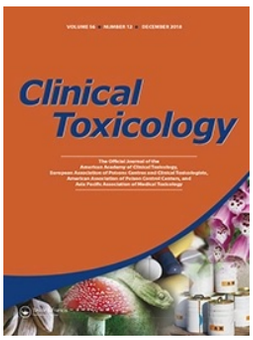

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CLINICAL RESEARCH

Coagulopathy and bleeding associated with salicylate toxicity

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ABSTRACT

Introduction: Salicylate toxicity is a common cause of morbidity and hospitalization. Animal and human studies suggest that salicylates cause a dose-dependent inhibition of the activation of factors 2, 7, 9, and 10. However, limited reports of coagulopathy or major bleeding from salicylate toxicity exist.

Methods: This is a retrospective study examining subjects from January 1, 2001 to December 31, 2011 in whom at least one serum salicylate concentration was measured above 30 mg/dL. Cases were patients with elevated salicylate concentration and coagulopathy (INR > 1.5). Major bleeding cases were those with elevated salicylate concentration who developed hemorrhagic death; or bleeding from an intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intramuscular site; or hemoglobin decrease of >2 g/dL, or transfusion of at least 2 units of packed RBCs during hospitalization.

Results: Twelve percent of all cases of elevated salicylate concentration developed coagulopathy, 6% developed major bleeding, and 3% died. In a multivariate model, duration of elevated salicylate concentration and renal impairment were associated with coagulopathy and no variable was associated with major bleeding. Patients were more likely to develop major bleeding if they had coagulopathy, but not all cases of major bleeding had coagulopathy.

Discussion: Coagulopathy and major bleeding during salicylate toxicity has been underrecognized. Renal impairment and duration of salicylate elevation contribute to the risk of coagulopathy, but no factors predict major bleeding. Patients with coagulopathy have a high risk of bleeding but some bleeding occurs without coagulopathy, suggesting that other factors, such as platelet dysfunction, may play a role.

Conclusion: Coagulopathy and major bleeding develop in a clinically relevant percentage of cases of salicylate toxicity.

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Salicylate; blood coagulation disorders; hemorrhage; hematology

Introduction

Salicylate toxicity is a common cause of morbidity and hospitalization in the United States [1]. Both animal [2] and human studies [3] suggest that salicylates may produce coagulopathy via inhibition of the activation of factors 2, 7, 9, and 10 [4, 5]. However, there are limited reports in the medical literature of elevations of prothrombin time (PT)/international normalized ratio (INR) [6–11] or bleeding [12–16] in humans with salicylate toxicity.

We sought to describe the incidence and demographics of patients with salicylate toxicity who develop coagulopathy or major bleeding and to examine factors that may be associated with salicylate-associated coagulopathy and bleeding.

Methods

This is an 11-year, single-hospital, retrospective study. Charts from a single hospital were identified by selecting all cases from January 1, 2001 to December 31, 2011 in whom at least one serum salicylate concentration was measured above 30 mg/dL. A search of the electronic medical record system for this laboratory value was performed by institutional information technology as the mechanism for initial case finding. Charts were reviewed by two trained abstractors for inclusion criteria and data extracted by using an a priori established standardized data extraction form. Ten percent of charts were abstracted by both reviewers and inter-relator agreement calculated.

Inclusion criteria were patients with at least one single serum salicylate concentration that was >30 mg/dL. There were no exclusion criteria. This study was approved by the Institutional Review Board of the Oregon Health and Science University.

For this retrospective chart review, eligible charts were defined as patients with serum salicylate concentration >30 mg/dL. Cases were defined as those with salicylate associated coagulopathy, exhibiting an INR > 1.5 within 15 days of the elevated salicylate concentration. INR > 1.5 was chosen to delineate coagulopathy as 1.5 is the upper limit of normal

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for the hospital assay. A 15-day measurement window was used to ensure that even late coagulopathy would be captured given that factor 2 has a half-life of 2.5–3 days. Controls were defined as patients without coagulopathy, defined as an INR that was not above 1.5 within 15 days of the elevated salicylate concentration, including those without a documented INR. If an INR was not measured, it was assumed to be 1.0. Sensitivity analyses excluding cases with missing INR demonstrated more pronounced effect size but did not change the key predictors identified. Univariate comparisons were made using *t*-tests for continuous variables and chi-squared tests for categorical variables. Odds ratios were estimated with univariate logistic regression. Variables with a $p \leq .1$ on univariate analysis were included in the main effects multivariate model.

For the case-control analysis of bleeding risk, patients with both coagulopathy and major bleeding were considered to be cases. Major bleeding was defined as any of the following: hemorrhagic death; or bleeding from an intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intramuscular site; or hemoglobin decrease of >2 g/dL, or transfusion of at least 2 units of packed RBCs during hospitalization. Controls were defined as patients with coagulopathy but no major bleeding. Univariate analysis of clinical features in cases of major bleeding compared to controls without was performed. Variables with a *p*-value ≤.1 were included in a multivariate model.

Features recorded on the data collection instrument included demographic information, co-morbidities, co-ingestion, history of liver disease, maximum concentration of salicylate in serum, maximum duration of salicylate concentration >30 mg/dL, chronicity of toxicity (i.e., acute vs. chronic), mass of salicylate ingested, serum creatinine concentration, glomerular filtration rate(GFR), use of hemodialysis, use of urinary alkalinization, metabolic acidosis, alteration of mental status, seizure, maximum INR, duration of INR >1.5, therapy or co-ingestion with anti-coagulants, therapy with N-acetylcysteine, presence of disseminated intravascular coagulopathy (DIC), major bleeding, minor bleeding, PRBC transfused, FFP transfused, and vitamin K administration.

Results

A total of 105 patients with salicylate concentration >30 mg/dL were identified and were included in the study. Fifty-eight patients had an INR measured. No charts were excluded for incomplete information. Inter-relator reliability of reviewed charts was 100% for each of 10 variables.

Thirteen percent (14/105) of patients with salicylate toxicity developed coagulopathy, 6% (6/105) developed major bleeding, and 3% (3/103) died. Restricting to those with measured INR, 24% (14/58) developed coagulopathy. The majority of cases were acute ingestions of salicylate (83%), single substance ingestions (52%), and female (63%). The majority of patients were adolescents (45%) or adults (48%). Ages ranged from 2 years to 89 years with a mean of 29 years old. Maximum salicylate concentration ranged from 30.4 to 101.2 mg/dL with a mean of 53.6 mg/dL. Ten percent (11/105) of patients underwent hemodialysis.

Perioperative bleeding requiring transfusion

Of the 14 patients with coagulopathy, one was taking therapeutic Coumadin, had an elevated INR prior to overdose, and was eliminated from the primary analysis. No other case was taking anti-coagulants. Of the remaining 13 (12% of total), 8 (54%) were female, 8 (54%) were acute ingestions, and 8 (62%) were adults with ages ranging from 13 years to 73 years. Coagulopathic patients had INRs that ranged from 1.67 to 6.52 with a mean of 2.72 and a median of 2.02. There was no correlation between maximum salicylate concentration and INR. Of note, several patients with coagulopathy had relatively low concentrations of salicylate (Figure 1).

Of the 6 bleeding episodes, 3 were GI hemorrhage, 1 was intracranial hemorrhage, 1 developed a neck hematoma at a dialysis catheter site placed for treatment of salicylate toxicity, 4 received 2U of PRBCs, and 3 patients received ≥4 units of PRBCs (Table 1). Two of the 6 major bleeding events occurred in patients who did not have an INR > 1.5; one with a GI bleed and one with the neck hematoma. The 3 deaths were not related to hemorrhage and were attributed to autoimmune hepatitis, polydrug overdose, and trauma.

Univariate model of coagulopathy amongst patients with elevated salicylate concentration suggested that older age, longer duration of elevated serum salicylate concentration, renal impairment, pre-existing liver disease, and administration of N-acetylcysteine were associated with coagulopathy. In the multivariate model, only duration of elevated salicylate concentration and renal impairment were associated with an increased odds of coagulopathy (Table 2).

Univariate analysis of major bleeding amongst patients with elevated salicylate concentration and elevated INR, the degree of renal dysfunction and coagulopathy were significantly associated with major bleeding ($p < .05$). In a multivariate analysis, no individual variable remained significant .

Patients who developed coagulopathy were significantly more likely to suffer major bleeding (28.6% vs. 4.7%; OR 8.2 [95%CI 1.3–52.3], $p = .01$).

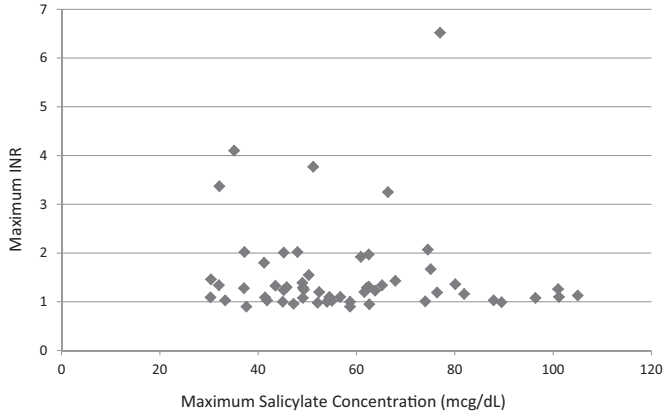

Figure 1. Comparison of maximum salicylate concentration with maximum INR during hospitalization.

Table 1. Cases of major bleeding.

Major bleeding episode	Outcome	Max INR	Max [ASA] (mg/dL)	
Epistaxis with 4U PRBC infusion	Survived ICU LOS 6 days, hospital LOS 13 days	1.97	63	29 years old M Acute overdose Bicarb & HD
GI bleed	Survived ICU LOS 2 days, hospital LOS 9 days	2.02	48	73 years old F Chronic toxicity Bicarb & HD
GI bleed	Survived ICU LOS 2 days, hospital LOS 2 days	1.1	57	38 years old M Acute ingestion Upper GI bleeding with Hgb drop > 2 mg/dL
Intracranial hemorrhage, 12U PRBC	Died	2.01	45.2	19 years old F Trauma Acute overdose
Neck hematoma	Survived ICU LOS 2 days, hospital LOS 4 days	1.13	105	20 years old M Acute overdose Bicarb & HD
Perioperative bleeding requiring transfusion	Survived ICU LOS 12 days, hospital LOS 35 days	3.37	32.1	73 years old M Chronic toxicity taking ASA for back pain found to have epidural abscess

Table 2. Predictors of coagulopathy in patients with elevated salicylate concentrations.

Analysis	Patient variable	Odds ratio (OR)	95% CI (OR)	*p*-Value
Univariate	Age	1.04	1.01, 1.07	.018
	Duration ASA >30	1.13	1.04, 1.24	.006
	Chronic toxicity	3.61	1.02, 12.75	.047
	Min GFR	0.97	0.95, 0.99	.005
	GFR <60	6.08	1.85, 19.97	.003
	Received NAC	4.69	1.16, 18.87	.030
	Preexisting Liver Disease	11.86	1.78, 79.00	.011
Multivariate	Duration ASA >30 (h)	1.12	1.02, 1.24	.022
	GFR <60	5.333	1.34, 21.23	.017

Discussion

Coagulopathy and major bleeding have rarely been reported to be associated with salicylate toxicity [3, 6–10, 12–16]. In this study, 12% of all cases of patients with elevated salicylate concentrations had an elevated INR (>1.5), suggesting that this phenomenon has been under recognized.

Salicylate has been shown in vitro to inhibit the activation of coagulation factors 2, 7, 9, and 10 [4, 5] and to produce a prolongation of the prothrombin time with salicylate concentrations between 30 and 50 mg/dL [3]. This effect is reversible in humans with treatment with vitamin K [3]. While this has been demonstrated in vitro [4, 5] and in case series of therapeutic use [3, 6–10, 12–16], few clinical cases of salicylate toxicity have been reported with clinically relevant coagulopathy or significant bleeding. Comprehensive reviews of salicylate toxicity have not noted coagulopathy or bleeding as clinical factors of concern [1, 17].

We found a clinically relevant incidence of coagulopathy (12%) and major bleeding (6%) in our cohort. In addition, we found that the only risk factors for developing coagulopathy included renal impairment and increased duration of salicylate concentration elevation. Notably, chronicity of toxicity (acute versus chronic), maximum salicylate concentration, altered mental status, acidosis, use of hemodialysis, and ingested mass of salicylate did not predict coagulopathy. This suggests that there is a subset of salicylate toxicity where renal impairment either develops prior to, or as a result of, elevated salicylate concentrations. Patients with impaired renal function may be at higher risk of coagulopathy and bleeding, potentially due to prolonged exposure of the liver to elevated salicylate concentrations having a proportionally greater impact on Vitamin K dependent coagulation factors.

Bleeding occurred more frequently in patients with coagulopathy. However, bleeding also occurred in a small percentage of patients with elevated salicylate concentrations who did not have an INR > 1.5, suggesting that other causes of hemorrhage, including platelet dysfunction during salicylate toxicity should be further studied.

This study is limited by several factors. The study was retrospective and is not able to definitely determine causation of coagulopathy and bleeding episodes. Since the study was retrospective, it was not possible to control for time of laboratory testing. It is possible that higher, or lower, serum concentrations or INR values were missed due to the timing of blood draws. For example, we were not able to determine that the max INR was correlated chronologically with the maximum salicylate concentration or bleeding episode.

Conclusion

Coagulopathy and major bleeding occur in a notable minority of patients with salicylate toxicity. In patients with salicylate toxicity, major bleeding occurs more commonly in patients with coagulopathy, but may also occur rarely in patients without coagulopathy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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