JPPT | Review

Diphenhydramine: A Review of Its Clinical Applications and Potential Adverse Effect Profile

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Diphenhydramine (Benadryl) is a first-generation antihistamine that is primarily used to treat allergic reactions including anaphylaxis, urticaria, and allergic rhinitis. Despite its availability as an over-the-counter medication, adverse physiologic effects and toxicity may occur with its use especially when administered rapidly via the intravenous route or when administered in large or excessive doses. The development and history of diphenhydramine is presented, its physiologic effects and clinical uses outlined, previous reports of clinically significant and potentially life-threatening adverse effects reviewed, and options to limit these effects discussed.

ABBREVIATIONS AAP, American Academy of Pediatrics; AE, adverse effect; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; FDA, Food and Drug Administration; H_1, histamine one receptor antagonist; ICU, intensive care unit; IV, intravenous; OTC, over the counter; pGp, P-glycoprotein; PONV, postoperative nausea and vomiting

KEYWORDS allergic reactions; antihistamine; arrhythmia; diphenhydramine; histamine; local anesthetic agents

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Introduction

Diphenhydramine (Benadryl) is a first-generation antihistamine that works by competitively blocking the binding of histamine to H_1 receptors in smooth muscle, endothelium, and the brain.[1,2] Synthesized first in 1943 by George Rieveschl at the University of Cincinnati while investigating the development of medications for the treatment of muscle spasms. These investigations led to the synthesis of the compound, dimethylaminoethyl benzhydryl ether, which was determined to have significant antihistamine properties. Subsequent development and investigation in conjunction with the pharmaceutical company, Parke-Davis, led in 1946 to its approval as the first prescription antihistamine by the US Food and Drug Administration (FDA).

Diphenhydramine was introduced into the clinical market under the brand name, Benadryl. The original chemical name, diphenymethoxyethyamine, later changed to diphenhydramine. During the 1980s, the FDA approved diphenhydramine as an over-the-counter (OTC) medication. Although it was the first antihistamine approved for clinical use by the FDA, it was not the first drug of that class to be synthesized. Neoantergan, was the first antihistamine compound synthesized originally produced by a Swiss-born Italian pharmacologist, Dr Daniel Bovet, who later received the Nobel prize for his work. However, as neoantergan caused severe drowsiness, it was never released for clinical use.

Cellular Effects and Metabolism

As a competitive antagonist for histamine at the H_1 receptor, diphenhydramine blunts the end-organ effects of histamine at various end organs. The H_1 receptor is located on respiratory smooth muscle cells, vascular endothelium, the gastrointestinal tract, cardiac tissue, immune cells, the uterus, and the central nervous system (CNS). There are 4 identified histamine receptor subtypes (H_1, H_2, H_3, and H_4), each with a unique spatial and temporal expression pattern across diverse cellular populations. Notably, H_1 receptors can be found across neurons in the CNS as well as on endothelial cells, white blood cells, and smooth muscle cells. Stimulation of the H_1 receptor, primarily by histamine in these tissues, results in increased vascular permeability, promotion of vasodilation causing flushing, decreased atrioventricular node conduction time, stimulation of sensory nerves of the airways producing bronchial irritation with cough, smooth muscle contraction of the bronchi and gastrointestinal tract, and eosinophilic chemotaxis promoting the allergic immune response. As a competitive antagonist at the H_1 receptor, diphenhydramine inhibits these physiologic effects in a dose dependent manner.

Additional clinical effects related to the central nervous may occur as diphenhydramine crosses the

blood–brain barrier and binds to central H_1 receptors in the brain, resulting in drowsiness. This effect has resulted in its clinical use as a sleep aid. Additional central effects, specifically on the vomiting center and the chemoreceptor trigger zone of the medulla, result in antiemetic properties, making it useful for motion sickness and certain types of nausea.[2] Subsequent work and the observation that a secondary effect of diphenhydramine is to inhibit the reuptake of serotonin led to the discovery and development of antidepressant medications with a similar chemical structure such as fluoxetine.

While its primary pharmacologic uses relate to its effects through antagonism at the H_1 receptor, diphenhydramine interacts with various other receptors systems throughout the body. It exhibits anticholinergic effects through antagonism of acetylcholine at muscarinic receptors. These latter cellular effects are not only responsible for additional activities of the adverse effect profile but led to its investigation as a potential treatment for Parkinson's disease. Diphenhydramine acts as an intracellular sodium channel blocker, resulting in local anesthetic properties, but also the potential to affect the electrophysiologic function of the cardiac conduction system.[3]

For clinical use, diphenhydramine can be administered orally by tablet, capsule, or solution, topically to provide analgesia through its local anesthetic effects, or systemically by intramuscular and intravenous (IV) injection. It undergoes hepatic metabolism and N-demethylation by the P450 enzyme system (primarily CYP2D6 with lower affinity for CYP1A2, CYP2C9, and CYP2C19). A small fraction (1%–2%) is eliminated unchanged in the urine.[4] The oral bioavailability of diphenhydramine ranges from 40% to 70%, due in part to pre-systemic extraction as it exhibits significant, first pass hepatic metabolism. The usual adult dose for a hypnotic effect is 25 to 50 mg.[4] See section below regarding diphenhydramine use as a sleep aid in children.

Clinically, diphenhydramine is primarily used in the treatment or prevention of allergic reactions including anaphylaxis, urticaria, and allergic rhinitis.[5,6] Other applications include the treatment of common cold symptoms, motion sickness, nausea, and insomnia.[7] Despite its availability as an OTC medication, toxicity including CNS and cardiovascular effects may occur, especially when it is administered in high or toxic doses, in off-label scenarios, or in patients with associated comorbid conditions. The remainder of this manuscript discusses the reported clinical uses of diphenhydramine, reviews previous reports of life-threatening adverse effects, and suggests options to improve the safety of its clinical use.

Clinical Uses and Applications

The clinical uses of diphenhydramine relate primarily to the treatment of symptoms related to allergic phenomena including urticaria, rhinorrhea, or pruritus. Although not a first-line medication, diphenhydramine and other first-generation antihistamines have also found anecdotal and sporadic use to produce sedation for patients in the pediatric critical care setting. Despite its wide therapeutic window, adverse effects may occur with the therapeutic use of diphenhydramine.

Treatment of Allergic Phenomena. As an antihistamine, diphenhydramine originally was released and marketed as a medication to treat minor allergic phenomena. The activation of H_1 receptors by histamine results in the onset of symptoms characteristic of acute allergic reactions, including pruritus, sneezing, and heightened vascular permeability.[7] As a consequence, antihistamines such as diphenhydramine have found widespread clinical use in the clinical management of histamine-mediated allergic responses including allergic rhinitis, urticaria, and allergic conjunctivitis. Additionally, they have been used to manage the clinical manifestations associated with minor upper respiratory infections including sneezing, rhinorrhea, and itching.[8,9] In specific clinical scenarios with acute allergic manifestations, the IV administration of antihistamines may provide swifter alleviation of symptoms than oral administration.[10]

Although not used as a first-line medication, systemic administration of diphenhydramine may be used as an adjunct to epinephrine and corticosteroids to treat severe and potentially life-threatening allergic conditions such as histamine-mediated angioedema.[11,12] In these settings, diphenhydramine is administered in conjunction with H_2-antagonists such as ranitidine or famotidine. The Centers for Disease Control and Prevention (CDC) has recommended IV diphenhydramine as adjunct therapy for vaccine-related anaphylaxis, including instances related to COVID-19 vaccinations.[13] When used in these scenarios, diphenhydramine and an H_2-antagonist should be used only as an adjunct and not as a primary therapy. Administration should follow treatment with epinephrine and other resuscitative efforts, which remain the primary and indispensable therapeutic agent in the context of anaphylaxis.[13] Despite their longstanding use as adjuncts in anaphylaxis management, there is a notable absence of randomized controlled trials evaluating the efficacy of H_1-antagonits (antihistamines) in the treatment of anaphylaxis. In addition to their use after anaphylaxis has occurred, H_1 and H_2 antagonists may be administered prophylactically in patients at risk for allergic reactions.

Pre-treatment with an H_1 antagonist may protect against bronchospasm induced by histamine.[14] Although antihistamines were previously suggested as a potentially useful treatment adjunct in alleviating the clinical symptoms of asthma, more recent work has failed to support their involvement in this scenario. Although histamine may provoke bronchospasm and may be a mediator of asthma, numerous other pathways, mediators, irritants, comorbid factors, and environmental

causes participate in the etiology and pathophysiology of asthma. Given the varied mechanisms, and the limited impact of the histaminergic pathways, there is currently no role for the acute or chronic administration of antihistamines in the treatment of asthma.

Sleep Aid. Given its impact on quality of life and cognitive development, sleep disturbances and insomnia in children remain a focus for ongoing clinical investigations to develop effective treatment paradigms. These may integrate cognitive/behavioral therapy with pharmacological interventions. One potentially effective pharmacological agent employed in this context is diphenhydramine.[15,16] Although, generally considered an adverse and undesirable effect, the sedative properties of diphenhydramine have been used in the treatment of insomnia and sleep disorders.

Histamine is a neurotransmitter that plays a pivotal role in promoting wakefulness and attentiveness. H_1 receptors have widespread distribution throughout the CNS with highest levels in areas involved in wakefulness including the thalamus, cortex, mesopontine tegmentum, and basal forebrain. H_1 receptors are also present in the limbic system with the receptors localized to the tuberomammillary nucleus in the posterior hypothalamus, which has been described as the wakefulness center. These neurons relay mainly to H_1 and H_3 receptors in the orexin-rich perifornical hypothalamus and cholinergic neurons in the basal forebrain, with their activity highest during attentive periods and lowered during steady wakefulness or rest and completely suppressed during periods of NREM and REM sleep. By antagonizing H_1 receptors in this area, diphenhydramine counteracts the wakefulness-inducing influence of histamine, leading to a pronounced sedative effect. Blockade of these H_1 receptors by diphenhydramine curtails the histaminergic signaling, thus diminishing arousal, and promoting a state conducive to sleep. The pathways have therefore suggested the potential utility of diphenhydramine as a sleep aid.

Various investigators have evaluated the clinical utility of diphenhydramine in preventing insomnia and promoting the re-establishment of healthy sleep patterns and a reduction of sleep latency. In a randomized, placebo-controlled trial of 50 children with varied sleep disorders including prolonged sleep latency (greater than 45 minutes), interrupted sleep, restless sleep, recurrent nightmares/night terrors, and recurrent sleepwalking, diphenhydramine (1 mg/kg) administered orally at bedtime was significantly better than placebo in reducing sleep latency time and the number of awakenings per night, while sleep duration was marginally increased.[15] There were no differences between diphenhydramine and placebo in other evaluated parameters including restlessness, nightmares, and difficulty awakening.

Similarly in a cohort of 111 adults with mild to moderate insomnia, oral diphenhydramine (50 mg) at bedtime was compared with placebo.[16] The comparison was made using a 2-week crossover in which the patients received diphenhydramine or placebo for 1 week each. Diphenhydramine improved sleep latency and patients reported feeling more restful the following morning. Additionally, patients preferred diphenhydramine to placebo despite the fact that there were more adverse effects which included daytime drowsiness and fatigue.

Despite the efficacy suggested by these studies, others have failed to show a positive response. Paul et al[17] performed a prospective, randomized trial in 100 children with an upper respiratory tract infection and a nocturnal cough affecting their sleep. The frequency, severity, and bothersome nature of the nocturnal cough were assessed on the day of presentation and following treatment with placebo (no medication), diphenhydramine, or dextromethorphan. All of these outcomes were significantly improved on the second night and no difference was noted between the 3 groups, diphenhydramine, dextromethorphan or placebo. Insomnia was reported more frequently in those who received dextromethorphan while drowsiness was reported more commonly in those who received diphenhydramine. No efficacy was noted in a cohort of forty-four infants, 6 to 15 months of age, who received placebo or diphenhydramine as a sleep aid at bedtime.[18] The primary outcome was parental assessment of the number of night awakenings requiring parental assistance during the intervention week. The authors concluded that diphenhydramine was no more effective than placebo in reducing nighttime awakening or improving overall parental happiness with sleep for infants.

In general, diphenhydramine is no longer recommended as a sleep aid in children primarily due to its lack of significant efficacy, as shown by the above-mentioned studies. One major drawback that has been cited is excessive sedation, which may seem beneficial at first, but often leads to excessive daytime drowsiness and impaired function, especially in school-aged children. A second potential adverse effect is paradoxical hyperactivity which is experienced by approximately 10% to 15% of children, resulting in restlessness. Additionally, potential anticholinergic effects may include dry mouth or throat, urinary retention, and constipation. There is the potential risk of life-threatening overdose leading to hallucinations, seizures, arrythmias, and cardiac arrest making it less suitable to use in children. The American Academy of Pediatrics (AAP) recommends alternatives to diphenhydramine, such as establishing a consistent bedtime routine, a comfortable sleeping environment, and promoting better sleeping habits including a limitation of screen time before bedtime. When pharmacologic adjuncts are needed, melatonin may be considered.

Treatment of Motion Sickness, Antiemetic Effect. Diphenhydramine, as the active constituent of dimenhydrinate (~55%), may have clinical efficacy in managing vestibular disturbances, notably in conditions such motion sickness, vertigo, and related disorders. However, to date, the majority of experience is anecdotal with limited evidence in pediatric-aged patients. Diphenhydramine works through a central antimuscarinic effect at higher doses and H_1-receptor antagonism within the CNS, acting on the area postrema and vomiting center in the vestibular nucleus. Diphenhydramine functions by inhibiting the histaminergic signal transmission from the vestibular nucleus to the vomiting center in the medulla. This action may be effective for the prevention and treatment of nausea and vomiting across various conditions including pregnancy, chemotherapy, and during the postoperative period.[19–22] Lu et al[20] demonstrated the efficacy of diphenhydramine and metoclopramide in preventing postoperative nausea and vomiting (PONV) following total abdominal hysterectomy as an additive to the patient-controlled analgesia solution.

Dimenhydrinate must be metabolized via multiple CYP enzymes (i.e., CYPs 2D6, 1A2, 2C9, 2C19) into its active ingredient, diphenhydramine, to attain antiemetic efficacy. Therefore, dimenhydrinate has a slower onset of action and has half the potency of diphenhydramine. Transdermal scopolamine has been compared to oral dimenhydrinate (100 mg) in a randomized, crossover trial on experimental motion sickness in 16 healthy adult volunteers.[21] Both pharmacologic agents were effective in treating nausea induced by rotation and head tilting (Coriolis maneuver). Additional studies suggesting the efficacy of dimenhydrinate in preventing or treating PONV including 5 pediatric trials are reviewed by Kranke et al[23] in their meta-analysis. However, the pooled relative benefit was only 1.2 to stay completely free of PONV during the early period and 1.5 for the overall investigated period.

ICU Sedation and Procedural Sedation. Given its sedative and sleep-inducing properties, diphenhydramine has been used in various clinical scenarios as a primary or adjunctive agent for sedation (Table 1).[24–27] In a case-controlled study, diphenhydramine decreased onset time to sleep and increased sleep duration in a cohort of 12 burn patients. Two prospective, randomized trials demonstrated improved sedation and decreased use of sedative/analgesia agents during

Table 1. Anecdotal Reports of Diphenhydramine Use for Procedural or ICU Sedation

Authors and Reference	Demographic Data and Clinical Scenario	Outcome
Yangzom[24]	Effect of diphenhydramine on sleep in 12 pediatric patients in the burn unit (mean age 10.5 ± 1.2 yr). Control group was case-matched non-DPH patients.	DPH patients took 4.3 ± 1.6 min vs 15.8 ± 1.6 min in non-DPH patients ($p = 0.06$). Total sleep was increased in DPH patients (297.6 ± 29.9 vs 209.2 ± 29.9 min, $p < 0.05$). No significant difference in stage 3 or 4 sleep. DPH group had 50% more rapid eye movement sleep time compared with the non-DPH group.
Tu[25]	Prospective, randomized trial in 270 adult patients presenting for colonoscopy. DPH (50 mg) administered intravenously 3 min before the start of the procedural sedation with intravenous meperidine and midazolam.	DPH patients had a 10.1% reduction in meperidine use and 13.7% reduction in midazolam use. Evaluation and efficacy scores were by faculty, fellows, nurses, and the patients scores were higher with DPH.
El Shahawy[26]	Prospective, randomized trial in 100 adult patients presenting for colonoscopy. DPH (50 mg) administered intravenously 3 min before the start of the procedural sedation with meperidine.	Total meperidine dose was decreased with DPH (61.2 ± 21.0 vs 69.9 ± 35.4 mg, $p < 0.01$) with no difference in the midazolam dose. More patients in the DPH were very satisfied with the procedure compared with placebo (88.67% vs 59.57%, $p < 0.001$) and more endoscopists were very satisfied (77.35% vs 51.06%, $p < 0.001$).
Cengiz[27]	Prospective, randomized trial in 96 children (aged 1–7 yr), who received either oral DPH (1.25 mg/kg) and midazolam (0.5 mg/kg) or oral midazolam alone for sedation during MRI.	There was an earlier onset of sedation and higher sedation scores in children who received DPH and midazolam. With midazolam alone, 20 children (41%) were inadequately sedated compared with 9 (18%) children who received midazolam and DPH.

DPH, diphenhydramine; MRI, magnetic resonance imaging

colonoscopy, while a final study suggested that oral diphenhydramine with oral midazolam improved sedation compared with oral midazolam alone during magnetic resonance imaging.

Local Anesthetic Effects. In addition to its antihistamine properties, topical diphenhydramine has properties similar to that of local anesthetics. The physiologic effects of diphenhydramine as a local anesthetic are attributed to its structural similarities to local anesthetic agents and sodium channel blockade.[28] Following initial animal studies in the 1950s, clinical work demonstrated the potential efficacy of diphenhydramine as a local anesthetic agent. Using an animal model, Landau et al[29] concluded that the local anesthetic effect of diphenhydramine (0.05%) was 2 to 4 times that of 0.05% procaine. In adults during superficial skin surgery, 1% injected diphenhydramine was as effective as 2% procaine while other investigators reported the efficacy of injected diphenhydramine during dental surgery including tooth extractions.[30–32] Injected diphenhydramine has subsequently been suggested as an alternative local anesthetic agent in patients with sensitivity or allergies to commonly used local anesthetic agents of the amide and/or ester class.[33–36] As a 1% solution, diphenhydramine is as effective as 1% lidocaine for superficial and dental procedures. Higher concentrations are not generally recommended with the caveat being that skin sloughing has been reported with concentrations ≥ 5%.[37]

Adverse Physiologic Effects

CNS Effects. As the first-generation H_1 receptor antagonists (antihistamines) cross the blood–brain barrier and bind to CNS H_1 receptors, these interactions can result in drowsiness, sedation, fatigue, decreased cognition, and other adverse effects on CNS functions.[38] First-generation antihistamines also bind nonselectively to muscarinic, serotonin, and α-adrenergic receptors and may result in dry mouth, balance issues, and dizziness. The sedative effects of H_1 antihistamines can pose an indirect risk to patients, particularly considering that individuals may drive themselves to medical appointments, a task demanding heightened mental alertness. The use of antihistamines has been linked to an increased risk of work-related injuries.[39] In a driving simulator study conducted by the University of Iowa, adult volunteers who had received a 50-mg dose of diphenhydramine performed more poorly than drivers with a blood alcohol concentration of 0.1%.[40] Consequently, prescribing information for diphenhydramine emphasizes the need to caution patients about engaging in activities requiring mental alertness, such as driving or operating machinery. Patients experiencing sedation, dizziness, or drowsiness may need to prolong their stay in the infusion center or emergency department for their own safety, especially following the IV administration of these agents. Medications with anticholinergic effects may have the potential to impact the development of dementia in individuals with prolonged exposure to first-generation H_1 antihistamines.[41] Additional anticholinergic effects may include delirium, agitation, confusion, restlessness, hallucinations, xerostomia, elevated body temperature, mydriasis and blurred vision, tachycardia, and urinary retention.

Perhaps of more concern is the potential impact of first generation antihistamines on the EEG pattern of young children and their potential association with or ability to provoke seizures. First-generation antihistamines have been shown to alter electroencephalographic (EEG) patterns, and induce symptomatic seizures, especially in susceptible individuals.[42–44] These concerns are support by animal studies showing that H_1 antihistamines increase seizure susceptibility in mice.[45] In a retrospective study of 49 children with febrile seizures (14 with simple febrile seizures and 35 with complex febrile seizures), the time from fever detection to seizure onset was significantly shorter (3.11 ± 0.79 vs 4.15 ± 1.16 hours, $p < 0.001$) and the duration of the seizure significantly longer (39.3 ± 14.2 vs 28.1 ± 15.6 minutes, $p < 0.05$) in patients who had received antihistamines.[46] The authors also postulated a mechanism as interleukin-1b is thought play an etiologic role in febrile seizures by both causing fever as well as being a pro-convulsant mediator through increasing the turnover of histamine within the hypothalamus and the CNS. Through this mechanism, antihistamines may deplete hypothalamic neuronal histamine and increase neuronal excitability. Similar findings with shortened time from onset of fever to seizure and longer seizure duration were reported in a second retrospective cohort of 250 infants and children (mean age 28.3 months) presenting with febrile seizures.[47] Eight-four patients had received an antihistamine (first or second generation) while 166 had not. When separating out first and second generation antihistamines, the impact (time from onset of fever to seizure and seizure duration) was greater with the first generation group.

The association of antihistamines with seizures may extend beyond the spectrum of febrile seizures.[48,49] Using a hospital-based database, 363 patients with new-onset seizures were retrospectively evaluated and the underlying etiology of new-onset seizures was determined.[48] Seven general etiologic categories were identified including medication, alcohol, encephalitis, stroke, hypoxic-ischemic injury, metabolic, and unclassified. The most common causative or temporally-related medications were antihistamines, followed by stimulants, and antibiotics. The majority of patients with antihistamine-induced seizures were receiving therapeutic doses. The authors concluded that given their widespread use as OTC medications, antihistamines around should be considered as a possible cause of new-onset seizures.

The same investigators more recently provided additional information regarding the potential association of antihistamines with seizures.[49] Using the National Health Insurance Database base in Korea, the authors identified a total of 11,729 children who had a seizure event, and then used a self-controlled, case-crossover design to determine the association and odds risk of antihistamine use with the seizure event. Use of first-generation antihistamines was associated with an increased adjusted odds ratio (AOR) of a seizure event during the hazard period of 1.22 (95% CI, 1.13–1.31). Subsequent analysis suggested that the AOR was higher in children aged 6 to 24 months compared with those who were 25 months to 6 years of age (AOR 1.49 [95%CI, 1.31–1.70] vs 1.11 [95%CI, 1.00–1.24], p = 0.04). The authors concluded that prescriptions for first-generation antihistamines were associated with a 22% higher seizure risk in children.

Cardiovascular Effects. Potential cardiovascular effects that have been reported with diphenhydramine use include tachycardia (anticholinergic effect) and conduction disturbances such as bundle branch block, atrioventricular dissociation, atrioventricular block, and widening of the QRS complex.[50–59] Arrhythmias may be related to alterations in repolarization or prolongation of the QT interval. The electrophysiologic and conduction effects of diphenhydramine are the result of blockade of fast sodium channels and prolongation of phase 1 of the cardiac action potential, thereby increasing the duration of depolarization. QT interval prolongation can also occur especially with high doses of diphenhydramine, which can result in lethal ventricular arrhythmias including *torsade de pointes*. Prolongation of the QT interval results from the blockade of potassium channels with lengthening of phase 3 repolarization of the cardiac action potential. Cardiac conduction effects are seen with other antihistamines. Terfenadine, a second-generation non-sedating antihistamine drug, was removed from the United States market due to the drugs ability to prolong the QT interval. The impact of these effects on cardiac conduction and arrhythmogenesis has

Table 2. Anecdotal Reports of Cardiac Conduction Disturbances or Arrhythmias With Diphenhydramine

First Author and Reference	Case Summary
Cole[51]	13-mo-old ingested 1000 mg of diphenhydramine. Two hr prior to presentation, the child was found with an empty bottle which had contained 24 of the 25-mg tablets. Wide QRS complex tachycardia. ECG changes improved after the administration of sodium bicarbonate.
Shah[52]	55-yr-old with hypertension, cardiac disease, and renal failure. Two doses of diphenhydramine (50 mg) on 2 consecutive days during hemodialysis. Prolonged QTc noted on telemetry and confirmed by a 12-lead ECG. The prolonged QTc resolved on subsequent ECGs.
Thakur[53]	17-yr-old adolescent with diphenhydramine overdose. Ingested an entire bottle of diphenhydramine tablets and was found unresponsive on a park bench. Time between ingestion and presentation was unknown. Anticholinergic symptoms noted including tachycardia, tachypnea, hyperthermia, and hypertension. ECG demonstrated right bundle branch block with a prolonged QT interval (522 ms).
Husain[54]	44-yr-old woman ingested ≥ 3 grams of diphenhydramine with alcohol. QTc prolongation with non-sustained polymorphic ventricular tachycardia.
Sype[55]	40-yr-old woman ingested 625 mg of diphenhydramine as a suicide gesture, several hours prior to admission. QTc prolongation with abnormal ventricular repolarization and biphasic T waves. Airway protection and mechanical ventilation due to progressive lethargy. ECG changes reverted to normal during monitoring of serial ECGs without therapeutic intervention
Zareba[56]	Cohort of 126 patients, including 12 children less than 15 years of age, presenting with diphenhydramine overdose (>500 mg). Signs and symptoms included tachycardia, decreased T wave amplitude, and prolonged QTc interval.
Chen[57]	49-yr-old woman with diphenhydramine dependence who injected diphenhydramine intramuscularly with increasing frequency and dose over 6 mo. Total daily dose ranged from 30 to 450 mg per day. QTc prolongation on ECG which resolved with supportive care.
Andersen[59]	3-mo-old with trisomy 21 status post-surgical repair of atrioventricular septal defect. Intravenous diphenhydramine (1.25 mg/kg) administered intravenously for agitation. Within 1–2 min after diphenhydramine administration, acute cardiac decompensation occurred with bradycardia, wide QRS complex, and cardiac arrest. Successful resuscitation.

ECG, electrocardiogram

been highlighted by previous anecdotal reports of arrhythmias following the ingestion or administration of diphenhydramine (Table 2).[51–57,59] These effects occurred most commonly with high serum concentrations related to toxic doses or rapid IV administration.

Summary

In the United States, diphenhydramine maintains approval as the sole first-generation H_1 antihistamine for IV use. Intravenous diphenhydramine continues to have several potential clinical applications (Table 3). However, as with any medication, the potential adverse effect profile and risk-benefit ratio must be weighed. Adverse CNS effects related to its sedative properties include drowsiness, sedation, fatigue, and decreased cognition. Additional adverse effects related to cholinergic-receptor blockade (anticholinergic effects) include dry mouth, balance issues, and dizziness. Anticholinergic effects may include delirium, agitation, confusion, restlessness, hallucinations, xerostomia, elevated body temperature, mydriasis and blurred vision, tachycardia, and urinary retention. Recent attention has been focused on the potential association of antihistamine use and new onset seizures or development of febrile seizures. Consideration of these concerns may impact prescribing practices especially in young children or those with febrile illnesses.[60]

Some aspects of adverse effect profile may be improved with second generation antihistamines such as cetirizine (Zyrtec) with limited CNS penetration and more specificity for peripheral H_1 receptors. As summarized in their review of three studies in adults, Blaiss et al[61] noted that second-generation antihistamines have an improved adverse effect profile when compared with first-generation antihistamines including less drowsiness and decreased impact on cognitive function. The decreased adverse-effect profile is related to the functional groups attached to the ethylamine side chain, which results in decreased CNS penetration and a greater selectivity for the H_1 receptor. P-glycoprotein (pGp)-mediated efflux and passive permeability contribute to the low cetirizine brain concentrations and may account for the differences in the sedation side-effect profiles of second generation antihistamines. However, given the maturation of the blood–brain barrier, the impact of these pharmacologic alterations may less in infants and young children than in adults.

Of primary concern, especially in critically ill patients or those with underlying cardiac comorbid conditions relate to effects on cardiac conduction. The electrophysiologic effects of diphenhydramine result from blockade of fast sodium channels and prolongation of phase 1 of the cardiac action potential, thereby increasing the duration of depolarization. The majority of the reported cardiovascular toxicity related to diphenhydramine have resulted from excessive or toxic doses. As diphenhydramine offers no particular benefit as a sedative in the Pediatric ICU setting or in critically ill patients, its use in this scenario warrants evaluation. In addition to its potential effects on conduction, medications with pronounced anticholinergic properties, such as diphenhydramine, have demonstrated an association with an increased incidence and heightened severity of delirium in the Pediatric ICU patient. Since the cardiovascular effects are dose-dependent, rapid IV administration which may result in high blood concentrations should be avoided. Whenever feasible, oral administration is recommended and in cases where IV administration is deemed necessary, it is advised to utilize a prolonged infusion time ranging from 3 to 5 minutes.

Table 3. Potential Clinical Applications Indications for Intravenous Diphenhydramine

1. To alleviate allergic reactions to blood or blood products.
2. As an adjunct after the administration of epinephrine in the treatment of anaphylaxis.
3. The treatment of uncomplicated allergic (non-anaphylactoid) conditions of the immediate type when oral therapy is not possible or contraindicated.
4. Treatment of motion sickness.
5. For use in Parkinsonism, when oral route is not feasible or is contraindicated. In combination with centrally acting anticholinergic agents.
6. To optimize sleep pattern, improve quality or quantity of sleep, and reduce sleep latency in the hospitalized patient. This indication is not currently endorsed by the American Academy of Pediatrics.
7. As an adjunct to sedative and analgesic agents during procedural sedation (colonoscopy).
8. As an alternative to standard local anesthetic agents for minor superficial surgical procedures in patients with documented allergies.
9. As part of a topical anesthetic agent for minor abrasions or as a mouthwash to treat mucositis associated with chemotherapy.

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