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CLINICAL RESEARCH



## Clinical and patient characteristics associated with severe outcome in diphenhydramine toxicity

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### ABSTRACT

**Background:** Diphenhydramine is frequently misused and ingested recreationally for its antihistaminergic and antimuscarinic effects and is often involved in both serious and fatal poisonings, either in isolation or in combination with other xenobiotics.

**Objective:** This analysis sought to determine which patient and encounter characteristics were associated with severe outcome after diphenhydramine overdose.

**Methods:** This is an analysis of the multi-center ToxIC registry (2010–2016). Descriptive analysis of all cases with diphenhydramine listed as the “primary agent” contributing to toxicity were included. Analysis sought to determine which patient and encounter characteristics were associated with severe outcome, defined as occurrence of seizure, ventricular dysrhythmia, or intubation. To determine which patient and encounter characteristics were individually associated with severe outcome, we performed chi-square tests. Fisher’s exact tests were used in the case of sparse data. We also performed multivariable logistic regression to further determine independent risk factors for severe outcome in diphenhydramine overdose.

**Results:** Eight hundred and sixty-three cases remained after exclusion with 15.6% ( $n=135$ ) of all patients having one or more severe outcome. The most common severe outcome was seizures which occurred in 98 (11.6%) of all ingestions. Females comprised 59.1% ( $n=510$ ) of all ingestions. Most ingestions were intentional (86.0%,  $n=742$ ) with the most common known reason for an intentional ingestion being self-harm, accounting for 37.5% ( $n=324$ ) of all ingestions. Self-harm ingestions and ingestions in males were more commonly associated with intubation. When examining outcomes by age, there were no significant differences overall or in any individual outcome except intubation in which children 0–12 were less likely to be intubated as compared to teens and adults. Signs and symptoms most strongly associated with a severe outcome included acidemia ( $\text{pH} < 7.2$ ), QRS prolongation ( $\text{QRS} > 120 \text{ ms}$ ), and elevated anion gap ( $\text{AG} > 20$ ).

**Discussion:** Acidemia, QRS prolongation, and elevated anion gap are associated with severe outcomes in diphenhydramine toxicity. Further research is warranted to determine their predictive characteristics.

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### KEYWORDS

Diphenhydramine; severe toxicity; seizures; dysrhythmias; endotracheal intubation

### Introduction

Diphenhydramine, a first-generation H1 histamine receptor antagonist, is found in numerous over-the-counter (OTC) allergy, cough, and cold preparations. Given its ease of access and frequency of use, diphenhydramine poisoning remains a serious public health problem.

Diphenhydramine is among the most common substances involved in suicidal ingestions and one of the most common causes of central nervous system (CNS) depression, seizures, and conduction disturbances in the United States [1,2]. In 2018, more than 44,000 cases of isolated diphenhydramine overdoses were reported to US Poison Centers [1]. Numerous fatalities due to diphenhydramine toxicity have been reported [1,3–9] and it remains among the top drugs involved in drug overdose deaths [10].

Our current knowledge of diphenhydramine toxicity is based mostly on case reports, small case series, and

retrospective poison center data. It is unclear which clinical characteristics may be associated with severe toxicity. Early clinical predictors of the severity of diphenhydramine poisoning are needed to help identify patients who require early aggressive treatment and monitoring. The first step in identifying predictors is to identify clinical associations with severe outcomes so they may be further tested prospectively. In this analysis of the Toxicology Investigators Consortium (ToxIC) Registry, we aimed to determine which patient and clinical characteristics are associated with severe outcomes in patients presenting with acute diphenhydramine poisoning, so that a prospective study can be designed.

### Methods

This is a multicenter analysis of registry data from the American College of Medical Toxicology (ACMT) ToxIC

between 1 January 2010 and 31 December 2016. The ToxIC case registry is a database of poisoned patients who are managed by medical toxicologists at the bedside. Participation in the registry was approved by, and analysis of de-identified data was exempted by, the Institutional Review Board of the Oregon Health and Science University. During the study period, the ToxIC registry consisted of cases from over 40 sites throughout the United States and internationally. Participating sites prospectively enter de-identified clinical and diagnostic data on all patients using a standardized online data collection form. Cases are included in the registry if a bedside consultation was performed by a participating medical toxicologist. The data collection form consists of demographics, substance exposure, reason for exposure, source of consultation, reason for consultation, clinical presentation, laboratory findings, medical complications, treatments, and disposition.

The following were established by the ToxIC registry: tachycardia (heart rate > 140 beats per minute); acidemia (pH < 7.2); QRS prolongation (QRS > 120 ms); QT prolongation (QT > 500 ms); acute kidney injury (AKI) (Cr > 2 mg/dL); hyperthermia ( $T > 105$  F). However, clinical signs and symptoms, such as agitation or hallucinations, are determined by physical examination findings and interpretation of these findings by the consulting medical toxicologist.

The medical toxicologists also determine the substance that has caused the patient's toxicity and enter this information into the "agent" section. Cases were included if they listed diphenhydramine as the "primary agent". "Primary agents" are those substance(s) believed to be primarily responsible for the patient's symptoms. Cases were excluded if they listed any agents other than diphenhydramine as a "primary agent". "Secondary agents" are not considered to be the most likely etiologic agent(s) responsible for the patient's symptoms as determined by the medical toxicology team managing the patient. As such, cases were included for analysis if "secondary agents" were listed. Data were provided by ToxIC in a standardized spreadsheet format and were organized by a single-study investigator.

Based on prior literature, we defined severe outcome as the occurrence of any of the following: (A) seizure, (B) ventricular dysrhythmia, or (C) intubation [11–18]. This analysis sought to determine which patient demographic and clinical characteristics were associated with a severe outcome so that these factors may be used in a prospective study. To determine which patient and encounter characteristics were individually associated with severe outcomes – both overall and within each severe outcome – we performed chi-square tests. Fisher's exact tests were used in the case of sparse data. Patient and encounter characteristics included demographics, reason for exposure, source of consultation, location of encounter, clinical characteristics, and specific interventions. We further examined which signs and symptoms were associated with a severe clinical outcome. We also evaluated cases with a recorded ingested dose to determine if dose was associated with a severe outcome. Cases with an exact ingested dose (in mg or g) were included. Those cases reporting only dose ranges (e.g., 100–400 mg),

weight-based dose (e.g., mg/kg), or pill count (e.g., 20 tablets) were excluded. We used two-sample tests for proportions to test for specific differences in proportions, and to assess the strength of relationship between signs and symptoms with any severe outcome, we calculated odds ratios.

We performed multivariable logistic regression to further determine independent risk factors for severe outcome in diphenhydramine overdose. Factors included in the model were the following: intentionality, age, sex, and additional clinical factors that achieved highest univariate significance. All statistical analyses were performed in Stata 15 (College Station, TX). All tests were two-sided with an alpha of 0.05.

## Results

We identified 2464 cases with diphenhydramine listed as the "primary agent" during the seven-year study period. 1601 were excluded because multiple "primary agents" were listed, leaving 863 isolated cases of diphenhydramine ingestion. Females comprised 59.1% ( $n = 510$ ) of all cases and 51.3% ( $n = 443$ ) involved children under 18 years old. Most ingestions were intentional (86.0%,  $n = 742$ ) with the most common known reason for an intentional ingestion being self-harm, accounting for 37.5% ( $n = 324$ ) of all ingestions, followed by intentional ingestions with reasons unknown (37.0%,  $n = 319$ ), abuse/misuse (11.5%,  $n = 99$ ), and unintentional ingestion (11.1%,  $n = 96$ ).

The most common presenting signs and symptoms were delirium/toxic psychosis (40.1%,  $n = 346$ ) and agitation (33.1%,  $n = 286$ ). Of the 863 cases, 135 (15.6%) had one or more severe outcome and three (0.2%) died. The most common severe outcome was seizure, which occurred in 98 or 11.6% of all cases. All patients who died had one or more severe outcome prior to death. Baseline clinical characteristics of subjects who were included are summarized in Table 1.

### Bivariate analysis

The following characteristics were associated with severe outcome in bivariate analysis: male gender, prolongation of QRS ( $\geq 120$  ms) or QT ( $\geq 500$  ms), tachycardia ( $p > 140$  bpm), coma/CNS depression, extrapyramidal symptoms/dystonia/rigidity, elevated anion gap (AG > 20), acidemia (pH < 7.2), AKI (Creat > 2.0), rhabdomyolysis (CPK > 1000), and hyperthermia ( $T > 105$  °F) (Table 1). Seizures were associated with tachycardia, prolongation of QRS and QT, coma/CNS depression, elevated anion gap, acidemia, and rhabdomyolysis (Table 1). Ventricular dysrhythmias were associated with prolongation of QRS and QT, coma/CNS depression, elevated anion gap, acidemia, and rhabdomyolysis (Table 1). Intubation was associated with self-harm ingestions, age > 12 years, and ingestions in males (Table 1).

The signs and symptoms most strongly associated with severe outcome were acidemia, prolonged QRS, hyperthermia, elevated anion gap, and AKI. Unadjusted analyses found that patients with acidemia had 35.4 (95% CI: 7.8–160.2,  $p < .01$ ) times the odds of having a severe outcome as

**Table 1.** Clinical characteristics of patients in the study.

	Overall n=# of patients, (%)	Severe clinical outcome	p Value	Seizures, n (%)	p Value	Ventricular dysrhythmias, n (%)	p Value	Intubation, n (%)	p Value
Total # of patients (%)	863 (100%)	135 (15.64%)	NA	98 (11.6%)	NA	10 (1.2%)	NA	66 (7.6%)	NA
Age groups <sup>a</sup>									
Children (age 0–12 years)	109 (12.63%)	10 (9.17%)	.07	9 (8.25%)	.06	1 (0.91%)	.52	0 (0.00%)	<b>&lt;.01</b>
Adolescents (age 13–18)	334 (38.70%)	61 (18.26%)		49 (14.67%)		2 (0.59%)		26 (7.78%)	
Adults (age 19–89)	412 (47.74%)	63 (15.295%)		40 (9.71%)		6 (1.46%)		40 (9.71%)	
Sex									
Female	510 (59.1%)	69 (13.52%)	<b>.04</b>	54 (10.58%)	.39	8 (1.56%)	.18	27 (5.29%)	<b>.02</b>
Male	353 (40.9%)	66 (18.69%)		44 (12.46%)		2 (0.56%)		39 (11.04%)	
Primary reason for encounter <sup>a</sup>									
Self harm	324 (37.54%)	59 (18.21%)	.05	38 (11.73%)	.29	5 (1.54%)	.46	38 (11.73%)	<b>&lt;.01</b>
Abuse	99 (11.47%)	12 (12.12%)		9 (9.09%)		1 (1.01%)		4 (4.04%)	
Unintentional	96 (11.12%)	7 (7.29%)		6 (6.25%)		1 (1.04%)		0 (0%)	
Intentional-reason unknown	319 (36.96%)	52 (16.3%)		41 (12.85%)		1 (0.31%)		23 (7.21%)	
Source of referral									
ED	570 (66.05%)	74 (12.98%)	<b>&lt;.01</b>	55 (9.65%)	<b>.03</b>	5 (0.88%)	.28	34 (5.96%)	<b>&lt;.01</b>
Admitting service	167 (19.35%)	38 (22.75%)	<b>&lt;.01</b>	26 (15.56%)	.06	4 (2.39%)	.10	21 (12.57%)	<b>&lt;.01</b>
Critical care/ICU	2 (0.23%)	0 (0.00%)	1.00	0 (0.00%)	1.00	0 (0.00%)	1.00	0 (0.00%)	1.00
Outside hospital transfer	113 (13.09%)	22 (19.46%)	.23	17 (15.04%)	.19	1 (0.88%)	.77	10 (8.84%)	.61
Poison center	12 (1.39%)	4 (33.33%)	.10	3 (25.00%)	.15	0 (0.00%)	1.00	1 (8.33%)	1.00
Request from another hospital service (not ED)	50 (5.79%)	9 (18.00%)	.64	5 (10.00%)	.76	0 (0.00%)	.43	4 (8.00%)	.92
Other	8 (0.93%)	1 (12.50%)	1.00	1 (12.50%)	1.00	0 (0.00%)	1.00	0 (0.00%)	1.00
Nature of tox encounter									
Consult (ED or inpatient)	660 (76.47%)	105 (15.90%)	.69	74 (11.21%)	.89	9 (1.36%)	.58	54 (8.18%)	.31
Attending (inpatient)	181 (20.97%)	28 (15.46%)		22 (12.15%)		1 (0.55%)		12 (6.62%)	
Other, unknown, or not recorded	22 (2.54%)	2 (9.09%)		2 (9.09%)		0 (0.00%)		0 (0.00%)	
Location of encounter									
Obs unit	10 (1.16%)	0 (0%)	.17	0 (0%)	.26	0 (0%)	.73	0 (0%)	.36
ED	321 (37.2%)	39 (12.15%)	<b>.03</b>	29 (9.03%)	.1	4 (1.25%)	.85	18 (5.61%)	.08
Hospital floor	180 (20.86%)	17 (9.44%)	<b>.01</b>	13 (7.22%)	.05	2 (1.11%)	.95	5 (2.78%)	<b>&lt;.01</b>
ICU	255 (29.55%)	76 (29.8%)	<b>&lt;.01</b>	52 (20.39%)	<b>&lt;.01</b>	7 (2.75%)	<b>&lt;.01</b>	45 (17.65%)	<b>&lt;.01</b>
Signs/symptoms									
Tachycardia (HR > 140)	258 (29.9%)	62 (45.93%)	<b>&lt;.01</b>	47 (47.96%)	<b>&lt;.01</b>	5 (50%)	.16	30 (45.45%)	<b>&lt;.01</b>
Prolonged QTc (>500 ms)	60 (7%)	19 (4.07%)	<b>&lt;.01</b>	13 (13.27%)	<b>.01</b>	4 (40%)	<b>&lt;.01</b>	12 (18.18%)	<b>&lt;.01</b>
Prolonged QRS (>120 ms)	19 (2.2%)	12 (8.89%)	<b>&lt;.01</b>	7 (7.14%)	<b>&lt;.01</b>	4 (40%)	<b>&lt;.01</b>	10 (15.15%)	<b>&lt;.01</b>
Agitation	286 (33.1%)	41 (30.37%)	.46	29 (29.59%)	.43	3 (30%)	1.00	16 (24.24%)	.11
Coma/CNS depression	151 (17.5%)	53 (39.26%)	<b>&lt;.01</b>	28 (28.57%)	<b>&lt;.01</b>	5 (50%)	<b>&lt;.01</b>	41 (62.12%)	<b>&lt;.01</b>
Delirium/toxic psychosis	346 (40.1%)	52 (38.52%)	.68	35 (35.71%)	.35	3 (30%)	.75	24 (36.36%)	.52
EPS/dystonia/rigidity	9 (1%)	4 (2.96%)	<b>.04</b>	2 (2.04%)	.27	0 (0%)	1.00	2 (3.03%)	.15
Hallucinations	179 (21%)	24 (17.78%)	.36	19 (19.39%)	.73	1 (10%)	.70	5 (7.58%)	<b>&lt;.01</b>
Hyperreflexia/myoclonus/clonus/tremor	40 (4.6%)	11 (8.15%)	.04	8 (8.16%)	.08	1 (10%)	.42	4 (6.06%)	.57
Acidemia (pH < 7.2)	14 (1.6%)	12 (8.89%)	<b>&lt;.01</b>	10 (10.2%)	<b>&lt;.01</b>	2 (20%)	<b>&lt;.01</b>	7 (10.61%)	<b>&lt;.01</b>
Elevated anion gap (AG > 20)	14 (1.6%)	8 (5.93%)	<b>&lt;.01</b>	6 (6.12%)	<b>&lt;.01</b>	1 (10%)	<b>.04</b>	6 (9.09%)	<b>&lt;.01</b>
Acute kidney injury (Creat > 2.0)	8 (0.9%)	4 (2.96%)	<b>.02</b>	3 (3.06%)	.05	0 (0%)	1.00	2 (3.03%)	.12
Rhabdomyolysis (CPK > 1000)	36 (4.2%)	13 (9.63%)	<b>&lt;.01</b>	9 (9.18%)	<b>&lt;.01</b>	3 (30%)	<b>&lt;.01</b>	11 (16.67%)	<b>&lt;.01</b>
Hyperthermia (Temp > 105°)	5 (0.6%)	3 (2.22%)	<b>.03</b>	1 (1.02%)	.45	0 (0%)	1.00	3 (4.55%)	<b>&lt;.01</b>
Death	3 (0.2%)	3 (2.22%)	<b>&lt;.01</b>	2 (2.04%)	<b>.04</b>	2 (20%)	<b>&lt;.01</b>	2 (3.03%)	<b>.02</b>
Specific interventions									
Lipid resuscitation therapy	4 (0.7%)	4 (2.96%)	<b>&lt;.01</b>	4 (4.08%)	<b>&lt;.01</b>	3 (30%)	<b>&lt;.01</b>	2 (3.03%)	<b>.03</b>
Physostigmine	171 (19.8%)	22 (16.3%)	.26	16 (16.33%)	.36	0 (0%)	.11	7 (10.61%)	.05
Sodium bicarbonate	37 (4.3%)	24 (17.78%)	<b>&lt;.01</b>	18 (18.37%)	<b>&lt;.01</b>	6 (60%)	<b>&lt;.01</b>	16 (24.24%)	<b>&lt;.01</b>
Antipsychotics	15 (1.72%)	0 (0%)	.09	0 (0%)	.16	0 (0%)	.67	0 (0%)	.26
Benzodiazepines	377 (43.6%)	91 (67.41%)	<b>&lt;.01</b>	66 (67.35%)	<b>&lt;.01</b>	7 (70%)	.11	49 (74.24%)	<b>&lt;.01</b>
Vasopressors	7 (0.8%)	7 (5.19%)	<b>&lt;.01</b>	6 (6.12%)	<b>&lt;.01</b>	3 (30%)	<b>&lt;.01</b>	5 (7.58%)	<b>&lt;.01</b>
Activated charcoal	55 (6.4%)	13 (9.63%)	.09	11 (11.22%)	<b>.04</b>	1 (10%)	.64	9 (13.64%)	<b>.01</b>
ECMO	0 (0%)	0 (0%)	NA	0 (0%)	NA	0 (0%)	NA	0 (0%)	NA
IV fluid resuscitation	248 (28.7%)	69 (51.11%)	<b>&lt;.01</b>	47 (47.96%)	<b>&lt;.01</b>	6 (60%)	<b>.03</b>	44 (66.67%)	<b>&lt;.01</b>
Hemodialysis	0 (0%)	0 (0%)	NA	0 (0%)	NA	0 (0%)	NA	0 (0%)	NA

Italicized bold values indicate statistically significant comparisons. *p* Values generated from chi-square tests or Fisher's exact test for sparse data (source of referral critical care/ICU, poison center, QRS, EPS/dystonia/rigidity, acute kidney injury, hyperthermia, death, lipid resuscitation, vasopressors).

<sup>a</sup>Age unknown for eight ingestions; reason for encounter unknown for 25 ingestions.

compared to patients without acidemia, and patients with prolonged QRS had 10.0 (95% CI: 3.9–26.0,  $p < .01$ ) times the odds of having a severe outcome as compared to patients without prolonged QRS.

We found gender differences by age group, reason for encounter, tachycardia, prolonged QT, acidemia, AKI, and rhabdomyolysis (Table 2). Tachycardia and prolonged QT

were more common in females, while acidemia, AKI, and rhabdomyolysis were more common in males. There was a significant difference in the proportion of self-harm ingestions by gender, with 45.9% of ingestions in females being self-harm compared to 25.5% of ingestions in males ( $p < .01$ ). Furthermore, there was a significantly larger proportion of males who were children (0–12 years of age,  $p < .01$ ) and a

**Table 2.** Sex differences in patient and ingestion characteristics.

	Overall n=# of patients (%)	Female	Male	p Value
	863 (100%)	510 (59.1%)	353 (40.9%)	NA
Age groups <sup>a</sup>				
Children (age 0–12 years)	109 (12.63%)	50 (9.8%)	59 (16.71%)	<b>&lt;.01</b>
Adolescents (age 13–18)	334 (38.7%)	221 (43.33%)	113 (32.01%)	
Adults (age 19–89)	412 (47.74%)	234 (45.88%)	178 (50.42%)	
Primary reason for encounter <sup>a</sup>				
Self harm	324 (37.54%)	234 (45.88%)	90 (25.5%)	<b>&lt;.01</b>
Abuse	99 (11.47%)	40 (7.84%)	59 (16.71%)	
Unintentional	96 (11.12%)	36 (7.06%)	60 (17%)	
Intentional-reason unknown	319 (36.96%)	186 (36.47%)	133 (37.68%)	
Signs/symptoms				
Tachycardia (HR > 140)	258 (29.9%)	169 (33.14%)	89 (25.21%)	<b>.01</b>
Prolonged QTc (>500 ms)	60 (6.95%)	44 (8.63%)	16 (4.53%)	<b>.02</b>
Prolonged QRS (>120 ms)	19 (2.2%)	10 (1.96%)	9 (2.55%)	.64
Agitation	286 (33.14%)	163 (31.96%)	123 (34.84%)	.38
Coma/CNS depression	151 (17.5%)	87 (17.06%)	64 (18.13%)	.68
Delirium/toxic psychosis	346 (40.09%)	193 (37.84%)	153 (43.34%)	.11
EPS/dystonia/rigidity	9 (1.04%)	4 (0.78%)	5 (1.42%)	.50
Hallucinations	179 (20.74%)	107 (20.98%)	72 (20.4%)	.84
Hyperreflexia/myoclonus/clonus/tremor	40 (4.63%)	24 (4.71%)	16 (4.53%)	.91
Acidemia (pH < 7.2)	14 (1.62%)	3 (0.59%)	11 (3.12%)	<b>&lt;.01</b>
Elevated anion gap (AG > 20)	14 (1.62%)	6 (1.18%)	8 (2.27%)	.21
Acute kidney injury (Creat > 2.0)	8 (0.93%)	0 (0%)	8 (2.27%)	<b>&lt;.01</b>
Rhabdomyolysis (CPK > 1000)	36 (4.17%)	13 (2.55%)	23 (6.52%)	<b>&lt;.01</b>
Hyperthermia (Temp > 105°)	5 (0.58%)	1 (0.2%)	4 (1.13%)	.08
Death	3 (0.35%)	1 (0.2%)	2 (0.57%)	.57

p Value generated from chi-square tests except in the case of sparse data (QRS, EPS/dystonia/rigidity, acute kidney injury, hyperthermia, death). Italicized bold values indicate statistically significant comparisons.

<sup>a</sup>Age unknown for eight ingestions; reason for encounter unknown for 25 ingestions.

**Table 3.** Multivariate analysis: factors associated with a severe outcome.

	Odds of a severe clinical outcome (95% CI)	p Value
Age groups		
Children (age 0–12 years)	1.06 (0.44–2.55)	.23
Adolescents (age 13–18)	<b>1.54 (1.01–2.34)</b>	
Adults (age 19–89)	Referent	
Age unknown	0.68 (0.07–6.59)	
Sex		
Female	Referent	.07
Male	1.47 (0.97–2.21)	
Primary reason for encounter		
Self harm	Referent	.46
Abuse	0.63 (0.31–1.30)	
Unintentional	0.45 (0.16–1.28)	
Intentional-reason unknown	0.97 (0.62–1.52)	
Unknown	0.99 (0.30–3.22)	
Signs and symptoms		
Acidemia	<b>14.66 (2.74–78.36)</b>	<b>&lt;.01</b>
Prolonged QRS	<b>7.48 (2.58–21.69)</b>	<b>&lt;.01</b>
Hyperthermia	2.08 (0.12–36.59)	.62
Elevated anion gap	<b>5.75 (1.71–19.37)</b>	<b>.01</b>
Acute kidney injury	2.20 (0.35–13.92)	.40

Italicized bold values indicate statistically significant comparisons.

larger proportion of females who were teenagers (13–18 years of age,  $p < .01$ ). There was not a significant difference in the proportion of ingestions in adults by gender ( $p = .19$ ).

Ninety-three cases had a recorded ingested dose. Of these, 32 were excluded because the ingested dose was listed either as a dose range, pill count, or weight-based dose. Of the remaining 61 cases with a documented ingested dose (in mg or g), 50 had no severe outcome and 11 had one or more severe outcome. The median dose (IQR) for patients with severe outcome was 2.5 g (1.7–3.6 g,  $n = 11$ ) compared to 0.5 g (0.2–1.5 g,  $n = 50$ ) for those with no

severe outcome (Wilcoxon two-sample test (Mann–Whitney,  $p = .005$ )).

The mainstay of therapy for diphenhydramine overdose consisted of benzodiazepines (43.6%,  $n = 377$ ), intravenous (IV) fluid resuscitation (28.7%,  $n = 248$ ), and physostigmine (19.8%,  $n = 171$ ). The following medical interventions were associated with severe clinical outcome in bivariate analysis: lipid resuscitation therapy, sodium bicarbonate, benzodiazepines, vasopressors, and IV fluid resuscitation. The use of physostigmine and antipsychotics were not associated with a severe outcome. Lipid resuscitation therapy (0.7%,  $n = 4$ ) and vasopressor use (0.8%,  $n = 7$ ) were infrequently reported as treatments. Of the 98 seizure cases, 66 (67.35%) received benzodiazepines. The use of activated charcoal, though not associated with severe outcomes overall, was associated with both seizures and intubation alone.

### Multivariable analyses

Multivariable logistic regression was performed to further elucidate independent risk factors for severe outcomes (Table 3). Factors included into the final model were the following: age, sex, intentionality, and those factors with highest univariate significance (acidemia, prolonged QRS, elevated anion gap, and AKI). When the model was adjusted with the above factors, acidemia, prolonged QRS, and elevated anion gap remained statistically significant. Although males and adolescents had higher odds of a severe clinical outcome, these were not statistically significant. Additionally, we found no significant difference in odds of a severe outcome when comparing primary reason for ingestion (e.g., self-harm, abuse, unintentional, etc.).

## Discussion

Predicting which patients with suspected diphenhydramine overdose will go on to have severe outcomes remains difficult. In this study, we evaluated the demographic and clinical characteristics of diphenhydramine mono-intoxications reported to the ToxIC registry and derived factors that are associated with a severe outcome. Further studies will have to evaluate if these factors may be used to predict severe toxicity.

Routine emergency department (ED) evaluation of patients with a suspected drug overdose typically includes a basic metabolic panel and electrocardiogram (ECG). This information, along with clinical factors, assists providers in determining appropriate disposition and level of monitoring for a patient. In this study, the factors most strongly associated with severe outcome in diphenhydramine overdose, when controlling for age, sex, and intentionality, were acidemia, QRS widening, and elevated anion gap. Hyperthermia and AKI were found to be associated, but not when controlling for age, sex, and intentionality.

The most common severe outcome in our study was seizure, accounting for 72.5% of severe outcomes. Data from a retrospective review of cases reported to the California Poison Centers reported that 8% of drug-induced seizures were due to diphenhydramine [19]. In children (<12 years old), we found similar rates of seizures compared to a recent study evaluating adverse events in children after exposure to diphenhydramine-only products (8.3% vs. 5.5%) [20]. The slightly higher seizure rate in children in our study may represent a higher acuity group of patients who received a bedside consultation from a medical toxicologist.

Epileptogenic activity of diphenhydramine is thought to be related to central histaminergic inhibition [21]. Drug-induced seizures can result in anoxic brain injury, acidosis, hyperthermia, and aspiration pneumonitis, with almost 2% mortality [19,22]. In the current study, acidemia was the factor most strongly associated with all severe outcomes in diphenhydramine overdose, including seizures. The association between acidemia and neuronal injury has been well established [23]. Neuronal injury may be exaggerated by acidemia, which facilitates free radical formation and intracellular calcium dysregulation [24]. A prospective poison center study found initial acidemia to be an independent clinical predictor of complications from drug-induced seizures, including endotracheal intubation, status epilepticus, anoxic brain injury, prolonged hospitalization, and death [19]. Due to study design, we were unable to determine whether acidemia was the primary seizure trigger or merely a manifestation of tonic-clonic muscle activity with secondary hypoxia. However, acidemia may reflect seizure duration or severity and these patients should be considered high risk for further clinical decompensation, necessitating aggressive monitoring and treatment.

In this study, the most commonly reported clinical features were those of CNS dysfunction, manifesting as delirium, agitation, hallucinations, and coma/CNS depression. These clinical findings are consistent with prior reports in the literature [13,14,20,25–27]. Though both symptoms of CNS

excitation and depression were commonly reported, only those of CNS depression were significantly associated with severe outcome. Here, coma/CNS depression may simply be a measure of dose-dependent diphenhydramine pathophysiology. In a large case series of diphenhydramine mono-intoxications, severe symptoms, including coma, seizures, and dysrhythmias, significantly increased in frequency with ingestions over 1.0–1.5 g in adults or 15–20 mg/kg in children [27]. Our data further confirm these results and those of prior studies regarding an association between reported ingested diphenhydramine dose and severity of poisoning [27–29]. Additionally, progressive obtundation and other CNS abnormalities frequently occur with acidemia [30]. Those with coma often have a blunted respiratory drive, which further impairs acid–base homeostasis. In severe cases, endotracheal intubation and mechanical ventilation may be indicated to ensure airway patency and adequate ventilation.

Endotracheal intubation was the second most common severe outcome reported in this study. Anticholinergic medications represent 2.6% of exposures managed with intubation in the ToxIC registry [31] and 1.1% of intubations in adolescents (ages 13–19) in the national poison center database [32]. We found that both teenagers and adults were more likely to be managed with intubation than children. In fact, no children <12 years of age in this series required endotracheal intubation. Similarly, the incidence of intubation (1.9%) and mechanical ventilation (1.6%) was low in a recent study of diphenhydramine exposures in children <12 years of age [20]. These findings may be largely explained by differences in ingested dose and type of exposure (e.g., intentional vs. accidental) as diphenhydramine exposures in children more frequently occur as a result of accidental unsupervised ingestions [20]. In the present series, self-harm ingestions and ingestions in males were also more commonly associated with intubation. Other findings associated with severe outcome, including acidemia, AKI, and rhabdomyolysis, occurred more frequently in males. These data suggest that in addition to airway management, male patients with diphenhydramine poisoning may require more aggressive supportive care and pharmacologic support.

The use of activated charcoal, though not associated with severe outcomes overall, was individually associated with both seizures and intubation. Similarly, a review of cases managed with endotracheal intubation in the ToxIC Registry from 2010 through 2014, found that decontamination and elimination processes, including the use of activated charcoal, was used more frequently in this sub-group when compared to overall use in both 2013 (4.5%) and 2014 (4.3%) in the ToxIC registry [31]. Authors hypothesize that use of activated charcoal and other decontamination and elimination procedures may have been used more liberally in those patients requiring intubation since their airway was protected with an endotracheal tube. Unfortunately, it cannot be concluded from our data whether activated charcoal was administered before or after endotracheal intubation.

The current study demonstrated that ventricular dysrhythmia was the third most common severe outcome in diphenhydramine poisoning. In a 10-year retrospective analysis of

drug exposures associated with ventricular dysrhythmias, 12.1% were associated with diphenhydramine [33]. Diphenhydramine inhibits fast sodium channels and delayed rectifier potassium channels in the heart, which may cause cardiac conduction abnormalities, including QRS widening and QT prolongation, as well as ventricular dysrhythmias [34,35]. These electrocardiographic findings are similar to those seen with a tricyclic antidepressant (TCA) overdose [36]. Despite frequent reports in the literature [7,11,12,18,35,37–39], rates of cardiac conduction abnormalities (QRS/QT prolongation) and wide complex dysrhythmias were low in the current study. Nevertheless, our data did demonstrate that both QRS > 120 ms and QT > 500 ms were associated with severe outcome. These data suggest that a prolongation of QRS and QT should be further studied as predictors of severe outcome. These findings also demonstrate the clinical utility of the ECG in the evaluation of patients with acute diphenhydramine poisoning, especially with regard to risk stratification.

Manini et al. reported similar findings in a study evaluating ECG predictors of adverse cardiovascular events (ACVE) in patients with suspected poisoning [40]. ACVE were defined as a composite endpoint that included shock, myocardial injury, ventricular dysrhythmia, and cardiac arrest. In this heterogeneous population of patients with suspected poisoning, authors found that prolonged QTc as well as a QTc cut-off of  $\geq 500$  ms on the initial ECG were both independent predictors of ACVE in suspected acute poisoning. While their data did not demonstrate an association between the QRS interval and ACVE, a secondary analysis showed an association between QRS > 120 ms and ventricular tachycardia/ventricular fibrillation alone ( $p < .01$ ). Although that study was designed for a heterogeneous group of suspected poisonings as opposed to isolated diphenhydramine intoxications, these findings further support the importance of initial ECG in prediction of cardiovascular complications in the setting of acute poisoning.

In a subsequent study, Manini et al. derived independent clinical risk factors for ACVE in patients with acute drug overdose [41]. Authors found that metabolic acidosis (bicarbonate <20 mEq/L), present on the initial basic metabolic panel, was one of the strongest predictors of ACVE in patients with acute drug overdose. Similarly, our data demonstrate that acidemia, as well as elevated anion gap, both are strongly associated with a severe outcome in acute diphenhydramine overdose. These findings are not unexpected, as cardiac abnormalities, such as dysrhythmias and hypotension, are often present at arterial pH values less than 7.20 mEq/L [42]. Therefore, the presence of acidemia, especially if present early in the clinical course, may be a useful indicator of those patients at higher risk of developing serious clinical outcomes.

Another factor strongly associated with severe outcome in this study was AKI. AKI can lead to serious complications, including volume overload, electrolyte derangements, metabolic acidosis, altered mental status, and decreased clearance. Following diphenhydramine overdose, intrinsic renal failure may be associated with rhabdomyolysis and is often

associated with seizure activity, severe agitation, coma, or hyperthermia [29,43–48]. Furthermore, diphenhydramine, as well as other agents with antimuscarinic properties, may lead to urinary retention, delayed bladder emptying, and post-renal injury from increased upstream pressure [49].

Lastly, hyperthermia (Temp > 105 °F) was found to be another factor strongly associated with severe outcome in this study. The etiology of hyperthermia in diphenhydramine poisoning is multifactorial and correlates with the extent of agitation, ambient temperature, and humidity. Peripheral muscarinic blockade impairs sweat-gland function and cutaneous heat loss [50]. The combination of anhidrosis and increased muscle activity from agitation or seizures, may be profoundly thermogenic. Life-threatening complications of hyperthermia include rhabdomyolysis, disseminated intravascular coagulation, renal failure, hyperkalemia, acidemia, cardiac dysfunction, and death [51–53]. The severity and duration of hyperthermia are important determinants of patient outcome, particularly with respect to neurologic disability and mortality.

## Limitations

Our study has several limitations. The central inclusion criterion for entry into the ToxIC registry is consultation by a medical toxicologist. Since all cases are entered by an examining medical toxicologist, this likely creates a reporting bias toward more severe presentations and unusual exposures. This is partially addressed by an agreement between ToxIC and each participating site to report all cases, so that the database is more representative of all cases seen by a practicing medical toxicologist. Additionally, ToxIC case entries represent those individuals who presented to clinical care rather than follow symptoms at home. This would likely predict a bias toward more serious and consequential exposures as compared to the majority of exposures reported to poison centers. The ToxIC registry requires that individual sites report all of their cases. However, as data in the registry are limited to voluntary reporting, it is possible that some cases were not entered into the registry. Furthermore, the vast majority of these exposures were not confirmed in biologic samples, but rather relied on the clinical syndrome and subject's history obtained by the treating medical toxicologist. Similarly, data regarding intentionality, specifically self-harm versus abuse, were unknown in approximately 40% of cases. Although intentionality may have been a significant predictor in a multivariable sense, any effect was likely washed due to these missing data.

In this study, we included all cases in which diphenhydramine was considered to be the most significant contributor of toxicity and excluded all cases with at least one other primary agent listed. However, it is possible that some of the subjects suffered significant toxicity from exposures other than diphenhydramine or that subject histories were mis-charted. The data collection instrument also limits our ability to examine many variables as continuous. For example, heart rate is recorded as “tachycardia” only if it is >140 bpm. It is possible that heart rates that are elevated, but less than this

cutoff may correlate with severe outcome. Furthermore, although significant vital sign abnormalities, physical examination findings, medical interventions, and laboratory results are abstracted from the patient's medical records, illness severity is not directly described in registry cases. The data collection form also limits our ability to interpret certain variables in the context of age. For instance, as the normal heart rate varies with age, the definition of tachycardia is age dependent. A heart rate of 140 beats per minute has a very different significance and interpretation in a 1-year-old child compared to a 40-year-old adult.

Finally, the lack of access to patients' full medical records and the design of the registry precluded us from examining detailed information regarding their clinical course. It is impossible to determine chronology of events given the dataset. This is particularly important when evaluating acidemia. It is possible that acidemia may predispose to severe outcomes or be a symptom of severe outcomes, such as after a seizure or intubation. These associations must be used in a prospective evaluation before definitive statements can be made. Similarly, given the lack of chronology, associations of therapeutics such as IV lipid emulsion and sodium bicarbonate with severe outcomes may be simply that patients with severe outcomes are treated with more aggressive therapy. Again, a prospective evaluation of these interventions will answer this question. Therefore, it is unknown if certain patient and encounter characteristics occurred before or after a severe outcome.

## Conclusions

In the current study, we found several patient and encounter characteristics associated with severe clinical outcome in diphenhydramine poisoning. Signs and symptoms most strongly associated with severe outcome included acidemia, prolonged QRS (>120 ms), and elevated anion gap. Future studies should determine if these factors are useful predictors of severe clinical outcomes.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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