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Research Paper

Acute Intentional Antihistamine Poisoning in the Emergency Department: Predictors of Anticholinergic Symptoms

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ABSTRACT

Background: Antihistamines are widely used for allergic and respiratory conditions, but can cause severe toxicity when taken in overdose. Differences in pharmacokinetic properties between first and second-generation agents influence clinical presentation and outcomes. This study aimed to describe the epidemiological and clinical features of intentional antihistamine poisonings in patients consulting our emergency department (ED) in Tunisia and to identify drug-specific and dose-specific associations with anticholinergic symptoms.

Methods: A retrospective study was conducted at the ED of the Mahmoud Yaacoub Center for Urgent Medical Assistance in Tunis from January 2021 to July 2024. Patients presenting with acute intentional antihistamine poisoning were included. Epidemiological and clinical data were analyzed using univariate and multivariate logistic regression to identify independent predictors of anticholinergic symptoms.

Results: Among 134 included cases (median age 24 years; 83.6% female), most involved H1-antihistamines (91.8%), predominantly first-generation agents (58.6%). Cyproheptadine (32.1%) and chlorpheniramine (9.7%) were the most frequently implicated first-generation drugs, while cetirizine (23.9%) was the most common second-generation agent. Symptomatic presentations occurred in 47% of patients, being more common and more severe with first-generation drugs than second-generation (69.8% vs 25.4%, $p<0.001$). Cyproheptadine poisoning was associated with tachycardia (P=0.034, OR=2.441) and toxic psychosis (P=0.032, OR=6.206), with a cutoff dose of ≥108 mg determinant for toxic psychosis (P=0.025, OR=12.73). Chlorpheniramine was linked to sedation (P=0.022, OR=5.43) and hypotension (P=0.043, OR=16.38). ICU admission occurred in 9.7% of cases, and 2 patients required mechanical ventilation. The majority of patients (73.1%) were discharged home, and 12.7% were referred for psychiatric evaluation.

Conclusion: Most intentional antihistamine poisonings resulted in mild or no symptoms; first-generation agents, particularly cyproheptadine and chlorpheniramine, were linked to more severe toxicity and consequences. Recognition of dose thresholds and drug-specific clinical patterns can guide early management in acute antihistamine poisoning.

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Introduction

Antihistamines are widely used and prescribed for their antiallergy properties, as well as a treatment for motion sickness, itching, cold symptom relief, and as a sleep aid.

They work by blocking histamine's effects, targeting both H1 and H2 receptors, and are classified by their affinity for either receptor.

H1 receptor blockers are commonly used to alleviate symptoms of allergies and Rhinitis by stabilizing vascular permeability, reducing inflammation, and opposing histamine-mediated responses [1].

They are classified into first and second-generation drugs. First-generation agents are highly lipophilic, allowing them to cross the blood-brain barrier and causing sedation through muscarinic receptor blockade, 5-HT (serotonin) antagonism, and α-adrenoceptor antagonism [2].

In contrast, second-generation H1 antihistamines are more hydrophilic and have limited central nervous system (CNS) penetration. They are referred to as "non-sedating" because they primarily act on peripheral histamine-1 receptors. They also have a longer duration of action (12-24 hours) than first-generation agents (4-6 hours) [3].

On the other hand, H2 blockers primarily inhibit gastric acid secretion via the AC/cAMP signaling pathway, making them effective for treating conditions such as gastric or duodenal ulcers, dyspepsia, and gastroesophageal reflux disease (GERD) [4].

These differences in pharmacokinetics make the clinical symptomatology in cases of poisoning vary depending on the type and dose of the ingested antihistamine.

We aimed to describe the epidemiological and clinical features of intentional antihistamine poisonings in patients consulting an emergency department (ED) in Tunisia and to identify drug-specific and dose-specific associations with anticholinergic symptoms.

Materials and Methods

This was a retrospective study conducted at the ED of the Mahmoud Yaacoub Center for Urgent Medical Assistance in Tunis over 3.5 years, from January 2021 to July 2024.

Patient records were retrieved from the ED archives. Information was collected using a data collection form for each patient, then entered into a database.

Patients of all ages who presented to our ED for intentional acute antihistamine poisoning were included. Both single antihistamine drugs and multiple drug ingestions were included.

We did not include cases involving co-ingestion of antihistamines with drugs or substances known to induce secondary sedating effects or anticholinergic manifestations similar to those of antihistamines, as well as cases of co-ingestion with medications that have potential electrocardiographic abnormalities mimicking antihistamine-related cardiac effects. Cases not included were co-ingestions of antidepressants, benzodiazepines, antipsychotics, antiepileptics, opioids, beta-blockers, angiotensin2 receptor blockers, and angiotensin-converting enzyme inhibitors.

All statistical analyses were performed using Jamovi version 2.5.6. Simple frequencies and percentages were calculated for qualitative variables.

Means, standard deviations, medians, interquartile ranges, and extreme values (minimum and maximum) were calculated for quantitative variables.

In the univariate analysis, risk factors were examined using Odds Ratios (OR), which express the magnitude of risk associated with exposure to a given factor relative to non-exposure.

Comparisons between independent groups were made using Student's t-test. For risk analysis, quantitative variables were converted to binary variables using thresholds determined from ROC curves with an AUC> 0.5.

Multivariate logistic regression was performed to identify independent risk factors for an event, yielding adjusted Odds Ratios for each variable. Pairwise relationships were tested before model construction, and only factors with significant associations ($p < 0.05$) were included in the model.

Results

Patient characteristics

A total of 134 cases were included in our study. The median age of the population was 24 years old [20-33] (minimum 11, maximum 77), with 83.6% of patients

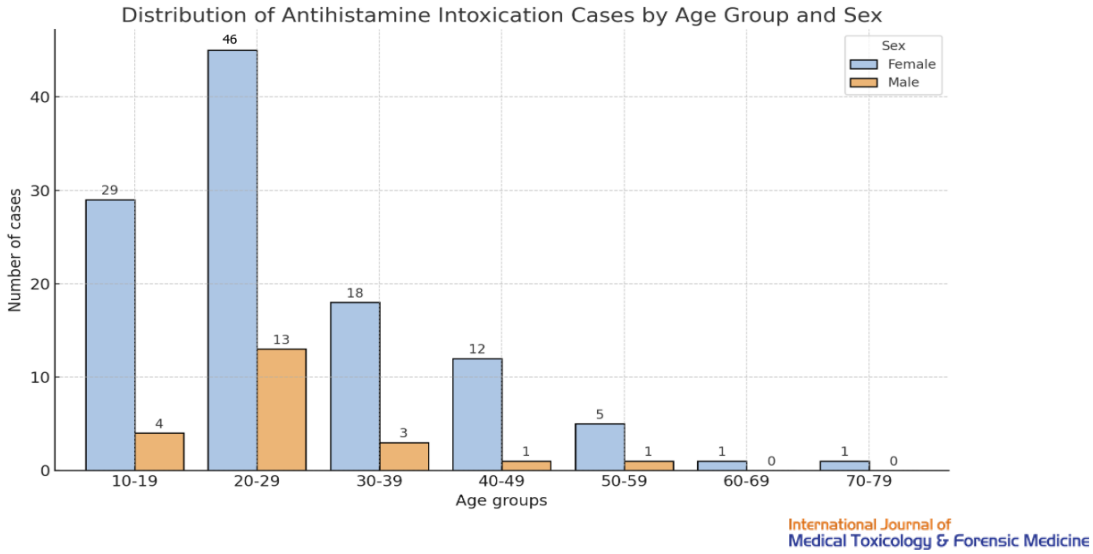

Figure 1. Age and sex distribution per decade.

being female and a sex ratio of M/F=0.19 (Figure 1).

The most common medical history among patients was psychiatric illness, documented in 11.9% of patients. It included major depressive disorder (6.7%), bipolar disorder (2.2%), panic disorder (1.5%), and schizophrenia (1.5%). Ten patients (7.5%) had a previous suicide attempt.

Other underlying medical conditions were Rhinitis in 7.5% of patients, as well as arterial hypertension, diabetes (type 2), and asthma in 2.2% each.

Involved drugs

Most intoxication cases involved antihistamines targeting H1-receptors (91.8%), including 58.6% first-generation and 42.4% second-generation agents. One patient reported a combined ingestion of both generation drugs (Figure 2).

Within the first-generation group, the most frequently implicated drugs were cyproheptadine (32.1%) and chlorpheniramine (9.7%), followed by hydroxyzine and triprolidine (4.5% each), pizotifen and diphenhydramine (2.2% each), and oxomemazine and promethazine (0.7% each).

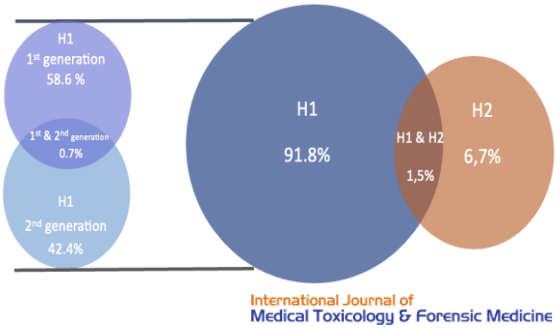

Figure 2. Distribution of ingested antihistamine target receptors and generations.

Among second-generation antihistamines, cetirizine (23.9%) and desloratadine (11.2%) were the most common, followed by levocetirizine (6.7%) and fexofenadine (0.7%).

H2-receptor antagonists were ingested by 6.7% and 1.5% of patients consulted for combined H1 and H2 antihistamine intoxication.

The only H2-antihistamine reported was Famotidine (8.2%).

Regarding the characteristics of the intentional poisoning, 44.8% were single antihistamine poisonings. The remaining 55.2% were multiple drug ingestions.

The most commonly co-ingested agents were acetaminophen (56.7%), antibiotics (44.5%), non-steroidal anti-inflammatory drugs (25.6%), pseudoephedrine (18.9%), and a second antihistamine (13.5%). The maximum number of co-ingested drugs along with antihistamines was five.

Clinical presentation

The median time of delay to consultation was 3 hours [2 - 5.25]. Symptomatic patients represented 47% of cases, and clinical manifestations were significantly more frequent in patients intoxicated by first-generation antihistamines (69.8%) compared to those who ingested second-generation agents (25.4%, p<.001).

Toxic psychosis, which is characterized by agitation, disorientation, and delirium, was observed in

Table 1. Symptoms per H1-antihistamine generation.

Symptoms	Total symptomatic patients (n=63)	
	First-generation H1-antagonists	Second-generation H1-antagonists
Symptomatic patients	44 (69.8)	16 (25.4)
Sedation (Drowsiness, dizziness)	16 (25.4)	4 (6.3)
Toxic psychosis	8 (12.7)	2 (3.1)
Hallucinations	3 (4.8)	0
Peripheral anticholinergic symptoms		
Tachycardia	31 (49.2)	11 (17.4)
Dry mouth	7 (11.1)	1 (1.6)
Dry eyes	3 (4.8)	0
Mydriasis	2 (3.1)	0
Flushed face	3 (4.8)	0
Hypertension	17 (27)	6 (9.5)
Hypotension	2 (3.1)	1 (1.6)
Prolonged QT in ECG	1 (1.6)	1 (1.6)
Coma	2 (3.1)	0
Admission to ICU	7 (11.1)	4 (6.3)

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7.5% of patients. They were intoxicated by either cyproheptadine (first-generation) or cetirizine (second-generation), with hallucinations present 30% of cases.

Following close observation, two of these patients, who overdosed on cyproheptadine (120mg and 240mg, respectively), exhibited a deterioration in their levels of consciousness, eventually developing coma. Both required intubation after rapid sequence induction and were transferred to the intensive care unit (ICU) for further management.

ICU admissions following antihistamine poisoning accounted for 9.7% of consultants.

First-generation H1 agents accounted for 53.8% of admissions, and second-generation agents accounted for 30.8%. The remaining 15.4% used H2-antihistamines and were admitted primarily for management of adverse effects related to co-ingested substances (Table 1).

Management was primarily symptomatic for all patients. However, N-acetyl cysteine (NAC) was given in severe acetaminophen co-ingestions (4.5%), and Midazolam was administered for agitation control in some toxic psychoses (4.5%). The majority of patients (73.1%) were home discharged, and 12.7% were transferred to a psychiatric ED for high suicidal risk (Table 2).

Analytical analysis

Our univariate analysis showed that first-generation antihistamines, specifically cyproheptadine and chlorpheniramine, were associated with distinct symptom profiles.

Cyproheptadine was associated with tachycardia (P=0.002) and toxic psychosis (P=0.002). Chlorpheniramine was associated with sedation (P=0.001) and hypotension (P=0.015).

Using the t-test, we subsequently determined that the ingested doses of cyproheptadine and chlorpheniramine were predictors of anticholinergic delirium (P=0.003) and sedation (P=0.043), respectively. The ROC curve identified cutoffs and found that the dose of 108mg of cyproheptadine was a predictor of delirium (P=0.015, AUC=0.802) and that a 25mg dose of chlorpheniramine was a predictor of sedation (Figure 3).

Multivariate logistic regression analysis confirmed that cyproheptadine was a predictor of tachycardia (P=0.034, aOR=2.441, 95% CI [1.0679—5.58]) and toxic psychosis (P=0.032, aOR=6.206, 95% CI [1.0679—5.58]) and that chlorpheniramine was associated with sedation (P=0.022, aOR=5.430, 95% CI [1.279—23.056]) and hypotension (P=0.043, aOR=16;379, 95% CI [1.090—246.035]).

In addition, an ingested dose superior to or equal to 108mg of cyproheptadine was confirmed to be associated with the occurrence of toxic psychosis (P=0.025, aOR=12.727, 95% CI [1.381—117.27]) (Table 3).

Table 2. Management and referral of patients.

Management	All patient n=134 (%)
Symptomatic treatment	
Normal saline infusion	53 (39.6)
Proton pump inhibitors	37 (27.6)
Midazolam	6 (4.5)
Mechanical ventilation	2 (1.5)
Specific treatment	
N-acetyl cysteine (NAC)	6 (4.5)
Decontamination	
Activated charcoal	8 (6)
Referral	
Home discharge with follow-up	56 (41.8)
Home discharge without follow-up	42 (31.3)
ICU admission	13 (9.7)
Psychiatric ED	17 (12.7)
Hospital of origin	2 (1.5)
Self-discharge	4 (3)

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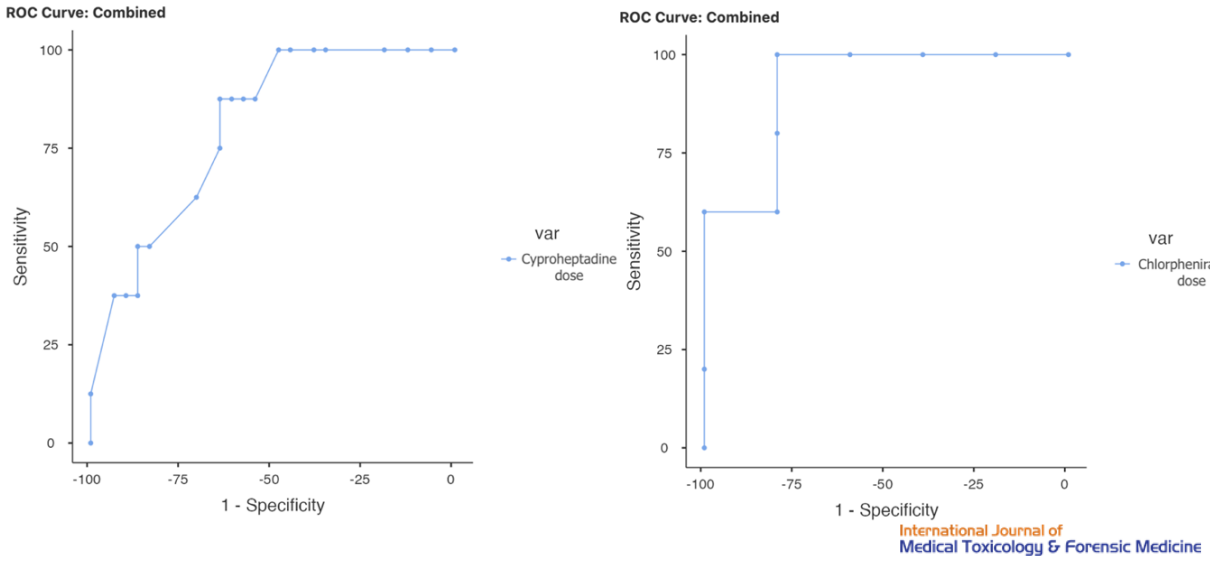

Figure 3. ROC Curves of molecule dose association with symptoms. ROC Curve of cyproheptadine dose association with toxic psychosis (A) ; ROC Curve of chlorpheniramine dose association with sedation (B).

However, the ingested dose of 25mg of chlorpheniramine was not associated with sedation. Interestingly, ICU admission was not statistically associated with first-generation drugs or ingested doses (P>0.05).

Discussion

Lately, the use of antihistamines has significantly increased, with these drugs ranking among the top 18 drug classes used in the USA between 1999 and 2012 [5].

This rise in exposure is reflected in the 40th Annual Report of America's Poison Centers, published in 2022 by the National Poison Data System, which highlighted antihistamines as the 5th most frequently involved substance class in human intoxications, accounting for 4.81% [6].

These are the reasons why understanding antihistamine poisonings and their main toxicity factors is key to optimizing intoxication management in the ED and preventing complications.

In our study, the most affected age group was females aged 20 to 29 years, with a median age of 24. This aligns with previous studies reporting a higher intoxication rate in young females [7, 8].

Most cases were multiple drug exposures, in line with recent international toxicology surveys and reports. Nevertheless, the pattern of antihistamines involved shows notable regional variation. In our Tunisian context, cyproheptadine was the most frequently implicated first-generation compound, unlike the main contributors in other countries. However, cetirizine was the most common second-generation agent, a finding consistent with observations from other regions [6, 9].

Our study confirms that first-generation H1 antagonists are associated with higher toxicity and

Table 3. Associations between drug type, dose, and toxicity symptoms in univariate and multivariate logistic regression analysis.

Dependent variable	Factor	P	OR	95% CI OR
Univariate analysis				
Cyproheptadine	Tachycardia	0.002	3.30	[1.52—7.16]
	Toxic psychosis	0.002	10.5	[2.12—51.8]
Chlorpheniramine	Sedation	0.001	7.27	[1.88—28.1]
	Hypotension	0.015	30.3	[2.47—370]
Multivariate analysis				
Cyproheptadine	Tachycardia	0.034	2.441	[1.0679—5.58]
	Toxic psychosis	0.032	6.206	[1.1749—32.78]
Cyproheptadine ingested dose≥108mg	Toxic psychosis	0.025	12.727	[1.381—117.27]
Chlorpheniramine	Sedation	0.022	5.430	[1.279—23.056]
	Hypotension	0.043	16.379	[1.090—246.035]

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more severe clinical outcomes than second-generation agents. In fact, at recommended medication dosing, first-generation agents occupy far more H1 brain receptors than second-generation drugs, causing more cognitive impairment [10—12]. When occupancy of brain H1 receptors exceeds 50%, it disrupts the sleep/wake cycle, leading to sedative effects [2].

Additionally, due to the similarity between H1 and muscarinic receptors, intoxication results in excessive blockade of histaminergic and cholinergic receptors, causing central and peripheral anticholinergic symptoms. These include anticholinergic delirium with agitation and hallucinations, tachycardia, mydriasis, dry mouth and eyes, flushed skin, urinary retention, and decreased sweating [13].

In Tunisia, cyproheptadine is sold as 4mg tablets for the control of allergic symptoms, but is also often prescribed by physicians for its appetite-stimulating and weight-gain properties. This drug, which has strong serotonergic and anticholinergic blocking activity, was the drug most often associated with toxic psychosis and tachycardia in our study.

In Hong Kong, a study investigating cyproheptadine poisonings found that 17.5% of their patients developed anticholinergic delirium following overdoses. They concluded that the average dose that caused delirium (170mg) was significantly higher than those causing sedation (70.7mg) or no symptoms at all (49.8mg). Our determined cutoff for delirium was 108mg of cyproheptadine [8].

Cyproheptadine-induced delirium remains insufficiently documented in the literature. Nevertheless, first-generation blockers in general have been associated with toxic psychosis resembling that observed in schizophrenia, as well as other acute psychiatric emergencies [14-16]. They induce electroencephalogram changes similar to those observed in schizophrenia, as well as anxiety and hallucinations. These alterations were not seen with second-generation H1 antagonists [17-19].

The two coma cases necessitating mechanical ventilation in our cohort were cyproheptadine overdoses. Other cyproheptadine coma cases have been reported in Tunisia and in other countries [20, 21].

Antihistamines interfere with cardiac ion channels, notably hERG, promoting rhythm disturbances (tachycardia, prolonged QT, widened QRS, cardiac arrest) [22, 23]. Tachycardia, which was the most frequent clinical manifestation following an antihistamine in our patients, was cited in Goldfrank's toxicologic emergencies guidebook as a consistent and typical finding following an H1-antihistamine overdose [24, 25].

Physicians should consider an elevated heart rate as an early intoxication warning sign, indicating the need to assess for additional toxic effects and anticipate possible anticholinergic complications.

Chlorpheniramine was the second most ingested first-generation drug in our population. It is usually found in combination with cold and flu medication, most often with acetaminophen and/or an alpha-adrenergic receptor agonist such as pseudoephedrine for nasal decongestion.

Chlorpheniramine was associated with hypotension and sedation. Although a link between 25mg and sedation was not maintained in the multivariate analysis, the literature suggests a dose-effect relationship. Higher doses, while more effective at reducing certain symptoms such as motion sickness, are associated with increased somnolence, greater central H1 receptor occupancy, and reduced alertness [26, 27].

Despite the well-documented cardiotoxicity of antihistamines in the literature, the effects of antihistamines on blood pressure, specifically chlorpheniramine [23, 28], are poorly studied.

In contrast, second-generation antihistamines such as cetirizine and desloratadine showed a lower frequency of anticholinergic symptoms, supporting their improved safety profile due to minimal CNS penetration and limited receptor cross-reactivity [29].

Management was symptomatic for all patients. After observation in the ED, as recommended by recent evidence-based consensus guidelines, 73.1% were discharged home, with or without a follow-up arrangement [30].

The limitations of this study are primarily related to its retrospective design. Ingested doses were based on patient-reported information. In future studies, urinary toxicology screening or antihistamine plasma concentrations would be valuable for assessing the relationship between the presumed ingested dose, drug concentration, and the clinical effect. Additionally, the potential use of antidotes, such as physostigmine, for the management of severe anticholinergic syndrome was not assessed and warrants consideration in prospective studies to evaluate both efficacy and safety.

Conclusion

The majority of patients with intentional antihistamine poisoning were asymptomatic or were home discharged after observation in the ED. Acute intentional poisoning with first-generation antihistamines was associated with greater anticholinergic toxicity than that with second-generation agents.

Cyproheptadine accounted for the most severe outcomes, including toxic psychosis, ICU admissions, coma when ingested in high doses, particularly at doses exceeding 108mg.

Chlorpheniramine intoxications primarily manifested with sedation and hypotension.

Therefore, clinical vigilance and careful management are required in cases of poisoning involving these frequently prescribed, readily available over-the-counter medications.

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None.

Conflicts of Interest

The authors report there are no competing interests to declare.

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