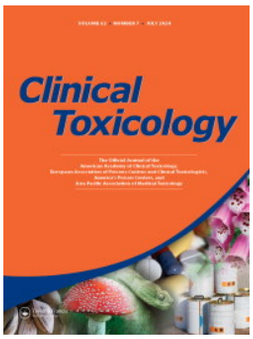

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POISON CENTRE RESEARCH

Physostigmine reversal of delirium from second generation antipsychotic exposure: a retrospective cohort study from a regional poison center

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ABSTRACT

Introduction: Physostigmine is an effective antidote for antimuscarinic delirium. There is little evidence for its use to reverse delirium following second generation antipsychotic exposure. The purpose of this study is to describe the safety and effectiveness of physostigmine in reversing delirium from second generation antipsychotic exposure.

Methods: This is a retrospective cohort study of all patients reported to a single regional poison center treated with physostigmine following a second generation antipsychotic exposure from January 1, 2000 to April 15, 2021. The poison center electronic medical record was queried to identify cases and for data abstraction. The primary outcome was the positive response rate to physostigmine, as determined by two trained abstractors. Secondary outcomes included physostigmine dosing, and adverse events.

Results: Of 147 charts reviewed, 138 individual patients were included, and the response to physostigmine was reported in 128 patients. The most common second-generation antipsychotic exposure was quetiapine (97; 70.3 percent). A positive response to physostigmine was noted in 106/128 (82.8 percent) patients [95 percent confidence interval 68.9–83.6 percent]. Median number of physostigmine doses was 1 (interquartile range 1–3; range 1–9). The median total physostigmine dose received was 2 mg (interquartile range 2–6 mg; range 0.15–30 mg). The positive physostigmine response rate for patients with an antimuscarinic co-ingestion was not significantly different compared to patients with a different co-ingestion or no co-ingestion (25/34 versus 81/94; $P = 0.09$). Adverse events were reported in four (2.9 percent) patients, including one death.

Discussion: A positive response to physostigmine to treat antimuscarinic delirium from second generation antipsychotic exposure was reported in 82.8 percent of patients, which is similar to previous physostigmine studies. Adverse events were infrequent, and included diaphoresis (one 0.7 percent), seizure (one; 0.7 percent), and bradycardia (one; 0.7 percent). One (0.7%) patient suffered a cardiac arrest 60 minutes after receiving physostigmine to treat antimuscarinic delirium following having received increasing clozapine doses over the previous month.

Conclusions: In this study, physostigmine appears to be a safe and effective treatment for antimuscarinic delirium from second generation antipsychotic exposure. Further studies are needed to validate the safety and effectiveness of physostigmine for this indication.

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Physostigmine; second generation antipsychotic; atypical antipsychotic; antimuscarinic delirium; anticholinergic delirium

Introduction

Physostigmine, a tertiary amine carbamate acetylcholinesterase inhibitor, is a safe and effective antidote for antimuscarinic delirium [1–6]. It has been reported to reverse the delirium following second generation antipsychotic exposure, particularly those with antimuscarinic properties such as quetiapine [7, 8].

Second generation antipsychotics are commonly prescribed worldwide [9]. In 2022, America's Poison Centers received 43,822 calls for cases of a second generation antipsychotic exposure, and over 12,000 of these required treatment in a hospital setting [10]. Second generation antipsychotics are antagonists of both dopamine D_2 and serotonin 5-HT_{2a} receptors, with varied effects on muscarinic receptors [11, 12]. Second-generation antipsychotic poisoning is typically characterized by central nervous system depression and delirium treated with supportive care [13–15]. Physostigmine may be beneficial in treating delirium, particularly after exposure to second generation antipsychotics with antimuscarinic properties. Evidence for this treatment is limited to case reports and small case series [8, 16]. The purpose of this study is to describe the safety and

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This study was previously presented as a lightning platform presentation for the 2021 North American Congress of Clinical Toxicology in Atlanta, GA (presented virtually due to COVID-19): Arens A, Sheikh Said H, Driver B, Cole J. Physostigmine reversal of delirium from second generation antipsychotics: A retrospective study from a regional poison center. Clin Toxicol. 2021; 59(11):1143–1144 (abstract #221).

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effectiveness of physostigmine in reversing delirium from second generation antipsychotic poisoning.

Methods

Study design and setting

This is an institutional review board-exempted retrospective cohort study of all patients reported to a single regional poison center for whom physostigmine was administered following exposure to a second-generation antipsychotic from January 1, 2000 to April 15, 2021. This poison center covers three states (Minnesota, North Dakota, and South Dakota) in the United States and has an existing guideline for the use of physostigmine in antimuscarinic delirium [2]. Briefly, this guideline recommends physostigmine for the treatment of patients with antimuscarinic delirium. Contraindications to physostigmine include QRS complex duration >120 ms, or an R wave in aVR >3 mm on the electrocardiogram (ECG). The guideline also recommends patients receive a dose of intravenous lorazepam prior to receiving physostigmine to prevent seizure. Three institutions included in this area also provide bedside toxicology consultations, which are reported to the regional poison center.

Selection of participants

The poison center electronic medical record (ToxiCALL®) was queried for any exposure cases involving a second generation antipsychotic (America's Poison Center code: 201122) with "physostigmine" coded as "performed whether or not recommended" as a therapy. Patients of any age were included if they had a reported exposure to a second generation antipsychotic and received physostigmine after review of case notes. Patients were excluded if they did not receive physostigmine, did not have a reported exposure to a second generation antipsychotic, or were duplicate cases.

Measurements

Patient demographic information included age and sex, and the year of exposure. All cases treated by the poison center are entered into ToxiCALL®, and subsequently reviewed and coded by symptom, treatment, and outcome as outlined by guidelines and definitions defined by the National Poison Data System (NPDS), the database owned and operated by America's Poison Centers. The reason for exposure was the recorded "reason for exposure" coded for each case using NPDS definitions (intentional and subcategories, unintentional, adverse reaction, and unknown reason) [17]. The specific second generation antipsychotics, and any antimuscarinic co-ingestants were gathered from the substance list entered by the poison center staff for each patient.

The primary outcome measure was whether there was a positive response to physostigmine (coded as yes or no), determined by two trained abstractors who reviewed case notes for every patient. A positive response to physostigmine was defined as a subjective improvement in mental status, delirium, or confusion as noted by care providers and documented in the case notes, or improvement in mental status, delirium, or confusion as determined by the reviewer on review of case notes. Secondary outcomes included physostigmine dosing, and adverse events were also determined by review of case notes by the trained abstractors. Adverse events reported included: asystole, bradycardia, cardiac arrest, any dysrhythmia, ventricular tachycardia, seizure, status epilepticus, or any other noted adverse events following physostigmine administration determined by the abstractor on review of case notes.

Data analysis

Descriptive statistics are reported. Medians, interquartile ranges (IQR), ranges, and 95% confidence intervals (CI) were calculated and reported when appropriate. Comparisons between groups were performed using the chi-square test, with a P value < 0.05 considered statistically significant. All data were analyzed using STATA® (Version 15.1; StataCorp®, College Station, TX)

Results

Data query returned 147 charts. Seven duplicate charts were excluded. After chart review it was unclear if two patients received physostigmine and were also excluded. After exclusions, 138 individual patients were included. Demographic and ingestion data are included in Table 1. The most common second generation antipsychotic involved was quetiapine (97; 70.3%), followed by olanzapine (27; 19.6%).

Details of physostigmine dosing and effectiveness are reported in Table 2. The response to physostigmine was reported in 128 patients and unclear in 10 patients. A positive response to physostigmine was noted in 106/128

Table 1. Demographic and ingestion data.

Age, years	Median 30, (range 1–65)
Sex, female, *n* (%)	65 (47.1)
Reason for exposure	
Suspected suicide, *n* (%)	110 (79.7)
Abuse, *n* (%)	4 (2.9)
Misuse, *n* (%)	2 (1.4)
Unintentional, *n* (%)	2 (1.4)
Adverse reaction, *n* (%)	3 (2.2)
Unknown reason, *n*	17
Second generation antipsychotics	
Quetiapine, *n* (%)	97 (70.3)
Olanzapine, *n* (%)	27 (19.6)
Risperidone, *n* (%)	6 (4.4)
Lurasidone, *n* (%)	3 (2.2)
Clozapine, *n* (%)	2 (1.4)
Ziprasidone, *n* (%)	2 (1.4)
Brexpiprazole, *n* (%)	1 (0.7)
Antimuscarinic co-ingestants	
Unique patients with antimuscarinic co-ingestion, *n* (%)	37 (26.8)
Hydroxyzine, *n* (%)	13 (9.4)
Diphenhydramine, *n* (%)	11 (7.9)
Benztropine, *n* (%)	6 (4.3)
Cyclic antidepressants, *n* (%)	6 (4.3)
Cyclobenzaprine, *n* (%)	5 (3.6)
Doxylamine, *n* (%)	1 (0.7)
Oxybutynin, *n* (%)	1 (0.7)

Table 2. Physostigmine dosing and response rate.

Number of physostigmine doses ($n = 112$)	Median 1, interquartile range 1–3, range 1–9
Total physostigmine administered (mg) ($n = 86$)	Median 2, interquartile range 2–6, range 0.15–30
Positive response to physostigmine[a]	
Quetiapine, *n* (%)	80/93 (86.0)
Olanzapine, *n* (%)	18/24 (75.0)
Risperidone[b], *n* (%)	3/4 (75.0)
Lurasidone[b], *n* (%)	2/3 (66.6)
Clozapine, *n* (%)	2/2 (100.0)
Ziprasidone[b], *n* (%)	1/2 (50.0)
Brexpiprazole, *n*	0
Total, *n* (%)	106/128 (82.8)

[a]$n = 128$, response was unclear in 10 patients.
[b]All patients with positive responses involved another antimuscarinic co-ingestion except for two risperidone cases.

(82.8%) patients [95% CI 75.1–88.9%]. The median number of physostigmine doses was 1 (IQR1–3; range 1–9). The median total physostigmine dose received was 2 mg (IQR 2–6 mg; range 0.15–30 mg). Two patients were treated with physostigmine infusions. One of these patients was started on a physostigmine infusion at 1 mg/h and weaned down for a total of 2 mg total. A second patient received multiple individual doses of physostigmine before an infusion was initiated. The details of the infusion rate were not reported. Neither patient experienced any adverse events. Eighty-nine (64.5%) patients received concomitant benzodiazepines. Of the 92/138 (66.6%) patients with a co-ingestion, 37/138 (26.8%) co-ingested a drug with antimuscarinic properties. The physostigmine response rate for patients with an antimuscarinic co-ingestion was 25/34 (73.5%) and for those with a different co-ingestion or no co-ingestion the response rate was 81/94 (86.2%) with an absolute difference of 12.6% [95% CI −3.7–29.0%]. There was no significant difference in the physostigmine response rate between these groups ($P = 0.09$).

Adverse events occurred in four (2.9%) patients. A 60-year-old male reportedly ingested an unknown amount of quetiapine with duloxetine and was described as "sweaty" after receiving physostigmine, with no additional effects and no treatment required. A 14-month-old child reportedly took an unknown amount of risperidone, and received physostigmine 0.15 mg for altered mental status. Thirty minutes after receiving physostigmine, the patient became bradycardic (heart rate 60 beats/min), which was treated with one dose of atropine. A 35-year-old man reportedly overdosed on quetiapine approximately 300 mg, an unknown amount of lamotrigine and ethanol, and received physostigmine 1 mg. He experienced a seizure immediately after receiving physostigmine, which resolved with diazepam. The last patient suffered a cardiac arrest after receiving physostigmine. This patient was hospitalized for over one month for an exacerbation of schizophrenia, whereupon he developed hospital-acquired delirium in the setting of increasing clozapine dosing and was transferred to a medical unit from psychiatry. His past medical history included a 1 pack per day cigarette smoking history, and additional home medications included: haloperidol decanoate, citalopram, trazodone, and metoprolol. During his hospitalization, the patient was also intermittently febrile and hypotensive with evidence of aspiration pneumonia on chest radiograph. He was also evaluated by cardiology for non-specific ST segment elevation noted on his ECG with elevated cardiac troponin concentrations. An echocardiogram showed a normal ejection fraction and it was determined by the cardiology team that these abnormalities reflected a non-occlusive myocardial infarction. A clozapine blood concentration on the day of transfer was 1,126 μg/L (reference range: 451–5,000 μg/L); clozapine was subsequently withheld. Bedside consultation suspected antimuscarinic delirium. The patient was also experiencing worsening dyspnea and tachypnea (respiratory rate 35 breaths/min) with thick secretions, and sinus tachycardia (heart rate 140 beats/min). Physostigmine 1 mg was administered over 5 min, which resulted in resolution of delirium. During the period of delirium resolution, the patient's heart rate improved to 110 beats/min and he was noted to be alert and joking with caregivers. Thirty minutes after physostigmine administration, delirium recurred and the patient was noted to be in respiratory distress, and he was intubated. Twenty minutes after intubation, one hour after the dose of physostigmine, the patient suffered a brady-asystolic cardiac arrest. The patient was resuscitated but died one week later from multi-organ system failure. No ECG was completed within the 24 h prior to receiving physostigmine. All electrolytes including magnesium were within normal limits the day of physostigmine administration, and the patient had received benztropine and trazodone the night prior. Documentation from the attending medical toxicologist noted the cardiac arrest was unrelated to physostigmine. The cause of death on autopsy was reported by the coroner as multisystem organ failure due to complications of refractory schizophrenia. The institutional medication safety officer, who was also a certified specialist in poison information, assessed the case using the Naranjo Adverse Drug Reaction Probability Scale [19] and assigned a score of +3, consistent with a "possible" adverse drug reaction (Supplemental Table).

Discussion

In this retrospective review of patients who received physostigmine to treat delirium following second generation antipsychotic exposure, most patients (106/128; 82.8%) were noted to have an improvement in mental status, delirium, or confusion following physostigmine administration. The majority of patients received a single dose of physostigmine (IQR 1–3; range 1–9), and patients typically received a total physostigmine dose of 2 mg (IQR 2–6 mg; range 0.15–30 mg).

Some patients required multiple doses of physostigmine to treat recrudescence of symptoms after initial improvement including one patient receiving a total physostigmine dose of 30 mg. The need for multiple doses and relatively higher doses of physostigmine in these patients may be secondary to the multiple receptor effects of second generation antipsychotics contributing to delirium. The response rate of the patients in this retrospective case series of 138 patients with second generation antipsychotic exposure was 82.8%, which is similar to that reported previously in patients with antimuscarinic delirium, regardless of medication class (73–81%) [5, 6].

In this case series, most patients, (97; 70.2%) were exposed to quetiapine. Quetiapine undergoes metabolism by CYP3A4 to produce the major active metabolite, norquetiapine, or N-desalkylquetiapine [20, 21]. Norquetiapine is both a muscarinic and histamine receptor antagonist in at least one *in vitro* study [20], though the contribution to quetiapine associated delirium is unclear [21]. Given the significant number of patients exposed to an antipsychotic with potential antimuscarinic and antihistamine properties, generalization of the positive response rate observed in this cohort to patients exposed to other second generation antipsychotics may be limited.

As previously discussed, the regional poison center physostigmine guideline recommends patients receive a dose of intravenous lorazepam prior to physostigmine administration to prevent seizure [2]. Thus, most patients (89; 64.4%) received concomitant benzodiazepines with physostigmine. It is difficult to determine the contribution of benzodiazepines to the improvement of delirium in this case series of patients. Future studies without concomitant benzodiazepine administration would further clarify the effectiveness of physostigmine reversal of delirium from second generation antipsychotic exposure. Adverse events were rare in our review of patients (four; 2.9%). While the safety and effectiveness of physostigmine is well described elsewhere [1, 5, 6], adverse events including seizure, bradycardia, dysrhythmia, diaphoresis, and cardiac arrest are also described. The concern for brady-asystole is often cited, after reports of cardiac arrest following use of physostigmine for the treatment of seizures in patients with tricyclic antidepressant overdose [22–24]. These cases are rare and in the setting of severe tricyclic antidepressant toxicity, and while the events were temporally related, the physostigmine was not necessarily the proximate cause of arrest [25].

We did observe one case of cardiac arrest in a patient with a history of schizophrenia who was treated with physostigmine to treat antimuscarinic delirium attributed to escalating doses of clozapine during an admission for concomitant aspiration pneumonia. This cardiac arrest occurred following intubation after he clinically deteriorated and an hour after receiving the last dose of physostigmine. The treating toxicologist did not attribute the cardiac arrest to physostigmine therapy, and independent review by a review safety officer determined the contribution of physostigmine to this patient's cardiac arrest was unclear. Regardless of the contribution of physostigmine in this case, the use of physostigmine is associated with adverse events, and as with any treatment the risk and benefits must be considered for each individual patient. Patients being treated for clozapine overdose or toxicity may warrant specific caution when considering treatment with physostigmine. Compared with other second generation antipsychotics, clozapine is most often associated with seizures [26], and hypersalivation is reported in up to 92% of patients treated with clozapine therapeutically [27]. The risk of seizure and hypersalivation with even therapeutic treatment with clozapine may increase the risk of these adverse events with physostigmine administration, so additional caution may be prudent. Patients at high risk for brady-dysrhythmias should be monitored closely, and all patients receiving physostigmine should have appropriate observation and precautions in place for seizure [22–25]. An alternative diagnosis considered was clozapine-induced myocarditis. Clozapine-induced myocarditis is described in up to 3.2% of patients treated with clozapine and may present with fever, tachycardia, nausea, vomiting, and elevated troponins. [28] Normal echocardiography is observed in one third of patients. [28] The coroner did not comment on myocarditis as a cause of death in the patient described in our case series.

Limitations

This study has several limitations. The data gathered is dependent upon the completeness of poison center records as documented by the individual specialist and is limited by the information provided by the patient care teams. In addition, the retrospective nature of this study and the use of poison center data, temporal relationships with physostigmine response and adverse events are difficult to interpret. Similarly, there was no confirmatory testing available to confirm ingestions and thus the ingestion history is reliant on patient and care team history. A validated delirium scale was not utilized by providers prospectively to help verify improvement in delirium and thus reviewers had to retrospectively make subjective determinations. There are also several limitations to the Naranjo Adverse Drug Reaction Probability Scale [18, 19] used to determine the role of physostigmine in the one fatality identified in the case series. While this scale includes all of the usual features that are important in assessing causality, the scale is not weighted for the most critical elements in judging the likelihood of adverse drug reactions, such as: specific time to onset, and list of critical diagnoses to exclude. The scale also relies upon testing for drug concentrations, which is not always helpful in confirming adverse drug reactions. Finally, the scale was designed for use in clinical trials. In addition, the majority of patients received benzodiazepines prior to receiving physostigmine. The contribution of benzodiazepines to the treatment of delirium or the safety of physostigmine in this case series is unclear. The applicability of this data is also limited by the lack of availability of physostigmine.

Conclusions

In this study, physostigmine was an effective treatment for antimuscarinic delirium induced by second generation

antipsychotic exposure, primarily in cases of quetiapine and olanzapine poisoning. Delayed cardiac arrest occurred in a patient with antimuscarinic delirium related to gradually increased therapeutic doses of clozapine. The role of physostigmine in this patient's arrest was unclear. As we observed no life-threatening adverse events clearly and directly related to physostigmine. In this case series, physostigmine appears to be a safe and effective treatment in this patient population. More studies are needed to validate these findings.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

Data will not be made available to protect patient confidentiality

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