J. Med. Toxicol. (2015) 11:179–184
DOI 10.1007/s13181-014-0452-x

TOXICOLOGY INVESTIGATION

The Use of Physostigmine by Toxicologists in Anticholinergic Toxicity

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Published online: 16 December 2014

Abstract The anticholinergic toxidrome is well described and relatively common. Despite controversy, studies have shown that physostigmine is relatively safe and effective in reversing this toxidrome. We would expect toxicologists would be liberal in its use. We retrospectively analyzed data in the Toxicology Investigators Consortium (ToxIC) registry, representing data from medical toxicologists in multiple institutions nationwide, searching for patients who exhibited an anticholinergic toxidrome, determining what treatment(s) they received, and classifying the treatments as physostigmine, benzodiazepines, physostigmine and benzodiazepines, antipsychotics, or no definitive treatment. The causal agents of the toxidrome were as reported by the treating toxicologist. Eight hundred fifteen consecutive patients with anticholinergic toxidromes were analyzed. Benzodiazepines alone were given in 28.7 %, 12.4 % were given physostigmine alone, 8.8 % received both physostigmine and benzodiazepines, 2.7 % were given antipsychotics, and 47.4 % were given no definitive treatment. In patients who received only physostigmine, there was a significant difference in the rate of intubation (1.9 vs. 8.4 %, OR 0.21, 95 % CI 0.05–0.87) versus other treatment groups. Physostigmine was given at varying rates based on causative agent with use in agents with mixed or unknown effects (15.1 %) being significantly lower than those with primarily anticholinergic effects (26.6 %) ($p<0.001$). Patients with anticholinergic toxicity were more likely to receive benzodiazepines than physostigmine. Those patients who received only physostigmine had a significantly lower rate of intubation. Physostigmine was more likely to be used with agents exerting primarily anticholinergic toxicity than in those agents with multiple actions.

Keywords Physostigmine · Anticholinergic syndrome · Antidotes · Antidepressive agents · Tricyclic · Intubation

Background

The anticholinergic toxidrome is well described and relatively common. This generally occurs in the setting of acute overdose of antihistamines, antipsychotics, and botanicals, such as Jimson weed or Mandrake. Physostigmine, widely regarded as the antidote to anticholinergic toxicity [1], is a naturally occurring cholinesterase inhibitor found in the Calabar bean, which is endemic to Western Africa [2]. Historically, it was used by the tribespeople of the area as a "Trial by Ordeal" whereby those accused of a crime were made to ingest the beans, and those who merely vomited were innocent and those who succumbed to the muscarinic effects were deemed to have been guilty [3]. The first recorded case of physostigmine reversing anticholinergic delirium came in 1864, when a group of prisoners inadvertently overdosed on atropine after mistaking it for alcohol. Based upon the observed antagonistic effects between atropine and physostigmine in the pupil, one of the prisoners received Calabar bean extract with almost

These data have been presented as abstracts/posters at the following conferences:
The Use of Physostigmine by Toxicologists in Anticholinergic Toxicity. Poster and Platform Presentation at the American College of Medical Toxicologists Annual Scientific Meeting, Phoenix, AZ, March 28–30, 2014
The Differential Use of Physostigmine by Toxicologists in Anticholinergic Toxicity Based on Causative Agent. Poster presented at the North American Congress of Clinical Toxicology, New Orleans, LA, October 17–21, 2014

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immediate reversal of their delirium [2]. The first reported use in modern medicine was in 1970, when a toddler ingested amitriptyline, presented in delirium and was given physostigmine [4]. In the 1970s, anticholinergic toxidromes were so common, and its safety so certain, it was proposed that physostigime be added to the "coma cocktail" of naloxone, glucose, and thiamine for undifferentiated altered mental status [5].

In 1980, however, the *Annals of Emergency Medicine* published a case report authored by Pental and Peterson that effectively turned the tide against physostigmine. They described two patients, both severely poisoned by tricyclic antidepressants with evidence of conduction delay and seizures. Patient one had a heart rate of 75 with first degree AV block and a QRS duration of 240 ms. Patient two had a heart rate of 75 and a QRS duration of 120 ms. Each patient received physostigmine, which at the time was understood to be the treatment for TCA-induced seizures, and shortly afterward became bradycardic. Both were given atropine and then rapidly progressed to asystolic arrest. Both were resuscitated with epinephrine and sodium bicarbonate and regained a perfusing heart rhythm. Patient one survived, patient two was pronounced brain dead on hospital day three [6]. In light of our current understanding of TCA poisoning, both of these patients would have received benzodiazepines for seizure control and sodium bicarbonate for their conduction abnormalities. Given their pretreatment heart rates, neither of these patients would have received physostigmine.

Since that time physicians have shown a reticence to use physostigmine, though recent reports again assert its safety for anticholinergenic toxicity. In 2000, Burns et al. [7] published a retrospective study of 52 patients who had been referred to a toxicologist and had received either physostigmine, benzodiazepines, or both for a central anticholinergic toxidrome. They found that those who received physostigmine first had fewer complications (7 vs. 47 %) and had their delirium reversed more often (87 % vs. ineffective) when compared with those who received benzodiazepines first. Additionally, from an operational and cost analysis standpoint, no patients in the physostigmine group received a head CT, which was specifically attributed to clearing of delirium after the use of physostigmine in several patients. Data from Beaver et al. in 2000 [8], again demonstrated the relative safety of physostigmine during a rash of anticholinergic toxicity from scopolamine-adulterated heroin along the East Coast. In both of these studies, ECGs were used to evaluate for conduction delays that served as an exclusion (QRS duration >100 ms, PR interval >200 ms) to administration of physostigmine. Further, a review of physostigmine usage by a large toxicology service showed few adverse events and no cardiac complications over 7 years of data [9].

Our intent was to query the Toxicology Investigators Consortium (ToxIC) registry to establish the incidence of anticholinergic toxicity and the rate at which physostigmine was administered to these patients by toxicologists, as well as to examine the most serious consequences of anticholinergic toxicity. Secondarily, given the previously mentioned concerns about cyclic antidepressants, we further subdivided these data to look at the frequency of physostigmine use based on causative agents.

Methods

We retrospectively analyzed data in the ToxIC registry over a 27-month period (January of 2012 through March of 2014) searching for patients with reported anticholinergic toxidrome. The ToxIC registry provides us with a nationwide repository of clinical toxicology data to analyze. Presently, 47 unique sites, including two international sites, participate in the registry. Only patients consulted on by medical toxicologists are entered into the registry. De-identified, descriptive data obtained by medical toxicologists during bedside encounters are entered into the database. We classified the treatment(s) they received as physostigmine, benzodiazepines, physostigmine plus benzodiazepines, antipsychotics, or no definitive treatment. Within those treatment groups, we analyzed the prevalence of rhabdomyolysis (creatinine kinase >1000 IU/L) and intubations, the complications most easily extracted from the data and attributable to an anticholinergic toxidrome. We calculated an odds ratio by constructing a 2×2 table for each complication.

Further, we attempted to determine what agent(s) was likely causative based on "primary agent #1" as recorded by the toxicologist. If we found that "primary agent #1" was unlikely to cause an anticholinergic toxidrome (e.g., acetaminophen without diphenhydramine, acetylsalicylic acid, etc.), we looked at "primary agent #2." If "primary agent #2" was unlikely to contribute to an anticholinergic toxidrome, we characterized the causative agent as "unknown." If there were multiple agents listed for "primary agent #1" that could contribute to an anticholinergic toxidrome, we characterized the causative agent as "mixed." We then calculated the rate of physostigmine use in the following categories of agents: antihistamines, antipsychotics, cyclic antidepressants, botanicals, SSRI/SNRI, antiepileptics, benztropine, cyclobenzaprine, mixed, others, and unknown. These numbers were put into 2×2 contingency tables from which p values were calculated (http://statpages.org/ctab2x2.html). To account for small sample sizes, the significance of the differences between groups was calculated via two-tailed Fisher's exact test comparing each group to the remaining group as a whole. The Human Subjects Committee of our institution approved this study.

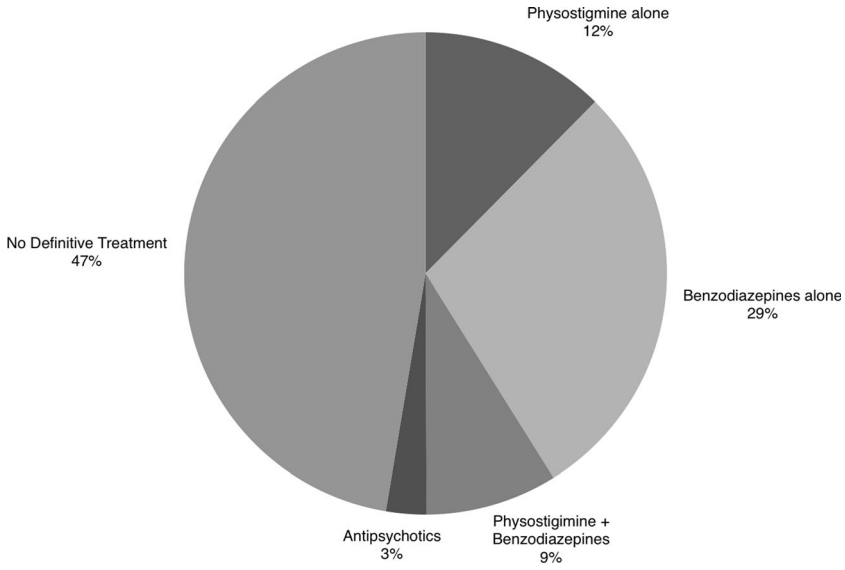

Fig. 1 Percentage of patients with anticholergic toxicity receiving specified treatment

Results

Participating toxicologists reported 815 patients exhibiting anticholinergic toxidromes from January of 2012 through March of 2014, of whom 47.4 % received no definitive treatment and 12.4 % received physostigmine alone (Fig. 1). When analyzing adverse events, receipt of antipsychotics was not considered, as numbers were small (22) and the majority (19) were also given benzodiazepines. Only one patient received antipsychotics alone. Those who received physostigmine alone or in combination with benzodiazepines had a lower rate of intubation (6.4 vs. 8.4 %) and rhabdomyolysis (1.7 vs. 3.63 %) than those who did not, but the differences were not significant (OR 0.73, 95 % CI 0.38–1.45 p=0.38 and OR 0.47 95%CI 0.14–1.60 p=0.23, respectively). Patients who received physostigmine alone (101) did have a significantly lower rate of intubation (1.9 vs. 8.4 %, OR 0.21, 95 % CI 0.05–0.87 p=0.031) than those patients who received other treatment regimens (714) (Fig. 2). The group that received physostigmine either alone or in combination had a significantly higher rate of rhabdomyolysis (6.4 vs. 2.3 %, OR 2.84, 95 % CI 1.28–6.30, p=0.01).

There was a wide variety of causative agents for anticholinergic toxidromes, and the rate of physostigmine use varied by agent (Fig. 3). The highest rate of physostigmine use was for exposure to cyclobenzaprine (23 of 44, 52 %) and the lowest was for cyclic antidepressants (4 of 57, 7 %). The rates of physostigmine use in each of these groups were

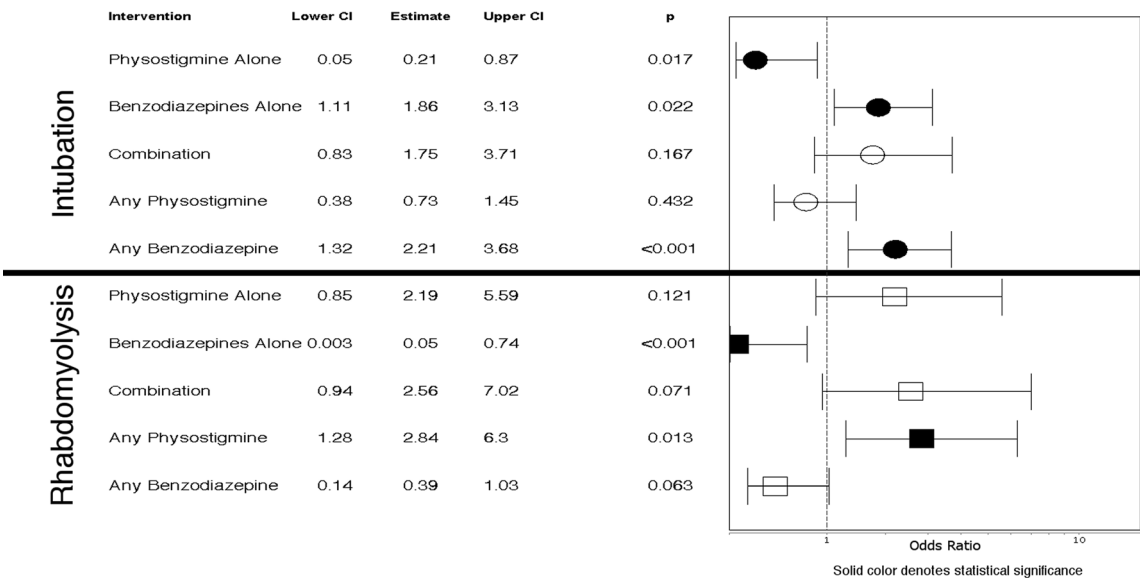

Fig. 2 Odds ratios for adverse events by treatment group [10]

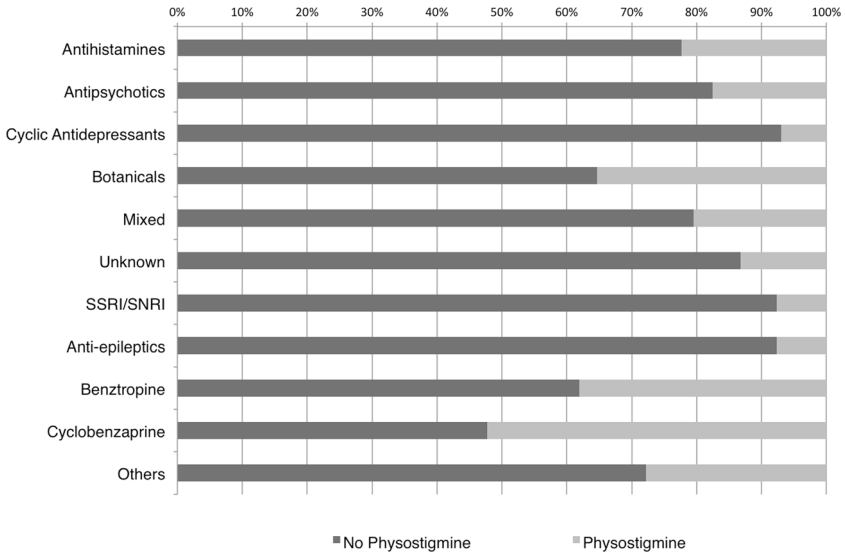

Fig. 3 Relative rates of physostigmine use by agent

significantly different than the remaining group as a whole (p=0.004 and p<0.001, respectively). Table 1 demonstrates the difference in physostigmine administration among causative agents. The difference in physostigmine use between agents with either mixed or unknown effects (antipsychotics, cyclic antidepressants, SSRI/SNRI, antiepileptics, "mixed," "unknown," or "others") and those with a primarily anticholinergic effect (antihistamines, botanicals, benztropine, cyclobenzaprine) was also statistically significant (15.1 vs. 26.6 %, p<0.001).

Table 2 shows physostigmine use by site. Twenty-nine sites reported using physostigmine in anticholinergic toxidrome during the study period. Four reporting sites accounted for 63 % of physostigmine given (109/173).

Discussion

These data suggest that patients with anticholinergic toxicity are more likely to receive benzodiazepines than physostigmine (28.7 vs. 12.4 %) as monotherapy, and a large number of these patients did not receive treatment for their toxidrome (47.4 %). Though the use of physostigmine in patients overall was not correlated with a decrease in intubation, in patients who received only physostigmine, there did exist a significant difference in the rate of intubation (8.4 vs. 1.9 %) versus other treatment groups.

These data also suggest that there was a differential use of physostigmine based on likely causative agents. Cyclobenzaprine overdoses that resulted in anticholinergic

Table 1 Rates of phystigmine use, intubation, and rhabdomyolysis in anticholinergic toxidromes stratified by causative agent

Causative agents	Anticholinergic toxidromes	Received physostigmine	p value	Intubated	p value	Rhabdomyolysis	p value
Antihistamines	350	78 (22.3 %)	0.545	18 (5.1 %)	0.013*	12 (3.4 %)	0.189
Cyclobenzaprine	44	23 (52.3 %)	<0.001*	4 (9.1 %)	0.771	1 (2.3 %)	1.000
Benztropine	21	8 (38.1 %)	0.055	1 (4.8 %)	1.000	0 (0 %)	1.000
"Primarily anticholinergic actions"	432	115 (26.6 %)	<0.001*	24 (5.5 %)	0.013*	14 (3.2 %)	0.269
Antipsychotics	114	20 (17.5 %)	0.326	15 (13.2 %)	0.036*	4 (3.5 %)	0.519
Unknown	98	13 (13.3 %)	0.040*	4 (4.1 %)	0.136	1 (1.0 %)	0.498
Cyclic antidepressants	57	4 (7.0 %)	0.004*	9 (15.8 %)	0.036*	0 (0 %)	0.390
Mixed	39	8 (20.5 %)	1.000	7 (17.9 %)	0.027*	0 (0 %)	0.618
Others	36	10 (27.8)	0.304	1 (2.8 %)	0.352	1 (2.8 %)	0617
SSRI/SNRI	26	2 (7.7 %)	0.086	3 (11.5 %)	0.450	1 (3.8 %) 0.498	
Antiepileptics	13	1 (7.7 %)	0.229	1 (7.7 %)	1.000	0 (0 %)	1.000
"Mixed actions"	383	58 (15.1 %)	<0.001*	40 (10.4 %)	0.013*	7 (1.8 %)	0.269
Total	815	137 (21.2 %)	–	64 (7.9 %)	–	21 (2.6 %)	–

*p<0.05

Table 2 Use of physostigmine in anticholinergic toxidrome by reporting site

Site	Physostigmine used (*n*)
Harrisburg, PA	40
Rochester, NY	35
St Paul, MN	17
Denver, CO	17
Dallas, TX	9
Phoenix, AZ	8
Worchester, MA	5
Philadelphia, PA	4
Manhasset, NY	4
St. Louis, MO	3
Oregon Health Sciences, OR	3
Kansas City, KC	3
Charlotte, NC	3
Pittsburg, PA	2
Omaha, NE	2
New York University, NY	2
Morristown, NJ	2
Houston, TX	2
Boston, MA	2
San Antonio, TX	1
Salt Lake City, UT	1
Richmond, VA	1
New Brunswick, NJ	1
Los Angeles, CA	1
Indianapolis, IN	1
Hartford, TC	1
Fresno, CA	1
Einstein, NY	1
Boston Beth Israel, MA	1
Total	173

toxidromes were seven times more likely to receive physostigmine than those whose causative agent was a cyclic antidepressant. In contrast, antihistamine poisoning had a relatively low rate of physostigmine use (22 %) despite its frequency of presentation. This may represent a selection bias in patients with mild toxidromes.

The weaknesses of this study are similar to most retrospective analyses, in that we should not infer causality from association. We do not know the order, timeframe, or the indications for which these medications were administered. It is conceivable that a benzodiazepine was used as an induction agent for intubation, or for seizure treatment, rather than for anticholinergic agitation. Perhaps benzodiazepines were used by the emergency physician to manage agitation initially, prior to the toxicology service giving physostigmine.

Additionally, the ToxIC database has several inherent limitations. It does not allow detailed analysis of patients, their demographics, or the order and dose of medications administered. Patients with polypharmacy ingestions may demonstrate subtle signs of multiple toxidromes. ToxIC does not allow weighting when multiple toxidromes are present.

Overall, the rate of physostigmine use in anticholinergic toxidromes was low. While acknowledging the possible selection bias of a retrospective analysis, it is interesting to note that those patients who received physostigmine as monotherapy were intubated at a lower rate than other patients. There is no current consensus for physostigmine use, so toxicologists may have varying thresholds for administration. One could expect that given the relative rarity of physostigmine use, it might be reserved for those patients who were more acutely ill and thus more likely to be intubated were physostigmine not administered. This position may be supported by the apparent relationship between overall physostigmine use and rhabdomyolysis. In our personal experience, when rhabdomyolysis occurs, it is present on admission and is likely indicative of case severity. Unfortunately, we are unable to determine from the ToxIC registry whether rhabdomyolysis was present on admission or developed subsequent to therapy. Alternatively, intubation may reflect an inability to control anticholinergic agitation with benzodiazepines alone. Toxicologists may resort to intubation for severe agitation control and thus intubation may not represent severity but rather discomfort with physostigmine use. Regardless, intubation is a resource-intensive intervention that requires an ICU admission, prolongs hospital stay, and has associated adverse outcomes such as ventilator-associated pneumonia. As such, these data suggest that those patients receiving physostigmine alone may utilize fewer resources than those that do not.

When stratified by causative agent, it appears that physostigmine was used more readily for cyclobenzaprine, benztropine, and botanicals, which exert primarily anticholinergic effects, whereas agents that have more complex physiologic or "mixed" effects, such as antipsychotics, mixed ingestions, or cyclic antidepressants, are less likely to be treated with physostigmine.

We find this of clinical importance in light of studies showing fewer complications when physostigmine is used [7], its proven effectiveness in clearing of delirium [7, 8], as well as lower resource utilization [7]. Studies in anesthesia literature have shown a trend towards improvement of delirium without significant safety concerns in controlled settings [11–13]. Unfortunately, though not surprisingly, no prospective trials have been undertaken to ascertain the true safety profile of physostigmine in a toxicologic setting, and concerns about its cardiotoxicity and neurotoxicity persist, particularly in the setting of cyclic antidepressants. Our data suggest that patients with

anticholinergic toxidromes due to cyclic antidepressants are the least likely to receive physostigmine among all the groups we analyzed. It is likely that the mechanism for cardiac dysrhythmias in cyclic antidepressant overdoses is a natural progression of severe sodium channel blockade, while the anticholinergic tachycardia initially maintains cardiac output. When administering physostigmine to these patients and increasing the cholinergic tone, it is conceivable that the cardiac output is compromised leading to death [14]. However, significant sodium channel blockade can be detected on an ECG done prior to treatment, thus the proposed risk of cardiac death should be extremely low in those with a normal QRS duration. Additionally, prolonged QRS is a proxy for the severity of cyclic antidepressant poisoning. Animal models have demonstrated a decrease in QRS duration with administration of physostigmine [15] and thus should decrease the incidence of fatal dysrhythmias. In those sentinel cases presented by Pentel and Peterson, both patients had a prolonged QRS without tachycardia and only one of them received sodium bicarbonate, as an infusion, prior to cardiac arrest [16].

Conclusions

While physostigmine is an ancient xenobiotic and has been used effectively for the anticholinergic toxidrome since the 1970s, there are still important questions that have gone unanswered. These data demonstrate an association between the use of physostigmine and an outcome, intubation, that is important both to the clinician and patient and deserves further evaluation. It is clear that a prospective study of physostigmine is needed to develop a more complete understanding of its safety and clinical usefulness and its effect on rate of intubation. A prospective study using a sub-registry may help address our current limitations. Perhaps this would implore us to more completely utilize a tool that toxicologists seem reticent to employ. Until that time, the data we currently have appear to support the use of physostigmine for the anticholinergic toxidrome.

Conflicts of Interest The authors have no conflicts to declare.

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