Procyclidine overdose induced central and peripheral anti-cholinergic toxicity

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ABSTRACT
Procyclidine is an anticholinergic agent that blocks excess acetylcholine at cerebral synapses. We describe central and peripheral anticholinergic toxicity in a 34-year-old male after 60 tablets of procyclidine (300 mg). He displayed acute agitation, tachycardia, mydriasis, dry mucous membranes, and urinary retention. Physostigmine is the antidote of anticholinergic toxicity but is unavailable in Qatar. He received supportive care in the ICU with repeated doses of diazepam and lorazepam. He improved sufficiently in three days to transfer to a psychiatric facility. We discuss and compare the roles of physostigmine and benzodiazepines in treating anticholinergic toxicity.

Introduction
Anticholinergic agents are effective adjuncts for the relief of extrapyramidal side effects. Procyclidine is a synthetic anticholinergic that can cross the blood–brain barrier causing cholinergic and dopaminergic activity balance in the basal ganglia. Food and Drug Administration (FDA) approved the use of procyclidine for the management of Parkinson’s disease and extrapyramidal side effects [1]. Although abuse of anticholinergic agents such as procyclidine seems to be rare, two cases have described abuse leading to anticholinergic toxicity [2,3]. The anticholinergic toxidrome can manifest with altered level of conscious, agitation, cardiac arrhythmias, hypothermia, blurred vision, dry mouth, and urinary retention. These manifestations are not all present in all patients with toxicity, and only 30% of patients may present with three classic symptoms such as mydriasis, tachycardia, and dry skin [4]. Other patients might present with delirium only [5]. We present a rare case of procyclidine overdose manifesting with anticholinergic toxicity.

Case details
A 34-year-old male with a history of schizophrenia on paliperidone 100 mg monthly injection and procyclidine 5 mg twice daily presented to the emergency department (ED) by family. The family reported that the patient ingested 60 tablets of procyclidine (300 mg) and he was agitated. The patient arrived at 00:02 to the ED and he ingested the tablets around 22:00. He was normotensive 132/80 mmHg, but he was tachycardic (heart rate = 126 B.M., normothermic (temperature = 37 °C), and tachypneic (respiratory rate = 26 RPM). His pupils were 3–4 mm in diameter and sluggishly reactive. He had dry mucous membranes, clear breath sounds on auscultation, and normal bowel sounds. The electrocardiogram showed a sinus tachycardia of 110 with QT interval of 303 ms and QTc 449 ms and premature atrial complexes. The patient’s complete blood count comprehensive metabolic panel, troponin, international normalized ratio (INR), and prothrombin time were normal and toxicology screen for acetaminophen, salicylate, and TCA were negative. As his initial lactate was 4.1 mmol/L, the patient received a 1 L bolus of intravenous (IV) lactated ringer over 1 hour followed by maintenance IV fluids. Ideally, physostigmine is the treatment for central anticholinergic toxicity [6]. Since physostigmine is unavailable in Qatar, the patient received diazepam 5 mg IV at 00:30 and a repeated dose at 3:35 as he became combative, agitated, and tried to remove the IV lines. The patient was admitted to the medical intensive care unit (MICU) for close monitoring; upon admission the patient was calm. At 6:00, the patient received lorazepam 2 mg IV as he started developing agitation, hallucinations, and urinary retention. Over his MICU stay, the patient received five doses of lorazepam for agitation and combativesness. The patient was vitally stable throughout his MICU stay. The patient had a slight increase in his serum CK (221 U/L normal range 30–200

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U/L), which came back to normal 24 hours later. The patient improved sufficiently to transfer to a mental health facility as he continued to have suicidal ideation.

Discussion

Procyclidine was prescribed for our patient for the prevention of dystonic effects of the antipsychotic medication paliperidone. The patient consumed 60 tablets (300 mg), while the maximum therapeutic dose is 20 mg/day [7]. Anticholinergics inhibit the muscarinic receptors that are present in the central nervous system (CNS) and the peripheral nervous system [4,8]. Our patient displayed symptoms secondary to anticholinergic toxicity. Central manifestations included agitation and delirium while peripheral manifestations included tachycardia, urinary retention, and dry skin.

Severity of anticholinergic overdose determines its management. In mild to moderate overdose, good supportive care and hydration is enough, but in case of severe CNS side effects (agitation and/or delirium), treatment options include physostigmine, benzodiazepines, and hydration. Physostigmine is an acetylcholinesterase inhibitor that crosses the blood–brain barrier, reversing the central anticholinergic effects [6]. Physostigmine can be administered at a dose of 0.5–2 mg IV over 5 minutes, when the patient has no contraindications to its use, including dysrhythmias, any degree of heart block or QRS >100 ms [8].

Burns et al. found physostigmine to be superior to benzodiazepines in the management of anticholinergic toxicity-induced agitation [9]. Their retrospective chart review compared physostigmine versus benzodiazepines in 52 patients with anticholinergic toxicity. The authors found that physostigmine controlled agitation in 96% patients compared to 24% of patients received benzodiazepines. Initial treatment with physostigmine significantly reduced the incidence of agitation and level of CNS stimulation compared to benzodiazepines. Moreover, patients in the physostigmine arm had a shorter time of recovery (median, 12 vs. 24 hours) compared to those treated with benzodiazepines [9]. Teoh et al. described a procyclidine overdose treated successfully with physostigmine after benzodiazepines (equivalent to 125 mg diazepam over 1 day) failed to control delirium [10].

Several studies showed that physostigmine is very effective in reversing the anticholinergic toxicity-induced agitation and delirium and physostigmine has a good safety profile [6,8–12]. Physostigmine is the antidote of choice for anticholinergic. Benzodiazepines, while safe, are generally ineffective in treating anticholinergic delirium [9,12].

Conclusion

Procyclidine toxicity inducing anti-cholinergic manifestations is rarely reported. Physostigmine in addition to supportive care should be considered a treatment option in the setting of anticholinergic toxicity. But if physostigmine is unavailable then the anticipated anti-cholinergic toxicity can be treated with benzodiazepines

Acknowledgement

The authors thank Dr. Rasha Al Anany, PharmD and Mr. Shamjith Kandaram Patta, RN for their help in this case.

Disclosure statement

No potential conflict of interest was reported by the authors.

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