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Acute Salicylate Poisoning: Risk Factors for Severe Outcome

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Key terms

aspirin; toxicity; mortality

Introduction

Salicylate is one of the most commonly used drugs worldwide.¹ In 2014, over 24,700 salicylate exposures were reported in the US and morbidity/mortality rates are reported to be as high as 30%.^{2,3} Of all drug poisonings that year, salicylate was the 14th most common fatal ingestion reported to US poison centers.² Moreover, given its ease of access, salicylate remains a serious public health threat. Early detection and treatment are essential, as the mortality rate for patients admitted to the hospital with undiagnosed salicylate poisoning is estimated to be up to three times higher than if the diagnosis is made in the Emergency Department (ED), especially for elderly and chronically poisoned patients.⁴

Previous studies have investigated risk factors for severe outcomes in salicylate poisoned hospitalized patients, acute ingestions, chronic ingestions, and those in the ED. In the 1960s, the Done nomogram was derived in order to predict severe outcome from acute poisoning using the salicylate concentration alone;⁵ however, subsequent validation studies failed, and use of the nomogram fell out of favor.⁶ Nevertheless, many subsequent studies have asserted that the serum salicylate concentration remains a predictor of severe outcome, in tandem with other clinical factors.^{6,7,8,9,11} Clinical factors that have been associated with severe outcome include age, central nervous system (CNS) features, metabolic acidosis, and delayed diagnosis.^{4,10,11}

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Early clinical predictors of the severity of salicylate poisoning are still needed in order to help identify patients who require aggressive treatment, and mobilize appropriate resources to hopefully prevent fatality. In this study, we aimed to derive early clinical predictors of severe in-hospital outcomes in ED patients presenting with acute salicylate poisoning. Given previous studies, we hypothesized that serum salicylate concentration, age, elements of the basic metabolic panel, and coma would predict severe outcomes.

Methods

Study Design

This was a secondary data analysis of salicylate overdoses from a retrospective cohort study of suspected acute drug overdoses performed on consecutive adult ED patients from 2009–2013.^{12,13} The study protocol was approved by the Institutional Review Board (IRB) for the two participating institutions with a waiver of informed consent.

Study Setting

Patients were enrolled from the EDs of two urban, tertiary-care hospitals. These EDs have a combined annual visit volume in excess of 150,000 and are staffed 24 hours per day by board-certified emergency physicians. Neither study hospital was affiliated with the regional Poison Control Center, but a medical toxicology consulting service was available.

Study Population

ED patients with acute drug overdoses within 24 hours of exposure were initially screened for inclusion by trained research assistants as previously described.^{12,13} Under the secondary analysis, only confirmed acute salicylate overdoses meeting the above criteria were extracted from the cohort's database. Exclusion criteria were the following: alternative diagnosis (e.g. trauma or infection), chronic presentation (i.e. not meeting acute criteria above), nondrug overdose (e.g. plant), exposures limited to dermal or inhalational means only, age younger than 18 years, anaphylaxis, patients with incomplete data (i.e. left against medical advice, transferred to an outside institution, or otherwise eloped from the hospital), and patients with prior Do-Not-Resuscitate (DNR) orders.

Study Protocol

Research assistants trained in data abstraction collected data from the medical chart in accordance with accepted guidelines, including training of abstractors and 95% agreement of a random sampling of 10 test charts prior to mass data abstraction.¹⁴ Medical record data (electronic medical records, paper medical records, and consult records) was used as the source for all data collection. Patients were followed prospectively during the hospital stay. Patients discharged from the hospital had no further follow-up. Data were abstracted to a de-identified electronic database with password protection.

Data

Demographics (age, sex), clinical parameters (vital signs, basic metabolic panel, blood gas, initial serum lactate), exposure information (timing of overdose, number of exposures,

intent, suicidality), initial serum salicylate concentration, co-ingestion identification (detail from history and physical interview, serum drug concentration and urine ELISA panel, if available), initial mental status (Glasgow Coma Scale [GCS] score and coma diagnosis), treatment modalities (activated charcoal, multi-dose activated charcoal, sodium bicarbonate, hemodialysis), and disposition (admission, death, discharge) were abstracted from the chart. For purposes of analysis, coma was used as one variable defined as a composite occurrence of GCS<10, mention of “coma” in the chart, and/or an ED diagnosis of “coma”.

Because serial measurements of serum salicylate concentration were not collected as part of the original study they were not available for this secondary data analysis. For this reason, and because this study intended to determine early predictors of severe outcome, only the initial serum salicylate concentration was included in the analysis. Treatment was determined by the primary medical team in coordination with the Poison Center recommendations, or medical toxicology consult, if applicable.

Study Outcome

Based on prior literature, we defined severe outcome as the composite occurrence of any of the following: (A) acidemia (pH<7.3 or bicarbonate <16mEq/L), (B) hemodialysis (any occurrence, any duration), or (C) death.^{4,7,9,15,16}

Statistical Analysis

Descriptive statistics calculation (percentage, quartiles, mean), univariate analysis, and multivariate analysis was performed using SPSS v20. We calculated 95% confidence intervals (CI) using the estimated standard error method. Chi-square (with two-tailed Fisher’s exact test when appropriate) and t-tests (with Mann-Whitney when appropriate) were calculated for categorical and continuous variables, respectively, with 5% alpha (two-tailed).

The multivariate regression model was performed with the NOMREG procedure using SPSS v20, and included candidate predictors based on prior literature that were approved by the senior investigators.^{5,6,7,8,9,11} In addition, candidate covariates that achieved univariate significance were also added to the multivariate regression model. Regression model fit was assessed by the Nagelkerke method with R² statistics. Missing data was handled by list-wise deletion. Multicollinearity was assessed using a variance inflation factor <5. No interaction terms were introduced. Odds ratios of the final model’s prediction of the primary outcome were calculated with 95% CI.

Results

Over the course of the prospective cohort study period, there were 1,997 suspected acute drug overdoses. Of those, 50 were identified in the secondary analysis as having acute salicylate overdoses. Two of these were excluded for age younger than 18.

Of the 48 patients who met inclusion and exclusion criteria, 21 (43.8%) were male, the median age was 32 (range 18–87) and the mean initial salicylate serum concentration was 28.1 mg/dL (SD 26.6). Ten (20.8%) were classified as severe outcome, of whom two (4.2%)

expired, two (4.2%) underwent hemodialysis and seven (14.6%) met acidemia criteria. Of the two deaths, neither received hemodialysis and both were endotracheally intubated in the ED.

Although all patients presented within 24 hours of ingestion, the exact time from ingestion to presentation data was missing in 40% of severe and 18% of non-severe patients. However, from available data, 2 (33.3%) in the severe group and 14 (36.8%) in the non-severe group presented within 4 hours of ingestion. Patients were treated with sodium bicarbonate in 16 (33.3%) of all cases (4 [40.0%] severe, 12 [31.6%] non-severe), while 26 (54.2%) (5 [50.0%] severe, 21 [55.3%] non-severe) received activated charcoal and 31 (64.6%) (9 [90.0%] severe, 22 [57.9%] non-severe) were admitted to hospital as inpatients. Baseline clinical characteristics of subjects who were included are summarized in Table 1.

Main Analysis

Univariate analysis indicated that increasing age ($p=0.04$), respiratory rate (RR) ($p=0.04$), lactate ($p=0.002$), coma ($p=0.05$), and presence of co-ingestions ($p=0.04$) were significantly associated with severe outcome, while initial salicylate concentration alone had no significant association. Glucose, creatinine, anion gap, suicidality, and male gender were also examined and found not to be associated. Finally, neither hyperthermia (temperature $> 100.4^{\circ}\text{F}$) nor hypoxemia (oxygen saturation $< 90\%$) were predictive of severe outcome ($p=0.22$ for both). Summary of univariate analysis is found in Table 2.

Multivariable logistic regression was performed to further elucidate independent risk factors for severe outcome. Factors included into the model were the following: literature-derived factors (salicylate concentration, age, gender, co-ingestions), and additional univariate factors with significance (lactate, respiratory rate, coma). When the model was adjusted with the above factors, only age (OR 1.13 per additional year; 95% CI 1.02–1.26) and RR (OR 1.29 per additional breath/min; 95% CI 1.02–1.63) remained statistically significant. Model fit was good, with an $R^2 = 0.68$ with negligible multicollinearity of each variable. Missing data resulted in the list-wise deletion of 10 patients, including 2 severe outcomes. The final derived model is summarized in Table 3.

Additionally, lactate was analyzed as a biomarker of salicylate poisoning. The receiver operating characteristic (ROC) area under the curve for prediction of severe outcome was 0.72 (95% CI: 0.51–0.94, $p=0.044$). The optimal lactate cutpoint was 2.25 mmol/L (78% sensitivity, 67% specificity), while the maximally specific cutpoint was 6.15 mmol/L. The ROC curve is illustrated in Figure 1.

Discussion

This study derived independent predictors of severe outcome from acute salicylate poisoning, which if validated in future studies, can be used as early clinical markers of severe salicylate poisoning. Once identified, high risk patients can be monitored and treated more aggressively (i.e., sodium bicarbonate, hemodialysis), with possible intensive care unit (ICU) triage for those at highest risk.

Prior studies have found the following to be correlated with severe outcome: salicylate concentration,^{5,6,8,9,11} age,^{4,8,9,10,11} CNS features,^{7,10,11,16} metabolic acidosis,^{7,10} coingestions,^{9,16} chronic poisoning,^{10,11} delayed diagnosis,⁴ delayed treatment,⁴ first episode drug overdose,⁴ accidental overdose,⁴ delayed presentation,⁷ hyperpyrexia,⁷ pulmonary edema,⁷ suicidality,⁸ comorbidities,¹⁰ smoking,¹¹ proteinuria,¹¹ and alcoholism.¹⁰ This study corroborated that age was related to severe outcome even when controlling for salicylate concentration. Co-ingestions and CNS features were found to be associated but not when controlling for salicylate concentration. Initial salicylate concentration, suicidality and accidental overdose were found to not be significantly correlated. Finally, the remainder of the above variables were not included in this study.

The strongest predictor of severe outcome was initial RR elevation. Here, tachypnea may simply be a measure for dose-dependent salicylate toxicity pathophysiology. Hyperventilation occurs as a result of direct stimulation of the medullary respiratory center. Furthermore, as salicylate uncouples oxidative phosphorylation, CO₂ is produced leading to indirect stimulation of respiration via chemoreceptor reflexes.¹⁷

The other predictor of severe outcome that maintained its significance when controlled for initial salicylate concentration was age. Age has been a well-known predictor of mortality with many toxic ingestions, possibly owing to the presence of co-morbidities and lack of physiologic reserve.^{11,18,19,20} Moreover, many aspects of drug pharmacokinetics are altered by aging.²¹ Specifically, age-related renal decline, hypoalbuminemia and change in end-organ sensitivity to medications are implicated in age's effect on salicylate toxicity.²²

Additionally, lactate was a candidate predictor, but lost significance when adjusted for initial salicylate concentration. However, the ROC area under the curve was significantly predictive, and allowed for calculation of an optimal cutpoint. This may indicate the more important toxicity exerted by uncoupled oxidative phosphorylation or be another marker of the work of breathing. This is compatible with other studies that have demonstrated the ability of lactate to predict mortality in general acute drug poisoning.²³ However, this is the first study to demonstrate lactate as a predictor of severe outcome in salicylate toxicity specifically.

Although not significant when controlled for initial salicylate concentration, co-ingestions and coma showed univariate significance. Mechanistically, this may be explained by a blunted hyperventilation response in the setting of coma and CNS-depressing co-ingestions. This principle was similarly demonstrated in the setting of worse clinical prognosis following orotracheal intubation.²⁴ Aside from CNS-depressants, other co-ingestions (e.g. acetaminophen) can lead to renal pathophysiology, which may also contribute to the overall severity of outcome (e.g. worse salicylate clearance, increased acidemia). Additionally, the individual toxicity of co-ingestants (e.g. hepatotoxicity, cardiotoxicity) may independently contribute to more severe outcomes.

It is likely that coma and co-ingestions lost their significance when controlled for initial salicylate concentration because of the overall low serum salicylate concentrations and the

confounding presented by age and respiratory rate. Additionally, there was a lower rate of CNS-depressant ingestions included in this study population.

Finally, creatinine demonstrated univariate significance, but also lost significance when controlled for initial salicylate concentration. Here, elevated creatinine may predispose to decreased salicylate clearance as well as impaired acid-base homeostasis.¹⁶ Nonetheless, as with coma and co-ingestions, low overall salicylate serum concentrations likely attenuated the significance of this effect.

The lack of correlation between serum salicylate concentration and severe outcome was not in line with some previous studies' findings.^{5,6,7,8,9,11} However, the study's small sample size and lower overall serum concentrations likely diminished its observed effect. Additionally, the outcome measure used was not equivalent to those in previous studies that used serial or peak salicylate concentrations.

Nevertheless, the initial serum salicylate concentration was analyzed intentionally, in order to develop a model for *early* prediction of outcomes. It would be warranted to assume that many concentrations rose over time given that most do not peak until 12–18 hours post-ingestion (although, data for time from ingestion to measurement of serum salicylate concentration was not available so this may not be true in every case).²⁵ Additionally, delayed salicylate absorption has been previously reported, with at least one case of mortality from salicylate ingestion occurring in a patient with an initially undetectable concentration.²⁶ Finally, acidemia will affect the correlation between serum salicylate concentration and CNS concentration, leading to potentially misleadingly low serum concentrations. Although the lack of serial measurements may have affected the ability to compare with previous salicylate toxicity outcome studies, serial measurements were not indicated in this study, as our goal was to develop a model for use in early discrimination. Regardless, trending serum salicylate concentrations and clinical exam in the first few hours post-ingestion remains extremely important in predicting morbidity and mortality.

Together these findings suggest that in patients with known salicylate overdose, the elderly and those presenting with higher RR should be triaged to a higher level of care. Additionally, although initial salicylate concentration can help guide triage, in patients with high likelihood of salicylate overdose but low serum concentration, those possessing these risk factors should especially be given priority. Finally, salicylate overdose patients possessing unexplained lactate concentrations above our cutpoint should also be considered for more intensive evaluation. For those who meet high risk criteria, early consultation with a medical toxicologist, early administration of activated charcoal (if not contraindicated), continuous monitoring, administration of sodium bicarbonate and consideration of hemodialysis is recommended.²⁷

Interestingly, in our study population, sodium bicarbonate was only provided to 40% of severe cases. This may be secondary to substandard care, late detection of salicylate toxicity or rapid deterioration to death or hemodialysis. Regardless, further studies should be performed to investigate potential barriers to sodium bicarbonate administration.

Limitations

Although the initial cohort size was large, significantly fewer patients qualified for the salicylate overdose secondary analysis. Similarly, the urban affiliate hospitals in this study represent only one center, which diminishes external generalizability, possibly with regard to non-urban non-teaching environments. This population also had lower serum salicylate concentrations than many studies; however, this is likely due to the fact that initial concentrations were used and these tend to rise over the course of an acute ingestion. This limits direct comparison to studies that used peak concentrations but it is consistent with our goal of early detection. Although early detection of salicylate toxicity is important as early intervention improves outcomes, salicylate toxicity is generally late onset so some important risk factors for severe outcome may not present themselves until later in the clinical course. This study does not diminish their importance as later predictors, but instead attempts to identify early predictors so patients meeting these criteria can be treated more deftly as they present.

Co-ingestions were not always confirmed/quantified through analytical testing. Similarly, RR recorded was based on hospital protocol and was not confirmed by study personnel evaluation; for this reason, precision in measurement may vary. Additionally, given the occurrence of ketosis in significant salicylate toxicity, serum creatinine values may have been falsely elevated. Salt and water depletion could also elevate serum creatinine; however, in our sample, this did not appear to be the case based on BUN/Cr ratio. Lastly, as we desired to make our sample specific and generalizable to acute adult salicylate poisoning, findings are not applicable to chronic and pediatric salicylate poisoning.

Our severe outcome definition was created based on previous studies and known consequences of severe salicylate poisoning with the goal of including all relevant outcomes. Although we included acidemia as a criterion for severe outcome based on multiple prior studies that have done the same, this precluded us from using initial pH, bicarbonate and base deficit as early predictors of severe outcome.^{15,16} This should be addressed in future studies. Additionally, as this was a secondary data analysis, we are unable to validate the appropriateness of hemodialysis. However, board-certified nephrologists were involved in both cases requiring hemodialysis; thus, we assume the decision to dialyze was appropriate. Moreover, as our database was pre-collected and de-identified, we were limited by its components, preventing us from including relevant measures that were not recorded, such as seizure activity. As with all composite outcomes, correlation cannot be presumed to apply to individual components of the composite alone. To this point, certain variables may disproportionately influence individual components (i.e. co-ingestions may contribute to acidemia through respiratory or lactic acidosis) while not exerting equivalent impact on the composite. Finally, our multivariate regression model removed several patients via list-wise deletion; however, the model still performed with a suitable 0.68 R^2 . Furthermore, given lack of available data, we were unable to perform analyses based on time from ingestion to presentation, though the percentage of early presenters did not vary dramatically between the severe and non-severe groups.

Conclusions

We determined that increased respiratory rate and older age were early predictors of severe outcome in ED patients with acute salicylate poisoning, even when controlled for initial salicylate concentration. Lactate concentrations above 2.25 mmol/L were shown to be significantly associated with severe outcome in acute salicylate poisoning. Consistent with previous literature, we found that the initial salicylate concentration is not prognostic. While this study can help guide treatment planning, further validation of these risk factors is warranted.

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Figure 1. ROC Curve for Prediction of Severe Outcome Using Initial Serum Lactate
The area under the curve of 0.72 was statistically significant. The optimal cutpoint (*), which maximized sensitivity and specificity, was 2.25 mmol/L (78% sensitivity, 67% specificity). The maximally specific cutpoint was 6.15 mmol/L.

Table 1**Clinical Characteristics of Patients in the Study**

Clinical Characteristics	Total n = 48	Severe Outcome n = 10 (21.3%)	No Severe Outcome n = 38 (78.7%)
Age (year)	32 (23.5–40.5)	37 (28–62)	29 (23–38.8)
Age subgroup 18–24	13 (27.1%)	2 (20%)	11 (28.9%)
Age subgroup 25–34	14 (29.2%)	2 (20%)	12 (31.6%)
Age subgroup 35–44	9 (18.8%)	3 (30%)	6 (15.8%)
Age subgroup 45–54	3 (6.3%)	0 (0%)	3 (7.9%)
Age subgroup 54–65	6 (12.5%)	1 (10%)	5 (13.2%)
Age subgroup 65+	2 (4.2%)	2 (20%)	0 (0%)
Men	21 (43.8%)	5 (50%)	16 (42.1%)
Respiratory Rate (breaths/min)	18 (18–20)	18 (18–28.5)	18 (18–20)
Creatinine (mg/dL)	0.9 (0.7–1.3)	1.2 (0.9–1.6)	0.9 (0.7–1.1)
Anion Gap (mEq/L)	10.5 (8–14)	14.5 (7.5–17.8)	10 (8.3–13)
Glucose (mg/dL)	109 (92–129.3)	111 (84.8–137)	107.5 (92–122.3)
Lactate (mmol/L)	2.1 (1.2–3.6)	3.6 (2.3–7.7)	2.0 (1.2–2.6)
Serum pH	7.41 (7.38–7.42)	7.32 (7.27–7.39)	7.41 (7.39–7.43)
Serum Bicarbonate (mEq/L)	24 (21–26)	21.5 (12–23.8)	24 (22–26)
Initial Salicylate Serum Conc. (mg/dL)	18.2 (9.0–39.2)	33.3 (4.7–71.9)	17.5 (10.5–31.7)
Coma	5 (10%)	3 (30%)	2 (5.3%)
Co-ingestions	40 (83.3%)	6 (60%)	34 (89.5%)
Opiate	6 (12.5%)	0 (0%)	6 (15.8%)
Benzodiazepine/barbiturate	7 (14.6%)	1 (10%)	6 (15.8%)
Acetaminophen	16 (33.3%)	3 (30%)	13 (34.2%)
Ethanol	18 (37.5%)	2 (20%)	16 (42.1%)
Other	29 (60.4%)	4 (40%)	25 (65.8%)
Presentation <4 hours post-ingestion *	19 (51.3%) *	2 (33.3%) *	14 (36.8%) *
Intubated	2 (4.2%)	2 (20%)	0 (0%)
Sodium Bicarbonate given	16 (33.3%)	4 (40%)	12 (31.6%)
Activated Charcoal	26 (54.2%)	5 (50%)	21 (55.3%)
Hemodialysis	2 (4.2%)	2 (20%)	0 (0%)
Admitted	31 (64.6%)	9 (90%)	22 (57.9%)

Age, respiratory rate, creatinine, anion gap, glucose, lactate, serum pH, serum bicarbonate and initial salicylate serum concentration are reported as median (interquartile range). The remainder of data, including age subgroups, are reported as n (%).

* A significant amount of time from ingestion to presentation data was not available for analysis. For this reason, percentages listed for time to presentation data are based on an n with available data for each group (total n=37, severe outcome n=6, no severe outcome n=31).

Table 2

Univariate Analysis: Predictors of Severe Outcome

Predictor	Severe Outcome	No Severe Outcome	P-Value
Age	45.6 (22.8)	33.2 (13.6)	0.04
Respiratory Rate (breaths/min)	22.4 (7.0)	19.2 (3.2)	0.04
Creatinine (mg/dL)	1.4 (0.8)	1.0 (0.4)	0.36
Lactate (mmol/L)	5.1 (4.5)	2.1 (1.1)	0.002
Coma	7.7 (1.1–55)	reference	0.05
Co-ingestions	0.2 (0.1–0.9)	reference	0.04
Anion Gap (mEq/L)	13.5 (5.9)	11.8 (5.7)	0.40
Initial Salicylate Serum Conc. (mg/dL)	41.6 (42.3)	24.6 (20.0)	0.07
Male Gender	1.4 (0.3–5.5)	reference	0.60
Suicidality	0.6 (0.14–2.6)	reference	0.70

Age, respiratory rate, creatinine, lactate, anion gap and initial salicylate serum concentration were analyzed with t-test and are reported as mean (standard deviation). Coma, co-ingestions, male gender and suicidality were analyzed with chi-square and are reported as odds ratio (95% confidence interval).

Table 3

Multivariate Analysis: Predictors of Severe Outcome

Clinical Predictor	Adjusted Odds Ratio	95% Confidence Interval
Age	1.13	1.02–1.26
Respiratory Rate	1.29	1.02–1.63
Lactate	2.00	0.70–5.61
Coma	0.32	0.00–92.32
Co-ingestions	5.43	0.05–583.41
ASA	1.04	0.96–1.13

Significant predictors in **bold**.