Neurology® Clinical Practice

Case

Chronic diphenhydramine abuse and withdrawal

A diagnostic challenge

Jagroop S. Saran, MD; Richard L. Barbano, MD, PhD; Rachel Schult, PharmD; Timothy J. Wiegand, MD; Olga Selioutski, DO

Diphenhydramine (DPH) acts on peripheral and central histamine H_1 receptors, causing reduction of allergic symptoms and sedation, respectively.[1] It is also a potent competitive antagonist of muscarinic acetylcholine receptors and can cause sinus tachycardia, xerostomia, mydriasis, blurred vision, ileus, urinary retention, CNS depression, agitation, hyperactivity, or psychosis. Given multiple potential mechanisms of action and its use for a variety of conditions, cases of medication misuse and abuse have been reported,[2–5] primarily due to behavioral effects such as elevated mood, increased energy levels, and mild euphoria.[6]

Practical Implications

Given widespread and unrestricted use of diphenhydramine, it is important to recognize signs and symptoms of chronic DPH abuse and acute withdrawal to provide timely and effective treatment while avoiding use of unnecessary and potentially harmful medications.

Case report

A 21-year-old man with multiple previous admissions for presumed toxic ingestions presented to an outside hospital with psychosis, tremors, and seizure-like events. Extensive diagnostic workup including basic laboratory testing, brain MRI, CSF analysis, and urine toxicology screen were unremarkable. Despite treatment with levetiracetam and phenytoin for presumed seizures along with haloperidol and benzodiazepines for symptomatic management of ongoing psychosis, his clinical status remained unchanged.

The patient was transferred to our facility for continuous EEG (cEEG) monitoring due to concern for recurrent seizures as reason for nonresolving encephalopathy. On examination, pertinent findings included sinus tachycardia, altered mental status, hypersalivation, diaphoresis, and flushed but cool and clammy skin. Neurologic examination revealed hypomimia, hypophonia, dysarthria, mydriasis, restricted upgaze, postural tremor, 4-limb rigidity with bilateral brisk reflexes, and recurrent episodes of tremors, staring, and decreased responsiveness. When alert and oriented, he was notably uncomfortable. The recurrent episodes of tremors, staring, and decreased responsiveness captured on cEEG monitoring were not epileptic seizures. cEEG monitoring revealed diffuse background slowing with preserved organization and a poorly sustained posterior dominant rhythm. Twenty-four-hour urine screen showed slightly elevated epinephrine and metanephrine levels, believed to be inconsequential.

Tachycardia, sweating, hypersalivation, and mydriasis were consistent with either sympathetic hyperactivity or anticholinergic agent withdrawal. Hypomimia and hypophonia, dysarthric speech, and restricted upgaze suggested either anticholinergic withdrawal or side effects of dopamine blockers. The differential possibilities included neuroleptic malignant syndrome, oculogyric crisis, serotonin syndrome, and toxic encephalopathy.

Departments of Anesthesiology (JSS), Neurology (RLB, OS), and Emergency Medicine (RS, TJW), University of Rochester School of Medicine and Dentistry; and Department of Pharmacy (RS), University of Rochester Medical Center, NY.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Correspondence to: Jagroop_Saran@URMC.rochester.edu

A history of chronic DPH abuse was uncovered including several hospitalizations related to acute intoxications and overdose from DPH. The history of persistent abuse of DPH suggested that a potential withdrawal syndrome from abrupt cessation of DPH was another possibility. IV administration of 50 mg of DPH resulted in immediate improvement of tremor, rigidity, tachycardia, and eye versions. The patient was started on oral DPH 50 mg 4 times a day and the dose was reduced by 25% every 3 days. Oral clonidine 0.1 mg 3 times a day and a weekly 0.1 mg transdermal patch was added to mitigate sympathetic side effects.

DISCUSSION

Abuse of DPH may be difficult to identify; overdose symptoms are similar to acute psychosis and often prompt hospitalization, which may precipitate unintentional withdrawal from the anticholinergic agent, symptoms of which are nonspecific and overlap with many other conditions. Moreover, dopamine antagonists used to manage psychosis have overlapping extrapyramidal effects with prominent autonomic features further confounding the diagnosis. Administration of DPH serves both diagnostic and therapeutic purposes. In addition to reinstatement of DPH and discontinuation of dopamine antagonists, symptomatic management of systemic symptoms should be provided. In our case, clonidine was used for its nonspecific sympatholytic effects by decreasing norepinephrine outflow via the presynaptic $\alpha 2$ receptors in the CNS and sedative effects via the imidazoline receptor to help reduce anxiety during DPH weaning.

Increased dopaminergic neurotransmission in the mesolimbic pathway is thought to be responsible for rewarding properties and drug-seeking behavior leading to antihistamine abuse but the exact mechanism leading to abuse is unknown.[2] In the CNS, the complex interaction between the cholinergic and dopaminergic systems in the cortex and basal ganglia is nonunidirectional but rather mutual, modulating synaptic transmission and plasticity and modifying dopamine release implicated in cognitive processes, motor responses, and reward-related information.[7] There are a number of other anticholinergic agents that have been abused. In the 1970s, tripelennamine, a first-generation antihistamine, was mixed with pentazocine, an opioid, for its euphoric effects, and this combination was known by its slang name, *Ts and blues*. Trihexyphenidyl has been used recreationally for its hallucinogenic effects. The use of DPH to treat a variety of conditions without regulatory control further contributes to the potential for misuse and abuse. Clinicians should consider DPH withdrawal in the differential diagnosis of acute onset mental status changes in any patients who might be taking this widely available over-the-counter medication.

REFERENCES

1. Khilnani G, Khilnani AK. Inverse agonism and its therapeutic significance. Indian J Pharmacol 2011; 43:492–501.
2. Thomas A, Nallur DG, Jones N, Deslandes PN. Diphenhydramine abuse and detoxification: a brief review and case report. J Psychopharmacol 2009;23:101–105.
3. Feldman MD, Behar M. A case of massive diphenhydramine abuse and withdrawal from use of the drug. JAMA 1986;255:3119–3120.
4. MacRury S, Neilson R, Goodwin K. Benylin dependence, metabolic acidosis and hyperglycaemia. Postgrad Med J 1987;63:587–588.
5. Gracious B, Abe N, Sundberg J. The importance of taking a history of over-the-counter medication use: a brief review and case illustration of "PRN" antihistamine dependence in a hospitalized adolescent. J Child Adolesc Psychopharmacol 2010;20:521–524.
6. Halpert AG, Olmstead MC, Beninger RJ. Mechanisms and abuse liability of the anti-histamine dimenhydrinate. Neurosci Biobehav Rev 2002;26:61–67.
7. Calabresi P, Di Filippo M. ACh/dopamine crosstalk in motor control and reward: a crucial role for alpha 6-containing nicotinic receptors? Neuron 2008;60:4–7.

Received June 15, 2016. Accepted in final form August 10, 2016.

AUTHOR CONTRIBUTIONS

J.S. Saran: drafting and revision of manuscript. R. L. Barbano: critical revision of manuscript. R. Schult: critical revision of manuscript. T. Wiegand: critical revision of manuscript. O. Selioutski: critical revision of manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

J.S. Saran reports no disclosures. R.L. Barbano serves on a scientific advisory board for Allergan; serves as an associate editor for *Neurology® Clinical Practice*; performs botulinum toxin injections at the University of Rochester (30% effort); receives research support from Allergan, Vaccinex, and Biotie; has received research support from NIH, NINDS, ORDR: Dystonia Coalition Projects, Site PI; holds stock/stock options in VisualDx; and has served as an expert witness in legal proceedings including malpractice, not involving commercial entities. R. Schult reports no disclosures. T. Wiegand is an Associate Editor of the *Encyclopedia of Toxicology*, 3rd ed.; receives publishing royalties from UpToDate; and serves as a consultant for Research Abuse Diversion and Addiction Related Surveillance (RADARS). O. Selioutski has received compensation from SAGE Therapeutics, Sepracor/Sunovion, Bial, and Upsher-Smith as a primary investigator in clinical research trials; and serves as adjunct faculty at Genesee Community College (Polysomnographic Technology Program). Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.