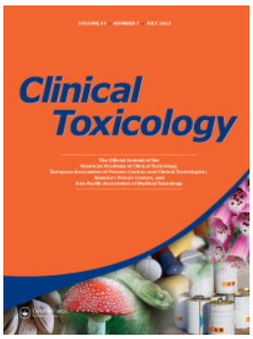

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

Incidence of rebound salicylate toxicity following cessation of urine alkalinization

Mary O'Keefe, Matthew Stanton, Ryan Feldman & Jillian Theobald

To cite this article: Mary O'Keefe, Matthew Stanton, Ryan Feldman & Jillian Theobald (2023) Incidence of rebound salicylate toxicity following cessation of urine alkalinization, Clinical Toxicology, 61:7, 536-542, DOI: 10.1080/15563650.2023.2227998

To link to this article: https://doi.org/10.1080/15563650.2023.2227998

CLINICAL TOXICOLOGY
2023, VOL. 61, NO. 7, 536–542
https://doi.org/10.1080/15563650.2023.2227998

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Incidence of rebound salicylate toxicity following cessation of urine alkalinization

Mary O'Keefe[a], Matthew Stanton[b,c], Ryan Feldman[b,c] and Jillian Theobald[b,c]

[a]Department of Pharmacy, Vanderbilt University Medical Center, Nashville, TN, USA; [b]WI Poison Control Center, Milwaukee, WI, USA; [c]Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

ABSTRACT

Introduction: Management of patients with salicylate toxicity frequently requires urine alkalinization to enhance excretion of salicylate. One strategy for determining when to stop urine alkalinization is to wait for two consecutive serum salicylate concentrations to be less than 300 mg/L (2.17 mmol/L) and declining. When alkalinization of the urine ceases, a rebound in serum salicylate concentration can occur from tissue redistribution or delayed gastrointestinal absorption. Whether this can lead to rebound toxicity is not well understood.

Methods: This was a single-center, retrospective review of cases with a primary ingestion of acetylsalicylic acid reported to the local poison center over a five-year period. Cases were excluded if the product was not listed as the primary ingestion or if there was no serum salicylate concentration documented after discontinuation of intravenous sodium bicarbonate infusion. The primary outcome was the incidence of serum salicylate rebound to a concentration greater than 300 mg/L (2.17 mmol/L) after discontinuation of intravenous sodium bicarbonate infusion.

Results: A total of 377 cases were included. Of these, eight (2.1%) had a serum salicylate concentration increase (rebound) after stopping the sodium bicarbonate infusion. All these cases were acute ingestions. Five of the eight cases had rebound serum salicylate concentrations that were greater than 300 mg/L (2.17 mmol/L). Of these five patients, only one reported recurrent symptoms (tinnitus). Prior to stopping urinary alkalinization, the last or the last two serum salicylate concentrations were less than 300 mg/L (2.17 mmol/L) in three and two cases, respectively.

Conclusions: In patients with salicylate toxicity, the incidence of rebound in serum salicylate concentration after cessation of urine alkalinization, is low. Even if serum salicylate rebounds to supratherapeutic concentrations, symptoms are often absent or mild. Routine repeat serum salicylate concentrations after urine alkalinization is stopped may be unnecessary unless symptoms recrudesce.

ARTICLE HISTORY
Received 23 March 2023
Revised 14 June 2023
Accepted 18 June 2023

KEYWORDS
Salicylates; acetylsalicylic acid; urine alkalinization; overdose

Introduction

Acetylsalicylic acid overdose is a common occurrence worldwide due to its presence in various different products and easy over-the-counter access [1,2]. Acetylsalicylic acid ingestions were the 19th most common cause of fatality from a single substance reported to United States poison centers in 2021 [3]. After ingestion, acetylsalicylic acid is quickly deacetylated to salicylic acid, which can then deprotonate to salicylate. Salicylate, in large overdose, causes severe metabolic acidosis and multisystem organ failure from mitochondrial oxidative phosphorylation uncoupling [4]. Salicylic acid has a pKa of 3 (pH at which 50% is in salicylic acid form and 50% is deprotonated to the negatively charged conjugate base, salicylate) [4]. As pH increases and solutions become more basic, more of the acid will deprotonate, becoming polar and unable to diffuse into tissues. As acidemia increases, more salicylic acid is present and is able to gain more organ compartment access [5]. Because of this, alkalinization of the urine with an intravenous sodium bicarbonate infusion is a cornerstone of therapy, which increases the excretion of ionized salicylate by trapping it in the urine [6].

The recommended therapeutic serum concentration of salicylate is 100–300 mg/L (0.72–2.17 mmol/L), but this varies by indication [5]. Serum concentrations greater than 300 mg/L (2.17 mmol/L) are usually not found unless there is a supratherapeutic, acute, or chronic toxic exposure. However, these serum concentrations should be interpreted in the context of the acuity of the exposure and the overall clinical condition. Factors that may influence the interpretation of the serum salicylate concentration include exposure acuity, product formulation, co-ingestions, comorbidities and clinical condition [7].

The American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) [8] state that urine alkalinization is recognized as first line therapy for patients with moderately severe salicylate poisoning who do not meet criteria for

CONTACT Mary O'Keefe mary.okeefe1@gmail.com Department of Pharmacy, Vanderbilt University Medical Center, Nashville, TN, USA.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2023.2227998.

hemodialysis; however, no specific laboratory values are recommended for what would be considered "moderately severe" and rather are based on the clinical presentation of the patient. A urinary pH of 7.5 – 8.0 is a standard goal of therapy [4,7,8]. Alkalinization of the urine often is discontinued when serum salicylate concentration has returned to therapeutic concentrations after an overdose [9]. There is variation between various toxicology groups and poison centers on the endpoints to use for appropriate cessation of urinary alkalinization. For example, the AACT/EAPCCT recommend stopping alkalinization of the urine when the serum salicylate concentration falls to less than 350 mg/L (2.53 mmol/L) in an adult or 255 mg/L (1.81 mmol/L) in a child [8]. In the Australia Therapeutic Guidelines, cessation of urinary alkalinization should occur when the patient is clinically well, serum salicylate concentration is less than 300 mg/L (2.17 mmol/L), and has a normal acid-base status [10]. Another source [2] states urinary alkalinization can be discontinued if the serum salicylate decreases to a therapeutic concentration (150–300 mg/L or 1.09–2.17 mmol/L) or the patient's symptoms resolve. When urine alkalinization stops, the pH of blood begins to fall, salicylate may become protonated to salicylic acid and diffuse out of tissues back into the blood. At least one report demonstrates a rebound of serum salicylate to toxic concentrations after stopping urine alkalinization [9]. The purpose of this study is to analyze the incidence of rebound serum salicylate concentrations after discontinuation of urine alkalinization in patients with salicylate poisoning.

Methods

This was a single-center, retrospective study of adult and pediatric cases with a primary ingestion of acetylsalicylic acid and sodium bicarbonate infusion listed as a part of the patient's treatment reported to the local poison center from 1 January 2015 through 31 December 2019. All data were queried from ToxSentry, the program at the local poison center used by the Specialists in Poison Information to input information received over the phone regarding cases. Cases were excluded if the salicylate product was not listed as the primary ingestion or if there was no serum salicylate concentration documented after discontinuation of intravenous sodium bicarbonate infusion. A "rebound serum salicylate concentration" was defined as any increase in serum salicylate concentration after discontinuation of the intravenous sodium bicarbonate infusion. "Salicylate toxicity" was defined as a serum salicylate concentration greater than 300 mg/L (2.17 mmol/L). "Rebound salicylate toxicity" refers to an increase in serum salicylate concentration greater than 300 mg/(2.17 mmol/L) after discontinuation of the intravenous sodium bicarbonate infusion. The local poison center recommends an endpoint of two decreasing serum salicylate concentrations less than 300 mg/L (2.17 mmol/L) as the internal guideline for cessation of alkalinization of the urine. However, due to a lack of a universal standard on when urine alkalinization should be stopped as described previously, cases were still included and analyzed even if they did not follow this internal guideline. The primary outcome was incidence of rebound salicylate toxicity following discontinuation of intravenous sodium bicarbonate infusion. This study was approved by the institutional review board.

Results

During the five-year period, 512 acetylsalicylic acid overdose cases who had intravenous sodium bicarbonate infusion listed as a treatment were reviewed. Of these, 135 did not have a documented serum salicylate concentration after discontinuation of the bicarbonate infusion and were excluded. Of the 377 remaining cases, eight (2.1%) had serum salicylate concentration rebound after stopping intravenous sodium bicarbonate (Figure 1, Table 1). All eight (100%) of these rebound cases were acute ingestions (meaning none were therapeutically taking acetylsalicylic acid prior to the overdose). The median time from sodium bicarbonate infusion discontinuation to repeat concentration was 3.0 h (interquartile range 3.55 h).

Five of the eight cases (63%) met the definition of rebound salicylate toxicity (rebound serum salicylate concentration greater than 300 mg/L (2.17 mmol/L). Prior to stopping urine alkalinization, the last or last two serum salicylate concentrations were less than 300 mg/L (2.17 mmol/L) in three patients (patients 6, 7, and 8) and two (patients 1 and 3) cases, respectively. One patient (Patient 8) experienced recurring symptoms (tinnitus) when serum salicylate concentrations rebounded from 260 mg/L (1.88 mmol/L) to 670 mg/L (4.85 mmol/L), while there was no mention of the other four (patients 1, 3, 6, and 7) experiencing any additional or new symptoms. In these five patients, the median rebound increase in serum salicylate concentration was 8.90 mg/L (0.65 mmol/L). Four of the five patients received at least one dose of activated charcoal. All five patients had urine alkalinization resumed. All patients who rebounded to greater than 300 mg/L (2.17 mmol/L) had a serum concentration between 200 – 300 mg/L (1.45–2.17 mmol/L) when urine alkalinization was stopped. Three of the five cases had only one serum salicylate concentration less than 300 mg/L (2.17 mmol/L) prior to stopping the infusion.

Discussion

The mechanism of rebound in serum salicylate concentration is not clear but may be related to delayed gastrointestinal absorption after activated charcoal administration (i.e., the activated charcoal/acetylsalicylic acid mixture acting as a slow release of acetylsalicylic acid as it transits the colon), delayed absorption of pharmacobezoars, or redistribution of salicylic acid from tissues as the blood/tissue pH rises [4,5,11]. In this retrospective cohort of patients with salicylate toxicity, the incidence of a rebound increase in serum salicylate concentrations after discontinuation of urine alkalinization was 2.1% (8 cases). Only five cases had rebound increases in serum salicylate concentration to greater than 300 mg/L (2.17 mmol/L) and all were retreated with intravenous sodium bicarbonate infusion. Only one patient who was

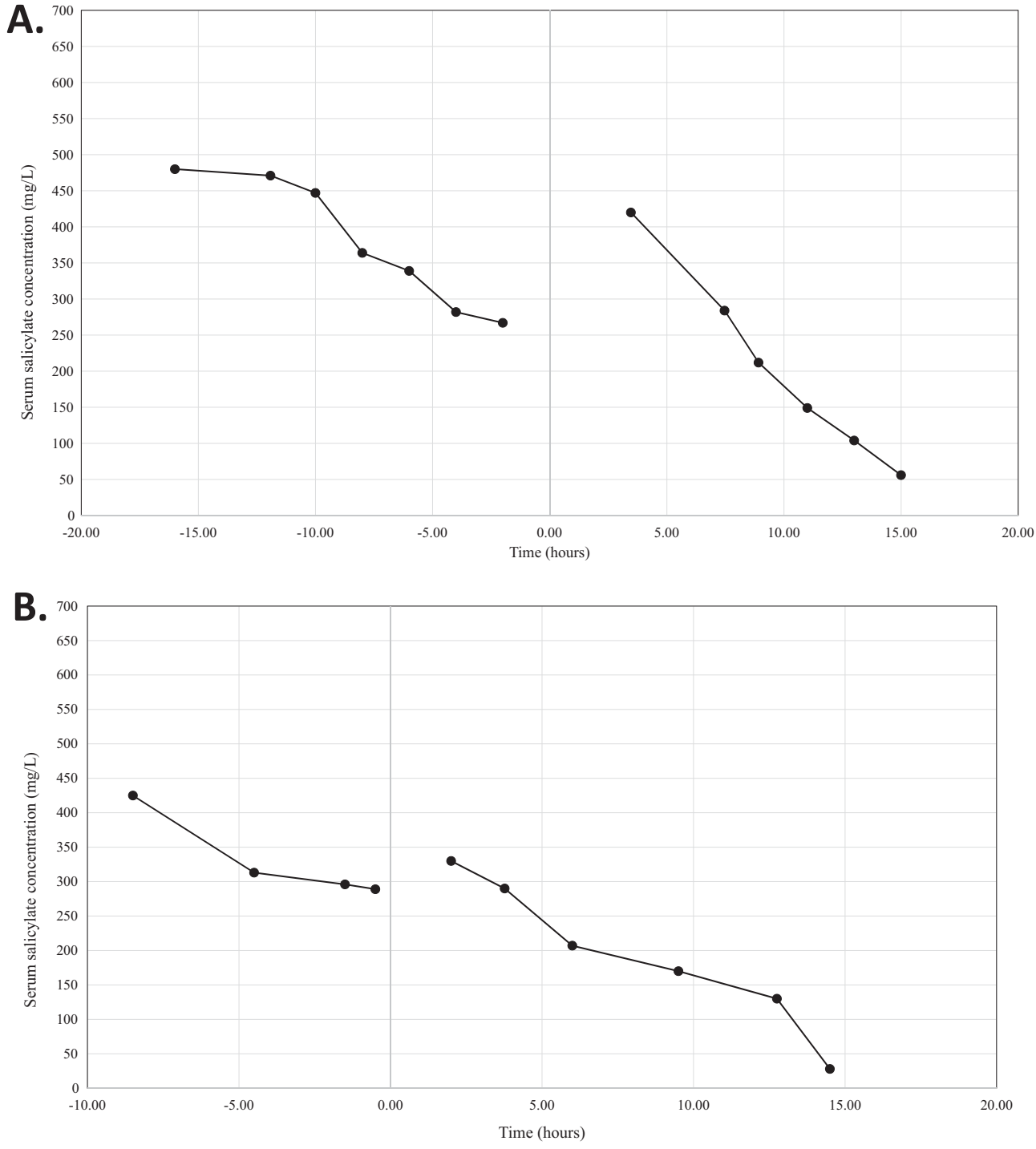

Figure 1. Changes in serum salicylate concentrations in eight cases of moderately severe acetylsalicylic acid overdose during intravenous sodium bicarbonate infusion (urine alkalinization) and after its discontinuation at hour 0. In five cases (graphs A–E for patients 1,3,6,7,8 respectively), serum salicylate concentrations rebounded to greater than 300 mg/L (2.17 mmol/L). in three cases (graph F, for patients 2,4 and 5), the rebound was less than 300 mg/L (2.17 mmol/L). To convert salicylate from mg/L to mmol/L multiply by 0.00724.

retreated was symptomatic. It is unclear if these patients may have had the same outcomes even without treatment.

These data also provide insight into the natural course of serum salicylate concentration rebound after stopping urine alkalinization. Patients in this series experienced delayed increases in serum salicylate concentrations as late as 10 h after sodium bicarbonate therapy was stopped, 20 h after presenting to the emergency department, and 42 h from assumed time of ingestion. Seven of the eight cases received activated charcoal upon arrival at the emergency department. One patient (patient 8) experienced a rebound increase in serum salicylate concentration to 410 mg/L (2.97 mmol/L) and symptom recurrence eight hours after discontinuing intravenous sodium bicarbonate infusion. It is possible that the patient was still absorbing acetyl salicylic acid from the gastrointestinal tract when the intravenous

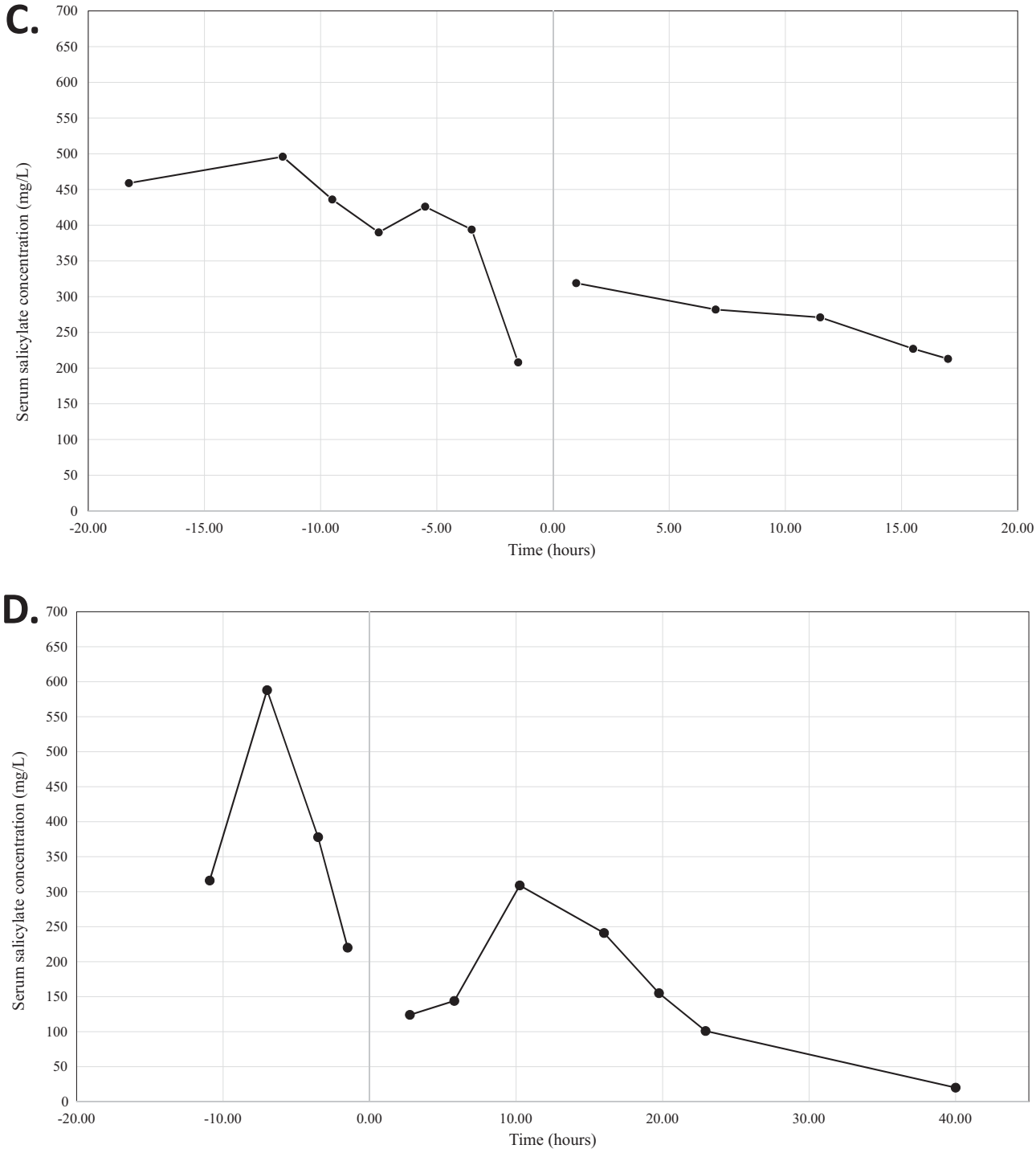

Figure 1. Continued.

sodium bicarbonate infusion was stopped 3.5 h later. One patient (patient 2) experienced a continued increase of 50 mg/L (0.36 mmol/L) between the first and second serum concentration after stopping sodium bicarbonate therapy. In this case, the patient also ingested diphenhydramine, a first-generation antihistamine with anticholinergic properties [12]. Due to altered gastric emptying and decreased intestinal motility, absorption of salicylic acid from the gastrointestinal tract could be delayed. No rebound to a concentration greater than 300 mg/L (2.17 mmol/L) occurred in patients whose serum salicylate concentrations were less than 200 mg/L (1.45 mmol/L) prior to cessation of alkalinization of the urine. Additionally, particular care in additional monitoring should be taken if patients are believed to have continued gastrointestinal absorption of acetylsalicylic acid, based on, for example, recent time of ingestion, serum salicylate concentrations, or the persistence of symptoms.

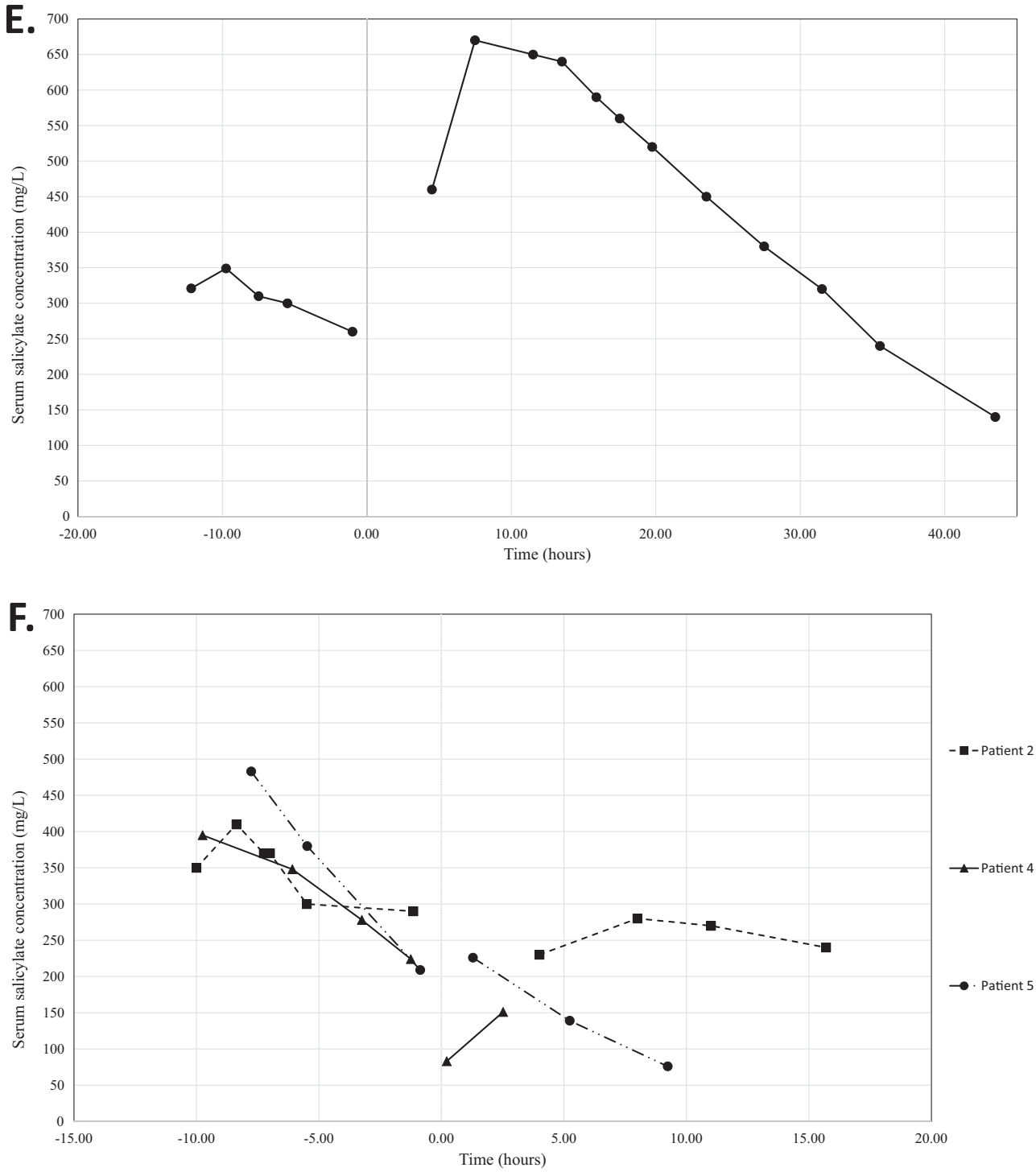

Figure 1. Continued.

Limitations

This is a single-center, retrospective review and was reliant on only the documentation within one poison center. Data are obtained through non-mandatory reporting to this poison center, and this relies entirely on accuracy of caller information, whether by healthcare professionals or laypeople, introducing the potential of transcription errors in data. Another limitation includes the inability to track a patient's urine pH throughout treatment, therefore it is unknown whether the patient achieved urine alkalinization. The reported cases were clinically diverse and confounding variables such as co-ingestion or comorbid condition could not be controlled for. Additionally, the clinical relevance of rebound is not clear as data on patient outcomes in those with rebound serum concentrations greater than 300 mg/L (2.17 mmol/L) who were not restarted on urine alkalinized is

Table 1. Cases of acetylsalicylic acid overdose with a rebound in serum salicylate concentrations after discontinuation of IV sodium bicarbonate infusion (urine alkalinization).

Case	Sex/ Age (y)	Formulation; Estimated ingested dose (g) [g/kg]	Co-ingestions	Activated charcoal; repeat doses; (Y,N)	Duration of sodium bicarbonate infusion (h)	Last two serum salicylate concentrations before stopping bicarbonate (mg/L) [mmol/L]	Peak in serum salicylate after stopping bicarbonate (mg/L) [mmol/L]	Time to rebound peak (h)
1	F/12	Unknown; Unknown	Methylphenidate, fluoxetine, ibuprofen	Y; N	15	282–267 [2.04–1.93]	420 [3.04]	3.5
2	F/18	ASA 325 mg tablet; (32.5)	Diphenhydramine	Y; Y	9.5	300–290 [2.17–2.1]	280 [2.03]†	8
3	F/41	ASA 325 mg tablet; (24.1) [0.21]	None	Y; Y	5.5	296–289 [2.14–2.09]	330 [2.39]	2
4	F/14	Unknown; Unknown	None	Y; N	7	224–83 [1.62–0.60]	151 [1.09]	2.5
5	F/16	ASA 325 mg tablet; Unknown	None	Y; N	6	380–209 [2.75–1.51]	226 [1.64]	1.3
6	F/62	Headache Relief medication (250 mg ASA per tablet); Unknown	Paracetamol, caffeine, doxylamine	N; N	16	394–208 [2.85–1.51]	319 [2.31]	1
7	F/74	ASA 325 mg tablet; (65) [1.01]	Ethanol	Y; Y	10.5	378 - 220 [2.74–1.59]	309 [2.24]‡	10.3
8	M/34	ASA 325 mg tablet; (146.3) [0.93]	None	Y; N	3.5	300 –260 [2.17–1.88]	670 [4.85]	8

After discontinuation of sodium bicarbonate infusion, serum salicylate concentration increased. †From 230 to 280 mg/L [1.67 to 2.03 mmol/L] and ‡From 124 to 144 and 309 mg/L [0.90–1.04 and 2.24 mmol/L].

not available for comparison given all five patients were restarted on urinary alkalinization.

Conclusion

After urine alkalinization for treatment of salicylate toxicity is stopped, any increase in serum salicylate concentration and a rebound greater than 300 mg/L (2.17 mmol/L) are uncommon, with an incidence of 2.1% and 1.3%, respectively. In the latter situation, there may be recurrence of symptoms. For patients with declining serum salicylate concentrations and resolving symptoms, repeated measurements may be unnecessary. However, particular care should be taken if ongoing gastrointestinal absorption of acetylsalicylic acid is likely, based on, for example, recent time of ingestion, serum salicylate concentrations or the persistence of symptoms. More study is needed regarding the role of urinary alkalinization in an asymptomatic patient who experiences a rebound in serum salicylate concentration greater than 300 mg/L (2.17 mmol/L).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

ORCID

Mary O'Keefe http://orcid.org/0000-0003-1905-5100
Jillian Theobald http://orcid.org/0000-0002-9906-4148

References

[1] Shively RM, Hoffman RS, Manini AF. Acute salicylate poisoning: risk factors for severe outcome. Clin Toxicol. 2017;55(3):175–180. doi: 10.1080/15563650.2016.1271127.

[2] Pearlman BL, Gambhir R. Salicylate intoxication: a clinical review. Postgrad Med. 2009;121(4):162–168. doi: 10.3810/pgm.2009.07.2041.

[3] Gummin DD, Mowry JB, Beuhler MC, et al. 2021 Annual report of the national poison data system© (NPDS) from America's Poison Centers: 39th annual report. Clin Toxicol. 2022;60(12):1381–1643. doi: 10.1080/15563650.2022.2132768.

[4] O'Malley GF. Emergency department management of the salicylate-poisoned patient. Emerg Med Clin North Am. 2007;25(2):333–346. abstract viii. doi: 10.1016/j.emc.2007.02.012.

[5] Lugassy DM, et al. Salicylates. In: Nelson LS, Howland MA, Lewin NA, editors. Goldfrank's toxicologic emergencies, 11th ed. New York: McGraw Hill; 2019. p. 555–566.

[6] Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med. 1981;141(3 Spec No):364–369. doi: 10.1001/archinte.1981.00340030096017.

[7] American College of Medical Toxicology. Guidance document: management priorities in salicylate toxicity. J Med Toxicol. 2015;11(1):149–152.

[8] Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. J Toxicol Clin Toxicol. 2004;42(1):1–26. doi: 10.1081/clt-120028740.

[9] West PL, Horowitz BZ. Delayed recrudescence to toxic salicylate concentrations after salsalate overdose. J Med Toxicol. 2010;6(2):150–154. doi: 10.1007/s13181-010-0070-1.

[10] Aspirin and other Salicylate Poisoning [published 2020 Aug]. In: Therapeutic guidelines. Melbourne: Therapeutic Guidelines Limited; 2023. https://www.tg.org.au

[11] Filippone GA, Fish SS, Lacouture PG, et al. Reversible adsorption (desorption) of aspirin from activated charcoal. Arch Intern Med. 1987;147(8):1390–1392. doi: 10.1001/archinte.1987.00370080026006.

[12] Huynh DA, Abbas M, Dabaja A. Diphenhydramine toxicity. In: StatPearls. Treasure Island, FL: StatPearls Publishing LLC; 2022.