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Selected Topics: Toxicology

CLINICAL EFFECTS OF PEDIATRIC CLONIDINE EXPOSURE: A RETROSPECTIVE COHORT STUDY AT A SINGLE TERTIARY CARE CENTER

Michael S. Toce, MD, MS,*† Eli Freiman, MD,* Katherine A. O'Donnell, MD,*‡ and Michele M. Burns, MD, MPH*†

*Harvard Medical Toxicology Program, Boston Children's Hospital, Boston, Massachusetts, †Division of Emergency Medicine, Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts, and ‡Division of General Pediatrics, Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts

Reprint Address: Michael S. Toce, MD, MS, Harvard Medical Toxicology Program, Boston Children's Hospital, 300 Longwood Avenue, Mailstop 3025, Boston, MA 02115

☐ **Abstract—Background: Pediatric clonidine ingestions frequently result in emergency department visits and admission for cardiac monitoring. Detailed information on the clinical course and specifically time of vital sign abnormalities of these patients is lacking. Objective: The objective of this study was to provide descriptive analysis of the rates and times to vital sign abnormalities, treatment, disposition, and outcomes in a single-center cohort of pediatric patients with report of clonidine poisoning. Methods: We performed a retrospective cohort study of patients younger than 21 years who presented to a large, urban, tertiary care center with a report of single substance clonidine exposure between January 2004 and November 2017. Patients were dichotomized into younger (≤9 years or younger) and older (10–21 years) groups based on the expected physiologic and psychologic differences between older and younger children. Results: Eighty-eight patients met our inclusion criteria. Younger patients (≤9 years or younger; n = 47) were more likely to be exposed to someone else's medication (53%) and older patients (10–21 years; n = 41) overwhelmingly (85%) were exposed to their own medication. Thirty-nine (45%) became bradycardic, 27 (32%) became bradypneic, and 38 (44%) became hypotensive. Eighty percent of patients had depressed mental status. Thirty-three (38%) patients received at least one dose of naloxone (median 0.07 mg/kg; interquartile range 0.03–0.11 mg/kg). Of those who received naloxone, 50% had a documented clinical response. Conclusions: In this study of patients at a pediatric tertiary referral center, pediatric patients with report of clonidine exposures were likely to exhibit altered mental status and frequently develop vital sign abnormalities. Naloxone exhibited some effectiveness; given its wide safety margin, high-dose naloxone should be used in critically poisoned non–opioid-dependent patients. Because adolescents are much more likely to ingest their own clonidine medication, counseling with parents and other caregivers regarding safe medication storage is paramount.** © **2020 Elsevier Inc. All rights reserved.**

☐ **Keywords—toxicology; clonidine; pediatric**

INTRODUCTION

Pediatric exposures to clonidine are common. In 2018, there were nearly 4000 clonidine exposures reported to the National Poison Data System involving patients younger than 20 years (1). Clinical findings of pediatric clonidine poisoning include mental status depression, bradycardia, hypotension, miosis, and respiratory depression (2–4). Treatment options include activated charcoal, isotonic fluid resuscitation, atropine, and naloxone; the need for vasopressor therapy or intubation is rare (5,6).

Clonidine is an α_2-adrenergic receptor and imidazoline-1 receptor agonist. Agonism of presynaptic α_2-adrenergic receptors in the medulla decreases norepinephrine release, which in turn contributes to a decrease in blood pressure and heart rate, and binding to α_2-adrenergic receptors in the pons induces sedation. In addition,

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clonidine binds to the I-1 receptor in the medulla, which leads to hypotension, bradycardia, and decreased myocardial contractility (7). Clonidine is used to treat hypertension, attention-deficit hyperactivity disorder, and Tourette syndrome, as well as a variety of other behavioral conditions in pediatric patients (8,9). In the intensive care setting, clonidine is used for sedation and management of iatrogenic withdrawal (10). In adults, clonidine is used in the treatment of both hypertension and opioid use disorder (11,12).

Clinical findings of pediatric clonidine exposure include mental status depression, bradycardia, hypotension, miosis, respiratory depression, and hypothermia (2,13,14). This pattern of findings closely mirrors the opioid toxidrome, making ascertainment of the correct diagnosis challenging. Occasionally, transient hypertension can be seen, likely due to peripheral stimulation of α_2-adrenergic receptors (15,16). Even exposure to small reported doses can have significant clinical consequences (3,15).

With the goal of further informing front-line clinicians who care for these patients, the objective of our study was to characterize the clinical course of a cohort of children younger than 21 years who presented to a large pediatric tertiary care center with report of clonidine exposure (unintentional ingestions or intentional overdoses). The primary outcome was time to vital sign abnormalities. Secondary outcomes included clinical effects, treatment, disposition, and outcomes.

METHODS

Study Design and Setting

We performed a single-center retrospective cohort study of patients younger than 21 years who presented to a large, urban, tertiary pediatric care center with a report of single substance clonidine exposure, many of whom were evaluated by a medical toxicologist between January 2004 and November 2017. The hospital carries a level I trauma center designation. The annual emergency department (ED) volume is approximately 60,000 visits. In addition, the hospital has a toxicology fellowship, as well as a toxicology consulting and admitting service. During the past 10 years, the toxicology service has averaged 220 consults per year. Finally, the hospital is the home for the regional poison control center.

Patient Identification

We identified patients using a tracking database maintained by the hospital's toxicology service of all patients in whom the admitting diagnosis was clonidine exposure and the toxicology team was consulted (n = 79). To ensure that no patients who met inclusion criteria were missed, a separate search of administrative data utilizing codes from International Classification of Diseases (ICD)-9 (972.6) and ICD-10 (T46.5X1, T46.5X2, T46.5X4) and subsequent chart review was performed. Nine additional patients were identified. Two authors (M.T. and E.F.) conducted chart review and were not blinded to study objectives. To measure inter-rater reliability, we used an intraclass correlation and measured absolute agreement of time to onset of bradycardia using a 2-way mixed-effect model, treating the raters as fixed effects. The intraclass correlation was 0.996 (95% confidence interval 0.988–0.999). Data were entered into a standardized Excel (Microsoft, Redmond, WA) spreadsheet for all patients. Inclusion criteria included all patients younger than 21 years who presented with a report of clonidine exposure and were evaluated in the ED, medical floor, or intensive care unit (ICU). Exclusion criteria included patients with report of polysubstance exposure.

Data Collection

We reviewed the medical records of all eligible patients and abstracted the following: age; sex; weight; time of exposure; estimated exposure dose; time to nadir; last occurrence of respiratory depression, bradycardia, or hypotension; disposition (ED, floor, or ICU); medication exposure medication source (self, sibling, parent, other, unknown); formulation (tablet, liquid, patch); reason (unintentional, intentional); pertinent clinical examination findings; and interventions (naloxone, activated charcoal, or intubation). Data were abstracted from our electronic health record, as well as records from outside hospitals that accompanied the patient and were scanned into our system.

Clinical Effects

We defined miosis as documentation of pupillary diameter or ≤ 2 mm, or documentation of "miosis" or "miotic pupils." Depressed mental status was defined as documentation of "sleepy," "lethargic," "somnolent," or "depressed mental status." Bradycardia and bradypnea were defined as a documented heart rate or respiratory rate below the first percentile by age (17). Hypotension was defined as a systolic blood pressure < 70 mm Hg in patients younger than 2 years, < 70 mm Hg + 2 × age in patients 2 to 10 years, and < 90 mm Hg in patients older than 10 years.

Statistical Analysis

We used IBM SPSS Statistics, version 23 (IBM Corp, Armonk, NY) for all statistical analysis. Mann-Whitney test

was used to compare for non-normally distributed, nonbinary, independent variables. Pearson χ^2 test and Fisher's exact test were used to compare categorical variables. When appropriate, we calculated medians and interquartile ranges (IQRs). Statistical significance was set at a p value < 0.05. Given the physiologic and psychologic differences between younger and older patients, we dichotomized patients into younger (≤9 years) and older (10–20 years) groups for analytic purposes. The study protocol was approved by the Institutional Review Board with a waiver of informed consent.

RESULTS

Demographics

We identified 143 patients who presented with concern for clonidine exposure, of which 88 (62%) met our inclusion criteria. Fifty-four patients were excluded due to polypharmacy exposure, and 1 patient was excluded due to presenting symptom of "clonidine withdrawal" (Figure 1). Age distribution is summarized in Figure 2. Estimated exposure dose was available in 72 patients (82%). The median reported clonidine exposure dose was 0.02 mg/kg (IQR 0.01–0.06 mg/kg). Seventy-five patients (85%) were exposed to a tablet formulation, 6 (7%) were exposed to a liquid formulation, 4 (5%) were exposed to patch, and 1 patient was exposed to both a tablet and a patch. Formulation was unknown in 2 patients (3%). Most patients (75%) initially presented to an outside hospital and were subsequently transferred to our institution. More than half (58%) of the patients in our cohort were unintentional exposures. The median age of the patients with an intentional exposure was 14.8 years (IQR 12.8–16.2 years), and the median age of the unintentional group was 3.4 years (IQR 2.0–8.3 years). Male patients (73%) were more likely to have an unintentional exposure, and female patients (67%) were more likely to intentionally take clonidine.

Vital Sign Abnormalities

Information on the time to vital sign abnormalities is summarized in Figure 3.

Bradycardia. Thirty-nine patients became bradycardic, with time to onset, nadir, and last occurrence available in 29 (74%), 27 (69%), and 24 (62%) patients, respectively. Bradycardia developed in a minimum of 36 min with a median of 3.5 h (IQR 1.8–8.0 h). There were no new episodes of bradycardia after 17 h. The median time to nadir was 7.3 h (IQR 2.7–9.7 h). Bradycardia resolved in a median of 10.0 h (IQR 7.7–17.4 h) and in 1 patient persisted for 38 h.

Bradypnea. Twenty-seven patients became bradypneic, with time to onset, nadir, and last occurrence available in 18 (67%), 18 (67%), and 17 (63%) patients, respectively. The earliest time to bradypnea was 1 h, with a median of 2.7 h (IQR 1.9–5.2 h). There were no new episodes of bradypnea after 10.2 h. Bradypnea reached a nadir at a median of 3.0 h (IQR 2.3–6.2 h), had resolved at a median of 10.7 h (IQR 5.3–17.5 h), and never lasted longer than 39 h.

Hypotension. Thirty-eight patients became hypotensive, with time to onset, nadir, and last occurrence available in 25 (66%), 25 (66%), and 26 (68%) patients, respectively. Hypotension occurred later than bradycardia and bradypnea, with earliest onset at 1.2 h and a median of 8.4 h (IQR 2.2–13.6 h). The latest time that hypotension presented was 50 h. Hypotension tended to nadir soon after presentation, with a median of 11.3 h (IQR 4.3–22.3 h), and had resolved by a median of 15.5 h (IQR 6.8–24.8 h), with 1 patient experiencing residual hypotension (not requiring vasopressors) past 53 h.

Clinical Effects and Treatment

In terms of clinical effects, 80% of patients had depressed mental status and 37% had miotic pupils. Thirty-nine patients (44%) were admitted to the ICU, 34 (39%) were admitted to the floor, and 15 (17%) were discharged from the ED. Thirty-three patients (38%) received at least one dose of naloxone, and 6 were placed on a naloxone infusion. Of those who received naloxone, 50% had a documented clinical response. The median naloxone dose of those with a documented positive and absent clinical response was 0.1 mg/kg and 0.04 mg/kg ($p = 0.084$), respectively. Twenty-three patients (26%) received activated charcoal. Six patients were intubated; no patients received vasopressors. Of the 6 patients who were intubated, the median age was 3.6 years (IQR 2.4–5.0 years) and the median reported exposure dose was 0.16 mg/kg (IQR 0.10–0.25 mg/kg). Four were intubated at an outside institution prior to transfer. Five of the 6 patients who were intubated received naloxone prior to intubation with a mean dose of 0.09 mg/kg.

Younger patients were more likely to be exposed to someone else's medication (53%), and older patients overwhelmingly (85%) ingested their own medication (Table 1). Younger patients were more likely to develop bradycardia (57% vs 33%) and bradypnea (55% vs 8%), and older patients were more likely to develop hypotension (61% vs. 28%), despite similar estimated exposure doses. In the younger group, the median naloxone dose was 0.1 mg/kg (IQR 0.06–0.2 mg/kg), and 3 patients were started on an infusion. Of the 19 younger patients who received naloxone and had documentation, 10

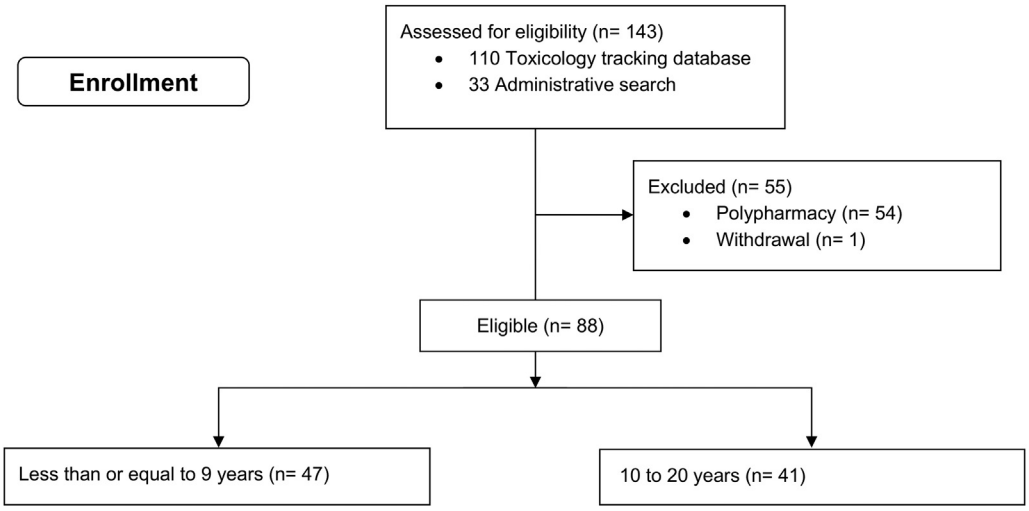

Figure 1. Study enrollment diagram.

(53%) had a positive response. In the older group, the median naloxone dose was 0.03 mg/kg (IQR 0.02–0.05 mg/kg), and 2 patients were given a naloxone infusion. Four of the 9 patients (44%) who received naloxone and had appropriate documentation had a positive response.

DISCUSSION

In our single-center retrospective cohort study of pediatric patients with reported clonidine exposure (unintentional ingestions or intentional overdoses), we found that bradycardia and bradypnea were common in patients ≤9 years, and hypotension was more common in older patients. The vast majority of patients developed depressed mental status. Miosis occurred in approximately 40% of patients. However, despite the high prevalence of vital sign abnormalities and depressed mental status, the need for critical interventions, like intubation or vasopressors, was rare and there were no fatalities.

This study design has advantages and weakness: by utilizing a cohort seen at a single center, we had access to each patient's electronic medical record and, in most

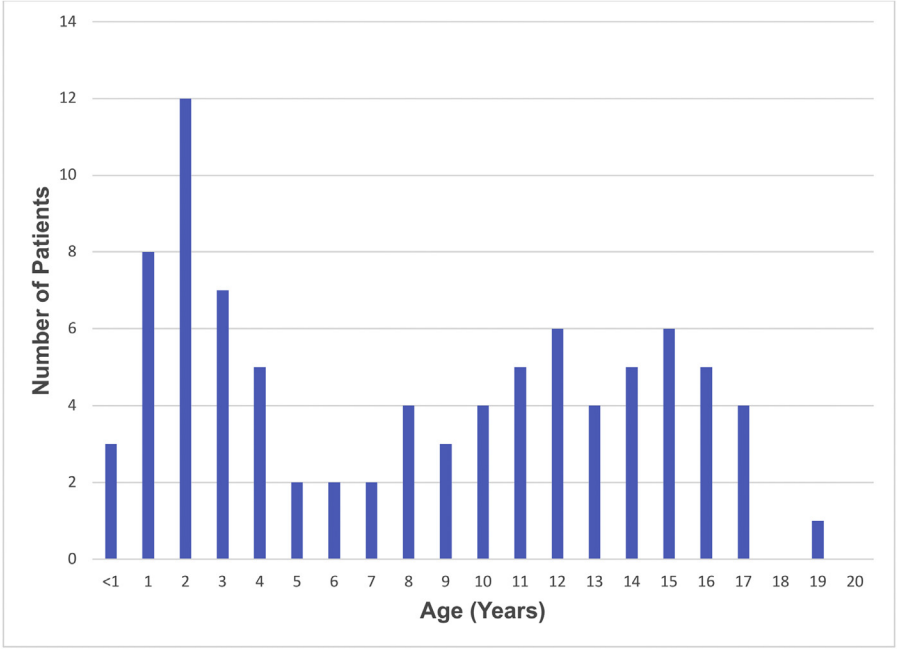

Figure 2. Number of clonidine exposures by child age (years), 2004–2017. A bimodal age distribution is seen with exposures concentrated in the toddler and adolescent age groups.

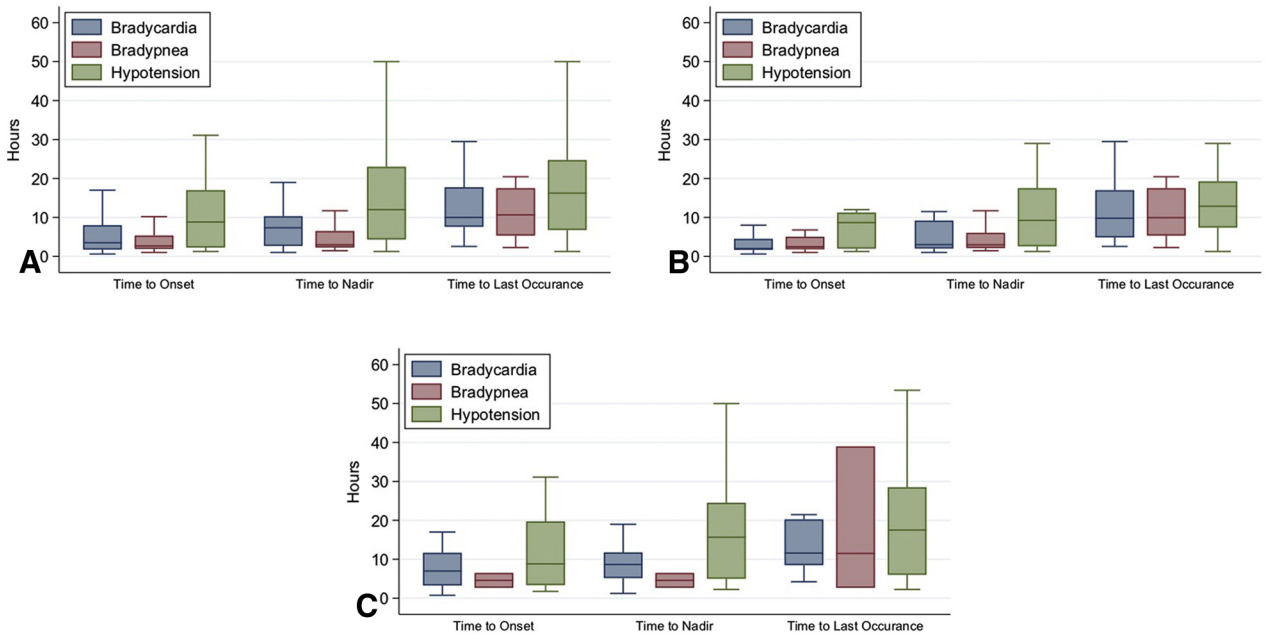

Figure 3. Timing to vital sign abnormalities. Box represents median, 25th percentile, and 75th percentile; whiskers represent adjacent values (1.5 times the absolute value of the difference between the 75th and 25th percentile). (A) Overall. (B) Age 0 to 9 years. (C) Age 10 to 21 years. Bradycardia and bradypnea occur, nadir, and resolve earlier than hypotension across all age groups. Although most patients had onset of vital sign abnormalities before 10 h, approximately 25% of patients had first episode of hypotension after 16 h. However, no patient received vasopressors.

cases, outside hospital documentation. Previous studies that use Poison Control Center databases are limited by cases that were voluntarily reported and by the information provided by the referring hospital (3,5,6,13,18). Key information, including time of exposure, time to onset of vital sign changes, duration of vital sign changes, and interventions, is frequently unavailable. In contrast, we had access to vital signs records, electronic medication administration records (which records the dose and timing of all administered medicines), bedside registered nurse assessment and documentation, and bedside consultative physician assessment and documentation. However, the majority of our patients were transferred to our institution, likely for subspecialist evaluation. This creates a selection bias for sicker patients and limits generalizability to all emergency settings.

One of the novel pieces of information that we report is more comprehensive data on time to onset, nadir, and resolution of various vital sign abnormalities commonly seen in acute toxic clonidine exposure. This information is key in assisting clinicians in deciding on disposition for patients with acute toxic clonidine exposure and for predicting hospital length of stay. Previous single-center studies have reported on vital sign abnormalities associated with clonidine exposures, but only discuss whether abnormalities occurred at presentation or during hospitalization, or present the mean time to appearance of "symptoms" (2,4,6,19). Fiser et al. provided a detailed account of 11 patients severely poisoned with clonidine, all of whom were admitted to the ICU, which may limit generalizability to the ED (15).

Nearly half of patients in our cohort developed bradycardia, which is in line with previously published rates of bradycardia ranging from 10% to 90% (5,20,21). Rates vary across studies, almost certainly due to differing patient populations and exposure amounts. Our study population experienced bradypnea at a rate of 32%, which is higher than these same studies (5,20,21). This difference is for two likely reasons: the first is that we used age-based percentile cutoffs for bradypnea that were not utilized in other studies (17). The second is that, due to the high number of patients referred to our institution, our patient population is likely more sick than those described in other population studies using poison center data. Despite these discrepancies, rates of intubation and mechanical ventilation remained low, suggesting that progression to respiratory failure is rare, despite relatively high rates of respiratory depression.

Our cohort developed hypotension at a rate of 44%, which is higher than described in the literature (4%–50%) (2–6,13,15,19–24). Again, this is likely due to a sicker patient population and because we defined hypotension as < 90 mm Hg systolic in adolescents when other studies used a cutoff of 80 mm Hg. Despite the higher rate of hypotension, no one received vasopressors.

Table 1. Age-Related Differences Between Younger (≤9 Years) and Older (10 to 20 Years) Patients

Characteristic	Patient Age		*p* Value
	≤9 Years (n = 47)	10–20 Years (n = 41)	
Age, y, median (IQR)	3.1 (2.0–4.9)	14.1 (12.6–15.8)	—
Sex, male, n (%)	34 (72)	16 (39)	—
Medication source, n (%)			—
Self	22 (47)	35 (85)	
Sibling	10 (21)	2 (5)	
Parent	10 (21)	0 (0)	
Other	5 (11)	1 (2)*	
Unknown	0 (0)	3 (7)	
Dose, mg/kg, median (IQR)	0.03 (0.01–0.11)	0.02 (0.01–0.05)	0.479
Intentional, n (%)	3 (7)†	30 (75)‡	< 0.001
Vital sign abnormality, n (%)			
Bradycardia	26 (57)§	13 (33)‡	0.026
Bradypnea	24 (55)‖	3 (8)‡	< 0.001
Hypotension	13 (28)§	25 (61)¶	0.002
Clinical effects, n (%)			
Depressed mental status	37 (79)#	33 (83)‡	0.658
Miosis	19 (42)#	13 (32)¶	0.314
Interventions, n (%)			
Naloxone	22 (47)#	11 (27)¶	0.053
Activated charcoal	10 (21)#	13 (32)¶	0.267
Intubation	6 (13)#	0 (0)¶	0.028
ICU admission	25 (53)#	14 (34)¶	0.148

ICU = intensive care unit; IQR = interquartile range.
* One patient was exposed to their sibling's medication and their medication.
† n = 45.
‡ n = 40.
§ n = 46.
‖ n = 44.
¶ n = 41.
# n = 47.

These data suggest that clinical observation for at least 4 to 8 h is reasonable to surveil for onset of vital sign abnormalities. If present, hospitalization for observation for cardiac monitoring is likely warranted, as vital sign changes can persist for the better part of a full day.

Our study included 88 patients younger than 21 years. The size is comparable with the cohort described by Nichols et al. in 1997, and is one of the largest single-center cohorts described in the literature (4). In more than one-third of our patient cohort, exposure to clonidine was viewed as intentional (knowingly taking extra doses, intent to harm). Female patients and patients older than 10 years were more likely to have an intentional exposure. Most patients (75%) in our cohort were referred to our institution for tertiary level care, likely selecting for a more symptomatic patient population. Although many other evaluated studies did not comment on specific inter-hospital transfer, studies based on national poison center data note hospital evaluation rates of 65% to 86% (3,5,18). This discrepancy suggests that their cohorts are likely less acutely ill, and rates of described clinical consequence of clonidine exposure could be understated compared with the population an emergency physician or toxicologist might see in an acute care setting.

Although older studies found that the source of toxic clonidine exposure was often a grandparent who had received a prescription, our data are consistent with more recent trends that exposures now are frequently a child's own medicine or from another sibling in the same home (2,3,15,18,19,21). This trend could be partially explained by the national increase of prescription clonidine to pediatric populations, and presents a risk to both patients with behavioral health disorders and their siblings (5,9,25,26). In our study, patients who had an intentional clonidine exposure were exposed to their own medicine in > 90% of cases, suggesting risk when considering prescribing clonidine for behavioral dysregulation to an older child with concomitant mood disorder.

The clinical findings of miosis, depressed mental status, and respiratory depression mirror the opioid toxidrome. When compared with a cohort of pediatric patients between 6 months and 7 years exposed to buprenorphine, there were comparable rates of depressed mental status (clonidine 80%, buprenorphine 80%), but respiratory depression (clonidine 32%, buprenorphine 83%) and miosis (clonidine 37%, buprenorphine 77%) occurred less frequently (27).

Substantial literature has debated the utility of naloxone as a reversal agent in acute toxic clonidine exposure. Hypothesized mechanisms of action center around reversing clonidine's effect at the endogenous *mu* receptors (either indirectly through release of endogenous opioids or directly). Data to date have been mixed, with the most compelling data in favor of naloxone use published in a study by Seger and Loden (6). In that study, 35 of 40 patients exposed to clonidine only experienced mental status improvement after high-dose naloxone (which the authors defined as > 10 mg). In our cohort, 33 patients (38%) received 1 or more doses of naloxone to attempt symptom reversal. Of those, 14 (50%) had a documented clinical response. The administered dose was much lower in our cohort (median dose 0.1 mg/kg) compared with the study by Seger and Loden, which likely explains the differing response rates. The retrospective nature of this study limits our ability to draw meaningful conclusions on the utility of naloxone in pediatric clonidine exposures. However, half of our cohort had a documented response to naloxone and, given the wide safety margin, a trial of high-dose naloxone (10 mg) to prevent intubation should be performed in non–opioid-dependent patients (6).

Limitations

Our study has several limitations. Information documented in the medical record is often incomplete and we do not have access to comprehensive records from outside institutions that initially cared for these patients prior to transfer. Although records from outside institutions that accompanied the patient were included in analysis, invariably some data are missing. Our analysis of exposure dose is limited by patient and family recall. There was also no testing done to confirm presence or degree of true clonidine exposure absent other polypharmacy exposures. Due to the tertiary care referral nature of our hospital, our reported cohort of patients likely represents a sicker subpopulation of patients exposed to clonidine compared with patients reported to national poison control centers. These limitations may reduce the external generalizability outside of ED settings.

CONCLUSIONS

In summary, we found that single-agent exposure to clonidine frequently caused depressed mental status, bradycardia, bradypnea, and hypotension. Vital sign changes generally nadir in the first 8 h after exposure, which may inform ED observation time. Although nearly half of all patients were admitted to an ICU setting, patients rarely required critical interventions such as endotracheal intubation or vasopressor support. Given the high rate of patients being exposed to their own medications, emergency physicians and pediatricians need to counsel parents on the importance of safe medication storage and assess for risk factors of adolescent self-harm at health care visits.

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ARTICLE SUMMARY

1. Why is this topic important?

Pediatric clonidine poisonings are common. Previous poison center–based studies suggest that pediatric clonidine ingestions frequently lead to altered mental status, bradycardia, hypotension, and bradypnea. However, detailed clinical information from direct bedside consultations, including time to vital sign abnormalities and treatment options, are frequently lacking.

2. What does this study attempt to show?

With the goal of further informing front-line clinicians who care for these patients, the objective of our study was to characterize the clinical course of a cohort of children who presented to a large pediatric tertiary care center with report of clonidine exposure (unintentional ingestions or intentional overdoses).

3. What are the key findings?

In our cohort of pediatric patients with report of clonidine exposure, we found that bradycardia and bradypnea were common in patients aged ≤ 9 years and hypotension was more common in older patients. Eighty-nine percent of patients with intentional exposures ingested their own medication.

4. How is patient care impacted?

This study provides detailed information on the time to vital sign abnormalities and supports an observation period of 4 to 8 h for pediatric clonidine ingestions. High-dose (10 mg) naloxone should be utilized in severe poisonings or prior to intubation. Given the high percentage of patients with intentional ingestions of their own medication, families and providers need to have discussions about safe medication storage in high-risk patients.