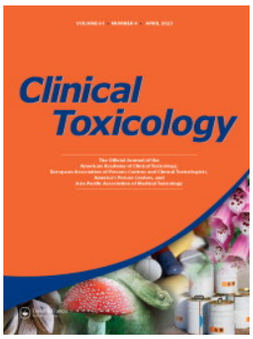

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CLINICAL RESEARCH

Are antimuscarinic effects common in hydroxyzine overdose? A cohort analysis of antimuscarinic effects in hydroxyzine and diphenhydramine-poisoned patients

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ABSTRACT

Introduction: Exposures to hydroxyzine, a first-generation H1 antihistamine, have increased rapidly over the last two decades. Many assumptions about hydroxyzine poisoning are based on other antihistamines, like diphenhydramine. However, the receptor affinities of hydroxazine suggest that there should be fewer antimuscarinic findings than diphenhydramine.

Methods: This was a cohort study that compared hydroxyzine and diphenhydramine exposures reported to the National Poison Data System between January 1, 2000, and December 31, 2020, and the Toxicologic Investigators Consortium Core Registry between January 1, 2010, and December 31, 2020. The primary outcome was to assess for antimuscarinic findings in hydroxyzine-poisoned patients, using diphenhydramine-poisoned patients as a comparison group. The secondary outcomes were to assess for markers of overall toxicity. Inclusion criteria were single-substance exposures with known outcomes. Exclusion criteria for National Poison Data System exposures were chronic exposures, unintentional exposures, and patients younger than 12 years old. There were no exclusion criteria for exposures reported to the Toxicologic Investigators Consortium Core Registry.

Results: There were 17,265 hydroxyzine and 102,354 diphenhydramine exposures reported to the National Poison Data System and 134 hydroxyzine and 1,484 diphenhydramine exposures reported to the Toxicologic Investigators Consortium Core Registry that met inclusion criteria. In both datasets, hydroxyzine-poisoned patients had lower rates and relative risk of developing antimuscarinic findings or receiving physostigmine, with the exception of hyperthermia in the Toxicologic Investigators Consortium Core Registry dataset. Coma/central nervous system depression (major), respiratory depression, seizures, ventricular dysrhythmias, intubation, and benzodiazepine administration were less likely in hydroxyzine-poisoned patients, but central nervous system depression (mild) was more likely in exposures reported to the National Poison Data System. The mortality in hydroxyzine-poisoned patients was rare: 0.02% and 0.8% of exposures reported to the National Poison Data System and Toxicologic Investigators Consortium Core Registry, respectively.

Discussion: The clinical manifestations of hydroxyzine exposures are consistent with the pharmacology of hydroxazine. The clinical effects were consistent across two United States national datasets. Clinicians should not generalize the illness script of diphenhydramine exposures to hydroxyzine exposures.

Conclusions: Hydroxyzine-poisoned patients were less likely to develop antimuscarinic findings than diphenhydramine-poisoned patients. Hydroxyzine-poisoned patients were more likely to have mild central nervous system depression than an antimuscarinic toxidrome.

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Introduction

Hydroxyzine, a first-generation H1 antihistamine, has multiple approved indications, including anxiety, pruritus, urticaria, and sedation [1]. The use of hydroxyzine in the United States has rapidly increased over the last two decades [2]. From 2009 to 2019, hydroxyzine prescriptions increased by 181 percent, and it became the 75th most-prescribed medication in the United States [2,3]. Correspondingly, the incidence of hydroxyzine poisonings has increased.

However, the literature on hydroxyzine poisonings remains sparse. Many assumptions about the clinical presentation of hydroxyzine poisonings are based on other more prevalent first-generation H1 antihistamines, such as diphenhydramine. As a class, first-generation H1 antihistamine poisoning is thought to produce antimuscarinic findings due to the antagonism of the human muscarinic receptor [4]. Yet, hydroxyzine has a much lower inhibitory binding affinity for this receptor (Ki = 3,800–15,000 nM) than many other antihistamines, such as diphenhydramine (Ki = 280–600 nM) [5,6]. Since hydroxyzine is a less potent inhibitor of the human muscarinic receptor, we expect that it should have a lower risk of developing antimuscarinic findings than diphenhydramine. The objective of this study was to quantify the antimuscarinic characteristics and overall toxicity of hydroxyzine-poisoned patients. These findings were

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compared to diphenhydramine, a prototypical first-generation H1 antihistamine.

Methods

This was a cohort study that compared hydroxyzine and diphenhydramine exposures through a retrospective review of data from the National Poison Data System (NPDS) from January 1, 2000, to December 31, 2020, and the Toxicologic Investigators Consortium (ToxIC) Core Registry from January 1, 2010, to December 31, 2020. As these data sources collect de-identified data, it was deemed to be exempt from review by our institutional review board and was approved by America's Poison Centers and the ToxIC Research Committee. The de-identified data was provided on standardized spreadsheets (Microsoft Excel 2022, version 16.70).

These two data sources were utilized to leverage the methodologic differences between the systems and display of consistency of the findings. The NPDS is a data repository maintained by America's Poison Centers. All calls made to the 55 poison centers in the United States are handled by specialists in poison information who collect exposure data and provide management recommendations. These calls are documented in a standardized electronic data collection format that is de-identified and submitted to the NPDS. Therefore, the NPDS contains all exposures reported by providers or laypersons to poison centers in the United States [7]. The ToxIC Core Registry is a repository of cases representing patients that received a medical toxicology consultation at 50 participating sites across the United States and internationally [8]. These two data sources were used because the NPDS captured the overall clinical picture while the ToxIC Core dataset served as an external source given medical toxicology evaluation.

The primary outcome was to assess the extent and relative risk of developing antimuscarinic findings in hydroxyzine-poisoned patients, using diphenhydramine-poisoned patients as a comparison group. The secondary outcomes were to assess the extent and relative risk of developing markers of overall toxicity.

The inclusion criteria were cases of single-substance hydroxyzine or diphenhydramine exposures with known outcomes. Those who were unable to be followed to an outcome were excluded. Additional exclusion criteria for the NPDS were chronic exposures, unintentional exposures, and exposures in patients younger than 12 years old. These criteria were chosen to capture exposures that would most accurately depict acute, intentional hydroxyzine and diphenhydramine poisonings. For the ToxIC Core dataset, all single-substance exposures with known outcomes were included.

The data utilized in this study were collected by America's Poison Centers and ToxIC and were entered through standardized data collection forms and stored as de-identified patient information. The variables chosen were intended to evaluate the primary and secondary outcomes. Antimuscarinic toxicity was assessed by tachycardia, mydriasis, hallucinations/delusions, erythema/flushed, urinary retention, fever/hyperthermia, blurred vision, ileus/no bowel sounds, and physostigmine administration. Overall toxicity was assessed by death, coma/major central nervous system (CNS) depression, respiratory depression, seizures, ventricular dysrhythmias, intubations, benzodiazepine administration, NPDS medical outcome, and NPDS level of health care facility care. The NPDS fatality reports were also obtained for any reported single-substance exposure to hydroxyzine or diphenhydramine.

These variables were defined using established criteria published by America's Poison Centers and ToxIC [8,9]. Some variables were only recorded in one of the datasets. The NPDS recorded mydriasis, erythema/flushing, urinary retention, blurred vision, and ileus/no bowel sounds, while ToxIC Core Registry recorded an anticholinergic toxidrome. Of note, the NPDS discontinued the use of the term 'coma' during the study period on December 31, 2018. 'Coma' had been defined as: "… all levels of CNS depression in which the patient cannot be awakened with a stimulus". The NPDS transitioned to a classification system of CNS depression: mild, moderate, and major. "CNS depression (major)" was defined as: "a state of unconsciousness in which the patient cannot be awakened with a stimulus," and "CNS depression (mild)" was defined as: "fatigue, drowsiness, normal sleep from which the patient can be awakened with minimal stimulation" [9].

Relative risk was calculated by contingency analysis of categorical variables. Relative risk was chosen to display differences in individual effects between the two medications. We calculated 95% confidence intervals for all relative risk ratios. Pearson's chi-squared testing was utilized to calculate the statistical significance between categorical variables, given the large population sample size. Statistical significance was defined as $P < 0.05$. JMP® Pro 16.0.0 statistical software was used for analyses.

Results

The NPDS database search provided 617,226 single-substance exposures, of which 64,452 were hydroxyzine and 552,774 were diphenhydramine. Single-substance hydroxyzine and diphenhydramine exposures reported to America's Poison Centers annually increased between 2000 and 2020 (Figure 1). Of the total exposures, 17,265 hydroxyzine and 102,354 diphenhydramine exposures remained after the exclusion criteria (Figure 2).

The ToxIC Core Registry search provided 1,618 single-substance exposures, of which 134 were hydroxyzine, and 1,484 were diphenhydramine. We included all exposures from this dataset to display cases that were deemed necessary by a medical provider to require a medical toxicology evaluation. The highest level of care that the patient required was documented in 1,478 exposures: critical care unit (33.6%), non-critical care unit (20.7%), observation unit (0.7%), emergency department (44.5%), outpatient (0.5%), and telemedicine visit (0.07%).

The median age, mean age, and interquartile range (IQR) of NPDS and ToxIC cases are displayed in Table 1. Females constituted a higher percentage of exposures in both datasets. A higher percentage of hydroxyzine patients in both

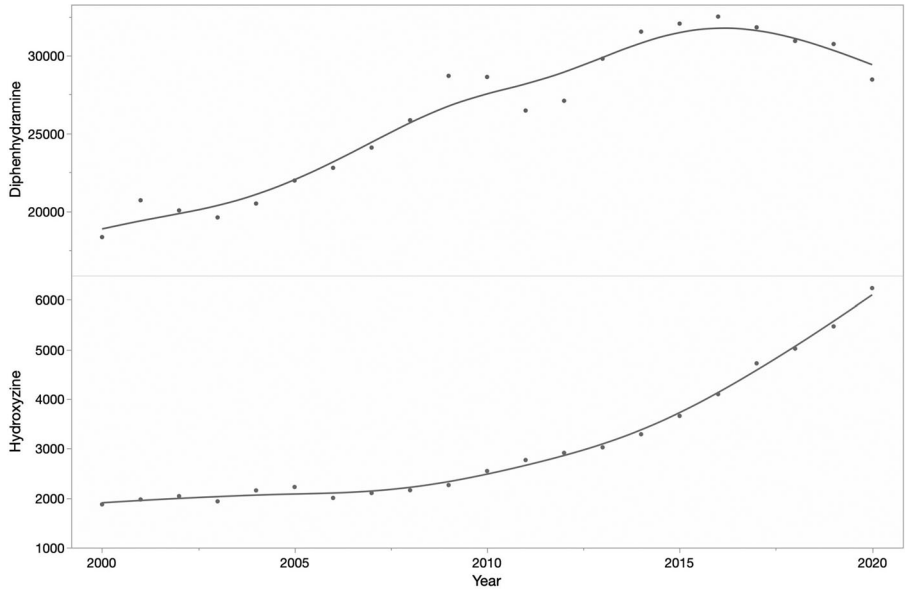

Figure 1. The total number of single-substance diphenhydramine and hydroxyzine exposures reported to America's Poison Centers annually between 2000 and 2020.

datasets reported that the exposure was a suicide or self-harm attempt.

Hydroxyzine-poisoned patients had a lower rate and relative risk of developing all antimuscarinic findings in both datasets, with the exception of hyperthermia in the ToxIC cases (Table 2). The NPDS cases display that each antimuscarinic finding, other than tachycardia, was present in less than 3% of hydroxyzine exposures. Additionally, hydroxyzine-poisoned patients were less likely to be administered physostigmine, which is an antidote for antimuscarinic toxicity. The demographics of patients who required physostigmine in the ToxIC dataset were similar between the hydroxyzine and diphenhydramine groups. Of the patients who received physostigmine, nine of 10 (90%) hydroxyzine and 255 of 279 (91.4%) diphenhydramine patients had tachycardia (pulse rate $>$ 140 beats/min), hyperthermia (temperature $>$ 40.6 °C), agitation, delirium/toxic psychosis, and/or hallucinations, which may be regarded as an indication for physostigmine administration for severe antimuscarinic toxicity. Of the patients who had at least one of these five findings, nine of 39 (23.1%) hydroxyzine patients and 255 of 1,048 (24.3%) diphenhydramine patients received physostigmine.

This study also looked at the rate and relative risk of markers of overall toxicity (Table 3). Coma/CNS depression (major), respiratory depression, seizures, ventricular dysrhythmias, intubation, and benzodiazepine administration were less likely in the hydroxyzine group compared to the diphenhydramine group in the NPDS cases. In the ToxIC Core dataset, coma/CNS depression and respiratory depression were more likely in the hydroxyzine group, while all other markers were more likely in the diphenhydramine group.

As discussed previously, the NPDS began categorizing CNS depression as mild, moderate, or major for the last two years of the study. During that two-year period, there were 3,837 hydroxyzine exposures and 15,606 diphenhydramine exposures that met the inclusion criteria. Mild CNS depression was reported in 30.5% of hydroxyzine exposures and 24.2% of diphenhydramine exposures during that period (relative risk 1.3; 95% confidence interval 1.2–1.3). Major CNS depression was only reported in 0.6% of hydroxyzine exposures compared to 2.4% of diphenhydramine exposures during that period (relative risk 0.2; 95% confidence interval 0.1–0.3).

Overall toxicity was further evaluated by the NPDS medical outcome and NPDS level of health care facility care. The NPDS cases are designated with a medical outcome based on all information that is available to the poison center that received the call [9]. Patients with hydroxyzine exposures were less likely to have the medical outcome of death, major effect, or moderate effect and were more likely to have the medical outcome of minor effect or no effect than diphenhydramine exposures (Table 4). Patients with hydroxyzine exposures were also less likely to be admitted to a critical care unit or noncritical care unit and were more likely to be discharged, transferred to psychiatric care, or remain at home than those with diphenhydramine exposures (Table 5).

Mortality was less likely in hydroxyzine (0.02%) than diphenhydramine (0.13%) exposures in the NPDS but was not different in hydroxyzine (0.8%) and diphenhydramine (0.6%) exposures in the ToxIC Core dataset (Table 3). To further evaluate the association between hydroxazine and mortality, we reviewed the six fatality reports provided by the NPDS and the one fatality in the ToxIC Core dataset (Table 6). The poison center or consulting medical toxicologist provided an assessment of the contribution of hydroxyzine to each fatality. Hydroxyzine was thought to be "probably responsible" in one case (14.3%), "contributory" in two cases (28.6%), "unlikely" in one case (14.3%), "unknown" in two cases (28.6%), and not recorded in one case (14.3%).

Finally, there was no correlation between the hydroxyzine dose and NPDS medical outcome in the 457 cases where the exact hydroxyzine dose was recorded (Figure 3). Therefore, the reported dose of hydroxyzine to which a patient was exposed in this dataset did not predict the severity of the medical outcome. There were an insufficient number of patients with recorded doses in the ToxIC Core dataset to

determine if there was a correlation between hydroxyzine dose and medical outcome, as ToxIC data collection does not require dose information.

Discussion

Hydroxyzine-poisoned patients were less likely to develop antimuscarinic findings compared to diphenhydramine-poisoned patients in both the NPDS and ToxIC Core dataset. The only exception was that the relative risk of hyperthermia in the ToxIC Core dataset did not reach statistical significance. These findings are consistent with the expected pharmacology of the two medications. Hydroxyzine is a less potent inhibitor of the human muscarinic receptors, as displayed by a larger inhibitory constant, Ki, than diphenhydramine. This has been shown in radioligand binding assays of the cerebral cortex [5] as well as in voltage-clamp measurements in mucosal cells [6]. Hydroxyzine (Ki = 3,800–15,000 nM) [5,6] belongs to the piperazine class of antihistamines, along with meclizine (Ki = 3,600 nM) [5]. In general, antihistamines in this class are less potent inhibitors of the human muscarinic receptor than members of the ethanolamine class of antihistamines, such as diphenhydramine (Ki = 280–600 nM) [5,6], dimenhydrinate (Ki = 160 nM) [5], and clemastine (Ki = 16 nM) [5].

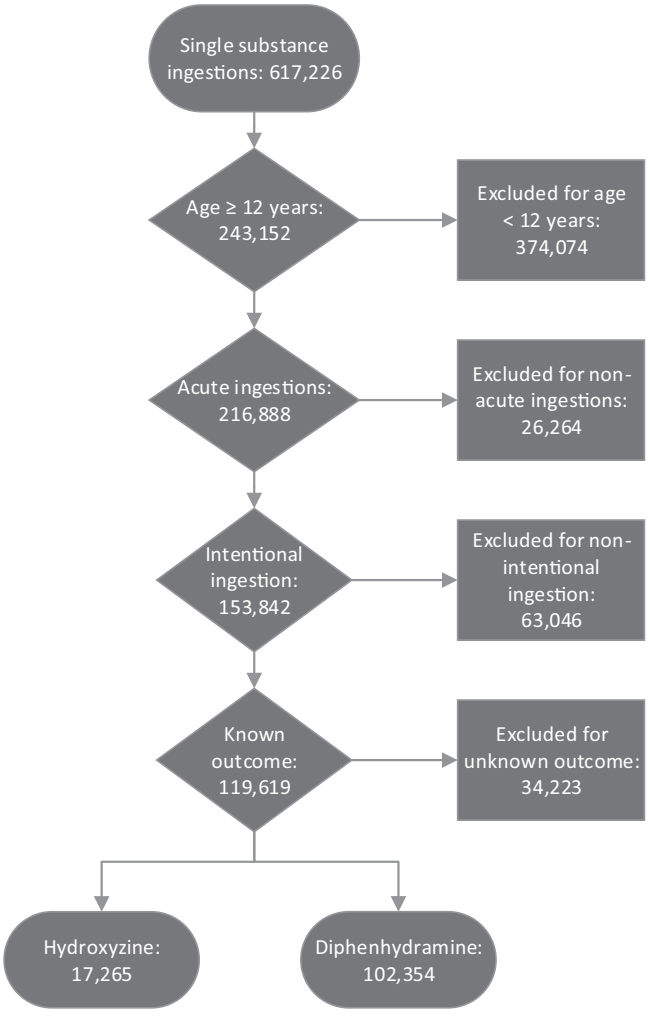

Figure 2. Flow diagram of the inclusion and exclusion criteria for single-substance cases from the National Poison Data System.

However, some hydroxyzine-poisoned patients still develop antimuscarinic findings. While inhibition of human muscarinic receptors by hydroxyzine is ten [5] to twenty-five-fold [6] lower than other first-generation H1 antihistamines such as diphenhydramine, hydroxyzine still acts as a weak inhibitor of the receptor. Therefore, patients who overdose on hydroxyzine may develop enough antagonism of human muscarinic receptors to exhibit antimuscarinic effects. However, these effects are infrequent, other than tachycardia, in hydroxyzine exposures. This was further supported by the lower risk of physostigmine administration to hydroxyzine-poisoned patients.

Given that antimuscarinic findings are infrequently reported in hydroxyzine-poisoned patients, we must develop a more accurate depiction of the clinical presentation of these patients. Clinical experience would suggest that somnolence and mild CNS depression are the most likely presenting findings. The NPDS exposures confirm this. During the two-year period where CNS depression was categorized, mild CNS depression was more common than any other finding that was followed for the entire study. Hydroxyzine-poisoned patients rarely developed major CNS depression or required intubation or ventilatory management.

The prevalence of sedation and CNS depression in hydroxyzine-poisoned patients is consistent with the inverse agonism of hydroxazine at the histamine H1 receptor [10–12]. Histamine H1 receptors modulate a multitude of physiologic functions, including the neuronal role of histamine in stimulating wakefulness and neurocognition [13]. The inhibition of Hydroxyzine at the H1 histamine receptor (Ki = 4.7–19 nM

Table 1. Demographic data of patients from the National Poison Data System and Toxicologic Investigators Consortium Core datasets.

Dataset	National Poison Data System		Toxicologic Investigators Consortium	
Medication	Hydroxyzine	Diphenhydramine	Hydroxyzine	Diphenhydramine
Total Cases	17,265	102,354	134	1,484
Age (years)				
Median	25	23	23	17
Interquartile range	18–37	17–35	16–36	14–27
Range	12–92	12–113	1–73	0.67–86
Sex				
Female	72.5%	64.8%	68.7%	61.6%
Male	27.5%	35.2%	29.9%	37.8%
Transgender	Not reported	Not reported	1.5%	0.5%
Reported suicidality/self-harm	90.6%	82.8%	84.1%	73.8%

Table 2. The rate and relative risk of developing antimuscarinic findings and physostigmine administration for the two datasets.

Effect	Diphenhydramine (%)	Hydroxyzine (%)	Relative risk	95% Confidence interval	Significance level
National Poison Data System					
Tachycardia	52.1	20.6	2.5	2.5–2.6	$P < 0.0001$
Mydriasis	11.5	2.1	5.6	5.0–6.2	$P < 0.0001$
Hallucinations/delusion	13.1	0.8	16.2	13.7–19.1	$P < 0.0001$
Erythema/flushed	2.2	0.6	3.8	3.1–4.6	$P < 0.0001$
Urinary retention	1.8	0.4	4.5	3.5–5.7	$P < 0.0001$
Hyperthermia/fever	1.6	0.3	6.3	4.7–8.5	$P < 0.0001$
Blurred vision	0.7	0.2	2.8	2.0–3.8	$P < 0.0001$
Ileus/no bowel sounds	0.1	0.0	9.8	2.4–39.6	$P < 0.0001$
Physostigmine given	1.7	0.1	16.2	10.2–25.7	$P < 0.0001$
Toxicologic Investigators Consortium					
Anticholinergic toxidrome	73.6	31.3	2.3	1.8–3.0	$P < 0.0001$
Tachycardia (Pulse > 140 beats/min)	33.3	5.2	6.4	3.1–13.2	$P < 0.0001$
Hallucinations	22.9	4.5	5.1	2.3–11.2	$P < 0.0001$
Delirium/toxic psychosis	43.5	19.4	2.2	1.6–3.2	$P < 0.0001$
Hyperthermia	0.4	0.0	3.9	0.5–30.0	$P = 0.18$
Physostigmine given	18.8	7.5	2.5	1.4–4.6	$P = 0.0028$

Table 3. The rate and relative risk for markers of overall toxicity in the National Poison Data System and Toxicologic Investigators Consortium Core datasets.

Effect	Diphenhydramine (%)	Hydroxyzine (%)	Relative risk	95% Confidence interval	Significance level
National Poison Data System					
Death	0.1	0.0	7.2	2.3–22.6	$P = 0.0007$
Coma	1.9	0.5	4.1	3.2–5.3	$P < 0.0001$
Central nervous system depression (major)	2.4	0.6	5.8	3.7–9.0	$P < 0.0001$
Respiratory depression	0.8	0.3	2.4	1.8–3.1	$P < 0.0001$
Seizure (single, multiple, or status)	4.8	1.2	4.0	3.5–4.5	$P < 0.0001$
Ventricular dysrhythmia	0.2	0.0	32.0	4.5–228.7	$P < 0.0001$
Intubation	3.8	0.7	5.3	4.4–6.3	$P < 0.0001$
Benzodiazepines given	24.7	8.7	2.8	2.7–3.0	$P < 0.0001$
Toxicologic Investigators Consortium					
Death	0.6	0.8	0.8	0.1–6.4	$P = 0.84$
Coma/central nervous system depression	22.4	39.6	0.6	0.5–0.9	$P = 0.0032$
Respiratory depression	2.9	3.1	0.9	0.3–2.6	$P = 0.92$
Seizure	13.2	6.3	2.0	1.0–3.9	$P = 0.056$
Ventricular dysrhythmia	1.3	0.0	3.5	0.2–58.4	$P = 0.38$
Intubation/ventilatory management	22.9	1.5	12.5	3.1–49.7	$P = 0.0003$
Benzodiazepines	85.5	19.6	2.8	1.9–4.1	$P < 0.0001$

Table 4. National Poison Data System medical outcome for diphenhydramine and hydroxyzine exposures.

National Poison Data System medical outcome	Diphenhydramine (%)	Hydroxyzine (%)	Relative risk	95% Confidence interval	Significance level
Death	0.1	0.0	7.2	2.3–22.6	$P = 0.0007$
Death, indirect report	0.0	0.0	4.2	0.2–71.2	$P = 0.32$
Major effect	5.1	1.2	4.4	3.8–5.0	$P < 0.0001$
Moderate effect	43.3	19.5	2.2	2.2–2.3	$P < 0.0001$
Minor effect	34.8	42.5	0.8	0.80–0.83	$P < 0.0001$
No effect	16.7	36.8	0.5	0.44–0.46	$P < 0.0001$

Table 5. National Poison Data System level of healthcare facility description in diphenhydramine and hydroxyzine exposures.

Level of healthcare facility	Diphenhydramine (%)	Hydroxyzine (%)	Relative risk	95% Confidence interval	Significance level
Admitted to critical care unit	26.0	11.8	2.2	2.1–2.3	$P < 0.0001$
Admitted to noncritical care unit	13.2	9.4	1.4	1.3–1.5	$P < 0.0001$
Admitted to psychiatric care facility	24.0	38.4	0.6	0.61–0.64	$P < 0.0001$
Treated/evaluated and released	31.2	36.7	0.9	0.8–0.9	$P < 0.0001$
Patient refused referral/did not arrive at healthcare facility	1.1	0.7	1.6	1.3–2.0	$P < 0.0001$
Patient lost to follow-up/left against medical advice	1.8	1.6	1.1	1.0–1.3	$P = 0.075$
Not documented	2.7	1.5	1.8	1.6–2.0	$P < 0.0001$

[14,15]) is three orders of magnitude greater than its inhibition of human muscarinic receptors. At a physiologic pH, hydroxyzine is an uncharged molecule, which allows it to readily cross the blood-brain barrier. When in the CNS, hydroxyzine can inhibit histamine-modulated neuronal transmission [16]. Two separate studies displayed that even therapeutic doses of oral hydroxyzine led to histamine H1 receptor occupancy of 67.6% and 53.95% in the brain [17,18]. Studies using positron emission tomography and mice with histamine-related gene knockouts have demonstrated that inhibition of histamine H1 receptors leads to decreased wakefulness and CNS depression [13]. This mechanism supports why sedation and CNS depression were seen commonly in hydroxyzine-poisoned patients. Hydroxyzine is also a weak potency antagonist at the serotonin 5-HT2, dopamine D2, and α_1-adrenergic receptors [16].

Table 6. A review of the six hydroxyzine-related fatality reports provided by the National Poison Data System and the one fatality in the Toxicologic Investigators Consortium Core dataset hydroxyzine cases.

Dataset	Year	Amount ingested (tablets)	Strength	Time of ingestion	Past medical history	Summary	Prehospital cardiac arrest	Autopsy hydroxyzine concentration	Contribution assessment
National Poison Data System	2000	180	Not recorded	Unknown	Not recorded	A 39-year-old male communicated a suicidal plan to family. Emergency medical services arrived to find patient seizing and in cardiac arrest. The patient arrived at the emergency department in cardiac arrest. The patient was pronounced dead several minutes later.	Yes	33 mg/L (postmortem, site not specified)	Not recorded
National Poison Data System	2011	60	50 mg	Unknown	Not recorded	A 37-year-old female's family reported that the patient ingested hydroxyzine. The patient arrived at the emergency department with central nervous system depression, tachycardia (130 beats/min), and hypertension (130/103 mmHg). The patient had a brief seizure and became hypotensive despite vasopressor agents and intravenous fluids. On hospital day 3, the patient was still unresponsive and expired.	No	Not recorded	Contributory
National Poison Data System	2011	36–40	50 mg	Over 24 h	Hepatitis C, drug use	A 50-year-old female reported ingesting hydroxyzine and arrived at the emergency department with central nervous system depression and a bradycardic junctional rhythm (40 beats/min). The patient developed a metabolic acidosis, hypotension, and renal failure despite vasopressor agents, intravenous fluids, intubation, and external pacing. On hospital day 2, care was withdrawn by the patient's family.	No	Not recorded	Contributory
National Poison Data System	2014	Unknown	Unknown	Unknown	Unknown	A 61-year-old male was found unresponsive at home with a bottle of hydroxyzine near the patient. The patient was intubated by the emergency medical services. Upon arrival, at the emergency department the patient was hypotensive and had diffuse bleeding. The primary team concluded that a gastrointestinal bleed was the cause of death. It is unknown if the patient ingested hydroxyzine.	No	Not recorded	Unknown
National Poison Data System	2015	Unknown	Unknown	Unknown	Unknown	A 46-year-old female was assessed by the emergency medical services when in cardiac arrest. The 911 caller reported a hydroxyzine ingestion and that 19 hydroxyzine tablets were missing. Cardiopulmonary resuscitation was performed for 30 min before the patient was pronounced dead on scene. The blood glucose concentration was 600 mg/dL (33.3 mmol/L).	Yes	Not recorded	Unknown
National Poison Data System	2017	Unknown	Unknown	Unknown	Suicidal ideation	A 29-year-old female developed "seizure-like activity" and was assessed by the emergency medical services and found to be in cardiac arrest. The 911 caller reported a hydroxyzine ingestion. The patient received advanced cardiac life support and benzodiazepines but was pronounced dead. On autopsy, the patient had a hydroxyzine concentration of 9.3 mg/L and an unspecified diphenhydramine concentration from a premortem venous sample.	Yes	9.3 mg/L (premortem, venous sample)	Probably responsible
Toxicologic Investigators Consortium	2014	Unknown	Unknown	Unknown	Asthma, intravenous drug use, HIV, Hepatitis C	A 28-year-old male was assessed by the emergency medical services with pulseless electrical activity. The roommate reported the patient had dyspnea preceding syncope after possible ingestion of amfetamine/dextroamfetamine. In the emergency department, the patient had return of spontaneous circulation but had hypotension and multiorgan dysfunction despite multiple vasopressor agents. Life support was withdrawn. Hydroxyzine was not mentioned, and the cause of illness was deemed "unlikely" to be toxicologic.	Yes	Not recorded	Unlikely

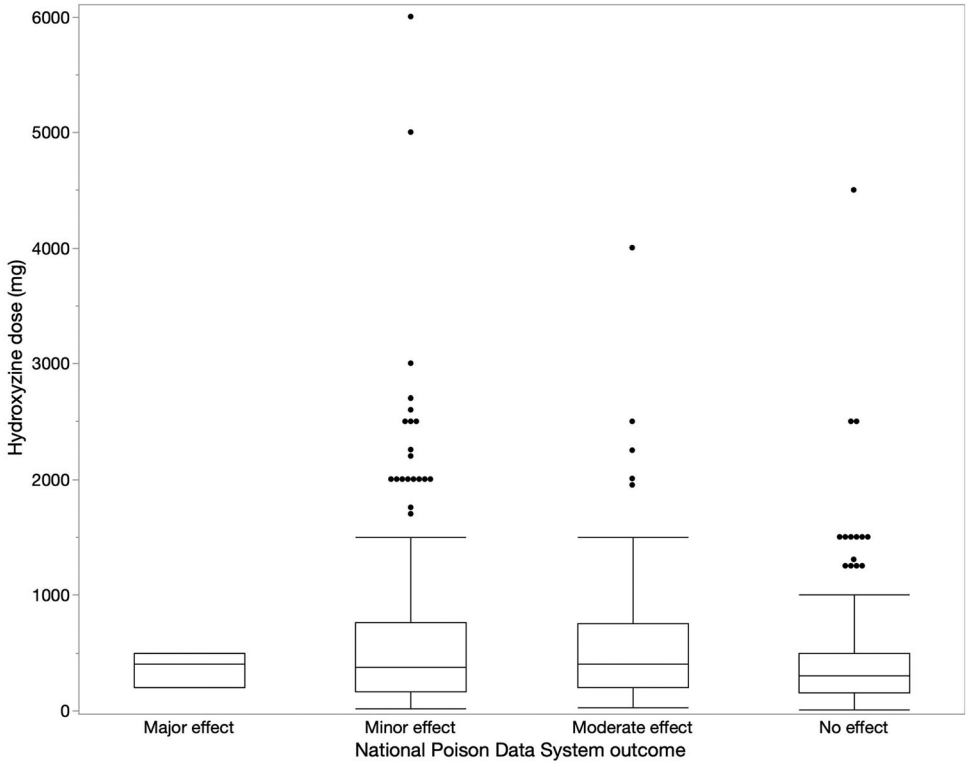

Figure 3. The relationship between hydroxyzine dose and National Poison Data System medical outcome. Each box plot represents the upper quartile, median, and lower quartile of hydroxyzine dose. Outliers are plotted on the graph but excluded from other calculations. The diamond represents the 95% confidence interval of the mean for each group.

Mortality in hydroxyzine exposures was exceeding rare. Despite an increasing prevalence, there were only seven hydroxyzine exposure fatalities reported to poison centers during the twenty-year study period. Two of the fatalities had recorded autopsies with measured hydroxyzine concentrations. One fatality had a hydroxyzine concentration of 33 mg/L on a postmortem sample from an unspecified site, and the other fatality had a concentration of 9.3 mg/L from a premortem, venous blood sample. The reported mean therapeutic plasma concentration following a 25 mg dose of hydroxyzine is 43 μg/L at 3 h with a half-life of 14 h [19]. The hydroxyzine concentrations of the two patients in this study are consistent with postmortem blood concentrations presented in other hydroxyzine-associated fatalities: 1.1 mg/L [20], 39 mg/L [21], and 4.2 mg/L [22]. Both fatalities in this study with measured supratherapeutic hydroxyzine concentrations had reported ingestions followed by "seizure-like activity" and cardiac arrest.

Despite the overall low mortality rate for hydroxyzine exposures in both datasets, the ToxIC Core dataset showed no difference in mortality rates between hydroxyzine and diphenhydramine exposures. There was only one death (0.8%) in the hydroxyzine group of the ToxIC Core dataset. This death was recorded as "unlikely" to be toxicologically related. The case summary reported that the patient had a possible amfetamine/dextroamfetamine exposure and made no mention of hydroxyzine. However, given that we were unable to verify that this was an erroneous hydroxyzine entry instead of an amfetamine/dextroamfetamine entry, this case was left in the dataset.

There are several limitations of this study regarding threats to internal and external validity. Internal validity is the extent to which the observed results represent the truth in the population being studied [23]. First, patients may have knowingly or unknowingly been exposed to different medications than were reported. Ingestion documentation was based on the history provided, not on laboratory confirmation. Therefore, this information relies on the accuracy of the history provided, the medical documentation of the providers, and data entry by dataset collection staff. Furthermore, exposure dose information is often obtained from sources other than the patient and was only recorded in 457 (2.6%) of the NPDS hydroxyzine exposures. While this represents a minority of the cases, the large population size still allows for many cases with reported doses. Second, data in the NPDS is collected primarily for clinical purposes. Therefore, aspects not thought to be clinically relevant may be omitted by providers or laypersons providing the history, and follow-up calls are made when clinically pertinent, not for means of data completeness. However, there is no reason to believe that there were categorical differences in how histories were obtained, or data was collected in hydroxyzine and diphenhydramine groups. Third, providers may experience confirmation bias in attributing or recognizing clinical effects that they expect to see with a poisoning. The conventional teaching that first-generation H1 antihistamines are antimuscarinic may affect how providers interpret the presentations for these medications. However, if this bias was present and could be accounted for, we suspect that this

would only strengthen the conclusion that hydroxyzine causes less antimuscarinic toxicity than diphenhydramine.

Furthermore, threats to external validity are those that affect whether a study is generalizable to daily practice [23]. The NPDS was chosen to help with generalizability as it captures all calls made to United States poison centers. However, some exposures are not reported to poison centers. Again, there is no reason to believe that there are categorical differences in hydroxyzine and diphenhydramine reporting. Furthermore, pediatric patients were excluded from the NPDS exposures in an attempt to minimize the effect of minor exploratory ingestions on the data. Because of this, we chose to include all ages from the ToxIC Core dataset to capture pediatric cases that developed findings. The limited pediatric sample size means that these results do not allow us to draw conclusions on pediatric patients, and further research is required in the pediatric population. Finally, the data from ToxIC does not represent all exposures like the NPDS. The ToxIC registry only captures patients who had a medical toxicology consultation. In most cases, this implies that patients were more complicated or ill, for which a primary team sought a formal expert consultation. Therefore, it may be expected that this dataset captures a sicker subset of exposures. Finally, some patients could have been present in both datasets. However, the data from these datasets were not pooled, and the calculations were done separately.

Conclusions

Hydroxyzine-poisoned patients were less likely to develop antimuscarinic findings than diphenhydramine-poisoned patients. Hydroxyzine-poisoned patients were more likely to have mild CNS depression than an antimuscarinic toxidrome. Based on the findings presented, clinicians should not generalize the illness script seen in diphenhydramine exposures to hydroxyzine exposures.

Disclosure statement

America's Poison Centers maintains the National Poison Data System (NPDS), which houses de-identified records of self-reported information from callers to the Country's Poison Centers. National Poison Data System data do not reflect the entire universe of US exposures and incidences related to any substances. Exposures do not necessarily represent a poisoning or overdose, and America's Poison Centers are not able to completely verify the accuracy of every report. National Poison Data System data do not necessarily reflect the opinions of America's Poison Centers.

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