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TOXICOLOGY OBSERVATIONS

Use of a Physostigmine Continuous Infusion for the Treatment of Severe and Recurrent Antimuscarinic Toxicity in a Mixed Drug Overdose

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Abstract
Introduction Physostigmine was once a widely used antidote for the treatment of antimuscarinic toxicity. However, reports describing the association of physostigmine with asystole and seizures in severe tricyclic antidepressant poisoning resulted in a decrease in use. Recent literature has demonstrated that physostigmine is a safe and effective antidote for the treatment of antimuscarinic toxicity. There are only two previously published articles regarding the use of physostigmine administered as a continuous intravenous infusion for persistent antimuscarinic toxicity. We present a case of physostigmine continuous infusion for the treatment of antimuscarinic symptoms in a polydrug overdose due to the ingestion of diphenhydramine along with bupropion, citalopram, acetaminophen, and naproxen.
Case Presentation A 13-year-old female presented with hyperthermia, myoclonus and rigidity, hallucinations, severe agitation, and antimuscarinic toxicity including inability to sweat after a polydrug overdose. Several doses of lorazepam were administered followed by physostigmine which produced resolution of hallucinations and attenuation of the antimuscarinic symptoms including perspiration, temperature improvement, and decreased agitation. After periods of improvement and recurrence of antimuscarinic effects, a continuous infusion of physostigmine was administered at 2 mg/h and continued for almost 8 h to maintain attenuation of symptoms. GABAergic agents including lorazepam and phenobarbital were used later in the hospital course for presumed symptoms of serotonergic and adrenergic toxicity after resolution of antimuscarinic effects. The patient did not experience any adverse effects of physostigmine administration.
Discussion Physostigmine administered as a continuous infusion may be a reasonable treatment option for severe and recurrent symptoms related to antimuscarinic toxicity.

Keywords Physostigmine · Anticholinergic antidote · Diphenhydramine · Delirium · Agitation · Antimuscarinic antidote

Introduction

Physostigmine has a storied history and checkered past. It was used prominently as an analeptic in the 1960s through the early 1980s. Case reports then described its adverse effects when used in severe tricyclic antidepressant (TCA) overdose including asystole and death [1, 2]. One case in particular describes the association of physostigmine use with asystole and seizures in severe TCA poisoning [1]. Physostigmine is not a benign antidote. There are predictable adverse effects when it is used inappropriately. Seizures tend to occur when physostigmine is administered too rapidly or in the setting of a pro-convulsant coingestant, and bradycardia and asystole are also associated with rapid administration and occur due to the potentiation of vagal effects on cardiac tissue [2]. Nausea, vomiting, bronchorrhea, hypersalivation, and incontinence of

The study entitled "Physostigmine continuous infusion for the treatment of anticholinergic toxicity in combined diphenhydramine and bupropion overdose" by Phillips MA, Acquisto NM, Gorodetsky RM, and Wiegand TJ was presented at the Annual Meeting of the North American Congress of Clinical Toxicology, Las Vegas, NV, last October 2012.

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stool and urine can occur when excess cholinergic tone predominates [3, 4]. Asystole occurs more commonly in patients with underlying cardiac arrhythmias or conduction disorders [5].

After the Pentel case report was published [1], the use of physostigmine changed dramatically and the pendulum of use swung from very liberal and even indiscriminate use to nearly no use and a "taboo" mentality in many settings[4]. Only in recent years has physostigmine had a resurgence and more rational pattern of use. It is still, however, underappreciated even in very pure anticholinergic drug overdose situations. There have been several excellent reviews with critical appraisal of the literature regarding the risk and benefits of physostigmine as an antidotal therapy, and these have essentially uniformly described overemphasis on toxicity and adverse effects related to its use in non-tricyclic antidepressant overdoses [2, 6]. While there are many case reports and robust literature describing the efficacy of physostigmine administered as an intermittent bolus for the treatment of anticholinergic toxicity, there are only a few case reports describing its use as a continuous intravenous infusion [7–10]. The goals of this paper are to present a patient with mixed drug overdose and illustrate the role of physostigmine in reversing severe antimuscarinic toxicity. Physostigmine was ultimately given via intravenous infusion, and indications and effects in this patient, along with a discussion of risk and benefit of a continuous intravenous infusion of physostigmine are included.

Case Presentation

A previously healthy 13-year-old female was brought to the emergency department (ED) following a polydrug overdose. The patient had left several suicide notes that were discovered 7 h after she was last seen. A text message indicated that she had taken "41 pills." Acetaminophen, bupropion, citalopram, diphenhydramine, naproxen, and omeprazole were found near the patient.

At presentation, the patient was agitated and hallucinating. She had markedly dilated pupils, her skin was very flushed although she was not sweating, and she had very dry axillae and mucous membranes. A Foley catheter was placed for urinary retention. She had tremors, developed "picking behavior," and had myoclonus in her upper extremities. She did not have any clonus at the ankles during her initial exam. Her initial ED vital signs showed that she was hypertensive (143/54 mmHg), hyperthermic (initial ED temperature obtained via temporal artery thermometer was 38 °C), tachycardiac (heart rate 160 beats per minute), and tachypneic (respiratory rate 46 breaths per minute). Her weight was 59 kg. An initial ECG demonstrated sinus tachycardia with a rate of 154 beats per minute, QRS interval of 74 ms, and QT/QTc of 324/518 ms. Magnesium sulfate was administered intravenously as empiric treatment for QTc prolongation. A total of 7 mg of lorazepam was administered intravenously in the ED for agitation and development of rigidity with minimal improvement in these symptoms. A core temperature documented persistent fever with a temperature of 38.5 °C (temperature monitored via a Foley catheter throughout). Despite the fever and agitation requiring restraints along with myoclonus and the development of lower extremity rigidity, the patient continued to have absence of sweating. She was hallucinating and exhibited picking behavior and tremors, her pupils were markedly dilated, and she had urinary retention and absent bowel sounds. A 2-mg dose of physostigmine was administered intravenously over 10 min which resulted in dramatic attenuation of agitation, hallucinations, and myoclonus. Within minutes of completing the intravenous administration of the physostigmine, the patient started to sweat and her skin, which had been quite red appearing, began to show less signs of cutaneous flushing. With the onset of her perspiration, the patient started to defervesce and her temperature dropped from 38.5 to 37.4 °C (core temperature via a Foley catheter). The patient's initial laboratory results returned with Na 138 mmol/L, K 3.0 mmol/L, Cl 106 mmol/L, HCO_3 18 mmol/l, BUN 10 mg/dL, Cr 0.58 mg/dL, glucose 165 mg/dL, Ca 8.2 mg/dL, and Mg 1.3 mEq/L. Immunoassay screen of urine drugs of abuse was positive only for amphetamines, and the acetaminophen level was 154 mg/L (treated with intravenous *N*-acetyl cysteine), salicylate level was <10 mg/dL, and ethanol level was <10 mg/dL. Two hours after the first dose of physostigmine had been administered, the patient required another 2-mg dose as her agitation and hallucinations returned. She had also stopped sweating again and her temperature rose concomitant with this to 39 °C. The repeat dose of physostigmine produced dramatic results with a calming effect and the hallucinations improved. She was able to sit and answer questions during an interview with the pediatric ICU provider at this point. After she started to sweat again and with the improvement in her agitation the patient's temperature improved to 37 °C. An hour after the second dose of physostigmine had been given, the patient became increasingly anxious, disoriented, agitated, and started thrashing around in her bed. She had stopped perspiring once more and her picking behavior returned. She was also noted to have extremely dry mucous membranes. She also had rigidity and tremors which had become more prominent as she was moved into the pediatric ICU. The rigidity and tremors had not resolved with the physostigmine administration whereas the absence of sweating, hallucinations, agitation, and hyperthermia had. Benzodiazepines and subsequently phenobarbital were administered once the patient got to the pediatric ICU for the rigidity, tremors, and other signs of neuromuscular excitation. It was thought that the patient's primary toxicity was from the antimuscarinic effects of diphenhydramine although it also appeared that the patient had suffered

serotonergic and adrenergic toxicity from the other coingestants including bupropion and citalopram. At this point, the patient's temperature was 38.5 °C, heart rate was 146 beats per minute, and respiratory rate was 36 breaths per minute. Due to the recurrence of symptoms and the improvement with the first two doses of physostigmine, a physostigmine continuous infusion (concentration 0.02 mg/mL) was initiated at 2 mg/h and was continued for nearly 8 h (7 h and 45 min). With the physostigmine continuous infusion administration, the patient's agitation, picking behavior, hallucinations, and fever were dramatically improved. She was sweating throughout the infusion and her skin was much less flushed. The patient required one additional 2 mg physostigmine intravenous bolus during the infusion as, despite the 2-mg/h rate, she had started to demonstrate antimuscarinic effects again. The bolus completely eliminated recurrence of picking behavior, hallucinations, and agitation. Atropine was readily available at the bedside in the event that bradycardia, hypersalivation, or bronchorrhea occurred; however, the patient never developed these signs or symptoms and administration of atropine was not required. Over the course of the physostigmine continuous infusion, the patient was calm, her heart rate began to decrease to 100–110 beats per minute, and it was ultimately discontinued when the heart rate decreased into the 90s. There were also improvements in cutaneous flushing and dryness throughout, and these signs did not recur after the physostigmine infusion had been stopped. The patient did not experience vomiting, seizures, bradycardia, or conduction block. The patient did not require additional physostigmine for the remainder of her hospitalization. While the antimuscarinic effects were improved, the patient had become more rigid and had myoclonus and clonus along with tremors. These symptoms were treated with benzodiazepines as well as phenobarbital which were administered in lieu of continued doses of lorazepam as her neuromuscular signs and symptoms were more persistent. The GABAergic agents were administered primarily after the physostigmine infusion had been turned off although she did get five 130-mg intravenous doses of phenobarbital while the infusion was running. The total amount of benzodiazepines included 7 mg lorazepam prior to the physostigmine infusion for agitation and 17 mg lorazepam administered intravenously after the physostigmine infusion was discontinued. After the physostigmine infusion was turned off, she required an additional 14 doses of 130 mg of phenobarbital over 36 h for a recurrence of myoclonus, rigidity, and tremor along with tachycardia and hypertension. She did not have seizures during her hospitalization. She remained afebrile after the physostigmine infusion was turned off for the duration of her hospitalization. The patient did not develop renal or hepatic failure. She did develop rhabdomyolysis with peak CK of 3,724 U/L on hospital day 2 [from an initial CK on arrival of <7 U/L (normal 34–145 U/L)].

Case Discussion

Our patient had a complex drug overdose. She had ingested multiple agents with different mechanisms of toxicity including antimuscarinic, serotonergic, and adrenergic effects. She exhibited clear signs of antimuscarinic toxicity including absence of sweating, hallucinations, stereotypical picking behavior, dry and flushed skin, urinary retention, and bowel sounds. The symptoms were readily reversed with physostigmine; however, they recurred several times and a continuous infusion of physostigmine was administered in this patient. While repeat bolus doses with increased frequency could have been administered, the infusion was chosen for the ease of administration while she was being closely monitored in the pediatric ICU. As she started to exhibit more prominent signs that the antimuscarinic effects were waning, the infusion were discontinued. We used the heart rate, bowel sounds, sweating, and presence of increasing saliva to make this decision. The continuous infusion was stopped when the heart rate had decreased from 140–150 beats per minute to 90–100 beats per minute. Atropine was not required and the patient did not have seizures nor did she vomit. Physostigmine was only part of the overall care in this patient. She required GABAergic agents adjunctively for presumed serotonergic and adrenergic effects of bupropion and citalopram. Her exam findings and course suggested that there was a significant drug effect and a high risk for seizures; however, she did not experience any seizures with the physostigmine continuous infusion. This was likely mitigated by our aggressive use of the GABAergic agents lorazepam and phenobarbital. Even with high doses of these drugs, she did not require intubation nor did she ever have any significant degree of somnolence.

Hail and colleagues recently described their experience using a continuous intravenous infusion of physostigmine in a 6-year-old pediatric patient with olanzapine-induced anticholinergic agitation and delirium. In their patient, the physostigmine was effective at reversing the agitation and delirium; however, the beneficial effects rapidly waned after each bolus dose. Ultimately, an infusion was used to manage the recurrent toxicity. Their patient received a total of 22.5 mg of physostigmine over 2 days including all bolus doses and infusion doses. There were no seizures or cardiac dysrhythmias reported in their case [7]. To our knowledge, the only other report in the literature of physostigmine continuous infusion use was in 1983 by Stern and colleagues. In this case, a 20-year-old female ingested benztropine and amitriptyline and was treated with a total of 77 mg of physostigmine [8]. This patient received a continuous infusion of physostigmine for 8 h and additional bolus doses over 52 h. The patient in this report had symptom resolution and no adverse effects.

Many authors suggest repeat bolus doses of physostigmine for recurrent anticholinergic toxicity as the use of a continuous

infusion is thought to have increased risk of escalating cholinergic effect and toxicity including seizure, vomiting, and dysrhythmia [4, 7]. Physostigmine given rapidly does have a higher risk for precipitating seizures [7]. The continuous infusion offers a way of decreasing the rate of administration and may in fact lower the risk for seizures. Much of the early toxicity with tricyclic antidepressants, in fact, was with higher doses of physostigmine given over only a few minutes, whereas more recent protocols suggest a 0.5–2-mg dose be given over 5–10 min. Our institutional protocol, which has gone through our Pharmacy and Therapeutics Committee, requires a physostigmine dose of 0.5–2 mg over 5–10 min for adult patients. We give this medication as a slow intravenous push and stop the push early if there are any signs of excessive cholinergic tone. Most of our overdose patients, however, end up receiving the full 2-mg dose over 10 min. The more prolonged initial administration time of up to 10 min with lower initial doses (0.5–2.0 mg incrementally) leads to less risk of seizures as well as less risk for other exaggerated cholinergic response [1, 6, 7, 11]. While we could have used repeat bolus doses of physostigmine to manage this patient, we chose to use intravenous infusion for ease of administration. Most patients in the literature with prolonged and severe antimuscarinic effects that recur after physostigmine initial reversal are in fact treated with bolus doses. There are reports of repeat bolus doses from 20 to nearly 200 mg of physostigmine given incrementally [12]. Physostigmine has a half-life of 16.4±3.2 min [3]. Many drugs have much longer antimuscarinic effects and toxicity, and many overdose patients require repeat bolus doses, often very frequently, in order to treat agitation, delirium, and other antimuscarinic effects. This case adds to the overall literature on physostigmine administered as a continuous infusion in that it was an important and successful antidote used as part of the treatment of a very severe mixed drug overdose. We felt it was particularly useful in avoiding escalating toxicity due to hyperthermia which may have occurred had the patient been unable to sweat and had the agitation persisted in this setting. Our patient never developed significant acidosis or end-organ failure. She did have rhabdomyolysis; however, it was not severe. GABAergic agents were also an important aspect of this patient's case; however, their use was adjunctive to physostigmine as we perceived the serotonergic and adrenergic effects to be from bupropion and citalopram.

There are several limitations of this case report. This case does not have confirmatory laboratory analysis regarding the ingested drugs; however, it is less a report of specific drug toxicity than a discussion on the role and usefulness of physostigmine in a mixed drug overdose for severe and recurrent antimuscarinic toxicity. Also, due to the different agents ingested and use of both GABAergic medications as well as physostigmine, it is difficult to specifically define the effect and degree of improvement related to each antidotal agent. That said, the Toxicology Team was at the bedside for the majority of the time that physostigmine was administered and was able to observe first-hand the response and changes before and after this medication was administered as well as the response to the bolus doses of lorazepam and phenobarbital.

Conclusion

Physostigmine was used successfully in our patient to reverse the antimuscarinic components of a mixed drug overdose. It was administered concomitantly with other antidotal agents including the GABAergic medications lorazepam and phenobarbital. The antimuscarinic features of this intoxication when combined with the serotonergic and adrenergic effects seen were problematic in this patient. Physostigmine was helpful in attenuating the fever, agitation, and hallucinations. In cases in which multiple repeat doses of physostigmine are administered with improvement but with rapid recurrence of antimuscarinic effects, a continuous infusion may be a reasonable alternative to frequent repeat bolus doses of physostigmine. Our patient did not have seizures, conduction block, bronchorrhea, or other adverse outcome from the continuous infusion of physostigmine. This case adds to the overall literature on physostigmine and addresses an important and infrequently used modality of administration.

Conflict of Interest Phillips MA, Acquisto NM, Gorodetsky RM, and Wiegand TJ have nothing to disclose.

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