COMIRB Protocol

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Protocol #: 16-1730
Project Title: A Randomized Trial comparing Physostigmine vs Lorazepam for Treatment of Adolescent Antimuscarinic (Anticholinergic) Toxidrome
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I. Hypotheses and Specific Aims:

- Specific Aim 1: Determine the effectiveness of physostigmine as compared with lorazepam for control of antimuscarinic agitation.
- Hypothesis: Physostigmine infusion will decrease agitation more effectively than lorazepam bolus

- Specific Aim 2: Determine the effectiveness of physostigmine as compared with lorazepam in the reversal of antimuscarinic delirium.
- Hypothesis: Physostigmine bolus will reverse a greater proportion of patients with antimuscarinic delirium compared to lorazepam bolus.

- Specific Aim 3: Demonstrate the safety of physostigmine infusion as compared to lorazepam bolus dosing for antimuscarinic toxicity.
- Hypothesis: The proportion of adverse events will not differ between physostigmine infusion compared to lorazepam bolus dosing.

II. Background and Significance:

Overdose or abuse of xenobiotics, such as antihistamines or Jimson Weed, with resulting antimuscarinic toxidrome is a common scenario in medical toxicology. In 2014, National Poison Data System (NPDS) annual report revealed 103,327 antihistamine ingestions reported to US regional poison centers, making it the 6th most common human exposure.[1] In addition to antihistamines, several medications are direct muscarinic antagonists, including antipsychotics.[2,3] The result of antagonism of muscarinic receptors is a constellation of signs and symptoms (toxidrome) which can consist of mydriasis (large pupils), decreased sweat, decreased bowel sounds, agitation, delirium, hallucinations, urinary retention, tachycardia, flushed skin and seizures.[2,3] This toxidrome is common after supratherapeutic ingestions (overdoses) of these medications.

Treatment for antimuscarinic toxidrome consists of supportive medical care including hemodynamic support with adequate fluid resuscitation, cooling if hyperthermia develops, and treatment of seizures. [4] In addition to hemodynamic support, the goal of therapy is control of agitation and delirium. Most medical therapy consists of

administration of sedative hypnotic pharmaceuticals such as benzodiazepines to achieve adequate sedation.[4] However, significant amounts of benzodiazepines can be required, which can be a risk factor for hypotension and over sedation, and in loss of airway protection leading to intubation and mechanical ventilation.[5] Furthermore, benzodiazepines do not reverse antimuscarinic delirium, and some patients may have a paradoxical worsening of symptoms.

Physostigmine is a reversible acetylcholinesterase inhibitor that increases the concentration of acetylcholine at the synapse. The increase in acetylcholine overcomes the competitive antagonism of acetylcholine muscarinic receptor.[2,3] Physostigmine crosses the blood-brain barrier, reversing both the agitation and delirium associated with the antimuscarinic toxidrome.[6] Safe and adequate control of agitation and delirium with physostigmine in the setting of antimuscarinic toxicity from various xenobiotics has been described. [7-16] Retrospective comparisons of physostigmine to benzodiazepines for treatment for antimuscarinic toxicity revealed physostigmine controlled all but 1 of 28 patients, while 16 of 22 patients still had agitation after benzodiazepine alone.[17] Delirium was also reversed in 87% patients receiving physostigmine compared with zero with benzodiazepine treatment. Adverse effects were not different between the treatment groups.

In the absence of high quality randomized trials, physostigmine has not been widely adopted for treatment of antimuscarinic toxicity. In 2014, NPDS annual review reported only 316 patients received physostigmine, while 35,337 patients received benzodiazepines for ingestions and exposures.[1] Concerns over the use of physostigmine stem from concerns of adverse events exist due to two case reports in the setting of tricyclic antidepressant overdose complicated by seizures and asystolic arrest.[18,19] However, more detailed evidence has shown that physostigmine can be administered safely and effectively in antimuscarinic toxicity without development of these severe adverse effects.[4,7-16,20-22] Another criticism of physostigmine is the short duration of action. The onset of effect after IV administration is rapid, with reversal or antimuscarinic toxidrome within several minutes. The duration of action is also short, lasting typically 30-60 minutes (elimination half-life is 16 minutes).[6,7] Even though physostigmine has a short duration of action, continuous physostigmine infusion for persistent antimuscarinic delirium and agitation of at least 8 hours has been demonstrated to be safe and effective even in pediatric patients.[23,24]

Although the antimuscarinic toxidrome occurs commonly, physostigmine has been used sparingly despite evidence of safety and efficacy. To demonstrate the utility and safety of physostigmine, we propose a randomized clinical trial of physostigmine compared to benzodiazepine for antimuscarinic toxicity.

III. Preliminary Studies/Progress Report:

From August 1, 2013 through January 31, 2016, 56 patients were evaluated by a medical toxicology consultation at Children's Hospital Colorado for antihistamine overdose. Several more were evaluated for antimuscarinic toxidrome from other ingestions (antipsychotics and *Datura*). Of the antihistamine overdose patients, 8 received physostigmine with complete reversal of agitation and delirium and no reported side effects; the

remaining received benzodiazepines. Twenty-seven patients were admitted to the intensive care unit, with the remaining being admitted to the inpatient ward or observed in the emergency department. There were no cardiac dysrhythmias or seizures from physostigmine, and no deaths.

IV. Research Methods

A. Outcome Measure(s):

Primary outcome measures for this study include evaluation and assessment of delirium and agitation, as measured by the Richmond Agitation-Sedation Score (RASS) and modified 3D-Confusion Assessment Delirium (CAM) scores. Secondary outcomes include adverse effects, which include the following: seizures, bradycardia, dysrhythmias, bronchospasm, increased secretions, diaphoresis, vomiting, intubation, and over-sedation. We will also evaluate treatment satisfaction scores from treating physicians, nursing staff, and parents. Total benzodiazepine doses given will be recorded for each patient enrolled. The total time requiring physical restraints will also be collected.
Immediately prior to study treatment, after each medication bolus, and during every hour of treatment, the following will be obtained: vital signs, RASS, determination of delirium, adverse effects (seizures, bradycardia (<60), bronchorrhea, bronchospasm, diaphoresis, vomiting, intubation and over-sedation) and clinical examination (specifically, symptoms of antimuscarinic toxicity: flushed skin, dry axillae, dry mucous membranes, mydriasis, decreased bowel sounds, seizures, tachycardia, hyperthermic (>38.0C)).

Previously validated RASS score will be used to assess agitation: -5 (nonarousable) to 0 (alert and calm) to +4 (combative).[25](Table 1) Two separate providers (MD or RN) will provide assessment of agitation score. Modified 3D-CAM score will be used to assess delirium.[26] All patients meeting inclusion criteria for RASS scores will automatically have the first 2 criteria for 3D-CAM met: fluctuating course of mental status and inattention.[26] Thus, questions on disorganized thinking will be asked to further assess for delirium: 1) Will a stone float on water? 2) Are there fish in the sea? 3) Does one-pound weight more than two? 4) Can you use a hammer to pound a nail? Reversal of delirium will be defined as ability to correctly answer at least 3 of 4 questions. Sensitivity analysis will be performed to compare 2-3 questions correct. At the end of the treatment protocol, the study will terminate and treating physicians can medically treat patient at their discretion. A urine sample from either a pre-existing foley catheter bag collection, or volunteer void, will be sent for a comprehensive urine drug screen.[27]

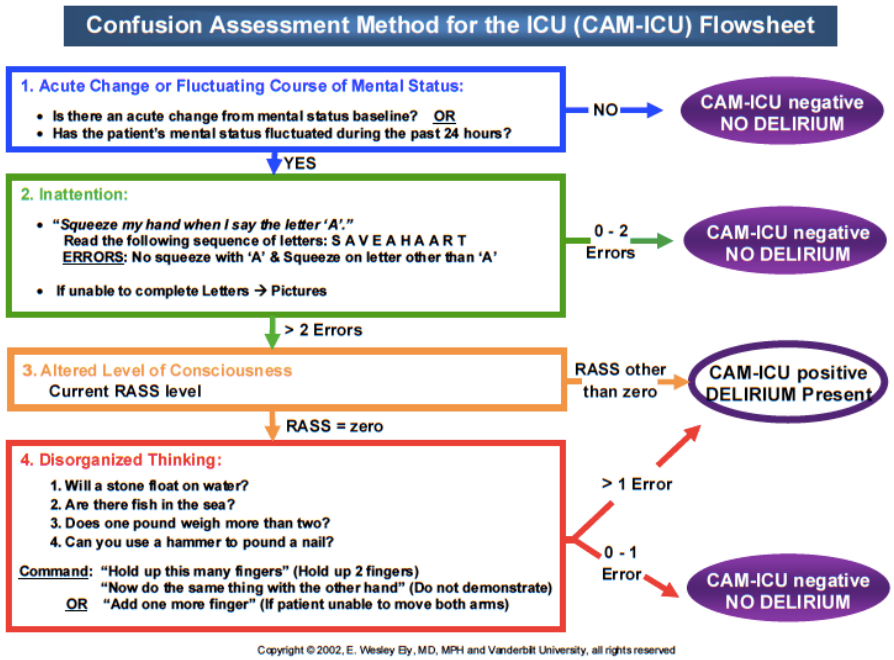
Table 1. The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)	Verbal stimulation
−2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical stimulation
−5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment

1. Observe patient
   - Patient is alert, restless, or agitated. — Score 0 to +4
2. If not alert, state patient's name and say to open eyes and look at speaker.
   - Patient awakens with sustained eye opening and eye contact. — Score −1
   - Patient awakens with eye opening and eye contact, but not sustained. — Score −2
   - Patient has any movement in response to voice but no eye contact. — Score −3
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   - Patient has any movement to physical stimulation. — Score −4
   - Patient has no response to any stimulation. — Score −5

Adapted with permission.[29]



B. Description of Population to be Enrolled:

Inclusion Criteria:

- >=10 and < 18 years of age
- Present to the Children's Hospital Colorado Emergency Department or Intensive Care Unit for an antimuscarinic toxidrome from either a pharmaceutical agent such as antihistamine overdose (diphenhydramine, chlorpheniramine, doxylamine, cyclobenzaprine), or natural toxins/products such as *Datura stramonium*
- Antimuscarinic toxidrome will be defined with at least one central nervous system agitation effect (agitation, delirium, visual hallucinations, mumbling incomprehensible speech), and at least 2 peripheral nervous systems adverse effect (mydriasis, dry mucus membranes, dry axillae, tachycardia, decreased bowel sounds).
- If the patient has one IV, does the medical team deem it appropriate to discontinue IVF during the 4-hour infusion period (due to drug compatibility)
- Patients will also be required to have a RASS score of ≥ +1 AND have a positive delirium score on the modified 3D CAM Score on initial assessment.
- Parent/legal guardian providing consent for the subject is >18 and <85

Exclusion Criteria:

- History of epilepsy or seizures during acute clinical course
- History of asthma or wheezing during clinical course
- Bradycardia (Heart Rate <60)
- Concomitant use of atropine or choline ester or depolarizing neuromuscular blocker during present illness and hospital course
- Diabetes gangrene, known intestinal obstruction or urogenital tract, vagotonic state
- QRS interval > 120 ms on electrocardiogram
- History of current overdose of tricyclic antidepressant
- Child is known to be pregnant at the time of enrollment
- Known ward of the state
- Child has a history of developmental delay
- Previous administration of physostigmine during the current illness*
  *(Previous benzodiazepine administration does not exclude subjects as long as agitation score meets inclusion criteria.)

C. Study Design and Research Methods

This is a double-blinded, randomized clinical trial, comparing physostigmine and benzodiazepines for treatment for antimuscarinic toxicity. The study will be registered with Clintrials.gov. Patients will be initially screened by research assistants (RA) or by primary medical treatment team by chief complaint of "Ingestion," "Overdose," "XXXX," or "Altered Mental Status" via EPIC electronic medical record. The diagnosis of antimuscarinic toxidrome will also be verified by the medical toxicology service.

After signed or verbal phone consent from the child's parent/legal guardian, randomization will be performed by the pharmacy to determine the treatment protocol. Investigational pharmacy will be notified by the RA and the initial pharmaceutical treatment regimen will be provided to the treatment team. The patient, caregiver, nursing staff, and treating physician will be blinded to the treatment. To maintain blinding, the bolus and infusion medications will only be labeled with a study protocol identifier. Physostigmine and lorazepam are both clear, and the bolus and infusion volumes will be similar and syringe will be covered to allow for adequate blinding. Patients will be on continuous cardiorespiratory monitoring, receive intravenous fluid resuscitation, laboratory assessment (basic metabolic panel, acetaminophen and salicylate concentrations, and electrocardiogram) and urine foley placement (if needed) per standard treatment protocol for their presenting diagnosis. They will be allowed to receive other medications, including antipsychotic or other benzodiazepines, during their treatment timeline while in the study. They will not be excluded from the study if they have received these medications prior to enrollment, as long as they have otherwise met study criteria.

Enrolled patients will be randomized to a treatment arm of:

- Physostigmine 0.02 mg/kg IV bolus (max of 2 mg), which can be repeated at 10 minutes, followed by a 0.02 mg/kg/hr (max of 2 mg/hr) infusion for 4 hours.

OR

- Lorazepam 0.05 mg/kg IV bolus (max 2 mg), which can be repeated at 10 minutes if inadequate patient response, followed by a NS infusion for 4 hours.

During either treatment arm, lorazepam 0.05 mg/kg IV bolus (max 2 mg) can be administered every 2 hours as needed for continued elevated agitation scores.

Urine samples will be obtained (10-30ml), and sent to LabCorp for analysis using the TOXASSURE Comprehensive Drug Analysis which includes 26 drug categories and 180 compounds using UPLC/MS-MS analysis platform. They will be stored at the Research Institute Freezer at < 20C until sent to LabCorp for analysis.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Human subjects included in our study will consist of patients greater than or equal to 10 years and less than 18 years of age. Our study does not involve fetuses, prisoners, institutionalized individuals, neonates, or pregnant women. This study will include women, minorities, and children. Parent/Legal Guardian consent will be obtained prior to study procedures being performed. Each patient enrolled will be given a unique study identifier which will be used for the laboratory samples and data collection. Any and all protected health information and data obtained will be stored in a password-secured, REDCap data system.

- Intravenous (IV) administration of medications: These patients will have existing IV's for their standard care and treatment. Risks of this procedure include pain, infection, local redness and irritation. Physostigmine, lorazepam, nor normal saline can lead to caustic injury with IV infiltration.

- Urine Sample: If a foley is being placed for their standard care, urine sample will be obtained from foley bag. If the patient can void, they will voluntarily void into a collection cup.
- There is a slight but unlikely risk of loss of confidentiality. To help protect against this, a password-protected REDCap database will be used to collect and store all data. Only study team members will have access to the database.
- Reports of seizures and cardiac dysrhythmias have rarely been reported with the use of physostigmine and from anticholinergic toxicity. Other rare but potentially serious side effects can include bronchospasm, bradycardia, and bronchorrhea. Standard label contraindications will be used for physostigmine (as listed in the exclusion criteria) to avoid these complications, and atropine will be at bedside to reverse any potential clinical effects which may occur. Adverse effects from lorazepam include over sedation and respiratory depression. Supportive care will be used for any adverse effects from lorazepam. Patients will be on a full cardiorespiratory monitor for their diagnosis per standard protocol, and will be constantly monitored for adverse events associated with their diagnosis, in addition to their treatment protocol.
- Stopping/Exit Criteria during study protocol:
    - Physician discretion
    - Bradycardia (HR <60)
    - Seizures
    - Cardiac Dysrhythmias
    - Wheezing
    - Intubation

Any possible adverse events reported by the research staff or parent/legal guardians that might occur from the urine collection or from medications received during their visit will be documented and reported to the primary investigator and appropriate IRB authorities in real time. They will be reviewed and determined if any immediate action will need to be taken.

E. Potential Scientific Problems:

One potential issue is misclassification of the patient at the time of enrollment. The anticholinergic toxidrome is a clinical diagnosis and there are many conditions that may mimic parts of this toxidrome. However, members of the medical toxicology service will be evaluating the patients to verify presentation of antimuscarinic toxidrome. There may be provider variability in rating delirium and agitation. We are using standardized scales to decrease this variability. Although standard dosing is used, the dose of physostigmine or lorazepam used for this study may not be adequate in treatment of delirium or agitation, depending on the exposure and amount ingested.

F. Data Analysis Plan:

Data will be analyzed by SAS 9.4 (SAS Institute, Cary, NC). Two-tailed Fisher exact and Mann-Whitney U tests will be used for independent samples. McNemar's and Wilcoxon signed rank tests will be used to assess variable change before and after

treatment. If continuous or ordinal data is non-normally distributed, non-parametric tests will be performed. Due to multiple comparisons, statistical significance will be adjusted using Bonferroni's correction. To compare intergroup changes in agitation score, repeated-measure analysis of variance will be used. When number of observed events was small, the exact binomial distribution was used to compute 95% confidence intervals. Kappa score for agreement will be performed for provider determination of agitation score. Our power calculations, based a retrospective study evaluating after initial control of agitation with treatment of where 96% of physostigmine and 27 % of benzodiazepine treated patients had control of agitation, suggested that 22 subjects (11 in each arm) provides 92% power to detect at least 70% difference assuming an alpha of type 1 error rate of 5%. To account for study withdrawal and attrition, study protocol and budget will be prepared for enrollment of 28 during the study time period.

G. Summarize Knowledge to be Gained:

Our study promotes the study of health effects and treatment of a common ingestion (antihistamines) and toxidrome (antimuscarinic), and will ultimately improve clinical care and practice of clinical toxicology, specifically in this very common patient population. It will help expand knowledge of safety and efficacy of physostigmine by providing top level evidence, and help define the use of this antidote for clinical toxicologists and other treating physicians.

H. References:

1. Mowry B, Spkyer DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. Clin Toxicol (Phila). 2015;53(10):962-1147.
2. Rumack BH. Anticholinergic Poisoning: Treatment with Physostigmine. Pediatrics. 1973;52(3):449-451.
3. Lieberman JA. Managing Anticholinergic Side Effects. Prim Care Companion J Clin Psychiatry. 2004;6(suppl 2):20-23.
4. Watkins JW, Schwarz ES, Arroyo-Plasencia AM, Mullins ME; Toxicology Investigators Consortium. The Use of Physostigmine by Toxicologists in Anticholinergic Toxicity. J Med Toxicol. 2015;11(2):179-84.
5. Beauchamp GA, Giffin SL, Horowitz BZ, Laurie AL, Fu R, Hendrickson RG. Poisonings associated with intubation: US National Poison Data System Exposures 2000-2013. J Med Toxicol. 2015. [epub ahead of print].
6. Dawson AH, Buckley NA. Pharmacological management of anticholinergic delirium- theory, evidence and practice. Br J Clin Pharmacol. 2015. [epub ahead of print].
7. Beaver KM, Gavin TJ (1998) Treatment of acute anticholinergic poisoning with physostigmine. Am J Emerg Med 16(5):505–507.
8. Rasimas JJ, Sachdeva K, Salama AM, Helmick TJ, Donovan JW. A review of bedside toxicologic experience with physostigmine and flumazenil. Clin Toxicol. 2010;48(6):648.

9. Crowell EB Jr, Ketchum JS. The treatment of scopolamine induced delirium with physostigmine. Clin Pharmacol Ther. 1967. 8(3): 409–414.
10. Slovis TL, Ott JE, Teitelbaum DT, Lipscomb W. Physostigmine therapy in acute tricyclic antidepressant poisoning. Clin Toxicol. 1971;4(3):451–459.
11. Teoh R, Page AV, Hardern R. Physostigmine as treatment for severe CNS anticholinergic toxicity. Emerg Med J. 2001 Sep;18(5):412.
12. Beaver KM, Gavin TJ. Treatment of acute anticholinergic poisoning with physostigmine. Am J Emerg Med. 1998 Sep;16(5):505-7.
13. Arnold SM, Arnholz D, Garyfallou GT, Heard K. Two siblings poisoned with diphenhydramine: a case of factitious disorder by proxy. Ann Emerg Med. 1998 Aug;32(2):256-9.
14. Martin B, Howell PR. Physostigmine: going…going…gone? Two cases of central anticholinergic syndrome following anaesthesia and its treatment with physostigmine Eur J Anaesthesiol. 1997 Jul;14(4):467-70.
15. Ceha LJ, Presperin C, Young E, Allswede M, Erickson T. Anticholinergic toxicity from nightshade berry poisoning responsive to physostigmine. J Emerg Med. 1997 Jan-Feb;15(1):65-9.
16. Centers for Disease Control and Prevention (CDC). Anticholinergic poisoning associated with an herbal tea--New York City, 1994. MMWR Morb Mortal Wkly Rep. 1995 Mar 24;44(11):193-5.
17. Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann Emerg Med. 2000;35(4):374–381
18. Falletta JM, Stasney CR, Mintz AA (1970) Amitriptyline poisoning treated with physostigmine. South Med J 63:1492–1493
19. Pentel P, Peterson CD (1980) Asystole complicating physostigmine treatment in tricyclic antidepressant overdose. Ann Emerg Med 9(11):588–590.
20. Tobis J, Das BN. Cardiac complications in amitriptyline poisoning. Successful treatment with physostigmine. JAMA. 1976 Apr 5;235(14):1474-6.
21. Snyder BD, Blonde L, McWhirter WR. Reversal of amitriptyline intoxication by physostigmine. JAMA. 1974;230(10):1433-4.
22. Goldberger AL, Curtis GP. Immediate effects of physostigmine on amitriptyline-induced QRS prolongation. J Toxicol Clin Toxicol. 1982;19(5):445-54.
23. Phillips MA, Acquisto NM, Gorodetsky RM, Wiegand TJ. Use of a physostigmine continuous infusion for the treatment of severe and recurrent antimuscarinic toxicity in a mixed drug overdose. J Med Toxicol. 2014;10(2):205-9.
24. Hall SL, Obafemi A, Kleinschmidt KC. Successful management of olanzapine-induced anticholinergic agitation and delirium with a continuous intravenous infusion of physostigmine in a pediatric patient. Clinc Toxicol (Phila). 2013;51(3):162-6.
25. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessier CN, Dittus RS, Bernard GR. Monitoring sedation stats over time in ICU patients, reliability and validity

of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983-2991.
26. Marcantonio ER, Ngo LH, O'Connor M, Jones RN, Crane PK, Metzger ED, Inouye SK. 3D-CAM: Derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium. Ann Intern Med. 2014;161(8):554-461.
27. Quest Drug Testing. http://education.questdiagnostics.com/system/FAQ101DL.pdf. Last accessed 2/24/2016.