Adverse Effects of Physostigmine

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Abstract

Introduction Physostigmine is a tertiary amine carbamate acetylcholinesterase inhibitor. Its ability to cross the blood-brain barrier makes it an effective antidote to reverse anticholinergic delirium. Physostigmine is underutilized following the publication of patients with sudden cardiac arrest after physostigmine administration in patients with tricyclic antidepressant (TCA) overdoses. We completed a narrative literature review to identify reported adverse effects associated with physostigmine administration.

Discussion One hundred sixty-one articles and a total of 2299 patients were included. Adverse effects occurred in 415 (18.1%) patients. Hypersalivation (206; 9.0%) and nausea and vomiting (96; 4.2%) were the most common adverse effects. Fifteen (0.61%) patients had seizures, all of which were self-limited or treated successfully without complication. Symptomatic bradycardia occurred in 8 (0.35%) patients including 3 patients with bradyasystolic arrests. Ventricular fibrillation occurred in one (0.04%) patient with underlying coronary artery disease. Of the 394 patients with TCA overdose, adverse effects were described in 14 (3.6%). Adverse effects occurred in 7.7% of patients treated with an overdose of an anticholinergic agent compared with 20.6% of patients with non-anticholinergic agents. Five (0.22%) fatalities were identified.

Conclusions In conclusion, significant adverse effects associated with the use of physostigmine were infrequently reported. Seizures were self-limited or resolved with benzodiazepines, and all patients recovered neurologically intact. Physostigmine should be avoided in patients with QRS prolongation on EKG, and caution should be used in patients with a history of coronary artery disease and overdoses with QRS prolonging medications. Based upon our review, physostigmine is a safe antidote to treat anticholinergic overdose.

Keywords Physostigmine · Antidote · Antimuscarinic · Delirium · Review

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Introduction

Physostigmine is a tertiary amine carbamate acetylcholinesterase inhibitor. Its unique ability to cross the blood-brain barrier makes it an invaluable antidote to reverse the central and peripheral effects of anticholinergic toxicity. Despite its effectiveness, physostigmine is underutilized following the publication of patients with sudden cardiac arrest after physostigmine administration in patients with tricyclic antidepressant (TCA) overdose [1]. Multiple studies have since demonstrated the safety of physostigmine; however, patients with anticholinergic toxicity are still more likely to be treated with benzodiazepines alone, even when cared for by a medical toxicologist [2]. Physostigmine administration avoids unnecessary invasive testing, and decreases rates of complications including intubation and length of stay when compared with benzodiazepines [2, 3]. We completed a literature review of the use of physostigmine to identify adverse effects

associated with physostigmine administration described in the literature. Our intent is to clarify the risk-benefit assessment for the use of physostigmine as an antidote to manage anticholinergic toxicity.

Background

Physostigmine is a tertiary amine carbamate and dose-dependent reversible inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) in the brain, erythrocytes, and plasma [4]. Physostigmine inhibits AChE by interacting with the anionic and esteratic sites of the enzymes to yield a carbamylated nonfunctional enzyme [4]. The tertiary amine structure of physostigmine allows it to penetrate the blood-brain barrier and exert central and peripheral cholinergic effects [5]. It also has nonspecific analeptic (arousal) effects [6] as the result of cholinergic stimulation of the reticular activating system of the brain stem [7–12]. After parenteral administration of physostigmine, the onset of action is within 3–8 min [9], though one case series noted a mean response time to physostigmine of 10.9 ± 5.3 min [3]. The average elimination half-life is 22 min (range: 12–40 min) [4, 9]; however, the half-life of cholinesterase inhibition is notably longer ranging at 83.7 ± 5.2 min [13]. Physostigmine's effects on cholinesterase inhibition are noted to be approximately five times longer than its elimination half-life [13].

The indirect central and peripheral cholinergic effects are responsible for the desired antidotal and adverse effects of physostigmine administration [4]. Signs and symptoms of cholinergic excess including: visual hallucinations, excessive salivation, sweating, bronchorrhea, and seizure have been described following intentional physostigmine overdose [14]. Peripheral muscarinic effects of physostigmine include activation of nonvascular smooth muscle with resultant intestinal hyperperistalsis and potential bronchospasm [4]. Seizure has also been described and may be attributed to stimulation of hippocampal nicotinic receptors [15–17]. However, myoclonus and choreoathetosis associated with a central anticholinergic syndrome may be inaccurately classified as seizures [18], and are reversed by physostigmine [18, 19]. The cardiovascular effects of physostigmine are likely multifactorial. Peripheral acetylcholine effects including vasodilation and atrial pacemaker cell-mediated bradycardia contribute to hypotension and bradycardia [4]. Central acetylcholine-related sympathetic effects have also been shown to contribute to bradycardia in animal studies [4]. Physostigmine may also oppose protective antimuscarinic-mediated tachycardia. In patients with

impaired cardiac myocyte depolarization from TCA toxicity, this may contribute to bradysystolic events [20].

The cardiac-related adverse effects of physostigmine have had the most consequential impact on the risk assessment and utilization of physostigmine as a reversal agent for patients with severe anticholinergic toxicity. Providers may be hesitant to treat patients with physostigmine to reverse an anticholinergic delirium based on unfounded risk assumptions. The aim of this review is to evaluate adverse effects associated with physostigmine reported in the literature to determine the frequency of adverse effects in patients receiving physostigmine.

Methods

In order to identify appropriate articles, the primary author conducted a review of the PubMed and Medline databases using the MESH terms “physostigmine,” “physostigmine AND antidote,” and “physostigmine AND treatment,” limited to the English language and human studies. Abstracts written in the English language were reviewed by the primary author, and relevant articles were selected. Articles were excluded if the causative substance or pharmaceutical class of the substance was unclear, and/or adverse effects were not described or could not be determined from the text, with the exception of well-described case reports. The “related articles” function of the PubMed database was also utilized to help identify articles. In addition, the references included in the chosen articles were reviewed by the primary author in order to identify additional articles. A secondary review of randomly selected articles was conducted by the second author to assess consistency in the reviewer interpretation.

Adverse Effects

A total of 161 articles were included in this review: 26 clinical studies including 13 randomized controlled trials, 51 case series, and 85 case reports. A summary of the articles can be found in the table in the [Appendix](#). The appendix table provides a compilation of the patient demographics, causative agents (that produced clinical effects in which physostigmine was intended to reverse), and the physostigmine doses, response, and adverse effects associated with the administration of physostigmine.

Of a total of 2299 patients was included in this review, 415 (18.1%) adverse effects, including 5 (0.22%) fatalities were identified and are listed in Table 1. The following are adverse effects identified in our literature review, detailed by organ system.

Table 1 Adverse effects identified in our narrative review, reported as incidence and percentage of total patients included ($n = 2299$)

Adverse effect	<i>N</i> (%)
Hypersalivation	206 (9.0)
Nausea/vomiting	96 (4.2)
Diaphoresis	27 (1.2)
Abdominal cramps	17 (0.74)
Seizure	14 (0.61)
Arrhythmia	10 (0.44)
Symptomatic bradycardia	8 (0.35)
Restless sleep	7 (0.30)
Diarrhea	6 (0.26)
Asymptomatic bradycardia	4 (0.17)
Fatality	5 (0.22)
Shivering	5 (0.22)
Cardiac arrest	4 (0.17)
Dreams/nightmares	3 (0.13)
Agitation	3 (0.13)
Tearing	2 (0.09)
Hiccups	2 (0.09)
“Depression”	2 (0.09)
Fecal incontinence	1 (0.04)
Hyperperistalsis	1 (0.04)
Tremor	1 (0.04)
Tachycardia	1 (0.04)

Neurologic

Seizure was reported in 15 (0.65%) patients, agitation was described in 3 (0.13%) patients, and tremor in 1 (0.04%) patient. A 13-month-old female arrived to the emergency department (ED) with sedation and seizures 2.5 h after an accidental hydroxyzine overdose [21]. Her seizures resolved with 0.5 mg physostigmine with 1 mg diazepam. Twenty minutes after the first dose of physostigmine, the patient had additional seizures that resolved with the same doses of physostigmine and diazepam. She had multiple additional seizures over the following 24 h, treated successfully with physostigmine and diazepam and ultimately recovered neurologically intact. Another patient experienced a seizure after receiving 2 mg of physostigmine to treat a quetiapine overdose [22]. One patient had a seizure approximately 5 min after receiving a total of 6 mg of physostigmine over 3 min following an imipramine overdose [23], and a 45-year-old male had a seizure 3–4 min after a second dose of 2 mg physostigmine given to reverse coma following amitriptyline overdose [24]. Seizure activity in both patients resolved with 10 mg of diazepam and both patients recovered uneventfully. A 22-year-old female presented to the ED agitated 2 h after ingesting between 750 and 1000 mg of amitriptyline [25]. She became obtunded with a wide QRS complex on EKG. She received three 2-mg IV doses of physostigmine with minimal effect on her mental status followed

by a total of 22 mg of physostigmine over the next 48 h with noted improvement in both QRS prolongation and tachycardia. Seven days after ingestion, she had atrioventricular dissociation with junctional premature contractions on EKG, and received two 1-mg doses of physostigmine 5 min apart. After the second dose, the patient had a seizure and her EKG returned to a normal rhythm. The patient recovered uneventfully. A patient with a doxylamine overdose had a witnessed generalized tonic-clonic seizure on arrival to the ED and had an additional seizure 12 min after receiving two 0.5-mg IV doses of physostigmine [26]. Rasimas et al. reported 9 patients with seizure following physostigmine administration in patients with stimulant, selective serotonin reuptake inhibitors (SSRI's)/serotonin-norepinephrine reuptake inhibitors (SNRI's), antidepressants, antipsychotics, lithium, or tramadol overdoses but provided details for only 2 of these patients [27]. A 62-year-old male with a history of seizure disorder had a seizure after receiving physostigmine to reverse delirium from a quetiapine overdose. He was found to have subtherapeutic serum concentrations of his antiepileptics and received additional doses of physostigmine with lorazepam without additional seizures [27]. A 39-year-old male had a seizure after being treated with physostigmine to reverse delirium from a clozapine and trifluoperazine overdose [27]. He also received additional doses of physostigmine with lorazepam without additional seizures. No patients in our review developed status epilepticus as the result of physostigmine administration, and all 14 patients with seizure identified in our review recovered neurologically intact.

Cardiovascular

Bradycardia was described in 12 (0.52%) patients, including 4 (0.17%) patients with asymptomatic bradycardia [3, 28–30]. Eight (0.35%) patients developed bradycardia with associated hemodynamic changes, arrhythmia, or required pharmacologic intervention. One patient complained of feeling faint and nauseated 12 min after receiving physostigmine to reverse diazepam sedation [31]. After vomiting, he became bradycardic, was treated with atropine, and subsequently developed atrial flutter. He converted to a sinus rhythm 4 h after he was given 0.5 mg digoxin IV [31]. Similarly, a 45-year-old male received 2 doses of 2 mg physostigmine to reverse a quetiapine overdose in addition to ethanol [27]. The second dose was given by a fast IV push, after which the patient developed bradycardia and atrial fibrillation. He converted to a sinus rhythm spontaneously within 75 min and received additional doses of physostigmine given slowly without additional adverse effects [27]. A 30-day-old infant received multiple doses of physostigmine to reverse presumed central anticholinergic syndrome following general anesthesia [32]. After a third dose of physostigmine, the patient developed

wheezing, hypersalivation, hyperperistalsis, and a relative bradycardia with a heart rate of 100 bpm. All of these symptoms were reversed with glycopyrrolate IV. Bradycardia with associated hypotension was described in 1 patient treated for an imipramine overdose [23], and 1 patient received atropine to treat bradycardia without associated hypotension after receiving physostigmine to treat gamma-hydroxybutyrate (GHB) sedation [33].

Three (0.13%) patients developed bradycardia and subsequent cardiac arrest [1, 34]. Pentel et al. described 2 patients with cardiac arrest after physostigmine administration: a 32-year-old male with a 2300-mg amitriptyline overdose, and a 25-year-old male with a 5000-mg imipramine and 150-mg propranolol overdose [1]. The 32-year-old male developed status epilepticus and a widened QRS complex soon after arrival to the ED, and was given 2 mg physostigmine IV over 3 min. Within 5 min of physostigmine administration, the patient became bradycardic, treated with 0.5 mg atropine followed by asystole 2 min later. He was resuscitated, a temporary transvenous pacer was placed, and he ultimately survived. The 25-year-old male had two generalized tonic-clonic seizures within 1 hour of arrival to the ED and received 2 mg physostigmine IV over 5 min following each of the two seizures in the ED, totaling 4 mg of physostigmine IV over 20 min. Five minutes after the second dose of physostigmine, he developed bradycardia, hypotension, and had an asystolic cardiac arrest. He was resuscitated, but never regained signs of neurologic activity and ultimately died on hospital day 3. Shannon et al. described a 15-year-old female with a 7500 to 9000 mg desipramine ingestion [34]. She had two generalized tonic-clonic seizures in the ambulance en route, and a third on arrival to the ED. She was obtunded and tachycardic with an initial QRS of 0.12 s on EKG and received 2 mg physostigmine IV in the ED. Within 3 to 4 min of receiving physostigmine, she developed bradycardia followed by an asystolic arrest and could not be resuscitated. While these three bradyasystolic arrests had temporal relationships to the administration of physostigmine, they are also consistent with the terminal effects of a severe TCA overdose [35, 36]. In two of the above cases, the patients were noted to have QRS prolongation on an EKG prior to receiving physostigmine [1, 34]. The 25-year-old male with an imipramine and propranolol overdose did not have evidence of QRS prolongation prior to receiving physostigmine; however, his course may have been complicated by a concurrent propranolol overdose that also results in QRS prolongation, bradycardia, and cardiac arrest.

Arrhythmia was described in 10 (0.44%) patients. Atrial fibrillation or flutter was described in 4 (0.17%) patients. Two of these patients were previously discussed [27, 31]. Atrial fibrillation also occurred in 2 patients treated for GHB overdose [37]. One of these patients required beta and calcium-channel blocker therapy and spontaneously converted to a sinus rhythm later the same day. The second patient required no specific therapy and also converted spontaneously

later the same day [37]. A 55-year-old female was given 2 mg physostigmine over 5 min to reverse sedation from general anesthesia and immediately became nauseated, vomited, and developed atrial fibrillation [38]. Three patients developed junctional rhythms after receiving physostigmine to treat ventricular arrhythmia, with subsequent conversion to sinus tachycardia in 1 patient [39], abolition of ventricular arrhythmia in a second patient [40], and improved hemodynamics in a third [41]. Sinus tachycardia was described in 1 patient receiving physostigmine following a GHB overdose [12]. One patient was noted to have several “ventricular ectopic beats” without associated change in blood pressure after physostigmine administration to reverse scopolamine anesthesia [42]. In addition, a 25-year-old female had premature ventricular contractions (PVC’s) without any hemodynamic changes following physostigmine treatment of a diphenhydramine overdose [27].

One patient with a previous history of myocardial infarctions and hypertension treated with physostigmine to reverse central anticholinergic syndrome (CAS) in the setting of general anesthesia developed ventricular fibrillation and cardiac arrest within 5 min of receiving 2 mg physostigmine IV [43]. He was initially resuscitated and recovered neurologically intact; however, he was later noted to have an occlusive aortic thrombus and died the following day. The authors conclude that bradycardia following physostigmine use, or the sudden catecholamine surge from waking following the use of physostigmine in conjunction with this patient’s significant underlying cardiovascular disease, may have been the cause of the patient’s cardiac arrest. They caution against the use of physostigmine in patients with known underlying cardiac disease.

Respiratory

Of the 2299 patients in this review, hypersalivation without airway compromise was the most common adverse effect, described in 206 (9.0%) patients. One 30-day-old infant was noted to have wheezing on exam after physostigmine reversal of CAS, successfully treated with glycopyrrolate [32]. Of note, Burns et al. treated 4 patients with known asthma with physostigmine without asthma exacerbation [3]. No patients developed bronchorrhea or airway compromise in our review.

Gastrointestinal

Nausea and/or vomiting was the second most common adverse effect, described in 96 (4.2%) patients. None of these patients had significant complications as the result of nausea and vomiting including aspiration of gastric contents. Gastrointestinal distress including diarrhea or fecal incontinence, abdominal pain or cramping, and/or hyperperistalsis was reported in 25 (1.1%) patients, without associated complications.

Other

Several additional adverse effects were identified in this review. Cholinergic effects including diaphoresis was described in 27 (1.2%), shivering in 5 (0.22%), and tearing in 2 (0.09%) patients. Psychiatric effects, including restless sleep (7; 0.30%), “dreams” or “nightmares” (3; 0.13%), and depression (2; 0.09%) were also described. These effects did not result in significant complications for any patients.

Fatalities

Five (0.22%) fatalities were identified [1, 34, 43–45]. Three of these patients were previously discussed [1, 34, 43]. A 3-year-old male arrived to the ED in cardiac arrest following an approximate 1500-mg imipramine overdose [45]. He was resuscitated in the ED and received 2 mg physostigmine IV every 60 min over 24 h without change in neurologic or cardiovascular status any each dose. Brain death was confirmed within 24 h [45]. A 60 year-old-male became obtunded after initiation of cimetidine treatment for a large gastric ulcer [44]. He received multiple doses of physostigmine without adverse effect and ultimately died of sepsis. Based upon our review, physostigmine did not contribute significantly to these two fatalities [44].

Inability to Reverse Delirium

The primary indication for the use of physostigmine is the reversal of agitated delirium associated with severe anticholinergic syndrome. Patients identified in our review also received physostigmine to reverse sedation and coma associated with anticholinergic and non-anticholinergic agents. Effectiveness of physostigmine to reverse mental status changes of patients with toxicity from an anticholinergic agent was reported in 297 patients. Physostigmine was ineffective in reversing altered mental status in 18 (6.1%) of these patients, with minimal effect in 2 (0.67%) patients. Adverse effects were described in 23 (7.7%) of these patients. In comparison, the effectiveness of physostigmine to reverse mental status changes of patients with toxicity from non-anticholinergic agents was described in 692 patients. In these patients, physostigmine was ineffective in reversing altered mental status in 8 (1.2%) patients with increased sedation in 1 (0.14%) patient. Compared with patients with anticholinergic overdose, 143 (20.6%) adverse effects were reported in patients with non-anticholinergic overdose or toxicity. As previously discussed, physostigmine does have nonspecific analeptic effects [6] as the result of increased synaptic acetylcholine and thus may

play a role in the arousal of patients with sedation following overdose. However, given the concern for the introduction of a cholinergic agent to a patient with normal cholinergic tone and subsequent adverse effects in the absence of convincing data to support its use, we do not recommend it as a general analeptic.

Use of Physostigmine in Tricyclic Antidepressant Toxicity

Reports of seizure and bradycardia following physostigmine administration in the treated of TCA overdose were first published in the mid-1970s [23]. In 1978, a 25-year-old female had a possible sudden cardiac arrest following physostigmine to treat an amitriptyline overdose in 1978 [46], but it was not until reports of asystole following administration of physostigmine in the setting of severe TCA toxicity were reported by Pentel et al. in 1980 that the concern for use of physostigmine in the setting of TCA toxicity was advocated. In our review, 394 patients with TCA overdose were treated with physostigmine, and adverse effects were reported in 15 (3.8%) of these patients. Three (0.76%) patients became diaphoretic, two (0.51%) developed hypersalivation, and 1 (0.25%) patient had diarrhea. Seizures occurred in 3 (0.76%) patients: 1 patient with an imipramine overdose, and another with an amitriptyline overdose, as previously discussed [23, 24]. Six (1.5%) patients experienced cardiovascular-related effects. Two (0.51%) patients developed bradycardia [3, 23], only one of which had associated hypotension [23]. A 2-year-old male developed seizures and hypotension after a 2-g imipramine overdose, followed by a cardiopulmonary arrest on arrival to the ED [41]. The patient was resuscitated from this arrest and had multiple wide complex arrhythmias unresponsive to antiarrhythmics. After a third dose of physostigmine, the patient was noted to have improved QRS duration followed by a junctional rhythm. The authors noted a more stable rhythm and improved hemodynamics with additional doses of physostigmine [41]. As previously discussed, 3 patients experienced bradyasystolic cardiac arrests [1, 34]. Three fatalities were identified, including 2 patients with bradyasystolic arrests [1, 34] and 1 patient who experienced brain death as the result of a large imipramine overdose [45]. Tricyclic antidepressant overdose may result in severe sodium-channel blockade and decreased depolarization frequency [20]. When combined with the loss of antimuscarinic-mediated tachycardia, physostigmine administration may result in bradycardia and asystole in severe TCA toxicity [20, 36]. Closer inspection of patients with these bradyasystolic events suggests they are more likely the result of severe TCA toxicity heralded by bradycardia and wide complex

arrhythmias rather than the administration of physostigmine alone [20, 47]. While these cases serve as cautionary tales, in our review, life-threatening bradyarrhythmias were isolated to TCA overdose patients with evidence of QRS prolongation prior to receiving physostigmine and in 1 patient with a concurrent propranolol overdose.

Dosing to Minimize Risk of Adverse Effects

The optimal dosing regimen for physostigmine is uncertain, but utilizing a titration approach with low doses given slowly and extended dosing intervals may minimize the risk of adverse effects. Other authors have adverse effects following rapid physostigmine administration [27]. Our experience has been to use lower initial doses (0.5 mg diluted in 10 mL of D5W or normal saline) infused over 2–5 min while observing for improvement or side effects with continuous cardiac monitoring [189]. If no effect is noted, then use a titration of additional 0.5-mg doses at 5- to 10-min intervals up to a maximum total dose of 2 mg over the first hour. We have noted that delirium reversal is usually achieved with an initial total dose of ≤ 2 mg [189]. Other authors also recommend at least a minimum delay of 10–15 min before re-dosing to allow for a maximal effect and greater safety after each dose [24].

Limitations

There are several limitations to this review. As previously mentioned, conclusions were made based largely on case reports and observational case series and thus there were no a priori criteria for diagnosis and response to therapy. Case reports are subject to selection bias and thus reports of a significant response to physostigmine; devoid of adverse effects may be preferentially published and included in this review. There was a wide variation in the severity of intoxications making it difficult to compare clinical effects, adverse effects, and outcomes between patients. Similarly, many patients received multiple concomitant therapies. Confirmatory testing of reported ingestions was rarely completed. In addition, this search was limited to two search engines, and publications written in the English language. Furthermore, publications were chosen at the discretion of the authors, with clinical data abstracted and interpreted by the authors.

Discussion

Physostigmine's unique pharmacology allows reversal of antimuscarinic delirium preventing unnecessary invasive

testing [3] when used appropriately. Despite its effectiveness, the use of physostigmine was discouraged following reports of cardiac arrest after physostigmine administration to 2 patients with TCA overdoses [1]. Our literature review demonstrates significant adverse effects including seizure, arrhythmia, bradycardia, and cardiac arrest following physostigmine administration were infrequent (40; 1.7%), and no patients developed respiratory distress. Of the five fatalities identified, cardiac arrest was concurrent with physostigmine administration in only 3 (0.13%) patients. The most common adverse effects were hypersalivation (206; 9.0%) and gastrointestinal distress (121; 5.3%) without significant complication from either.

Seizures, described in 15 (0.65%) patients, were self-limited or treated successfully without complication. It is unclear whether seizure in these cases was the result of the ingestion, physostigmine administration, or a combination thereof. At least two of the patients with seizure identified in this review had seizures prior to and after receiving physostigmine [21, 26]. Given the small number of patients, it is difficult from this review to determine if the presence of seizure is a contraindication to physostigmine. While seizure was uncommon, it is reasonable to be prepared to treat patients with benzodiazepines, particularly in overdoses with increased risk of causing seizure. Some providers recommend pretreatment or concurrent treatment with benzodiazepines to prevent seizure [27]; however, this did result in hypoxia in a single case report [26].

No patients in this review experienced airway compromise as the result of physostigmine administration. One infant experienced transient airway wheezing treated successfully with glycopyrrolate [32]. Four patients with a known history of asthma were treated with physostigmine without asthma exacerbation [3]. While bronchospasm and bronchorrhea remain a theoretical concern, in our review, no patients suffered severe respiratory compromise following physostigmine administration.

Cardiovascular effects are the most concerning complications of physostigmine administration. In our review, bradycardia was infrequent (12; 0.52%) and fewer patients experienced bradycardia associated with hemodynamic changes, or required treatment (8; 0.35%). In comparison, sinus bradycardia is described in up to 28% of patients with organophosphate toxicity [48]. Bradycardia associated with physostigmine is likely multifactorial including increased vagal tone, increased synaptic acetylcholine at cardiac muscarinic receptors, and abolition of antimuscarinic-mediated tachycardia. While symptomatic bradycardia was uncommon in our review, patients should remain on continuous cardiac monitoring while receiving physostigmine, and atropine should be immediately available.

The most common arrhythmia identified in our review was atrial fibrillation (4; 0.17%). Increased vagal tone and

muscarinic receptor activation are both known triggers of atrial fibrillation, particularly in structurally normal hearts [49]. As previously discussed, bradycardia associated with cardiac arrest occurred in 3 (0.13%) patients with severe TCA toxicity, two of which did have evidence of QRS prolongation on ECG prior to physostigmine administration and one with concomitant propranolol overdose. These bradyasystolic events are more likely to be related to the severity of poisoning, but physostigmine-mediated bradycardia may contribute to bradyasystolic events in patients with prolonged QRS, including patients with severe TCA toxicity. In our review, 379 patients with TCA overdose received physostigmine without adverse effects, suggesting that the concern for arrhythmia after treating any TCA overdose with physostigmine is largely overstated. Ventricular fibrillation occurred in 1 (0.04%) patient with underlying coronary artery disease suggesting underlying cardiac disease may be a relative contraindication for physostigmine administration [43]. However, in a larger case series, 15 patients with known “cardiac disease,” including 4 patients with underlying “rhythm disorders,” were treated with physostigmine without evidence of arrhythmia [27]. Furthermore, May et al. described 20 patients who received physostigmine following open-heart surgical procedures without any cardiovascular adverse effects [50].

In patients treated with physostigmine following overdose of anticholinergic agents, adverse effects occurred in only 23 (7.7%) of patients, making it a reasonable treatment option. In comparison, adverse effects were reported in 143 (20.6%) patients’ physostigmine use as an analeptic to reverse sedation in patients with normal cholinergic tone. While these effects may be mitigated by low-dose administration and avoidance of rapid administration, the use of physostigmine in the treatment of patients without anticholinergic overdose is not recommended given the increased incidence of adverse effects.

In conclusion, significant adverse effects associated with the use of physostigmine were infrequently reported, including in patients with tricyclic antidepressant overdose. Seizures following physostigmine administration were self-limited or resolved with benzodiazepines, and all patients recovered neurologically intact. Physostigmine should be avoided in patients with QRS prolongation on EKG, and caution should be used in patients with a history of coronary artery disease and overdoses with QRS prolonging medications. However, these recommendations are based upon four case reports. Based upon our narrative review, physostigmine is a safe antidote to treat anticholinergic overdose.

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References

- Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. *Ann Emerg Med*. 1980;9(11):588–90.
- Watkins JW, Schwarz ES, Arroyo-Plasencia AM, Mullins ME. Toxicology Investigators Consortium i. The use of physostigmine by toxicologists in anticholinergic toxicity. *J Med Toxicol*. 2015;11(2):179–84. <https://doi.org/10.1007/s13181-014-0452-x>.
- 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):374–81.
- Triggle DJ, Mitchell JM, Filler R. The pharmacology of physostigmine. *CNS Drug Reviews*. 1998;4(2):87–136. <https://doi.org/10.1111/j.1527-3458.1998.tb00059.x>.
- Rumack BH. Anticholinergic poisoning: treatment with physostigmine. *Pediatrics*. 1973;52(3):449–51.
- Nilsson E, Meretoja OA, Neuvonen P. Hemodynamic responses to physostigmine in patients with a drug overdose. *Anesth Analg*. 1983;62(10):885–8.
- Larson GF, Hurlbert BJ, Wingard DW. Physostigmine reversal of diazepam-induced depression. *Anesth Analg*. 1977;56(3):348–51.
- Weinstock M, Davidson JT, Rosin AJ, Schnieden H. Effect of physostigmine on morphine-induced postoperative pain and somnolence. *Br J Anaesth*. 1982;54(4):429–34.
- Hartvig P, Wiklund L, Lindstrom B. Pharmacokinetics of physostigmine after intravenous, intramuscular and subcutaneous administration in surgical patients. *Acta Anaesthesiol Scand*. 1986;30(2):177–82.
- Schneck HJ, Rupprecht J. Central anticholinergic syndrome (CAS) in anesthesia and intensive care. *Acta Anaesthesiol Belg*. 1989;40(3):219–28.
- Rupprecht J, Dworacek B, Oosthoek H, Dzoljic MR, Valkenburg M. Physostigmine versus naloxone in heroin-overdose. *J Toxicol Clin Toxicol*. 2008;21(3):387–97. <https://doi.org/10.3109/15563658308990429>.
- Caldicott DG, Kuhn M. Gamma-hydroxybutyrate overdose and physostigmine: teaching new tricks to an old drug? *Ann Emerg Med*. 2001;37(1):99–102. <https://doi.org/10.1067/mem.2001.111642>.
- Asthana S, Greig NH, Hegedus L, Holloway HH, Raffaele KC, Schapiro MB, et al. Clinical pharmacokinetics of physostigmine in patients with Alzheimer’s disease. *Clin Pharmacol Ther*. 1995;58(3):299–309. [https://doi.org/10.1016/0009-9236\(95\)90246-5](https://doi.org/10.1016/0009-9236(95)90246-5).
- Cumming G, Harding LK, Prowse K. Treatment and recovery after massive overdose of physostigmine. *Lancet*. 1968;2(7560):147–9.
- Salas R, Cook KD, Bassetto L, De Biasi M. The alpha3 and beta4 nicotinic acetylcholine receptor subunits are necessary for nicotine-induced seizures and hypolocomotion in mice. *Neuropharmacology*. 2004;47(3):401–7. <https://doi.org/10.1016/j.neuropharm.2004.05.002>.
- Gholami M, Saboori E, Zare S, Roshan-Milani S, Hajizadeh-Moghaddam A. The effect of dorsal hippocampal administration of nicotinic and muscarinic cholinergic ligands on

- pentylentetrazol-induced generalized seizures in rats. *Epilepsy Behav.* 2012;25(2):244–9. <https://doi.org/10.1016/j.yebeh.2012.07.004>.
17. Trivisano M, Terracciano A, Milano T, Cappelletti S, Pietrafusa N, Bertini ES, et al. Mutation of CHRNA2 in a family with benign familial infantile seizures: potential role of nicotinic acetylcholine receptor in various phenotypes of epilepsy. *Epilepsia.* 2015;56(5):e53–7. <https://doi.org/10.1111/epi.12967>.
 18. Holinger PC, Klawans HL. Reversal of tricyclic-overdosage-induced central anticholinergic syndrome by physostigmine. *Am J Psychiatry.* 1976;133(9):1018–23. <https://doi.org/10.1176/ajp.133.9.1018>.
 19. Burks JS, Walker JE, Rumack BH, Ott JE. Tricyclic antidepressant poisoning. Reversal of coma, choreoathetosis, and myoclonus by physostigmine. *JAMA.* 1974;230(10):1405–7.
 20. Suchard JR. Assessing physostigmine's contraindication in cyclic antidepressant ingestions. *J Emerg Med.* 2003;25(2):185–91. [https://doi.org/10.1016/s0736-4679\(03\)00169-0](https://doi.org/10.1016/s0736-4679(03)00169-0).
 21. Magera BE, Betlach CJ, Sweatt AP, Derrick CW Jr. Hydroxyzine intoxication in a 13-month-old child. *Pediatrics.* 1981;67(2):280–3.
 22. Eyer F, Pfab R, Felgenhauer N, Strubel T, Saugel B, Zilker T. Clinical and analytical features of severe suicidal quetiapine overdoses—a retrospective cohort study. *Clin Toxicol (Phila).* 2011;49(9):846–53. <https://doi.org/10.3109/15563650.2011.624100>.
 23. Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdose. *JAMA.* 1975;231(9):941–3.
 24. Stewart GO. Convulsions after physostigmine. *Anaesth Intensive Care.* 1979;7(3):283.
 25. Tobis J, Das BN. Cardiac complications in amitriptyline poisoning. Successful treatment with physostigmine. *JAMA.* 1976;235(14):1474–6.
 26. Schneir AB, Offerman SR, Ly BT, Davis JM, Baldwin RT, Williams SR, et al. Complications of diagnostic physostigmine administration to emergency department patients. *Ann Emerg Med.* 2003;42(1):14–9. <https://doi.org/10.1067/mem.2003.232>.
 27. Rasimas JJSK, Donovan JW. Revival of an antidote: bedside experience with physostigmine. *J Am Assoc Emerg Psychiatry.* 2014;12(2):5–24.
 28. Artru AA, Hui GS. Physostigmine reversal of general anesthesia for intraoperative neurological testing: associated EEG changes. *Anesth Analg.* 1986;65(10):1059–62.
 29. Bidwai AV, Cornelius LR, Stanley TH. Reversal of innovar-induced postanesthetic somnolence and disorientation with physostigmine. *Anesthesiology.* 1976;44(3):249–52.
 30. Holzgrafe RE, Vondrell JJ, Mintz SM. Reversal of postoperative reactions to scopolamine with physostigmine. *Anesth Analg.* 1973;52(6):921–5.
 31. Avant GR, Speeg KV Jr, Freeman FR, Schenker S, Berman ML. Physostigmine reversal of diazepam-induced hypnosis. A study in human volunteers. *Ann Intern Med.* 1979;91(1):53–5.
 32. Gillick JS. Atropine toxicity in a neonate. *Br J Anaesth.* 1974;46(10):793–4.
 33. Henderson RS, Holmes CM. Reversal of the anaesthetic action of sodium gamma-hydroxybutyrate. *Anaesth Intensive Care.* 1976;4(4):351–4.
 34. Shannon M. Toxicology reviews: physostigmine. *Pediatr Emerg Care.* 1998;14(3):224–6.
 35. Kulig K, Rumack BH. Physostigmine and asystole. *Ann Emerg Med.* 1981;10(4):228–0.
 36. Krolecki PF, Curry SC. Poisoning by sodium channel blocking agents. *Crit Care Clin.* 1997;13(4):829–48.
 37. Zvosec DL, Smith SW, Litonjua R, Westfal RE. Physostigmine for gamma-hydroxybutyrate coma: inefficacy, adverse events, and review. *Clin Toxicol (Phila).* 2007;45(3):261–5. <https://doi.org/10.1080/15563650601072159>.
 38. Maister AH. Atrial fibrillation following physostigmine. *Can Anaesth Soc J.* 1983;30(4):419–21.
 39. Danze LK, Langdorf MI. Reversal of orphenadrine-induced ventricular tachycardia with physostigmine. *J Emerg Med.* 1991;9(6):453–7.
 40. Schmidt W, Lang K. Life-threatening dysrhythmias in severe thioridazine poisoning treated with physostigmine and transient atrial pacing. *Crit Care Med.* 1997;25(11):1925–30.
 41. Wright SP. Usefulness of physostigmine in imipramine poisoning. A dramatic response in a child resistant to other therapy. *Clin Pediatr (Phila).* 1976;15(12):1123–8. <https://doi.org/10.1177/000992287601501208>.
 42. Greene LT. Physostigmine treatment of anticholinergic-drug depression in postoperative patients. *Anesth Analg.* 1971;50(2):222–6.
 43. Boon J, Prideaux PR. Cardiac arrest following physostigmine. *Anaesth Intensive Care.* 1980;8(1):92–3.
 44. Mogelnicki SR, Waller JL, Finlayson DC. Physostigmine reversal of cimetidine-induced mental confusion. *JAMA.* 1979;241(8):826–7.
 45. Ryan R 3rd, Wians FH Jr, Stigelman WH Jr, Clark H, McCurdy F. Imipramine poisoning in a child: lack of efficacy of resin hemoperfusion. *Pediatr Emerg Care.* 1985;1(4):201–4.
 46. Ordiway MV. Treating tricyclic overdose with physostigmine. *Am J Psychiatry.* 1978;135(9):1114.
 47. Bigger JT Jr, Kantor SJ, Glassman AH, Perel JM. Is physostigmine effective for cardiac toxicity of tricyclic antidepressant drugs. *JAMA.* 1977;237(13):1311.
 48. Saadeh AM, Farsakh NA, Al-Ali MK. Cardiac manifestations of acute carbamate and organophosphate poisoning. *Heart.* 1997;77(5):461–4.
 49. Linz D, Elliott AD, Hohl M, Malik V, Schotten U, Dobrev D, et al. Role of autonomic nervous system in atrial fibrillation. *Int J Cardiol.* 2018. <https://doi.org/10.1016/j.ijcard.2018.11.091>.
 50. May AE, Machin JR, Wyatt R. Physostigmine in open-heart surgery. Reversal of hyoscine supplementation of morphine-oxygen-air-relaxant anaesthesia. *Anaesthesia.* 1978;33(6):547–50.