Acute delirium caused by diphenhydramine withdrawal in a medically complex patient

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BACKGROUND

The abuse potential of many over-the-counter (OTC) medications has been well-documented. Diphenhydramine is a first-generation H1 receptor blocker with a multitude of effects (**Table 1**) often misused for mood elevation, sedation, and hallucinogenic effects. Abrupt discontinuation of diphenhydramine may result in cholinergic rebound, although little literature exists on treatment recommendations.

CASE PRESENTATION

Patient is a 65-year-old female with history of hypertension, hyperlipidemia, type II diabetes mellitus, gastritis, migraines and chronic back pain, major depressive disorder (MDD) with psychotic features and multiple substance use disorders (diphenhydramine, alcohol, benzodiazepines and zolpidem) who presented to the emergency department for 4 days of headache and dizziness and was admitted for anemia and acute kidney injury (AKI). On the second day of admission, psychiatry was asked to consult on the patient for anxiety and tactile hallucinations. On examination, she appeared restless with tremors in all 4 extremities, reporting headache, urinary incontinence, tactile and auditory hallucinations of the noise of a "bee" in her left ear. Urine toxicology for drugs and alcohol were negative. She stated she last used one or two tablets of diphenhydramine the day before admission, though was unsure of the exact dose. There was no clonus or pupillary abnormality, and deep-tendon reflexes were normal. CT head without contrast was normal.

Psychiatry recommended alcohol withdrawal precautions due to unclear history of benzodiazepine use, despite negative urine toxicology. Quetiapine PO and olanzapine IM were recommended as needed for mild and severe agitation, respectively. Home medications of valproic acid and donepezil were resumed. Vital signs were stable, with blood pressure ranging from 90-120 mm Hg systolic and 50-70 mm Hg diastolic, with heart rate ranging from 70-90 bpm. Due to suspicion of anticholinergic withdrawal causing cholinergic rebound symptoms, patient was started on an oral diphenhydramine taper as detailed in **Table 2**. On the day of discharge, patient appeared bright in affect, denying physical complaints including tremors, restlessness or incontinence. She was discharged on hospital regimen of valproic acid 250 mg AM and 500 mg PM, and quetiapine 25-50 mg daily as needed for anxiety.

CASE PRESENTATION (CONTINUED)

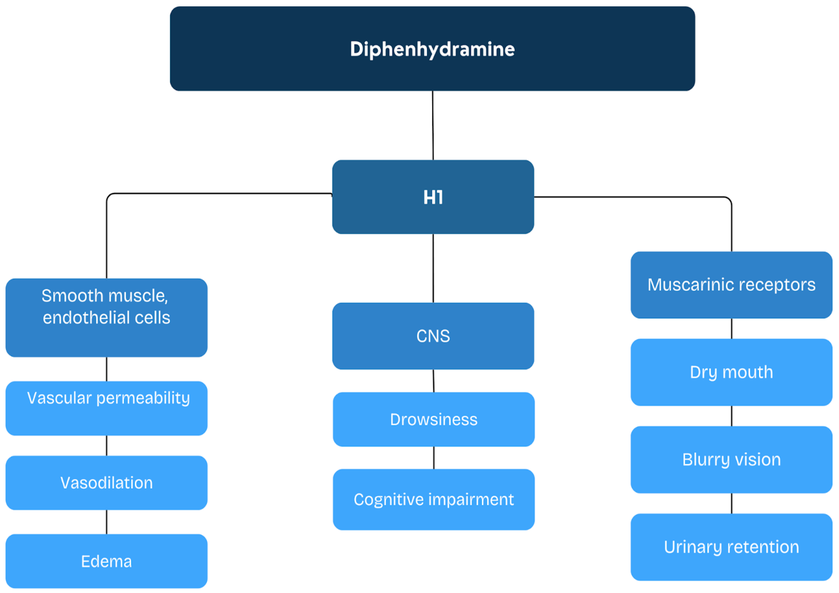

Table 1. Effects of diphenhydramine on H1 receptor causing changes within smooth muscle/endothelial cells, central nervous system (CNS), and muscarinic receptors.

Day 1	DPH 25 mg	DPH 25 mg	DPH 25 mg	DPH 25 mg	Total DPH dose = 100 mg
Day 2	DPH 25 mg	DPH 25 mg	DPH 25 mg		Total DPH dose = 75 mg
Day 3	DPH 25 mg	DPH 25 mg	DPH 25 mg		Total DPH dose = 75 mg
Day 4	DPH 25 mg	DPH 25 mg			Total DPH dose = 50 mg
Day 5	DPH 25 mg				Total DPH doce = 25 mg

Table 2. Table summarizing diphenhydramine (DPH) taper schedule over 5 days of inpatient hospitalization.

DISCUSSION

Acute diphenhydramine withdrawal may be difficult to detect in a patient with multiple comorbidities, history of psychosis or substance use disorders. Cholinergic rebound usually occurs after abrupt discontinuation of drugs that block acetylcholine receptors including agitation, confusion and psychosis. The biopsychosocial model is imperative to understanding patients' motivations and decisions in using OTC medications thought to be benign. It is the duty of the CL psychiatrist to help educate patients on safe use of medications while understanding and respecting barriers to implementing these practices, be it educational, cultural, or biological.

CONCLUSION

- The above case details the importance of recognizing acute diphenhydramine withdrawal and cholinergic rebound in patients with signs of delirium and agitation with known or suspected use of OTC agents
- Some literature suggests that patients who take antipsychotics may experience more rewarding effects from anticholinergic medications due to their potential to reverse negative symptoms associated with antipsychotics, suggesting elevated prevalence in this patient population
- Taper schedule should take into consideration dose the patient had been taking and the amount of time on the medication, as well as symptomatic improvement.
- CL psychiatrists have a unique role in assessing potentially overlooked OTC medication misuse and the unique features of dependence and withdrawal in psychiatric patients

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