Successful management of olanzapine-induced anticholinergic agitation and delirium with a continuous intravenous infusion of physostigmine in a pediatric patient

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Physostigmine effectively reverses anticholinergic delirium. However, continuous IV infusion of physostigmine is rarely used due to concern for cardiotoxicity and signs of cholinergic excess such as seizures, nausea, and vomiting. We report the successful use of continuous IV physostigmine in a 6-year-old boy with anticholinergic delirium. A 6-year-old, 30-kg boy with attention deficit hyperactivity disorder (ADHD) ingested 15–20 olanzapine (5 mg) tablets. He was agitated and was treated with lorazepam at a local hospital. His heart rate was 148 beats per min; respiratory rate, 32 breaths per minute; blood pressure, 111/70 mmHg; temperature, 96.8°F; and O₂ saturation of 98% on room air. His pupils were 5–6 mm, and his skin was warm and initially flushed. Blood chemistry results were normal. A 12-lead ECG showed sinus tachycardia with normal QRS and QT intervals. The agitation worsened and did not respond to benzodiazepines. The patient was then given a dose of 0.6 mg physostigmine (0.02 mg/kg) intravenously with reversal of the agitation. But the effect only lasted 45 min requiring administration of a second bolus of 0.6 mg (0.02 mg/kg). A physostigmine intravenous infusion was administered at a rate of 0.5 mg/h (0.0167 mg/kg/h). Overnight, the patient became more agitated. The physostigmine was discontinued, and IV dexmedetomidine (0.2 µg/kg/h) was started at 21:00. The patient became over-sedated with pinpoint pupils resulting in discontinuation of the dexmedetomidine at 04:00. The patient again became agitated and developed visual hallucinations. Three 1-mg (0.03 mg/kg) boluses of physostigmine were administered over 45 min, and the physostigmine infusion was restarted at a rate of 1 mg/h (0.03 mg/kg/h) for 16.5 h. He received 19.5 mg of physostigmine with no return of anticholinergic symptoms and no signs of cholinergic excess except for a tremor that resolved when the infusion was stopped. He was discharged home without further sequelae. There are few publications describing a continuous infusion of physostigmine to reverse anticholinergic delirium. Our patient received a total dose of 25.5 mg with complete resolution of symptoms. We report the successful use of continuous infusion of physostigmine to reverse anticholinergic delirium in a pediatric patient who unintentionally ingested olanzapine.

Keywords Antidote; Complications of poisoning; CNS/Psychological; Physostigmine; Olanzapine; Organ/tissue specific

Introduction

Central nervous system (CNS) toxicity due to anticholinergic agents ranges from mild agitation to marked delirium. Although effective in the management of such CNS toxicity, physostigmine is used infrequently mostly due to concern for cardiac dysrhythmias. Its use is also limited by the potential for cholinergic excess such as seizures, nausea, and vomiting that can lead to aspiration in an altered patient. Additionally, pediatricians have very little experience with the use of physostigmine and monitoring for side effects. When physostigmine is used, it is usually to confirm the suspicion of anticholinergic toxicity. The return to baseline mental status after its use obviates the need for further studies such as computed tomography of the brain or the performance of a lumbar puncture. While benzodiazepines may then be used to control agitation, they do not reverse anticholinergic delirium.

Once the diagnosis of anticholinergic delirium has been confirmed with physostigmine, the treatment of further agitation is traditionally done with benzodiazepines.1,2 However, benzodiazepines are not always effective at controlling agitation associated with anticholinergic toxicity. The problem with continued treatment with physostigmine is its short duration of action compared to the duration of delirium associated with anticholinergic toxicity.3,2 In these situations, repeat doses of physostigmine or a continuous intravenous infusion of physostigmine might be effective. Thus, physostigmine may also be a therapeutic agent in the treatment of persistent anticholinergic delirium and agitation.

The successful use of continuous intravenous physostigmine to treat anticholinergic delirium and agitation in a pediatric patient who ingested olanzapine is reported.
Case report

A 6-year-old, 30-kg boy with a history of attention deficit hyperactivity disorder (ADHD) and alleged bipolar disorder on multiple medications including olanzapine, sertraline, topiramate, melatonin, and guanfacine; cut open the individual packages of his olanzapine with a steak knife and ingested fifteen to twenty 5-mg tablets (2.5 mg/kg–3.3 mg/kg). He subsequently woke up his mother and told her “that he had taken all of his medicine like a big boy.” The mother confirmed that only the olanzapine had been ingested, but the shedding of the packages only allowed her to estimate the exact number. He was immediately transported to a local hospital. Upon arrival, vital signs observed were as follows: heart rate, 200 beats per minute (bpm); respiratory rate of 24 breaths per minute; blood pressure of 111/48 mmHg; axillary temperature of 96.8°F; and oxygen saturation of 99% on room air. Within 1 h of the ingestion, he was combative and screaming. On physical examination, he was flushed and his mental status fluctuated between sleeping and agitated. His pupil size was not documented. He had normal range of motion in his extremities. The results of the Laboratory tests included a serum salicylate less than 5 mg/dL, ethyl alcohol less than 10 mg/dL, urinalysis and urine toxicology screen were unremarkable, complete blood count was unremarkable with a white blood cell count of 6.5 Thsd/mm³, creatine kinase was 76 U/L, and a complete metabolic profile was only significant for potassium of 2.9 meq/L, and carbon dioxide of 16 meq/L. Electrocardiogram (ECG) revealed a sinus tachycardia with a rate of 155 bpm, QRS duration of 82 ms, and an incomplete right bundle branch block. He was not administered activated charcoal. Two doses of 1 mg of lorazepam (0.033 mg/kg) were given intravenously. He was then transferred to a pediatric facility.

On admission to the pediatric hospital, the vital signs were as follows: heart rate of 148 bpm, respiratory rate of 32 breaths per minute, blood pressure of 111/70 mmHg, axillary temperature of 96.8°F, and oxygen saturation of 98% on room air. He was sleepy but became agitated with even minimal physical contact, especially during examination. His pupils were 5–6 mm in size and minimally reactive to light bilaterally. His skin was warm but not flushed. His lungs were clear to auscultation, and he had hypoactive bowel sounds.

He received 2 mg of lorazepam (0.067 mg/kg) intravenously every 4 h as needed for agitation. Additionally, 25 mg of diphenhydramine (0.083 mg/kg) intravenously was administered every 8 h for extrapyramidal side effects, but the patient received only one dose. No laboratory results were obtained on the day of admission, since the tests were done at the referring hospital. A 12-lead ECG demonstrated sinus tachycardia with normal QRS and QT intervals. The plan was to continue supportive care with benzodiazepines for agitation and to monitor the patient for extrapyramidal symptoms.

On day two in the hospital, the patient’s agitation and delirium were progressively worsening despite the administration of 14 mg (0.47 mg/kg) of lorazepam since admission. His grandmother mentioned that he was “picking cherries in the air” thus increasing our suspicion for anticholinergic delirium. In addition, the patient also had hit, scratched, kicked, pinched, and bitten his mother and had violently grabbed the eyeglasses off from a nurse’s face.

His vital signs were blood pressure of 102/77 mmHg, heart rate of 136–168 bpm, temperature of 37.1°C, and a respiratory rate of 30 breaths per minute. He was very agitated and delirious, and was intermittently swarming and kicking. His pupils were 4–5 mm in size bilaterally with minimal reaction to light. There was no rigidity, clonus, tremor, or hyperreflexia to suggest serotonin syndrome. His lungs were clear, and he had decreased bowel sounds. He had sodium of 139 meq/L, potassium of 3.8 meq/L, chloride of 106 meq/L, bicarbonate of 20 meq/L, BUN less than 5 mg/dL, creatinine 0.6 mg/dL, glucose 108 mg/dL, and creatine kinase 229 IU/L. A repeated 12-lead ECG showed sinus tachycardia at 188 bpm, QRS of 64 ms and QT/QTc of 254 ms and 449 ms, respectively.

After discussion on the diagnosis and treatment options, the decision was made to administer physostigmine. The patient was placed on a continuous cardiac monitor, and atropine was available at the bedside. A dose of 0.6 mg (0.02 mg/kg) of physostigmine was administered intravenously over 3–5 min. His delirium cleared within 3 min, and the family noted that his behavior had returned to normal. The effect of the physostigmine lasted 45 min, and then, the patient again displayed delirium. A second dose of 0.6 mg (0.02 mg/kg) of physostigmine was administered. His mental status cleared again for 30 min. The risks and benefits were discussed regarding the administration of physostigmine in a continuous infusion.

The patient was transferred to the pediatric intensive care unit (PICU) where he was bolused with three doses of 0.6 mg (0.02 mg/kg) of intravenous physostigmine at 16:04, 16:52, and 16:57 for ongoing delirium. Six milligrams of physostigmine was placed in 250 cc of D₅W and administered at a rate of 0.5 mg/h (20.8 ml/h or 0.017 mg/kg/h). The plan was to titrate up to 3 mg/h as needed to control agitation. The PICU nursing staff were educated regarding the signs of cholinergic excess and instructed to stop the infusion if seizure, bradycardia, and/or bronchorrhea/bronchospasm developed. Atropine was maintained at the bedside to reverse any signs of cholinergic excess. For approximately 2 h, the infusion was administered at a rate of 0.5 mg/h (0.017 mg/kg/h). Due to continued restlessness, the infusion rate was increased to 1 mg/h (0.03 mg/kg/h). The patient’s agitation was controlled, and the patient was playful. His tachycardia improved. The mother reported that he was at his baseline mental status.

One hour later, the patient was restless and hyperactive similar to his baseline at bedtime as per the patient’s mother. She requested medication to assist with sleep. At 21:00 on day 2, intravenous dexmedetomidine was started at a rate of 0.2 µg/kg/h after one oral dose of 5 mg (0.17 mg/kg) of diazepam and stopped the physostigmine.
infusion at 23:17 after running for 6 h. There were never any signs of cholinergic excess. The patient became oversedated with pinpoint pupils resulting in discontinuation of the dexmedetomidine at 04:00 on day 3. After stopping the dexmedetomidine, the patient again became delirious and developed visual hallucinations so the patient was placed back on the dexmedetomidine infusion at 07:00 until 16:50. The risks and benefits were again discussed, and the decision was made to stop the dexmedetomidine infusion and restart the physostigmine infusion.

While awaiting the physostigmine infusion from pharmacy, physostigmine was re-bolused at a rate of 1 mg (0.03 mg/kg) for 3 doses at 16:52, 17:41, and 18:56 for a total of 3 mg prior to the administration of the continuous infusion. Since the maximum rate of 0.5 mg/h was insufficient to control agitation previously, the patient was treated at a rate of 1 mg/h (0.03 mg/kg/h) to be titrated to effect as previously advised. The patient was continued on a physostigmine drip for a total of 16.5 h with a clear sensorium and no agitation. The infusion was stopped on day 4 in the hospital. The patient had developed a slight tremor that resolved after discontinuation of the infusion. There were no other potential signs or symptoms of cholinergic toxicity, and his heart rate remained normal (Fig. 1).

While in the PICU, he remained on continuous cardiac monitoring. The patient received a total of 19.5 mg to include the three 1-mg boluses at the completion of this second infusion of physostigmine and had no return of anticholinergic symptoms. The patient received a total dose of 25.5 mg to include all boluses and both infusions over 2 days. He was discharged home without further sequelae.

Discussion

Although the diagnostic use of physostigmine has helped eliminate the need for unnecessary procedures in patients presenting with anticholinergic delirium, its therapeutic use has been potentially underused. Current evidence supporting, or refuting, its use is lacking. Further study on this topic could be beneficial.

Olanzapine is an atypical antipsychotic with significant antimuscarinic effects. There is minimal information in the literature regarding the use of physostigmine for olanzapine-induced anticholinergic delirium. Theisen and others reviewed the literature of all reported cases of olanzapine overdose in children and adolescents. In younger children (age range of 1–6 years), accidental ingestion produced mainly mental status changes, respiratory distress, and anticholinergic symptoms. In older children (age range of 9–15 years), combative behavior, tachycardia, hypotension, decreased gastrointestinal motility, extrapyramidal symptoms, opioid-like symptoms, initial agitation followed by lethargy, and anticholinergic symptoms have been reported.

Although anticholinergic delirium was the ultimate diagnosis in this patient, other differential diagnoses including neuroleptic malignant syndrome and serotonin syndrome were considered. Neuroleptic malignant syndrome has a gradual onset (1–3 days) and increased muscle tone. The patient’s symptoms developed rapidly after ingestion, and there were normal reflexes and muscle tone. Serotonin syndrome usually has an acute onset of symptoms that develop within 12 h associated with hyperreflexia, neuromuscular hyperactivity, and increased muscle tone. Anticholinergic delirium was the most likely diagnosis given the lack of neuromuscular findings and the characteristic “picking at cherries in the air.” Physostigmine was administered to confirm the diagnosis.

Physostigmine is a medicinal carbamate that inhibits acetylcholinesterase. Since it is a tertiary amine, physostigmine readily crosses the blood brain barrier and increases the level of acetylcholine available in synapses, reversing anticholinergic delirium. However, physostigmine is rapidly metabolized and patients often revert to an anticholinergic state. Weizberg and others reported two young adult patients, who had developed delirium after the ingestion of olanzapine and were successfully treated with bolus doses of physostigmine. Olanzapine has a half-life between 21 and 54 h. Comparatively, physostigmine has a half-life of 16.4 ± 3.2 min. Based on these pharmacokinetic parameters, it follows that the central and peripheral muscarinic effects of olanzapine will persist longer than the cholinergic effects...
of physostigmine. Consequently, physostigmine dosing would have to be administered repeatedly or continuously in order to treat anticholinergic toxicity. Concern about cardio-

toxicity has limited the use of physostigmine in the manage-

ment of anticholinergic delirium.1,8,2,9 In 1980, Pentel and

Peterson reported observations on two patients with tricyclic antidepressant (TCA) overdose who developed asystole fol-

lowing administration of physostigmine to treat seizures.

Bradycardias and hypotension are known adverse effects on

the heart from cholinesterase inhibitors. This is related to the

abundant cholinergic innervation of the ventricular conduct-

ing system. Their conclusion was that physostigmine carries

the risk of life-threatening bradyarrhythmias in patients who

have overdosed on TCAs and advised caution with its use.8

This occurrence of asystole has led some to categorically dismiss physostigmine as a treatment option when overdose with TCAs is known or suspected.1 The effects of TCAs are complex. Sodium channel blockade causes QRS interval prolongation, myocardial depression, and ventricular dysrhythmias. Physostigmine may further decrease cardiac output and enhance cardiac conduction defects by augmenting vagal effects.3 After these patient reports, the use of physostigmine as an antidote for anticholinergic poisoning declined and many physicians have been hesitant to use it.9

Because of the concerns for cardiotoxicity, the traditional treatment for anticholinergic delirium and agitation has been benzodiazepines.3,1,2

Burns and others conducted a retrospective study that compared the efficacy and safety of physostigmine with benzodiazepines for the treatment of agitation and delirium associated with anticholinergic poisoning. They evaluated 50 consecutive adult patients referred to a university hospital toxology service who were treated with physostigmine, benzodiazepines, or both for anticholinergic agitation and delirium. Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively. Benzodi-

azepines controlled agitation in 24% of patients and did not reverse delirium in any. They concluded that physostigmine is more effective and safer than benzodiazepines for the treat-

ment of anticholinergic agitation and delirium. To date, there

are no prospective studies to address that question. The first case of an intravenous infusion of physostigmine resulting in the successful reversal of anticholinergic delirium and agita-

tion was a 20-year-old female with schizoaffective disorder who had overdosed on benzotrope and amitriptyline. The patient received a total dose of 77 mg.10 Other authors have reported using doses from 20 to 192 mg with intermittent boluses of physostigmine.11

There are limited data addressing the role of physostig- 

mine as a therapeutic agent in the treatment of anticholinergic induced agitation and delirium.9 Most recently, Rhyee and others have described the brief resolution of anticholinergic delirium after a bolus dose of physostigmine in a 15-year-old female who ingested quetiapine.12 Pediatricians, including pediatric intensivists, have been hesitant to use physostig-

mine and have limited experience with it as an antidote. With repeated doses or a continuous infusion of physostig-

mine, the chance of physostigmine-induced adverse effects

increases as the underlying overdose resolves.2 Therefore, the medical toxicologist chose to remain at the bedside upon the initiation of the infusion to assist the pediatric staff with monitoring for any adverse effects of physostigmine.

Most physicians including pediatricians are unfamiliar with physostigmine as an antidote. Dexmedetomidine is a familiar sedative-hypnotic with a variety of clinical applica-

tions in the pediatric population. Dexmedetomidine is an α2-adrenergic agonist that is approved by the Food and Drug Administration for the provision of short term (less than 24 h) sedation of adults during mechanical ventilation. However, given its anxiolytic and sedative effects, there are benefits to the pediatric patient. Additionally, Tobias described the use of dexmedetomidine to control agitation and delirium from toxic ingestions of recreational drugs in three patients.13 Akingnola and Singh describe the successful use of dexmedetomidine to control the agitation of serotonin syndrome in a 6-year-old girl who had ingested lisdexamfetamine.14 Similar to benzodiazepines, dexme-

detomidine may control agitation but it does not reverse the anticholinergic delirium.

After risks and benefits were discussed, a continuous infusion of intravenous physostigmine was chosen because benzodiazepines had not provided a satisfactory outcome and the effects of the intermittent boluses of physostigmine wore off quickly. Before starting the continuous infusion, the patient had received seven boluses of physostigmine to total 4 mg and multiple doses of lorazepam without significant and persistent improvement in his mental status. His agita-

tion and delirium did improve with continuous physostig-

mine administration. He did experience transient tremor that resolved completely within 30 min of discontinuing the physostigmine infusion. The authors could not find a similar case involving the pediatric population in the literature.

Continuous intravenous infusion of physostigmine is infrequently described in the literature as an option for man-

agement of the anticholinergic toxidrome.10,6 To date, there has not been a randomized controlled trial that compares the relative efficacy of continuous intravenous infusion of physostigmine versus intermittent boluses of physostigmine and/or benzodiazepines in the management of anticholinergic-induced agitated delirium. Situations exist in which a need for continuous infusion may be desirable or necessitated by clinical circumstance.

Declaration of interest

The authors report no conflicts of interest. The authors alone

are responsible for the content and writing of the paper.

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