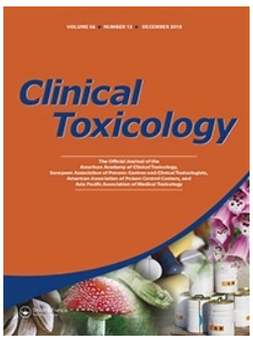

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RESEARCH ARTICLE

A randomized trial comparing physostigmine vs lorazepam for treatment of antimuscarinic (anticholinergic) toxidrome

George Sam Wang[a], Keith Baker[b], Patrick Ng[c], Gregory C. Janis[d], Jan Leonard[a], Rakesh D. Mistry[a] and Kennon Heard[e]

[a]Section of Emergency Medicine, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, CO, USA; [b]Departments of Emergency Medicine and Medical Toxicology, St. Luke's University Health Network, Bethlehem, PA, USA; [c]En route Care Research Center, Lackland AFB, San Antonio, TX, USA; [d]MedTox Laboratories, Laboratory Corporation of America Holdings, Saint Paul, MN, USA; [e]Department of Emergency Medicine, University of Colorado Anschutz Medical Campus, University of Colorado Hospital, Aurora, CO, USA

ABSTRACT

Background: Toxicity from antimuscarinic agents precipitates a constellation of signs and symptoms; two of the most significant are agitation and delirium. Benzodiazepines are commonly used for treatment; physostigmine is also effective but is underutilized due to concerns for safety and short duration of action. The objective of this study was to compare lorazepam to physostigmine for the treatment of antimuscarinic delirium and agitation.

Methods: This was a blinded, randomized clinical trial in patients presenting for antimuscarinic toxidrome. Inclusion criteria were: ≥10–<18 years old, at least one central and two peripheral antimuscarinic symptoms, delirium and moderate agitation. Subjects were randomized to either (1) lorazepam bolus (0.05 mg/kg) followed by a 4-h normal saline infusion, or (2) physostigmine 0.02 mg/kg bolus followed by a 4-h physostigmine infusion (0.02 mg/kg/h). Primary outcomes were the control of delirium and agitation after bolus and during the infusion.

Results: Ten (53%) subjects were enrolled in the lorazepam arm, 9 (47%) in the physostigmine arm. Diphenhydramine was the most common agent ingested (16, 84%). Fewer patients receiving physostigmine had delirium after the initial bolus (44% vs 100%, $p = 0.01$) and at the 4th hour of infusion (22% vs 100%, $p < 0.001$) compared to patients who received lorazepam. There was a significant decrease in agitation scores in the physostigmine arm compared to the lorazepam arm after the initial bolus (89% vs 30%, $p = 0.02$), but no difference at the 4th hour of infusion ($p > 0.99$). There were no seizures, bradycardia, bronchorrhea, bronchospasm, intubation, or cardiac dysrhythmias.

Conclusion: Physostigmine was superior to lorazepam in controlling antimuscarinic delirium and agitation after bolus dosing, and control of delirium after a 4-h infusion. There were no serious adverse events in either treatment arm. Physostigmine bolus and infusion should be considered in adolescent patients with significant delirium and agitation from antimuscarinic agents

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Introduction

Overdose of antimuscarinic xenobiotics, such as antihistamines, is a common scenario in medical toxicology. In 2018, the American Association of Poison Control Centers' National Poison Data System (NPDS) reported 14,139 antihistamine ingestion, which had the third greatest rate increase in exposures over the past 10 years, at a mean of 1,018 (CI 934, 1102) per year [1]. In addition to antihistamines, several medications and natural products are competitive muscarinic antagonists, including antipsychotics and plants such as *Datura stramonium* (Jimson Weed) [2,3]. The result of antagonizing muscarinic receptors is a constellation of signs and symptoms (toxidrome) which can consist of mydriasis, decreased sweat, decreased bowel sounds, agitation, delirium, hallucinations, urinary retention, tachycardia, flushed skin and seizures [2,3].

Treatment for these ingestions and exposures consists of supportive medical care including hemodynamic support with adequate fluid resuscitation, treatment of dysrhythmias, cooling if hyperthermia develops, and treatment of seizures [2–4]. In addition to these acute resuscitative measures, the main goal of therapy is control of agitation and delirium. Poorly controlled agitation and delirium can lead to hyperthermia, rhabdomyolysis, metabolic acidosis, and end organ damage. Most often medical therapy consists of administration of sedative pharmaceuticals, such as benzodiazepines [2–4]. However, substantial doses of benzodiazepines may be required to control the agitation and delirium, which may place patients at risk for hypotension, over sedation and respiratory depression [2–5]. Physostigmine is a reversible acetylcholinesterase inhibitor which is able to cross the blood-brain barrier. It increases the concentration of

CONTACT George Sam Wang George.wang@childrenscolorado.org Section of Emergency Medicine, Department of Pediatrics, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, 13123 E 16th Ave B251, Aurora, 80045, CO, USA

acetylcholine at the synapse overcoming the competitive antagonism of acetylcholine muscarinic receptors, reversing both the agitation and delirium associated with the antimuscarinic toxidrome [2–4,6,7].

Physostigmine has not been widely adopted for treatment of antimuscarinic toxicity. In 2018, the NPDS annual review reported only 417 patients received physostigmine, while over 32,000 patients received benzodiazepines for various ingestions and exposures [1]. Concerns over the use of physostigmine stem from adverse events in the setting of tricyclic antidepressant overdose complicated by seizures and asystolic arrest, although the relationship of physostigmine in causing these events is heavily debated [7–8]. Another criticism of physostigmine is its short duration of action. However, a a clinical trial comparing physostigmine to benzodiazepine for treating antimuscarinic toxicity has not been performed. To determine the utility and safety of physostigmine, the objective of this study was to prospectively compare physostigmine to lorazepam for the treatment of antimuscarinic delirium and agitation.

Methods

This was a double-blinded, randomized clinical trial, comparing physostigmine and benzodiazepines for the treatment of antimuscarinic delirium and agitation. Our local institutional review board approved this study and informed consent was obtained from a guardian. Inclusion criteria were patients $\geq$10 and $<$ 18 years of age who presented to our tertiary care children's hospital emergency department or intensive care unit for symptoms consistent with antimuscarinic toxidrome. Symptoms could be from ingestion of either a pharmaceutical agent such as antihistamine (diphenhydramine, chlorpheniramine, doxylamine, cyclobenzaprine), or natural toxins/products such as *Datura stramonium*. Antimuscarinic toxidrome was defined as having at least one central nervous system agitation effect (visual hallucinations, mumbling incomprehensible speech), and at least two adverse peripheral nervous system effects (mydriasis, dry mucus membranes, dry axillae, tachycardia, decreased bowel sounds). Patients needed a score of 1+ or greater on the Richmond Agitation-Sedation Score (RASS) and presence of delirium as determined by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) score (Appendix 1). Exclusion criteria included: history of seizures/epilepsy (or during clinical course), history of asthma (or wheezing during clinical course), bradycardia (heart rate $<$60 bpm), concomitant use of atropine or depolarizing neuromuscular blocker during present illness and hospital course, diabetes, gangrene, known intestinal or urogenital tract obstruction, vagotonic state, QRS interval $>$ 120 ms on electrocardiogram, history of current overdose of tricyclic antidepressant, pregnancy, or ward of the state. Previous administration of physostigmine during the current illness was also an exclusion criteria as we did not want any residual effect to impact the presence of agitation or delirium, nor did we want to impact to blind the treatment team and guardians to the effect of physostigmine. Previous benzodiazepine or antipsychotic administration did not exclude subjects if agitation and delirium met inclusion criteria.

Patients were initially screened by research assistants (RAs) or the primary medical treatment team by chief complaint of "Ingestion," "Overdose," or "Altered Mental Status" *via* EPIC electronic medical record. The medical toxicology team was consulted to verify the diagnosis and toxidrome. Signed consent from parent/legal guardian was obtained bedside by RA's or the study investigator. A block randomization using envelopes occurred in the clinical pharmacy to determine the treatment protocol. Enrolled patients were randomized to a treatment arm of either (1) physostigmine 0.02 mg/kg IV bolus (max of 2 mg) over 3–5 min, which could be repeated at 10 min, followed by a 0.02 mg/kg/h (max of 2 mg/h) physostigmine infusion for 4 h; or (2) lorazepam 0.05 mg/kg IV bolus (max 2 mg) over 3–5 min, which could be repeated at 10 min, followed by a NS infusion for 4 h. During either treatment arm, lorazepam 0.05 mg/kg IV bolus (max 2 mg) could be administered every 2 h as needed for treatment of continued agitation or delirium at the discretion of the treatment team. The research team, patient, guardian, nursing staff, and treating healthcare providers were blinded to the treatment. To maintain blinding, the bolus and infusion medications were labeled with a study protocol identifier. Physostigmine and lorazepam are both clear and colorless, and the bolus and infusion volumes were similar to allow for adequate blinding.

Vital signs were obtained before and after each bolus, and during every hour of the infusion. Two independent nurses or healthcare providers assessed RASS score and CAM-ICU before and after each bolus, and at every hour of the infusion. Kappa coefficients and 95% confidence intervals (CI) were calculated to assess inter-rater reliability.

The primary outcome measures for this study was the evaluation and assessment of the presence of delirium and agitation, as measured by the CAM-ICU and RASS scores, respectively (Appendix 1, [9,10]). For analysis, we took the average of the 2 RASS scores to use as the outcome and considered a patient positive for delirium if one provider obtained the presence of delirium. The secondary outcomes include rates of adverse events including: seizures, bradycardia, dysrhythmias, bronchospasm, increased secretions, diaphoresis, vomiting, intubation, and over-sedation. Treatment satisfaction scores were also evaluated from treating physicians, nursing staff, and guardian. Total benzodiazepine doses given during the clinical course were recorded, in addition to time in physical restraints (if needed) and hospital length of stay (total and ICU). A urine sample from either a pre-existing foley catheter or bag collection was sent to LabCorp for a comprehensive LC-MS/MS urine drug screen to confirm the presence of the ingested xenobiotics [11].

Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC). Descriptive statistics were calculated, including mean (standard deviation, SD) and median (interquartile range, IQR), when appropriate, for continuous variables and counts and percentages for categorical variables. Fisher's exact, *t*-tests, and Mann Whitney *U* tests were used to compare

demographics, clinical characteristics, and outcomes between study arms. With-in each study arm, Wilcoxon signed rank tests were used to assess changes in delirium and agitation before and after treatment. A Bonferroni correction was applied to the outcomes of delirium and agitation due to multiple comparisons; a significant p-value was set at 0.025. Our power calculation was based on a retrospective study evaluating the initial control of agitation with physostigmine versus benzodiazepine. The study found 96% of physostigmine and 27% of benzodiazepine treated patients had control of agitation, which suggested a sample size of 22 subjects (11 in each arm) would provide 92% power to detect at least 70% difference assuming an alpha of type 1 error rate of 5% [12].

Results

From March 20, 2017 to June 30, 2020, 175 patients presented to our hospital with a xenobiotic ingestion that can potentially result in antimuscarinic toxidrome. We excluded 156 patients and enrolled 19 patients, 9 (47%) to the physostigmine arm and 10 (53%) to the lorazepam arm (Figure 1). There was no significant difference in the demographics or clinical characteristics (vital signs) between the two treatment arms (Table 1). The most common antimuscarinic xenobiotic ingested was diphenhydramine (16, 84%), followed by doxylamine (1, 5%), hyoscyamine (1, 5%), and dicyclomine (1, 5%). All ingestions were confirmed *via* HPLC-MS/MS, with the exception of hyoscyamine and dicyclomine which were not targets on the expanded urine drug assay. Additional co-ingestants included ibuprofen (4), naproxen (1), sertraline (1), and one ingestion of a combination product containing pseudoephedrine, ephedrine, and phenylpropalanine. Although not significant, the median RASS score was slightly higher in the physostigmine arm (Table 1).

As previously stated, two individual healthcare personnel (nurses and/or providers) performed agitation and delirium assessments. The kappa was 0.49 (95% CI 0.40–0.59), with 59.7% agreement for the RASS agitation score and 0.79 (95% CI 0.68–0.90), with 90.6% agreement for the CAM-ICU assessment. All patients enrolled in the lorazepam arm received 2 mg bolus dose. Patients in the physostigmine arm received a mean bolus dose of 1.2 mg (range of 0.9 mg–1.7 mg), with a similar dose per hour during the infusion, When evaluating the response in improvement of delirium, subjects in the physostigmine arm had significantly less delirium both after the initial bolus and after the 4th h of infusion compared to subjects in the lorazepam arm (Table 2). Within the lorazepam arm, only 10% of subjects had resolution of their delirium by the end of the 4-h infusion ($p > 0.99$), and the rate of delirium was near 100% during the entire study period for subjects enrolled in the lorazepam arm (Figure 2). In contrast, resolution of delirium occurred in 78% of subjects in the physostigmine arm ($p = 0.02$) by the end of the 4-h infusion.

After the initial study bolus, 89% of patients in the physostigmine arm experienced a decrease in RASS agitation scores, whereas 30% of patients in the lorazepam arm had a decrease in their RASS agitation scores ($p = 0.02$). When comparing the change in the RASS agitation score from prior to the initial bolus until after the 4th h of infusion, there was a similar proportion of patients with a decreased RASS score in the two arms (100% of patients in the physostigmine arm and 80% of patients in the lorazepam arm, $p > 0.99$ (Table 3). The lorazepam group saw no significant difference in RASS agitation scores after the initial bolus (-0.05, 95% CI −0.71 to 0.61, $p > 0.99$), but the RASS agitation scores did significantly decrease by four hours post infusion (−1.5, 95% CI −2.83 to −0.17, $p = 0.02$). The RASS agitation scores within the physostigmine arm significantly decreased after the initial bolus (−1.44, 95% CI −2.41 to −0.48, $p = 0.02$) and four hours post infusion compared to prior to treatment (−2.11, 95% CI −3.14 to −1.08, $p = 0.004$). Subjects in the lorazepam arm

Table 1. Demographics of enrolled patients in each treatment arm.*

	Lorazepam ($n = 10$)	Physostigmine ($n = 9$)	p-Value
Mean age, years	14.4 (1.3)	13.4 (1.4)	0.14
Male (%)	3 (30.0%)	4 (44.4%)	0.65
Mean heart rate (bpm)	117 (10)	127 (18)	0.15
Mean temperature (Celsius)	37.1 (0.5)	37.3 (0.6)	0.49
Mean respiratory rate	24 (4)	29 (7)	0.09
Mean systolic blood pressure	127 (14)	131 (12)	0.50
Mean diastolic blood pressure	88 (17)	80 (11)	0.29
Mean oxygen saturation	97 (3)	96 (2)	0.49
Antimuscarinic xenobiotic ingested			
Diphenhydramine	10 (100%)	6 (66.7%)	0.09
Olanzapine	0 (0%)	0 (0%)	
Doxylamine	0 (0%)	1 (11.1%)	
Other**	0 (0%)	2 (22.2%)	
Median RASS score	1 (1–2)	2 (1–3)	0.16
Mean QRS (ms)	87.4 (13.2)	84.9 (8.3)	0.63

*Mean values include Standard Deviation, and median values include interquartile range.
**Other included hyoscyamine and dicyclomine.

Table 2. Proportions of subjects in each arm with delirium by CAM-ICU.

PRESENCE OF DELIRIUM	Lorazepam ($n = 10$)	Physostigmine ($n = 9$)	p-Value
Prior to first bolus	9 (90%)	9 (100%)	>0.99
After first bolus	10 (100%)	4 (44.4%)	**0.01**
End of 4 h infusion	10 (100%)	2 (22.2%)	**<0.001**

Bold values represents as statistically significant p-values

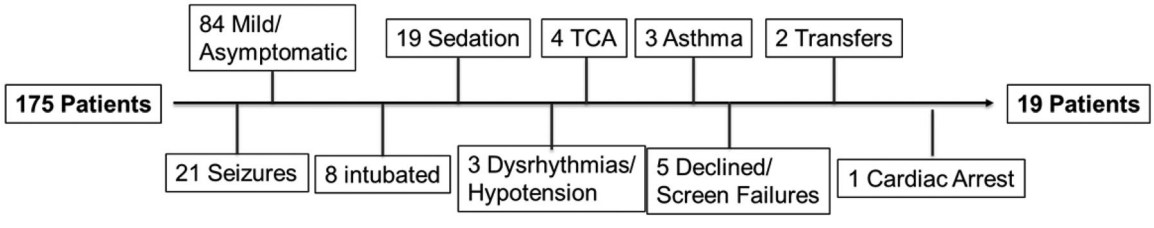

Figure 1. Subject enrollment.

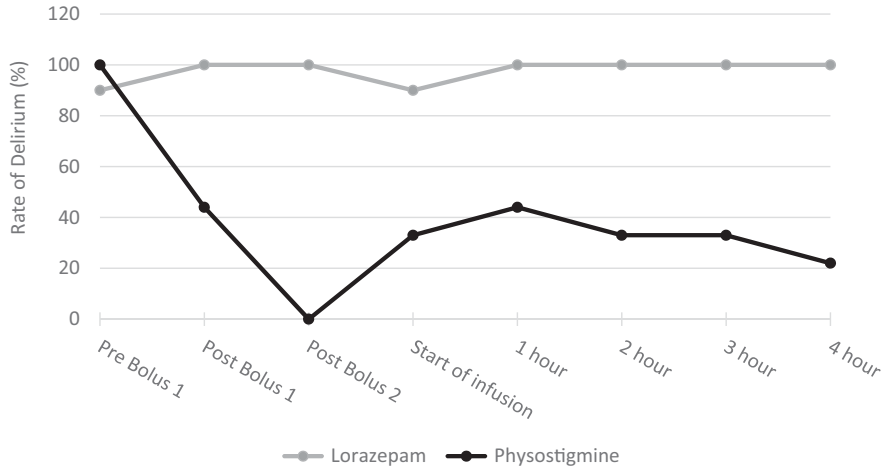

Figure 2. Rate of delirium during study period.

Table 3. RASS agitation scores in each arm, median (IQR).

RASS AGITATION SCORE	Lorazepam ($n = 10$)	Physostigmine ($n = 9$)	p-Value
Prior to first bolus	1 (1,1.5)	1.5 (1,2)	0.32
After first bolus	1 (1,2.5)	0 (0,0)	0.10
After 4th h of infusion	0.25 (−1.5,1.5)	0 (0,0)	0.58
Change in RASS score *before and after first bolus*			**0.02**
Increased	2 (20.0%)	1 (11.1%)	
Decreased	3 (30.0%)	8 (88.9%)	
Unchanged	5 (50.0%)	0 (0%)	
Change in RASS score from *before first bolus to end of infusion*			>0.99
Increased	1 (10.0%)	0 (0%)	
Decreased	8 (80.0%)	9 (100%)	
Unchanged	1 (10.0%)	0 (0%)	

Bold values represents as statistically significant p-values

Table 4. Amount of as needed (PRN) benzodiazepines administered to subjects in each treatment arm.

PRN BENZODIAZEPINE USE	Lorazepam ($n = 10$)	Physostigmine ($n = 9$)	p-Value
Doses *prior* to study treatment?			0.55
0	2 (20.0%)	1 (11.1%)	
1	5 (50.0%)	7 (77.8%)	
2	3 (30.0%)	1 (11.1%)	
Doses lorazepam *during* study			0.09
0	4 (40.0%)	8 (88.9%)	
1	3 (30.0%)	1 (11.1%)	
2	3 (30.0%)	0 (0%)	
Median *total* doses of benzodiazepines	2 (1–3)	1 (1–1)	0.07
Number of doses benzodiazepines (prior + prn)			
0	0 (0%)	1 (11.1%)	
1	4 (40.0%)	6 (66.7%)	
2	3 (30.0%)	2 (22.2%)	
3	2 (20.0%)	0 (0%)	
4	1 (10.0%)	0 (0%)	

received more "as needed" lorazepam dosing during the study, although the difference was not statistically significant (Table 4, $p = 0.09$). Six (60%) subjects in the lorazepam arm received 2 or more doses of lorazepam for agitation, compared to 2 (22%) subject in the physostigmine arm ($p = 0.17$).

During the study, no subjects experienced seizures, bradycardia, bronchorrhea, bronchospasm, diaphoresis, or required intubation in either treatment arm. Vomiting occurred in one subject in the physostigmine arm after a 2nd bolus. Vomiting also occurred in one subject in the lorazepam arm prior to the 4-h infusion, and at 2 h into the infusion. Over sedation was noted in one subject in each treatment arm, both occurred during the length of the 4-h infusion.

There was no difference in ICU length of stay and total hospital length of stay between subjects in the two treatment arms (Table 5). Of the nineteen patients enrolled, 10 required physical restraints upon arrival to our hospital due to agitation and delirium: 3 subjects in the lorazepam arm and 7 subjects in the physostigmine arm. Subjects in the physostigmine group had a shorter mean time in restraints of 13.4 h (SD 12.3) compared with 27.5 h (SD 18.2) for the

Table 5. Hospital length of stay, and time in restraints in each treatment arm.

	Lorazepam ($n = 10$)	Physostigmine ($n = 9$)	*p*-Value
Total Hospital Length of Stay (hours), Mean (SD)	51.9 (19.0)	46.5 (24.1)	0.60
ICU Length of Stay (hours), Mean (SD)	25.9 (13.2)	21.3 (16.9)	0.52
	Lorazepam ($n = 3$)	Physostigmine ($n = 7$)	
Time in Restraints (hours), Mean (SD)	27.5 (18.2)	13.4 (12.3)	0.18

Not all patients required physical restraints.

Table 6. Satisfaction score from guardian, nurses, and healthcare providers.

	Lorazepam ($n = 10$)	Physostigmine ($n = 9$)	*p*-Value
Guardian			
How satisfied are you with control of *delirium*? (1–5)	4 (3–4)	4.5 (4–5)	0.10
Not satisfied (1)	1 (11%)	0 (0%)	
Somewhat satisfied (2)	1 (11%)	1 (13%)	
Neutral (3)	2 (22%)	0 (0%)	
Satisfied (4)	4 (44%)	3 (38%)	
Very satisfied (5)	1 (11%)	4 (50%)	
How satisfied were you with control of *agitation*? (1–5)	4 (4-4)	5 (4-5)	0.14
Not satisfied (1)			
Somewhat satisfied (2)	1 (11%)	0 (0%)	
Neutral (3)	0 (0%)	0 (0%)	
Satisfied (4)	1 (11%)	1 (13%)	
Very satisfied (5)	5 (56%)	2 (25%)	
	2 (22%)	5 (63%)	
	Lorazepam ($n = 10$)	Physostigmine** ($n = 11$)	*p*-Value
Nursing*			
How satisfied are you with control of *delirium*? (1–5)	1 (1–3)	5 (4–5)	**<0.001**
Not satisfied (1)			
Somewhat satisfied (2)	6 (60%)	0 (0%)	
Neutral (3)	1 (10%)	1 (9%)	
Satisfied (4)	1 (10%)	0 (0%)	
Very satisfied (5)	2 (20%)	2 (18%)	
	0 (0%)	8 (73%)	
How satisfied were you with control of *agitation*?	1.5 (1–3)	5 (5–5)	**<0.001**
Not satisfied (1)			
Somewhat satisfied (2)	5 (50%)	0 (0%)	
Neutral (3)	2 (20%)	0 (0%)	
Satisfied (4)	2 (20%)	0 (0%)	
Very satisfied (5)	1 (10%)	2 (18%)	
	0 (0%)	9 (82%)	
	Lorazepam ($n = 10$)	Physostigmine** ($n = 10$)	*p*-Value
Healthcare provider*			
How satisfied are you with control of *delirium*? (1–5)	1 (1–2)	5 (4–5)	**0.001**
Not satisfied (1)			
Somewhat satisfied (2)	7 (70%)	0 (0%)	
Neutral (3)	1 (10%)	1 (10%)	
Satisfied (4)	0 (0%)	1 (10%)	
Very satisfied (5)	1 (10%)	2 (20%)	
	1 (10%)	6 (60%)	
How satisfied were you with control of *agitation*? (1–5)	2 (1–3)	5 (4–5)	**0.001**
Not satisfied (1)			
Somewhat satisfied (2)	3 (30%)	0 (0%)	
Neutral (3)	3 (30%)	0 (0%)	
Satisfied (4)	2 (20%)	1 (10%)	
Very satisfied (5)	1 (10%)	2 (20%)	
	1 (10%)	7 (70%)	

For one subject in the lorazepam group, and two subjects in the physostigmine group, bolus and treatment infusions were given in two locations (ED and ICU), which provided additional nursing and healthcare provider satisfaction scores.
*Nursing and Healthcare Provider were from either the Emergency Department or the Intensive Care Unit.
**There were additional providers and nursing providing scores in the physostigmine.
Bold values represents as statistically significant *p*-values

lorazepam group, however this was not statistically significant ($p = 0.18$). There was no significant difference in guardian satisfaction in control of delirium ($p = 0.10$) or agitation ($p = 0.14$) between patients treated with lorazepam versus physostigmine. The nursing staff and treating healthcare provider reported significantly more satisfaction with

physostigmine compared to lorazepam for controlling delirium and agitation (Table 6).

Discussion

Physostigmine bolus and infusion is an effective and safe treatment for antimuscarinic delirium and agitation. Our findings demonstrated that, as compared to lorazepam, physostigmine was superior in reversal/treatment of delirium after initial bolus and after the 4th h of the infusion. Physostigmine was also superior in control of agitation after the initial bolus, but not after the 4th h of the infusion. Patients in the lorazepam group required additional benzodiazepine dosing, and more subjects in the lorazepam group received multiple dosing of benzodiazepines to achieve similar control in agitation, although this was not statistically significant.

In addition to superior efficacy during the study, physostigmine did not result in significant adverse events including seizures, bradycardia, intubation, or other cardiopulmonary sequelae. Safe and adequate control of agitation and delirium from physostigmine in the setting of antimuscarinic toxicity has been previously described [13–22]. A retrospective comparison of physostigmine to benzodiazepines for treating antimuscarinic toxicity also demonstrated the superiority of physostigmine compared to lorazepam. Burns et al. described reversal of delirium with physostigmine in 87% of patients receiving physostigmine compared with 0% of patients receiving benzodiazepine treatment. In that study, physostigmine also controlled agitation in all but 1 of 28 patients, while 16 of 22 patients still had agitation after benzodiazepines alone [12]. Similar to the findings in our study, there were also no differences in adverse events between the two groups; however, physotigmine was associated with a lower incidence of complications and shorter recovery times.

Physostigmine has a rapid onset of action and can quickly reverse delirium and agitation. However, the disadvantage of physostigmine is that the duration of action is also short, typically lasting only 30–60 min (elimination half-life is 16 min) often requiring frequent re-dosing after clinical effects wane [2–4,6,7]. By using a continuous physostigmine infusion, we were able to successfully control delirium and agitation for a longer period of time without significant adverse events. We chose a continuous infusion rather than repeat dosing in order to attempt to achieve more continuous control of the delirium and agitation, rather than a waxing and waning state. Previous case reports have also demonstrated safe and effective use of physostigmine infusions for persistent antimuscarinic delirium and agitation for at least eight hours in pediatric patients [23,24]. However, we did not achieve control of delirium in all patients receiving physostigmine infusion. This may be due to inadequate dosing of physostigmine during an infusion. We dosed subjects by their bolus dose per hour during the infusion. Physostigmine may need to be titrated to achieve optimal effect for infusion rather than using the calculated bolus dose. Additionally, many of the patients were enrolled during the overnight period, where awakenings to assess agitation and delirium scores were difficult.

Although the number of restrained patients in the lorazepam group was small ($n = 3$), subjects in the physostigmine group were in restraints for half the time of patients receiving lorazepam (13 h compared with 27 h). Additionally, the need for physical restraints can be a subjective evaluation. However, the observed decreased time in restraints could lead to fewer patient complications associated with physical restraints such as traumatic injuries, worsening psychomotor agitation, and metabolic abnormalities such as rhabdomyolysis or acidosis. Furthermore, less time in physical restraints can improve the safety of the guardians, healthcare providers and staff caring for the agitated and altered patient. This benefit was reflected in the significant difference in satisfaction scores of bedsides nurses and healthcare providers of subjects receiving physostigmine compared with lorazepam. The lack of guardian satisfaction between subjects in each treatment arm was likely due to the inability to compare the response from each treatment protocol.

There were some limitations to our study. Due to time allotment from funding sources, and the limitations of patient enrollment due to the SARS-COV2 pandemic, we were only able to enroll 19 of the needed 22 patients based on our power calculation. Fortunately, the treatment effect was large enough to find a difference between the smaller groups. However, the smaller subject numbers decreased our ability to detect adverse events. Subjects were not enrolled if there was a history of seizures or asthma. Furthermore, all potential subjects were excluded if they had any hemodynamic instability upon initial evaluation. All patients in our cohort ingested antihistamines, the majority of which was diphenhydramine. There were no ingestions of other common antimuscarinic xenobiotics such as antipsychotics or Datura. Thus, we cannot comment on the effectiveness nor the safety of physostigmine bolus and infusion administration in these clinical situations or other ingestions. Many of the subjects were enrolled during the overnight hours. This time period, in addition to the underlying sedation effect of the ingested agent made an assessment of delirium challenging which may have led to more positive delirium scores in both treatment arms. The duration of the infusion was 4 h, and we did not assess efficacy or safety beyond this time period. A quantitative score to assess delirium may have been more helpful in quantifying and comparing the response between the two treatment arms. Finally, we only enrolled adolescent patients. Our results likely could be applied to adults, but may not generalize to younger pediatric patients or geriatric patients.

Conclusion

Physostigmine is superior to lorazepam in control of antimuscarinic delirium and agitation after bolus dosing, and control of delirium after a 4-h infusion, though not more effective in control of agitation after the 4-h infusion. Furthermore, physostigmine is efficacious without increased risk of adverse events. Additional research is needed to fully compare these treatments with other outcome variables

including adverse events, in addition to evaluating its utility in other age groups patients. Physostigmine bolus and infusion should be considered in adolescent patients with significant delirium and agitation from ingestion of antimuscarinic agents.

Disclosure statement

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