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TOXICOLOGY INVESTIGATION

Timing and Frequency of Physostigmine Redosing for Antimuscarinic Toxicity

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Abstract We sought to determine how frequently antimuscarinic-poisoned patients receiving physostigmine receive multiple doses of physostigmine, the length of time between physostigmine doses, and what impact multiple doses of physostigmine have on the disposition and total length of hospital stay. We performed a retrospective chart review of patients given physostigmine for likely antimuscarinic toxicity. A total of 45 patients met inclusion criteria. We abstracted patient demographics, vital signs, physical exam findings, electrocardiograms, the timing and dose of physostigmine, the implicated antimuscarinic agents, and disposition from the hospital. We counted the number of patients who required multiple physostigmine doses and calculated the time to repeat dosing. Fourteen of the 45 patients (31%) given physostigmine for antimuscarinic toxicity received multiple doses: nine patients (20%) received two doses, three patients (6.6%) received three doses, and two patients (4.4%) received four doses. Less than 5.5 h elapsed between sequential physostigmine doses, and less than 6.5 h elapsed between the first and last dose. Forty-five percent of patients receiving one dose of physostigmine were discharged from the emergency department (ED) and 36% of patients receiving more than one dose of physostigmine were discharged from the ED. Whether admitted or discharged, there was no statistically significant difference in the length of hospital stay between patients receiving one or multiple doses of physostigmine. Repeated physostigmine administration is not frequently needed in medication-induced antimuscarinic toxicity. Patients are not likely to require further physostigmine redosing more than 6.5 h from their first dose.

Keywords Physostigmine · Antimuscarinic · Anticholinergic · Toxicity

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Introduction

Background

Physostigmine is a naturally occurring plant alkaloid that was once used to determine innocence or guilt in the mid-nineteenth century [1]. Today, physostigmine is a diagnostic and therapeutic antidote that can reverse the agitated delirium and tachycardia of antimuscarinic poisoning (i.e., antimuscarinic toxidrome) [2]. The antimuscarinic toxidrome results from blockade of the neurotransmitter acetylcholine at central and peripheral muscarinic receptors, leading to varying degrees of tachycardia, agitation, delirium, dilated pupils, dry mucous membranes, dry skin, and hypoactive bowel sounds [3]. Unlike quaternary amine acetylcholinesterase inhibitors (such as neostigmine) that treat peripheral manifestations of the antimuscarinic toxidrome, physostigmine is a tertiary amine, and thus is able to cross the blood-brain barrier to treat both central (e.g., agitation and delirium) and peripheral (e.g., tachycardia) antimuscarinic manifestations [3].

Importance

The time to onset, time to peak effect, and duration of action for parenteral physostigmine are short: approximate-

ly 5 min, 15 min, and 1–3 h, respectively [3, 4]. However, there are no published clinical human data regarding the pharmacodynamics of physostigmine when used to reverse antimuscarinic toxicity. Our personal experience as consulting medical toxicologists suggests that multiple doses of physostigmine are sometimes necessary to maintain reversal of significant antimuscarinic effects (such as agitation and delirium). The ability to determine the frequency of physostigmine redosing could significantly impact patient care and disposition, especially from the ED. The current study was designed to address these clinical observations and hypotheses.

Goals of this Investigation

The goals of this investigation were to determine how frequently patients with antimuscarinic toxicity receive repeated doses of physostigmine, the length of time between physostigmine doses, and what impact multiple doses of physostigmine have on total length of hospital stay or disposition.

Materials/Methods

Study Design and Setting

We performed a retrospective chart review and descriptive case series study of hospitalized patients given physostigmine for suspected antimuscarinic toxicity. We identified inpatient and ED medical records given the *International Classification of Diseases—ninth revision* (ICD9) code 971.1 ("poisoning by parasympatholytics (anticholinergics and antimuscarinics) and spasmolytics") between January 1997 and December 2007 and pharmacy-recorded physostigmine orders between July 2005 and February 2008. The study was conducted from an urban Massachusetts tertiary care university teaching hospital, with an emergency medicine residency, a medical toxicology fellowship, and 24-h toxicology consultation services. The University of Massachusetts Medical School Institutional Review Board approved this study.

Selection of Participants

Adults with either ICD9-coded antimuscarinic toxicity or physostigmine orders through pharmacy records met inclusion criteria. Exclusion criteria were age <18 years, medical records lacking documentation of physostigmine administration, or physostigmine given in the postanesthesia care unit (PACU). Ultimately, we identified 45 patients given physostigmine for suspected antimuscarinic toxicity that met inclusion criteria (Fig. 1).

Methods of Measurement and Data Collecting/Processing

A single physician abstracted patient demographics, vital signs, physical exam findings, electrocardiogram (ECG) results, urine drug screens, timing and dosing of physostigmine, the implicated antimuscarinic agent(s), and disposition time from the hospital according to established criteria [5]. Medical records were available in a combination of paper and electronic formats. Data were entered directly into an Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet in a de-identified fashion. Data analyses and graphing were performed in Stata 11.0 (StataCorp, College Station, TX, USA) and GraphPad Prism (GraphPad Software, Inc, La Jolla, CA, USA).

Agitation was considered to be present if the word "agitated" or "agitation" appeared in the patient's medical record. Similarly, delirium was considered to be present if the patient was less than fully oriented or had "delirium," "delirious," "incoherent," "incomprehensible," "mumbling," or "mumbled" speech documented in the record [2].

We defined multiple doses of physostigmine as any single dose greater than 2 mg or doses given more than 30 min apart. In our hospital, physostigmine is supplied in 2 mL vials at a concentration of 1 mg mL^{-1}. We administer a test dose of 0.5 mg physostigmine over 1–2 min to observe for adverse effects such as bradycardia or vomiting. If no adverse effects are observed after roughly 5 min, further dosing of 1.5 mg is given over another 2–3 min. Thus, per our usual practice, a dose >2 mg or doses >30 min apart constitute more than a single dose. An implicated antimuscarinic agent was identified by ED or inpatient records, toxicology consult note, or if one or more antimuscarinic agents was detected on urine laboratory testing (GC-MS).

Primary Data Analysis and Outcome Measures

The implicated antimuscarinic agents and time between doses of physostigmine were tabulated. We determined the time from the first physostigmine dose to disposition from the hospital. We compared these times as well as total length of hospital stay between patients given single or multiple doses of physostigmine. Descriptive and comparative statistics via two sample *t* tests of means and medians with unequal variances were performed to compare patients given single vs multiple doses of physostigmine.

Results

Characteristics of Study Subjects

Of the 45 patients included for analysis, 41 patients (91%) received physostigmine in the ED and four (9%) received

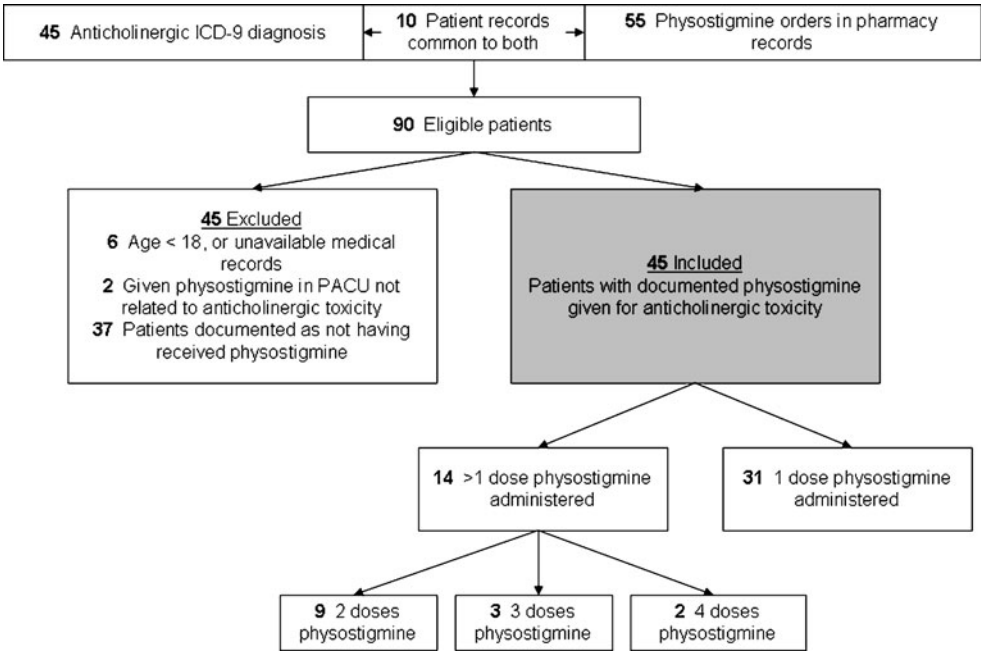

Fig. 1 Selection of participants

physostigmine in an Intensive Care Unit (ICU). Tachycardia (median heart rate 110 bpm, range 53–159 bpm) was documented in 67% of patients prior to physostigmine administration. One patient who was taking metoprolol had a heart rate <60 bpm. Agitation or delirium was documented in 32 patients (71%). Sinus tachycardia was the most common ECG abnormality, occurring in 26 of the 32 people who had ECGs prior to physostigmine administration. There were no ECGs with prolonged QRS complexes; median 88 [range 62–106 ms] (Table 1).

Main Results

Fourteen of 45 patients (31%) received multiple doses of physostigmine. In these patients, the greatest time between doses was <5.5 h (Fig. 2). The maximum interval between first and last dose was <6.5 h (Fig. 3). Whether admitted or discharged from the ED, there was no statistically significant difference in length of hospital stay between patients receiving single or multiple doses of physostigmine (Table 1, Fig. 4).

The mean length of hospital stay for patients receiving single vs multiple doses of physostigmine was 2.56 and 5.46 days, respectively, but the difference was not statistically significant (Table 1). The mean length of time from first dose of physostigmine to discharge was 2.78 and 3.1 days in the two groups, but this was also not statistically significant.

The most commonly implicated antimuscarinic agents were antihistamines or atypical antipsychotics. Nine individuals received physostigmine when amitriptyline was the implicated antimuscarinic agent (Table 2).

There was urine laboratory testing or chart documentation of implicated antimuscarinic agents for 37 patients (82%). The suspected medication was explicitly documented in the physician record for 20 patients (44%). In all 17 cases (38%) where comprehensive urine drug testing (GC-MS) was available, at least one antimuscarinic agent was confirmed to be present. Ten patients had two implicated agents, and no individuals had more than two implicated agents (Table 2).

Limitations

This study's small sample size and retrospective design lead to inherent limitations and biases. The small sample size precludes statistically significant comparisons and conclusions between groups. A prospective, multicenter study might yield more cases and thus improve the ability to draw conclusions and comparisons between patients who received single vs multiple doses of physostigmine.

The toxicology consultants may have introduced selection bias by preferentially recommending or discouraging physostigmine as an antidote for antimuscarinic toxicity. Also, antimuscarinic cases may have been missed due to inadequate ICD-9 coding. We addressed this selection bias by reviewing pharmacy records for physostigmine orders during the study period. However, these records were only available for a 30-month period.

Nine patients with pharmacy-identified physostigmine orders had no corroborating physician or nursing documentation of physostigmine administration, and these patients were excluded from the study (Fig. 1). These cases likely

Table 1 Characteristics

	Total	One dose of physostigmine	Multiple doses of physostigmine	*p* value (one vs multiple doses)
Number of patients	45	31	14	
Male sex (*n*)	28 (62%)	18 (58%)	10 (71%)	
Age median (range)	37 (19–59)	38 (19–59)	37 (19–36)	
Temperature Celsius median (range)	36.8 (35.9–39.6)	36.7 (35.9–39.6)	36.9 (36–38.9)	
Heart rate median 110 (range)[a]	110 (53–159)	108 (53–159)	117 (76–140)	
Agitation documented	24 (53%)	14 (45%)	10 (71%)	
Delirium documented	25 (55%)	17 (55%)	8 (57%)	
Agitation/delirium not documented or documented as not present	13 (29%)	9 (29%)	4 (29%)	
ECG QRS milliseconds median (range)	88 (62–106)	86 (64–106)	86 (70–106)	
ECG QTc milliseconds median (range)	446 (366–558)	439 (366–558)	465 (422–531)	
Discharged (*n*)	19 (42%)	14 (45%)	5 (36%)	
Admitted to floor (*n*)	14 (31%)	8 (26%)	6 (43%)	
Admitted to ICU (*n*)	12 (27%)	9 (29%)	3 (21%)	
Length of hospital stay (days)	3.59	2.56	5.46	NS
Time from first dose of physostigmine given to discharge (days)	2.87	2.78	3.1	NS
Physostigmine dose (mg) median (range)	2 (0.4–5)	2 (0.4–5)	2 (1–4)	

NS not significant

[a] Only ×1 HR <60 on Lopressor

represent ordering errors, changes in patient condition or diagnosis, or an order for physostigmine that was never administered. Regardless, these limitations do not fundamentally change the findings of this study.

We could not comment more precisely on patients' severity of antimuscarinic findings before or after physostigmine administration. Missing ED and ICU documentation of heart rates immediately preceding and following physostigmine administration as well as physical exam details (agitation, delirium, mydriasis, dry mucous membranes, loss of axillary sweat, hypoactive bowel sounds) made analysis of predictors for single vs multiple doses of physostigmine unattainable. Because ECG and vital signs were documented at varying times prior to physostigmine administration, it is difficult to draw greater conclusions regarding indications and contraindications for physostigmine. A prospective study is needed to collect that information as well as determine physostigmine's time to onset and duration of clinical effect.

Due to varying degrees of tachycardia and physical manifestations, antimuscarinic toxicity is often difficult to define. Because many medical records did not explicitly document antimuscarinic toxicity, we used the surrogates of agitation, delirium, tachycardia, or likely exposure to an antimuscarinic drug as previous investigators have done [2]. Despite this approach, we identified 13 cases in which agitation or delirium was not documented or documented as not present.

We intentionally excluded two postoperative patients who received physostigmine perioperatively, as it was not clear from the anesthesia record as to whether they were treated for anticholinergic toxicity or reversal of neuromuscular blockade. Because physostigmine has virtually no other use in the hospital (other than the possible reversal of

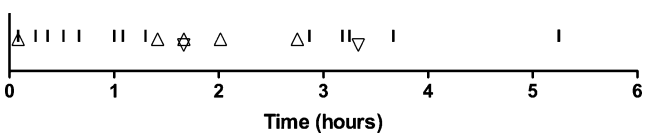

Fig. 2 Time (h) between physostigmine doses when more than one dose of physostigmine given. *Small vertical line* indicates interval between first and second dose, *n*=4; *triangle* indicates interval between second and third dose, *n*=5; *inverted triangle* indicates interval between third and fourth dose, *n*=2

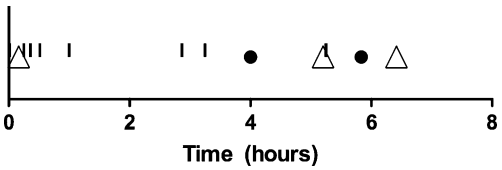

Fig. 3 Time (h) between first and last dose of physostigmine when more than one dose of physostigmine given. *Small vertical line* indicates first to second (max=2 doses), *n*=9; *triangle* indicates first to third (max=3 doses), *n*=3; *filled circle* indicates first to fourth (max=4 doses), *n*=2

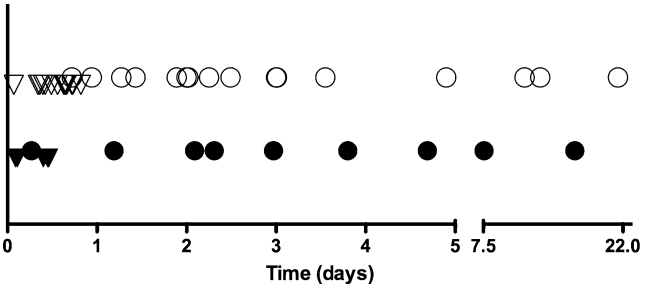

Fig. 4 Time (days) to discharge from first dose of physostigmine. *Unfilled circle* indicates one dose given, admitted, $n=16$; *inverted triangle* indicates one dose given, discharged, $n=14$; *filled circle* indicates one dose given, admitted, $n=9$; *filled inverted triangle* indicates more than one dose given, discharged, $n=5$

neuromuscular blocking drugs or treatment of postanesthetic shivering) [6], we feel confident that it was administered as an antidote for antimuscarinic toxicity in every case included in this study. There was no documentation to suggest that physostigmine was administered to reverse a paralytic agent other than the cases excluded from the PACU.

The use of multiple doses of physostigmine as previously defined was based on the local practice pattern of our medical toxicology service. This may not be representative of clinical practices elsewhere. Furthermore, some patients and antimuscarinic agents may require >2 mg to achieve reversal of symptoms. Likewise, antimuscarinic agents with longer duration of effect such as Jimson weed (*Datura* spp.) may require more frequent physostigmine administration and a longer period of observation than is needed for the patients in this study [7, 8].

Table 2 Antimuscarinic agents

Agent name (no. of times present as one of two suspected agents)	Number cases receiving one dose of physostigmine	Number cases receiving more than one dose of physostigmine
Diphenhydramine (8)	11	5
Amitriptyline (5)	8	1
Quetiapine (3)	5	4
Chlorpheniramine (3)	3	1
Olanzapine (1)	2	2
Benztropine	2	0
Doxylamine (1)	1	0
Cylclobenzaprine (2)	1	1
Trihexyphenidyl	0	1
Haloperidol (1)	0	1

Documented in medical record as suspected agent OR present in urine GC-MS screen. Ten patients had two implicated agents

Discussion

Physostigmine is a relatively short-acting acetylcholinesterase inhibitor that is the preferred antidote in antimuscarinic toxicity [2, 9, 10]. Physostigmine's tertiary amine structure allows it to effectively cross the blood-brain barrier, thus treating both central and peripheral antimuscarinic effects. While there are reports of continuous intravenous physostigmine infusions [11], the need for and timing of multiple discrete doses of physostigmine to maintain reversal of antimuscarinic toxicity has not been previously addressed in the medical literature. An understanding of the pharmacodynamics of physostigmine in this setting may have a significant impact on the disposition of patients to and from the ED and ICU.

Fourteen patients (31%) that received physostigmine for antimuscarinic toxicity required multiple doses, but in no cases was there >5.5 h between consecutive doses or >6.5 h between first and last dose. Consequently, clinicians may be reassured that a patient is not likely to require a repeat dose of physostigmine after >6.5 h of observation from the first dose of physostigmine. When comparing this small cohort of patients who received single vs multiple physostigmine doses, there was no statistically significant difference in total length of hospital stay, type of disposition, or time to disposition.

Of the 41 ED patients and four ICU patients, each patient received physostigmine in only one location (the ED or ICU, respectively). We intentionally omitted two postoperative patients who received physostigmine perioperatively, as they were likely given physostigmine to reverse neuromuscular blockade rather than antimuscarinic toxicity.

Many agents can cause antimuscarinic toxicity. In our study, antihistamines (primarily diphenhydramine) and antipsychotics (primarily quetiapine and olanzapine) were the most frequently implicated antimuscarinic agents. Diphenhydramine and quetiapine have relatively short durations of effect [12]. However, in overdose the relatively predictable pharmacokinetics and pharmacodynamics change, making estimates of duration of action difficult [13]. This is particularly applicable when one considers the frequent implication of quetiapine in our patients, which in standard doses has modest muscarinic receptor binding [14]. The frequency of quetiapine in this study is also likely accounted for by the high penetrance of quetiapine prescribing in our area. Because there is no single model for the toxicokinetics and toxicodynamics with antimuscarinic toxicity, each case must be evaluated independently.

There are a few relative contraindications to physostigmine administration. The transient and reversible inhibition of acetylcholinesterase may promote muscarinic effects [15, 16]. Therefore, diarrhea, urinary incontinence, bronchor-

rhea, bradycardia, emesis, salivation, and seizures may result from or be exacerbated by physostigmine administration [17, 18]. Any evidence of seizure or significant bradycardia in the absence of beta-adrenergic antagonists should be considered a contraindication to physostigmine administration. Some reports suggest that physostigmine may be safe to treat anticholinergic effects of amitriptyline toxicity [19–23]. However, other papers describe a theoretical and actual risk of seizure and asystole after physostigmine is given for tricyclic antidepressant poisonings [24–28]. A 1976 case report describes a 22-year-old who ingested up to 1 g of amitriptyline and received 22 mg of physostigmine without evidence of seizure. The patient was discharged to home but returned to the ED 6 days later after another TCA overdose, when she seized after receiving 2 mg of physostigmine. Her ECG prior to the seizure showed "atrioventricular dissociation with frequent junctional premature contractions"—a known cardiac effect of TCA overdose and one that should have excluded her from receiving physostigmine [27]. Furthermore, seizures after TCA overdose occur at serum concentrations lower than those that predispose to cardiac conduction abnormalities such as atrioventricular dissociation [12]. Therefore, it is not unexpected that a seizure would occur in this case even in the absence of physostigmine administration.

A case series from 1975 described 21 consecutive patients given physostigmine for suspected TCA overdose. Two comatose patients developed seizures. Of these, one patient received 6 mg of physostigmine and was described as having "recovered uneventfully" from his grand mal seizure. There was no description of the seizure in the second patient who received 2 mg of physostigmine [29]. No specifics regarding timing of suspected TCA overdose or onset of seizure in relation to the physostigmine administration were provided. Furthermore, no ECG data was provided regarding QRS duration before or after physostigmine administration for either of these patients [29].

Pentel published a case report in 1980 describing two patients with suspected TCA overdose who "developed asystole following the administration of physostigmine to treat seizures." [26] One patient, who ingested 2,300 mg of amitriptyline, had a wide QRS complex (~160 ms) and first-degree atrioventricular block prior to physostigmine administration. He developed asystole 2 min after physostigmine was given. Although vital signs and ECG abnormalities subsequently resolved, the patient's ultimate outcome was not described. The second patient with suspected 5,000 mg imipramine and 150 mg propranolol overdose had two "major motor seizures" and a systolic blood pressure of 90 mmHg prior to physostigmine. The QRS complex appeared to be ~120 ms prior to physostigmine. This patient's vital signs recovered after 10 min of closed cardiac massage, epinephrine, sodium bicarbonate, levarterenol, isoproterenol, and hemoperfusion. However, the patient remained comatose for 3 days and was subsequently pronounced brain dead.

These historic case reports help drive the current reticence to physostigmine use in the face of suspected TCA overdose. It is interesting that nine patients in our study received physostigmine after an implicated amitriptyline ingestion. None of these patients had any documented cardiac dysrhythmia or seizure during their hospital course, and none had a QRS duration greater than 106 ms prior to physostigmine administration. In lieu of the previously described case reports, it is not reasonable to assert physostigmine's absolute safety in the setting of tricyclic antidepressant related anticholinergic toxicity. However, our study suggests that in a patient with significant antimuscarinic toxicity and a normal QRS duration, it may be safe to administer physostigmine even in the setting of TCA poisoning [2, 30].

Despite the pharmacologic and mechanistic rationale for the use of physostigmine in the treatment of antimuscarinic toxicity, many clinicians forego its use in favor of benzodiazepines or no therapy at all [2]. Worse yet, due to either lack of recognition of the toxidrome or unfamiliarity with its therapy, some clinicians administer an antipsychotic such as haloperidol [31, 32]. Such inappropriate pharmacotherapy may worsen the patient's delirium and further delay appropriate therapy. Within our cohort, the antipsychotics quetiapine, olanzapine, and haloperidol were implicated in 14 patients (31%) presenting with antimuscarinic syndrome.

This study suggests that patients with evidence of antimuscarinic toxicity from common pharmaceuticals who are administered physostigmine in the ED or ICU setting will more often than not require just one dose of physostigmine. Furthermore, patients with an appropriate response to physostigmine will likely not require another dose >6.5 h after their first dose.

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