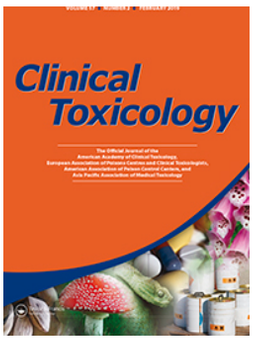

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POISON CENTRE RESEARCH

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Salicylate toxicity after undetectable serum salicylate concentration: a retrospective cohort study

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ABSTRACT

Background: Salicylates are usually rapidly absorbed and quickly measurable in serum. An undetectable serum salicylate concentration ([ASA]) may occur early after ingestion and may be interpreted as evidence of non-exposure and not repeated. Although cases of delayed salicylate detection are reported rarely, the risk factors associated with this phenomenon are not known.

Research question: What factors are associated with an early undetectable [ASA] in salicylate poisoning?

Methods: Records from a single regional poison center were searched from 2002 to 2016 for cases of salicylate toxicity treated with bicarbonate and [ASA] > 30 mg/dL. Cases were excluded if initial [ASA] was obtained >4 h after presentation. Case information, serial [ASA], and outcomes were recorded and compared between groups.

Results: A total of 313 records met all criteria with 11 initially undetectable [ASA] (3.5%) and 302 detectable [ASA] (96.5%). Time of first [ASA] occurred sooner in the undetectable [ASA] group (89 vs. 137 min, $p = 0.011$) while time to peak [ASA] was longer (640 vs. 321 min, $p < .001$). The longest interval between ingestion and undetectable [ASA] was 225 min. Peak [ASA] and reported mean ingested dose were similar in both groups (45 vs. 50 mg/dL, p = NS; 19.7 g vs. 32.9 g, p = NS). Coingestion of agents that delay gastric emptying were similar in both groups (18% [2/11] vs. 25% [76/302], p = NS, chi-square). Hemodialysis was performed in 9% (1/11) of undetectable [ASA] patients and 5.6% (17/302) of detectable [ASA] patients (p = NS, chi-square). A single death occurred in the entire cohort in a patient with an initially detectable [ASA].

Discussion: In this series, a small but significant proportion (3.5%) of patients who developed [ASA] > 30 mg/dL had an initially undetectable [ASA]. Those with an undetectable [ASA] were measured earlier after ingestion with a longer time to peak [ASA]. However, neither coingestion of agents prolonging gastric emptying nor reported dose ingested was different between groups. Formulation was infrequently recorded but one undetectable [ASA] did ingest a non-enteric coated product. Limitations include the small number of patients with undetectable [ASA], use of single poison center data and partial data on co-ingestants and aspirin formulation.

Conclusions: [ASA] may be undetectable early after an overdose and need for serial [ASA] in the evaluation of salicylate ingestion should be further explored. Additional research is needed to determine any causative factors and the optimal timing of [ASA] measurements.

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Aspirin; salicylate; poisoning

Introduction

According to the 2016 report from the United States National Poison Data System, salicylate exposure occurred 19,401 times with 22 deaths reported [1]. Absorption of salicylates is generally rapid and detectable in serum within minutes and peak concentrations reached in about an hour [2]. However, prolonged absorption with a late peak aspirin concentration ([ASA]) has been described [3, 4]. Perhaps more worrisome are reports of patients with initially undetectable serum salicylate concentrations who went on to develop salicylate toxicity [5–8]. Although some references have recommended obtaining an [ASA] 6 h after ingestion, this reflects the idea that absorption would be ongoing up to 6 h, not that it would be undetectable prior to this point. Thus, clinicians may be falsely reassured by an undetectable salicylate concentration obtained shortly after presentation and forego serial testing even with a reported history of salicylate exposure.

Although salicylate absorption is known to be prolonged in overdose, the factors associated with an initial undetectable [ASA] are not well described. We hypothesized that several variables may be associated with an early undetectable [ASA] such as a short interval between ingestion and testing, assay with a relatively high limit of detection, co-ingestion of agents delaying gastric emptying, enteric coated salicylate formulations, or a smaller total ingested dose. We reviewed a cohort of cases of salicylate toxicity presenting less than 4 h after ingestion to identify any risk factors associated with an early undetectable [ASA].

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Methods

Records from a single regional poison center were searched from 1 January 2002 to 31 December 2016. We searched for all records coded under acetylsalicylic acid or acetylsalicylic acid combination products (AAPCC generic codes 0041701, 0041703, 0041000, 0041708, 0041717, 0201064, 0041700, 0041707, 0041706, 0041718, 0041709) that received alkalinization therapy. Exclusion criteria were: peak [ASA] < 30 mg/dL, initial [ASA] obtained >4 h from ingestion, time of ingestion not clearly documented, time of initial [ASA] not clearly documented, and chronic ingestions. An undetectable [ASA] was defined a value less than that laboratory's lower limit of detection. Undetectable cases were compared to those with an [ASA] obtained <4 h after ingestion that was greater than the lower limit of detection.

Chart reviewers were trained in the study protocol. A senior reviewer evaluated an initial subset of each reviewer's records to ensure protocol adherence. All cases with an initial undetectable [ASA] were verified by a second reviewer. The following variables were collected: demographics, salicylate formulation, salicylate dose, quantity of tablets ingested, weight, co-ingested substances, treatments administered, GI decontamination, serial [ASA] measurements, symptoms, vitals, other laboratory data, length of stay, and death. A subset of co-ingested substances that could delay gastric emptying were examined for each group including antimuscarinics, opioids, and ethanol. Data were summarized with descriptive statistics. The Mann-Whitney U test for non-parametric data was used to compare means between groups and the chi-squared test to compare proportions. All analyses were done with JASP (Version 0.8.3, JASP Team 2017).

Results

There were 2343 cases included in the initial search for cases of salicylate exposure receiving alkalinization therapy. Three hundred thirteen records met all inclusion and exclusion criteria with 11 having an initially undetectable [ASA] and 302 with detectable [ASA]. Characteristics of both groups are summarized in Table 1. The only significant differences between the two groups were time of initial [ASA] ($p = 0.011$) and time to peak [ASA] ($p < .001$). There was wide variation in the reported ingested dose but this had weak correlation with peak [ASA] ($r = 0.321$). The longest interval between ingestion and an undetectable [ASA] was 225 min. The lower limit of detection of [ASA] in cases ranged from 1 to 5 mg/dL and was explicitly stated in 7 of 11 cases with the remaining 4 documented as "undetectable." A summary of cases with an initial undetectable [ASA] is shown in Table 2.

Discussion

Salicylate absorption is known to be erratic with symptoms and elevated aspirin concentrations ([ASA]) occurring many hours after ingestion. Though this phenomenon is now commonly recognized, patients with an undetectable initial [ASA] may have their ingestion history questioned or not have repeat testing at 4 h. While clinicians are accustomed to waiting until 4 h after acetaminophen ingestion to obtain a plasma acetaminophen concentration, no such practice is routinely in place for salicylates. In addition, recent evidence suggests that acetaminophen concentrations are frequently drawn on arrival and often not repeated at 4 h [9]. Some authors had previously recommended measuring [ASA] at 6 h after ingestion, but this reflects use of the Done nomogram and that [ASA] may not have peaked at 6 h, not that it would be undetectable before 6 h [10].

Several cases of salicylate toxicity with initially undetectable [ASA] have been reported. Kaufman reported an 18-month female who ingested 10 to 15 tablets of a delayed release aspirin, paramethasone, and propoxyphene product. Serum [ASA] was undetectable at 4 h but at 16 h a repeat urine ferric chloride test was positive and [ASA] was 33 mg/dL [8]. Wortzman described a 22-year-old male who ingested 88 tabs of 325 mg delayed release aspirin. [ASA] at 1 and 3 h were undetectable [11]. At 7 h [ASA] was 13.3 mg/dL and

Table 1. Case characteristics.

	Undetectable [ASA]	Detectable [ASA]	*p*-Value
Male	55%	30%	.283
Female	45%	70%	
Age (median, years, IQR)	29 (17–43)	20 (17–29)	.273
Reported ingested dose (median, grams, IQR)	14 (8.5–27.4)	25.5 (11.4–32.5)	.227
Formulation			
Enteric coated (*n*, %)	2, 18%	3, 1.0%	.084
Non-enteric coated (*n*, %)	1, 9%	13, 4.3%	
Unknown (*n*, %)	8, 73%	286, 95%	
Ingestion of agents delaying gastric emptying	18%	25%	.599
Single dose activated charcoal only	18%	42%	.406
Multi dose activated charcoal	82%	54%	.068
Gastric lavage	9%	12%	.990
Initial [ASA] (mg/dL)	undetectable	37.6	
Initial [ASA] time after ingestion (mean, minutes, IQR)	89 (60–120)	138 (90–180)	**.011***
Peak [ASA] (mg/dL)	45.2	50	.445
Peak [ASA] time after ingestion (mean, minutes, IQR)	641 (371–855)	321 (185–420)	**< .001***
Seizures, (*n*, %)	0, 0%	3, 1%	.740
Intubation, (*n*, %)	1, 9.1%	6, 2%	.118
Hemodialysis, (*n*, %))	1, 9.1%	17, 5.6%	.628
Death, (*n*, %)	0, 0%	1, 0.3%	.848

IQR: interquartile range, * $p < 0.05$

Table 2. Cases with an initially undetectable salicylate concentration.

Case	Age	Gender	Coingestants	GI Decon	Formulation	Initial [ASA] time after ingestion (min)	Assay lower limit of detection (mg/dL)	2nd [ASA] (mg/dL)	2nd time (min)	Peak [ASA] (mg/dL)	Peak time (min)
1	21	M	Ethanol	AC	NR	60	5	7.7	180	51.9	375
2	30	F	Cannabis	AC	NR	120	2	24	240	36	600
3	17	M		AC	Non-enteric coated	100	–	39	360	39	360
4	17	F		AC	NR	90	1	2.4	240	41.5	1362
5	37	F		AC	Enteric coated	60	–	41	240	43.9	460
6	15	F		AC	NR	120	3	–	–	58	780
7	43	M		AC	NR	40	–	16.6	160	55.5	480
8	29	F		AC, gastric lavage	NR	25	–	36.9	140	47.8	250
9	16	M		None	Enteric coated	120	4	22.7	420	43.6	660
10	51	M	Acetaminophen, trazodone	AC	NR	60	1	<1	225	35	1080
11	58	F	Quetiapine	None	NR	180	3	–	–	61	1740

GI decon: gastrointestinal decontamination; AC: activated charcoal; NR: not reported.

peaked at 35.8 mg/dL at 24 h after ingestion. Elko reported a 12-year-old female who ingested an unknown quantity of enteric coated aspirin 325 mg [6]. [ASA] was <2.8 mg/dL at 2 h and peaked at 34 mg/dL 20 h after ingestion. Herres reported a 53-year-old male who ingested 200 tablets of 325 mg aspirin [7]. Approximately 45 min after ingestion [ASA] was undetectable but was elevated to 33 mg/dL at 3 h. He was transferred to a psychiatric ward and ultimately died 20 h after ingestion with a peak [ASA] of 128 mg/dL. Grandey reported 13 cases of initial [ASA] that were <10 mg/dL but not necessarily undetectable [12]. They do specifically report one patient with an undetectable [ASA] that later peaked at 54.8 mg/dL though further detail is not available beyond an abstract. These authors hypothesized several factors that could contribute to delayed detection and absorption of salicylates such as enteric coated or delayed release preparations, ingestion of agents delaying gastric emptying, pylorospasm, pharmacobezoar formation, or repeated ingestions while under medical care and after initial blood draws.

In this series of patients with salicylate toxicity presenting less than 4 h after ingestion, 3.5% had an initially undetectable [ASA]. We were unable to identify any clinically significant risk factors for an initially undetectable [ASA]. The undetectable group did have an earlier time of initial [ASA] and longer time to peak [ASA]. Though the mean time to initial [ASA] was shorter in the undetectable group, there was substantial overlap in the two groups (IQR undetectable [ASA]: 60–120 min, detectable [ASA]: 90–180 min). Neither of these factors would be clinically useful to identify patients at risk for salicylate toxicity after an undetectable [ASA].

There was no significant difference with regard to patient demographics, reported ingested dose, co-ingestion of agents delaying gastric emptying, charcoal administration, gastric lavage, or peak [ASA]. Use of activated charcoal or gastric lavage would not be expected to affect the initial [ASA] unless there was significant delay between these interventions and collecting blood samples. None of the undetectable cases had a delay between gastric decontamination interventions and [ASA] measurement.

Antimuscarinic agents, opioids, and ethanol are known to delay gastric emptying [13–15] and could potentially lead to a delay in salicylate absorption and detection. There was no difference in the proportion of patients with reported co-ingestions of these agents between the two groups. The presence of co-ingestants is likely underreported, though overall 46% did have at least one co-ingestant listed.

Aspirin is known to have erratic and prolonged absorption [3, 4]. Enteric coated preparations have delayed absorption in therapeutic doses [16, 17]. Unfortunately the aspirin formulation was infrequently reported in both groups, though one patient in the undetectable group did ingest a non-enteric coated product with a peak [ASA] of 41.5 mg/dL at 23 h. We only reported the formulation if explicitly stated. We did not infer the formulation based on the reported dosage (e.g. 81 mg tablets as always enteric coated) as both 81 mg and 325 mg tablets are available in immediate release and enteric coated forms.

While specific details on the salicylate assays used were not available, cases of undetectable [ASA] occurred even with assays with a lower limit of detection of 1 mg/dL.

Overall, patients in both groups had good outcomes. This is likely influenced by only including patients who presented less than 4 h after ingestion, leading to timely diagnosis and treatment.

There are several interesting notes to detail about the cases with an initial undetectable [ASA]. Case #10 had an undetectable [ASA] on two consecutive measurements at 60 and 225 min after ingestion. Additionally there were two patients with detectable but very low [ASA] on the second measurement. Case #1 had an [ASA] of 7.7 mg/dL at 180 min and Case #4 had an [ASA] of 2.4 mg/dL at 240 min. It is possible these patients may have had a second undetectable [ASA] if an assay with a different lower limit of detection were used. We previously reported Case #4 in greater detail [5].

In case #11, the patient ingested 2000 mg of quetiapine and an unknown quantity of aspirin. She was intubated for airway protection on arrival to the emergency department. Salicylate concentration obtained 3-h postingestion was $<$3 mg/dL. Approximately 29 h after ingestion the patient developed hyperthermia (39.3°C). It was noted that a subsequent [ASA] was not performed following the initial undetectable concentration obtained at presentation. Repeat [ASA] at that time was 61 mg/dL. The patient received hemodialysis and made a good recovery after 7 days.

There are several limitations to this study. There were relatively few cases with an undetectable [ASA] making statistical comparisons relatively insensitive to small differences between the groups. Poison center data relies on voluntary reporting and is not able to capture all relevant cases. Additionally, data collected by poison centers may be incomplete and relies on accurate telephone reporting of history, dose, co-ingestants, laboratory findings, and treatments. Notably, the aspirin formulation was only specifically reported in 6% of all cases. It is possible that patients may have surreptitiously ingested aspirin while in the hospital and after blood was drawn, though this was not reported in any of these cases. Medical comorbidities, such as gastroparesis, could also influence salicylate absorption. We attempted to collect these data but only about 7% of charts had any specific medical history documented.

Conclusions

Delayed absorption and detection of salicylates in cases of salicylate ingestion is an infrequent but concerning phenomenon. Even very sensitive salicylate assays cannot exclude eventual salicylate toxicity early after an ingestion. We were unable to identify any risk factors clearly associated with an early undetectable [ASA] in this cohort. The longest interval from ingestion to undetectable [ASA] was nearly 4 h. Further research with a larger cohort of patients is required to identify any risk factors associated with an initial undetectable [ASA] and the optimal timing of [ASA] measurements to exclude salicylate ingestion.

Disclosure statement

No potential conflict of interest was reported by the authors.

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