CASE REPORT

Dexmedetomidine Infusion to Control Agitation due to Anticholinergic Toxidromes in Adolescents, a Case Series

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Dexmedetomidine is an α_2-adrenergic agonist approved by the US Food and Drug Administration for the sedation of adults who are intubated on mechanical ventilation and in non-intubated adults who are undergoing surgical procedures. However, it has also recently become a commonly used sedative agent in varied clinical settings for the pediatric patient as well. We present the use of dexmedetomidine for sedation in a unique clinical scenario, the severely agitated and combative patient following the intentional misuse of anticholinergic drugs. Its applications in this situation are discussed, and previous reports in the literature are reviewed.

INDEX TERMS: adolescent, anticholinergic toxidrome, dexmedetomidine, toxicity

J Pediatr Pharmacol Ther 2015;20(4):329–334

INTRODUCTION

Every year, approximately 90,000 calls are made to poison control centers for antihistamine and related anticholinergic exposures.[1] Of these, there are reported cases of adolescents who misuse these substances, likely due to ease of availability. Common anticholinergics include antihistamines (diphenhydramine, hydroxyzine, chlorpheniramine), atropine, carbamazepine, tricyclic antidepressants, jimsonweed (*Datura stramonium*), atypical antipsychotics (quetiapine and buspirone), and scopolamine (Table 1). The mnemonic "mad as a hatter, dry as a bone, blind as a bat, hot as a hare, and red as a beet" is often used to recall the symptom profile of the anticholinergic toxidrome. Clinically, this manifests as delirium, agitation, dry mouth, warm and dry skin, mydriasis, fever, tachycardia, hypertension, and flushing. The severe agitation, combativeness, and mental status changes that occur with toxic ingestions of anticholinergics are often what prompt the seeking of medical attention. This profound derangement in behavior results not only in potential self-harm but also in harm to the health care providers taking care of these patients. Given such safety concerns, sedation may be required until the effects of the medication(s) dissipate. Often, this situation requires inpatient admission for close observation.

Recent experience has demonstrated the potential usefulness of dexmedetomidine (Precedex, Hospira, Lake Forest, IL) in providing safe sedation in multiple scenarios.[2–9] Because of its minimal effect on respiratory function, dexmedetomidine is becoming more widely used as a sedative agent without the increased risk of respiratory compromise.[5,7] In addition, dexmedetomidine does not appear to potentiate the risks of dysrhythmias in the setting of QT prolongation, a common sequela in ingestion cases.[10–12] We present anecdotal experience with using dexmedetomidine to control the agitation related to the ingestion of pharmacologic agents causing anticholinergic side effects. Its application in these unique scenarios is discussed, and previous reports are reviewed.

CASE SERIES

Review of these cases and presentation in this format was approved by the institutional review board of Nationwide Children's Hospital (Columbus, OH).

Table 1. Common Agents Causing Anticholinergic Toxidrome

Antihistamines • Cetirizine • Chlorpheniramine • Cyproheptadine • Diphenhydramine • Fexofenadine • Hydroxyzine • Loratadine	**Antimuscarinics** • Atropine • Benztropine • Doxylamine • Glycopyrrolate • Hyoscyamine • Oxybutynin • Scopolamine • Trihexyphenidyl	**Antinicotinics** • Bupropion • Dextromethorphan	**Atypical Antipsychotics** • Clozapine • Olanzapine • Quetiapine
Phenothiazines • Chlorpromazine • Prochlorperazine • Thioridazine	**Plant Derivatives** • *Amanita muscaria* (fly amanita mushroom) • *Atropa belladonna* (deadly nightshade, atropine derivative) • *Brugmansia arborea* (angel's trumpet) • Datura stramonium (jimsonweed) • Hyoscyamus niger (henbane, stinking nightshade) • Mandragora officinarum (mandrake)		**Cyclic Antidepressants** • Amitriptyline • Chlorimipramine • Cyclobenzaprine • Desipramine • Doxepin • Imipramine • Nortriptyline

Case 1

A 13-year-old, 63-kg, previously healthy male was seen at an outside emergency department (ED) for acute mental status changes. The patient admitted that he "smoked a joint and drank some tequila." Laboratory results were negative for acetaminophen, aspirin, and ethanol. However, because of persistent combativeness, arrangements were made to transfer the patient to our tertiary care facility for further management. Before transport, the patient required intravenous (IV) lorazepam, 2 mg, for agitation.

In our ED, vitals were heart rate (HR), 120-140 beats/min; blood pressure (BP), 120-130/50-60 mm Hg; and respiratory rate (RR), 16-18 breaths/min. He was actively hallucinating and required 4-point restraints for staff safety, despite an additional dose of IV lorazepam, 2 mg, upon arrival. Other pertinent exam findings were minimally reactive, 6-mm pupils; hypoactive bowel sounds; and flushed skin. Comprehensive drug testing was positive for diphenhydramine and cotinine. The patient's initial electrocardiogram (ECG) was also concerning for a prolonged QTc of 475 ms (reference range, <450 ms). The patient was thus admitted to the pediatric intensive care unit (PICU) for close monitoring.

In the PICU, the patient continued to have severe agitation and aggression. Two more doses of lorazepam, 2 mg IV, were administered less than 30 minutes apart because of the short duration of effect. However, after these additional doses, the patient developed intermittent upper respiratory obstruction related to his sedation. Recognizing that this patient would require continued sedation and fearing further benzodiazepine administration would compromise his ability to protect his airway, a dexmedetomidine infusion was initiated. Dexmedetomidine was started at 0.5 mcg/kg/hr without a bolus dose by syringe pump. During the next 24 hours, no further episodes of agitation occurred, and no additional bolus doses of sedatives were needed.

The patient did not experience any hemodynamic instability while on dexmedetomidine, but he did have transient bradycardia to the 60s, which subsequently improved with a decrease in the infusion dose to 0.3 mcg/kg/hr. His QTc had normalized after 24 hours, and the dexmedetomidine was discontinued as the patient became more cooperative. The patient was discharged home on hospital day 2.

Case 2

A 15-year-old, 75-kg female was brought to a local ED after confessing that she had intentionally ingested 17 divalproex sodium, 500-mg, extended-release tablets; 17 quetiapine, 150-mg tablets; and 37 buspirone, 10-mg tablets. All of these medications were the patient's own bipolar medications. In the ED, she presented with decreased mental status. Evaluation was notable for a valproate level of 73 mg/L (therapeutic range: 50-100 mg/L). Her ECG also demonstrated a QTc of 450 ms, with occasional premature ventricular contractions. The patient was transferred to our

hospital for further management.

At our hospital, the patient continued to be sleepy. Pertinent exam findings were 3-4 mm, sluggish pupils; normoactive bowel sounds; and psychomotor agitation with noxious stimulation. Vital signs were HR, 70-90; BP, 86-102/40-62 mm Hg; and RR, 16-22. A repeat valproic acid concentration was 128.9 mg/L (approximately 6 hours after ingestion). She was thus admitted to the general pediatrics floor with continuous telemetry monitoring overnight.

As the patient's sensorium improved, however, she became more aggressive with staff. She would hit, bite, and scream with nursing care. Toxicology specialists attributed this behavioral change to the prolonged effects of quetiapine, also noting that her QTc had now peaked at 480 ms. Because of the patient's extreme behavior, hospital security had been called multiple times to the bedside for staff safety concerns. The patient ultimately received pharmacologic restraint with intramuscular haloperidol, 2 mg, and multiple doses of lorazepam, 4 mg IV, for her combativeness, but with only short-term effects. The patient was consequently transferred to the PICU for continuous dexmedetomidine.

In the PICU, dexmedetomidine was started at 0.3 mcg/kg/hr without a bolus dose. Within 30 minutes, the patient tolerated care, and restraints were able to be discontinued. Her vitals were HR, 80s; and BP, 86-95/40s. Without any fluid boluses, she remained warm and well-perfused with good urine output. Her BP results improved to 110s/60s with decreases in the dexmedetomidine infusion by 0.1 mcg/kg/hr every few hours based on sedation scoring. For the next 19 hours, the original offending medications were allowed time to metabolize, and the patient eventually became more coherent on low-dose dexmedetomidine, 0.1 mcg/kg/hr. After this period, her QTc had normalized, and the patient was allowed to reinitiate her bipolar therapy medications. Upon discontinuation of the dexmedetomidine, the patient was transferred out of the PICU for ongoing psychiatric treatment.

Case 3

A 17-year-old, 68-kg male was brought to a local ED after his family had noticed him acting confused. His mother had noticed that approximately half of her bottle of diphenhydramine (25-mg tablets) was missing (estimated 3 g ingested) and endorsed that the patient had been having recent behavioral issues. In the ED, the patient had altered mental status and combativeness. Toxicology screen results were positive for delta-9-tetrahydrocannabinol (THC) and tricyclic antidepressants. His ECG showed a QTc of 460 ms. Charcoal was administered via nasogastric tube, and arrangements were made for transfer to our hospital.

In the PICU, lorazepam, 4 mg IV, was administered for agitation shortly after arrival, as the patient was uncooperative and pulling off monitoring leads. His exam was significant for the reaching of non-existent objects in the air; 5-6-mm, sluggish pupils; flushed extremities; and decreased bowel sounds. Vital signs were HR, 120s; BP, 150-160/80-90s; and RR, 20. Comprehensive toxicology screen confirmed the presence of cotinine, lorazepam, and diphenhydramine. As observed in case 2, the frequency and amount of lorazepam that was required for agitation control led to immediate concerns for the patient's ability to protect his airway. As anticipated, he soon demonstrated upper airway obstruction, which was relieved with repositioning. As the effects of the lorazepam quickly waned, dexmedetomidine was started at 1 mcg/kg/hr without a bolus dose. Vitals were HR, 62-95; with BPs, 113-140/47-70. He remained warm and well-perfused, but because of the lower HRs, the dexmedetomidine infusion dose was decreased to 0.5 mcg/kg/hr. At this dose, HRs improved, and satisfactory control of his agitation continued. After 24 hours of incremental decreases in the dexmedetomidine infusion titrated based on sedation scoring, the patient was fully cooperative, and the infusion was stopped. His QTc normalized. The patient was transferred to an inpatient psychiatric facility for subsequent care.

DISCUSSION

Supportive care is often the only therapy for ingestion cases, particularly those that involve poly substances. Although prescription medications are commonly involved, over-the-counter (OTC) medications have also been used as substances of abuse. Many of these OTCs contain an antihistamine ingredient resulting in the anticholinergic toxidrome: delirium, agitation, dry mouth, mydriasis, tachycardia, hypertension, and skin flushing. The patients in the cur-

rent series displayed many of these symptoms, with the most troublesome being agitation and delirium. Specific issues related to observed agitation include the risk of self-injury, injury to health care providers, and the risks of oversedation. In support of the recent article by Walker et al,[4] our anecdotal experience also demonstrates the effectiveness of dexmedetomidine (Precedex, Hospira, Lake Forest, IL) in controlling the agitation caused by the anticholinergic toxidrome.

Dexmedetomidine is an α_2-adrenergic agonist, structurally similar to clonidine, but it has a much greater affinity for the central α_2 receptors. This selectivity, specifically the locus coeruleus of the brain stem, allows for its sedative and anxiolytic effects with minimal respiratory effect.[2,5,17] The recommended infusion rate of 0.2 to 0.7 mcg/kg/hr generally provides a moderate depth of sedation.[6] Our institutional experience of using a maximum infusion rate of 1.2 mcg/kg/hr has also been noted to preserve respiratory function.

In specific cases of anticholinergic toxidromes, and perhaps, even cases of sympathomimetic toxicity, dexmedetomidine may provide multiple advantageous therapeutic effects because of its mechanism of action. To illustrate, dexmedetomidine is widely observed to cause modest sinus bradycardia. The decrease in central sympathetic tone is thought to be primarily responsible, but there are studies that suggest dexmedetomidine may also directly affect the sinus and or atrioventricular (AV) nodal conduction pathways.[18] Nonetheless, dexmedetomidine provides control of the tachycardia related to the anticholinergic toxidrome without causing significant hemodynamic compromise. This is in contrast to the possible use of physostigmine, an anticholinesterase inhibitor, which is not as easily titratable as dexmedetomidine is and may inadvertently cause cholinergic toxicity with even a single dose.

Physostigmine is only useful in patients with confirmed acetylcholine depletion and is contraindicated in overdoses of tricyclic antidepressants, where it can exacerbate cardiotoxicity and cause seizures. Many overdoses manifest as the anticholinergic syndrome that are not related to acetylcholine excess. Lastly, dexmedetomidine interferes with thermoregulation by diminishing shivering, vasoconstriction, and non-shivering thermogenesis. These actions help address the anticholinergic toxidrome effects of fever and flushing ("red as a beet" and " hot as a hare"). The activation of α_2 receptors in the hypothalamus cause a decrease in centrally mediated metabolic heat production, as well the inhibition of lipolysis that converts brown fat into heat.[19]

Dexmedetomidine has been widely reported in the literature to be a versatile sedative option. Specifically, it has been used successfully for the sedation and symptom control of pediatric patients with toxic ingestions of other agents, such as methylphenidate, methylenedioxymethamphetamine (Ecstasy), atypical antipsychotics, and dextromethorphan (Table 2).[3,4,8,9,13] Another unique benefit of dexmedetomidine may be its stable hemodynamic profile, even in the presence of a prolonged QTc. Although deemed acutely necessary in the case our second patient, the use of haloperidol should be discouraged in the presence of any preexisting, prolonged QT because haloperidol itself may cause prolongation.[14,15] In support of dexmedetomidine use, Kim et al[12] reported that, in adults who developed spinal anesthesia-induced prolonged QTc, these patients may actually have had an expeditious return of QTc normalization when given dexmedetomidine versus saline. Moreover, Tsutsui et al[16] showed in the animal model that dexmedetomidine may also have a role in the prevention of arrhythmias in the setting of a prolonged QTc.

CONCLUSIONS

In summary, dexmedetomidine successfully controlled the agitation and combative behaviors from anticholinergic toxidrome in our 3 patients without any significant adverse effects on respiratory or cardiac function. Nevertheless, because bradycardia or hypotension may be seen with dexmedetomidine, more commonly following bolus dosing, this possibility does mandate the continuous monitoring of hemodynamics with its use.[2,6] There are mixed reports of significant hypotension requiring fluid administration.[8,20] In our experience, mild bradycardia was observed with higher doses, but it readily resolved with decreased infusion rates and yet still provided adequate sedative effect.

Our anecdotal data suggest that dexmedetomidine may offer significant advantages over other sedative agents when controlling the agitation and delirium related to the anticholinergic toxidrome. In our experience, we found that

Table 2. Reported Dexmedetomidine Use in the Management of Toxicity Cases

Reference	Patient Demographics	Ingested/Offending Agent	Dexmedetomidine Dosing	Outcomes
Akingbola et al[9]	6-yr-old	Lisdexamfetamine dimesylate	1 µg/kg bolus dose, infusion 0.5-0.7 µg/kg/hr	Effective control of signs and symptoms of serotonin syndrome
Bagdure et al[12]	7-yr-old	Methylphenidate	Infusion at 0.5 µg/kg/hr	Effective control of signs and symptoms of serotonin syndrome
Tobias[3]	3 patients (ages 14, 16, and 16 yr)	Dextromethorphan, methylenedioxymethamphetamine (ecstasy)	1 µg/kg bolus dose, infusion 0.5-1.5 µg/kg/hr	Control of agitation and combative behaviors without respiratory or hemodynamic compromise
Walker et al[4]	13-yr-old	Diphenhydramine	1 µg/kg bolus dose, infusion 0.5 µg/kg/hr	Control of patient agitation with RASS score 4^+ to a RASS score 3^- without respiratory or hemodynamic compromise

intermittent doses of lorazepam provided short-term control of symptoms and that the repeated dosages were harmful to respiratory function. Overall, the dexmedetomidine infusions were required for less than 48 hours, and patients were weaned off them without evidence of withdrawal or recurrence of delirium or agitation.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Abbrevations α_2, alpha-2; AV, atrioventricular; BP, blood pressure; ECG, electrocardiogram; ED, emergency department; HR, heart rate; IV, intravenous; OTC, over-the-counter; PICU, pediatric intensive care unit; RR, respiratory rate; THC, delta-9-tetrahydrocannabinol

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