory alkalosis as it tries to decrease levels of bicarbonate, can present very similarly to a type II RTA.[14] Overall, the renal loss of bicarbonate contributes to further acidification of the bloodstream and even quicker degradation of ASA into its toxic, acidic metabolites with eventual widening of the anion gap acidosis.[15]

While many of the physiologic effects of ASA on the body are known, the exact physiology of renal toxicity caused by salicylate overdose is unclear. There are several hypotheses based on animal studies, the most likely of which is that ASA (or its metabolites) covalently binds to mitochondria in the proximal tubular cells and causes uncoupling of ATP synthesis resulting in dysfunction of active transporters in the proximal tubule.[16-18] This pathophysiology is supported by the fact that the Na/K-ATPase on the basolateral surface of the proximal tubular epithelial cells is the main driving force for transport of most molecules within the proximal tubule. This broad effect on many transporters in the proximal tubule can lead to Fanconi syndrome, characterized by renal losses of phosphate, glucose, amino acids, uric acid, and bicarbonate. Animal studies of salicylate toxicity have also described instances of isolated glucosuria with normal blood glucose levels (as in our patient) in the absence of phosphaturia, uric aciduria and amino aciduria, suggesting that ASA may have more specific effects on individual transporters, such as those for glucose reuptake.[17] It appears that once the salicylate is cleared from the body, proximal tubule epithelial cells return to baseline function and the glucosuria and proteinuria that can develop with toxic levels of ASA are transient and resolve within 2 weeks in all of the cases of proximal tubule dysfunction described in children to date, including in our patient.[6-10]

In conclusion, our case report further substantiates the possibility of transient Fanconi-like syndrome following salicylate overdose, as previously documented.[6-10] These findings highlight the need for serial urinalyzes to monitor for proximal tubule dysfunction, even after clinical correction of salicylate toxicity, and to ensure resolution of the proximal tubule dysfunction if present.

## Author Contributions

ZT and VC contributed to conception of the article. ZT drafted the manuscript. ZT, VC and HP all contributed to acquisition, analysis and interpretation of data and critically revised the manuscript. All authors read and approved the final manuscript.

## Declaration of Conflicting Interests

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## Ethical Approval and Informed Consent

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