Pediatric clonidine and guanfacine poisoning: a single-center retrospective review

Kevin Baumgartner and Michael Mullins
Department of Emergency Medicine, Division of Medical Toxicology, Washington University School of Medicine, St. Louis, MO, USA

ABSTRACT
Clonidine and guanfacine are centrally acting sympatholytics (CAS). Poisoning with these agents is common in children, and management of this poisoning is controversial. We sought to characterize our experience with pediatric CAS poisonings. We used an internal database to identify patients with CAS poisoning seen by the medical toxicology service at our children’s hospital from January 2001 through November 2019. We performed a retrospective chart review. We identified 56 patients with clonidine poisoning and 19 patients with guanfacine poisoning. Sixty-six percent of patients with clonidine poisoning underwent any medical intervention, as did 32% of patients with guanfacine poisoning. The most common interventions were fluids and naloxone. Endotracheal intubation was uncommon. The median hospital length of stay was one day and the median ICU length of stay was one day. Two patients died; one co-ingested a large amount of bupropion and one aspirated charcoal, leading to pneumonitis and anoxic brain injury. No patient with isolated CAS poisoning died. In this retrospective single-center review, pediatric patients tolerated CAS poisoning well. CAS poisoning did not directly result in death. Most pediatric patients with CAS poisoning had short hospital lengths of stay and did not undergo critical care interventions.

KEYWORDS
clonidine; guanfacine; sympatholytic; pediatrics

Introduction
Clonidine and guanfacine are centrally acting sympatholytics (CAS) which are prescribed for multiple indications for both pediatric and adult patients [1]. Clonidine is an antihypertensive [2] with both oral and transdermal [3] formulations, and has also been used in the symptomatic treatment of opioid withdrawal [4]. Both clonidine and guanfacine are frequently prescribed to pediatric patients with attention deficit hyperactivity disorder and other neurobehavioral conditions [5]. Their use in these disorders may help control irritability and reduce hyperactivity and problematic behaviors.
CAS poisoning is quite common in children [6], with nearly 4,000 pediatric exposures reported to the National Poison Data System (NPDS) in 2018 [7]. Young children frequently engage in exploratory ingestion of their own medication or a sibling’s medication. Older children and adolescents may intentionally ingest large quantities of these medications in attempts at suicide or self-harm. Patients prescribed CAS may accidentally take or be given incorrect doses.
CAS poisoning produces a sympatholytic toxidrome, consisting of depressed mental status, miosis, bradycardia, and occasionally mild hypotension [8]. There is a lack of consensus among experts regarding the management of poisoning by clonidine, guanfacine, and related drugs. Multiple issues in management are controversial, including the need for endotracheal intubation and the role of naloxone as a possible antidote [9].
We thus sought to characterize our experience with pediatric CAS poisoning, with a specific focus on the rate of medical interventions, level of hospital care provided, and length of stay.

Materials and methods
The Section of Medical Toxicology maintains an internal database of all patients seen by our consulting service from January 2001 through the present day.
This database includes patients’ demographic information, date of service, and toxicologic diagnosis; it does not include any other clinical information such as vital signs, therapeutic interventions, or length of stay. We queried this database in November 2019 for the terms “clonidine” and “guanfacine.” We included patients with a diagnosis including “clonidine” or “guanfacine” who were seen at our affiliated children’s hospital through November 2019. We excluded patients seen at our affiliated adult hospital.

Both investigators designed a standardized data collection tool to extract relevant clinical and demographic data, including but not limited to the patient's age, presence of any reported co-ingestants, intention of overdose, highest level of care provided, intensive care unit (ICU) and hospital length of stay, medical interventions, and mortality. “Medical interventions” were defined as administration of any medication, administration of intravenous (IV) fluids other than maintenance fluids, endotracheal intubation (ETI), or any other invasive procedure. After identifying patients to be included in the study in our internal database, a single investigator reviewed the electronic medical record (EMR) to extract clinical and demographic data using the aforementioned data collection tool. Data were extracted from physician notes, nursing notes, medical administration records, and flow-sheets. When possible, we noted the clinical context in which medical interventions took place (ED, general ward, or ICU) and the doses of any medications administered. We recorded all medical interventions, including medical interventions performed before our service was consulted and medical interventions which we did not recommend. We recorded descriptive statistics using Microsoft Excel.

Our institution switched EMR software in July 2018; archived records for visits occurring before July 2018 are still available, but these data are frequently incomplete, especially regarding medication doses. Many patients included in the study were transferred to our children’s hospital from outside facilities. Data regarding their treatment at outside facilities were extracted from available physician notes, but key elements such as medication doses and insight into medical decision making were often lacking.

The study was reviewed and approved by the university Institutional Review Board.

**Results**

Fifty-six patients with clonidine poisoning met inclusion criteria, as did 19 patients with guanfacine poisoning. Demographics, including age, sex, single-substance or polysubstance ingestion, and intent of ingestion, appear in Table 1. Eight patients with clonidine poisoning (14%) and 8 patients with guanfacine poisoning (42%) had polysubstance ingestions by history. A plurality of poisonings (48%) was due to exploratory ingestions by young children, but a substantial minority (27%) was due to suicide attempts by older children and adolescents.

Outcomes and interventions for patients with clonidine poisoning appear in Table 2. All 56 patients with clonidine poisoning were admitted to the hospital; 37 (66%) were admitted to an intensive care unit (ICU). The median hospital length of stay was one day (range 1–9 days, 73% 1 day) and the median ICU length of stay was one day (range 1–4 days, 89% 1 day). No patient initially admitted to a general ward moved to the ICU after admission. Only 4 patients (7%) underwent any medical intervention after admission to the hospital. The most common medical interventions were naloxone and IV fluid resuscitation.

### Table 1. Demographics of pediatric patients with clonidine or guanfacine poisoning.

| Variable                  | Clonidine [n (%)] | Guanfacine [n (%)] |
|---------------------------|-------------------|--------------------|
| Age                       |                   |                    |
| <2 years                  | 11 (20)           | 1 (5)              |
| 2–6 years                 | 27 (48)           | 5 (26)             |
| 7–12 years                | 7 (13)            | 3 (16)             |
| 13–18 years               | 11 (20)           | 10 (53)            |
| Sex                       |                   |                    |
| Male                      | 27 (48)           | 11 (58)            |
| Female                    | 29 (52)           | 8 (42)             |
| Type of ingestion         |                   |                    |
| Single substance          | 47 (84)           | 11 (58)            |
| Polysubstance             | 9 (16)            | 8 (42)             |
| Intent of ingestion       |                   |                    |
| Exploratory               | 31 (55)           | 5 (26)             |
| Therapeutic misadventure  | 3 (5)             | 1 (5)              |
| Suicidal                  | 12 (21)           | 8 (42)             |
| Intentional non-suicidal  | 1 (2)             | 5 (26)             |
| Unclear                   | 9 (16)            | 0 (0)              |

### Table 2. Medical outcomes of pediatric patients with clonidine or guanfacine poisoning.

| Outcome                               | Clonidine [n (%)] | Guanfacine [n (%)] |
|---------------------------------------|-------------------|--------------------|
| ICU admission (any)                    | 37 (66)           | 6 (32)             |
| ICU admission >1 day                   | 3 (5)             | 2 (11)             |
| Hospital admission (any)               | 56 (100)          | 18 (95)            |
| Hospital admission >1 day             | 15 (27)           | 8 (42)             |
| Any intervention                       | 37 (66)           | 6 (32)             |
| Any intervention after admission       | 3 (5)             | 1 (5)              |
| Activated charcoal                     | 4 (7)             | 0 (0)              |
| Intravenous fluid resuscitation       | 19 (34)           | 4 (21)             |
| Naloxone                               | 24 (43)           | 1 (5)              |
| Atropine                               | 7 (13)            | 1 (5)              |
| Vasopressors and/or inotropes          | 1 (2)             | 1 (5)              |
| Endotracheal intubation                | 6 (11)            | 1 (5)              |
| Death                                  | 1 (2)             | 1 (5)              |
Outcomes and interventions for patients with guanfacine poisoning appear in Table 2. Eighteen patients (95%) with guanfacine poisoning were admitted to the hospital; one patient was discharged home after evaluation by the Toxicology service in the ED. Six patients (32%) were admitted to an ICU. The median hospital length of stay was 1 day (range 1–3 days, 56% 1 day) and the median ICU length of stay was one day (range 1–2 days, 67% 1 day). No patient initially admitted to the floor was moved to the ICU after admission. Only one patient underwent any medical intervention after admission to the hospital. The most common medical intervention was IV fluid resuscitation.

Table 3 summarizes the 25 cases (33%) in which naloxone was used. The total bolus dose of naloxone administered was available in 20 cases. Nine patients received less than 2 mg of naloxone, and no patient received more than 4 mg of naloxone, with the possible exception of one patient who received a 2 mg bolus followed by an infusion (rate not reported). The mean dose of naloxone administered was 0.11 mg/kg, with a median dose of 0.08 mg/kg. Naloxone infusions were used in 4 cases (5%); the rate of the naloxone infusion was available in three cases and ranged from 0.24–0.6 mg/kg/hr.

There were two deaths in the study population. One patient with clonidine poisoning aspirated AC, which resulted in chemical pneumonitis leading to severe hypoxic brain injury and cardiac arrest. Activated charcoal was administered and multiple attempts at endotracheal intubation were made at an outside hospital, prior to Toxicology involvement. One patient with guanfacine poisoning co-ingested a large amount of bupropion, and suffered recurrent seizures and refractory cardiovascular collapse, consistent with bupropion poisoning.

Excluding the two unusual patients described above, only two patients received any medical intervention after hospital admission. We reviewed these patients’ charts in detail to characterize their post-admission medical interventions. One 23 month old patient received naloxone after admission to the ICU; medical records are very limited and the indication, dose, timing, and clinical response could not be determined. One 3 year old patient received two doses of atropine after admission to the ICU and placed on scheduled glycopyrrolate due to bradycardia. The amount of atropine and glycopyrrolate administered was not recorded. His lowest recorded heart rate was 50 beats per minute, and he was never hypotensive for age. The same patient also received multiple boluses of IV fluids, for a total of 45 mL/kg, after admission to the ICU. The patient had a normal or acceptable mental status throughout his ICU admission.

We reviewed the charts of patients with an ICU length of stay longer than one day in detail. Five patients remained in the ICU for longer than one day. Two of these were the unusual patients described above who died. One 2 year old patient who ingested clonidine and clonazepam remained in the ICU for 2 days. The reason for the second ICU day is not clear; the ICU attending documented on day 1 that he intended to transfer her to the general pediatrics floor. One 2 year old patient who ingested clonidine remained in the ICU for 2 days due to the need for respiratory support for a coincident human metapneumovirus infection. One 4 year old patient who ingested guanfacine remained in the ICU for 2 days due to concern for ongoing bradycardia. She underwent no therapeutic interventions, suffered no complications, and was discharged directly from the ICU on hospital day 2.

We reviewed the charts of all patients who were treated with naloxone, vasopressors, atropine, and/or ETI (excluding the two unusual patients who died) to assess their vital signs and response to interventions. Only three patients received a trial of naloxone prior to intubation; naloxone doses were quite low in these patients (1.3 mg, 2.4 mg, and 0.4 mg). When vital sign data were available before and after interventions, atropine generally raised the heart rate as expected, but naloxone did not have any appreciable effect on heart rate or blood pressure. Four patients had a documented blood pressure that was hypotensive for age at any time. The hypotension was mild (median deviation from threshold value of the systolic blood pressure was 4.5 mm Hg, range 1–9 mm Hg). None of the mildly hypotensive patients received vasopressors or ETI.

Discussion

In this retrospective study conducted at a single pediatric hospital with a medical toxicology consult...
service, patients with CAS poisoning had excellent outcomes with no morbidity or mortality directly attributable to CAS ingestion. Our patients did not experience end-organ damage or serious clinical morbidity or mortality due to CAS poisoning. These results are consistent with those reported by Toce and colleagues in their recently published retrospective cohort study of pediatric clonidine exposure [10].

The treating toxicologists concluded that the two deaths identified were not directly related to CAS poisoning. One patient with clonidine poisoning developed iatrogenic charcoal pneumonitis, which led to hypoxemic respiratory failure, cardiac arrest, and hypoxic-ischemic brain injury. Activated charcoal was administered and multiple attempts at endotracheal intubation were made at an outside hospital, prior to Toxicology involvement. One patient with guanfacine poisoning also ingested a large amount of bupropion, and his symptoms and clinical course, with recurrent seizures and refractory cardiovascular collapse, were consistent with severe bupropion poisoning. This case, in which guanfacine poisoning likely obscured the early symptoms of bupropion toxicity, has been reported in detail elsewhere [11]. The remainder of our patients survived to hospital discharge with no clinically apparent sequelae of their ingestions.

Advanced therapeutic interventions such as ETI, vasopressors, and inotropes were infrequently used in this series. When the two patients listed above who died are excluded, no patients were treated with vasopressors or inotropes, and only five patients underwent ETI. All patients who underwent ETI were intubated prior to assessment by our service.

The retrospective nature of our study and the limitations of electronic medical records make it difficult to determine which patients, if any, truly required or benefited from ETI, or any other medical intervention reported here. The fact that an intervention was performed does not imply that it was required or necessary, and it is essentially impossible to prove that the patient would not have had a good outcome if the intervention was not performed. This problem is especially relevant in pediatric CAS poisoning, which, in our experience, can cause striking vital sign abnormalities or changes in mental status that, in other clinical contexts, would necessitate aggressive medical intervention.

Other authors have questioned the utility of ETI in patients with clonidine poisoning [9]. A review of ten years of NPDS data by Wang and colleagues [8] showed a very low rate of intubation (only 2% of patients) in pediatric CAS poisoning. A large retrospective review of pediatric patients admitted to an ICU by Even and colleagues found that only one of 35 (2.9%) patients with CAS poisoning was intubated for consequences of CAS poisoning [12]. An Australian poison center review of 802 pediatric CAS exposures found only two intubations [13]. It is striking that at least one or two of the patients in our study who were intubated successfully self-extubated after a brief period in the ICU. ETI in pediatric patients is not a benign procedure. One review of emergency airway registry data found a 17% adverse event rate [14]. ETI should be performed after careful preparation and with a well-considered medical indication.

One outcome of interest was the performance of any medical intervention after hospital admission, which has important implications for the required level of hospital care. Only four patients underwent any medical intervention after admission. After the two unusual patients who died were excluded, only two patients underwent any medical intervention after admission. Based on the available clinical information reported above, it is unclear that these patients’ vital signs and symptoms truly warranted repeated doses of antimuscarinic agents or aggressive fluid resuscitation.

These data suggest that patients with CAS poisoning typically do not require medical interventions after hospital admission. Most patients in our study who were admitted to the ICU underwent no medical intervention after ICU admission. No patient initially admitted to the general ward required transfer to the ICU, and the vast majority of ICU admissions lasted no longer than one day. In the few cases of ICU admission for longer than one day, the prolonged ICU stay was generally unrelated to the direct effects of CAS poisoning.

Naloxone has been proposed as a possible antidote for central nervous system depression in CAS poisoning. Our study did not yield much high-quality information about the efficacy or effects of naloxone. Authors who support administration of naloxone in clonidine poisoning typically suggest much higher doses, typically 10 mg [9]. Naloxone was administered in low and likely ineffective doses for the treatment of pediatric CAS poisoning in our case series (Table 3).

Limitations

The main limitation of our study is its reliance on retrospective medical record review of a relatively small sample in a single center. As in all retrospective record reviews, the quality of available data was not uniform and was sometimes difficult to interpret. As
noted in the methods, our institution changed EMR software in 2018, and all records predating July 2018 are available only in a limited legacy repository system. The nature of the available records prevented us from accessing information regarding specific medication doses and granular vital signs and also significantly limited our ability to understand medical decision making. Additionally, many patients included in the study were initially treated at outside hospitals; these records were not available for review, obliging us to rely on limited second-hand summaries of events at outside hospitals in admission and consult notes.

Additionally, the presence of CAS and/or co-ingestants was not confirmed by specific drug testing, requiring us to rely on patient histories and identification of relevant toxidromes on physical examination. This does, however, reflect real-world clinical practice; specific drug concentrations are rarely available in the acute care setting, and serum or urine drug testing rarely changes acute toxicologic management [15, 16].

Finally, the management of patients with CAS poisoning was not uniform during the duration of our study. In many cases, initial management was directed by emergency physicians (either at our hospital or an outside hospital) or by critical care physicians without Toxicology involvement. Toxicology was frequently consulted after the patient’s initial disposition and management had been determined. It is highly likely, although not demonstrable from the data, that our service would have made different management decisions if involved early.

Conclusion
In conclusion, in our single-center retrospective study, pediatric patients tolerated clonidine and guanfacine poisoning well. Clonidine or guanfacine poisoning did not directly cause death in our series. It may be reasonable to admit pediatric patients with clonidine and guanfacine poisoning to a general pediatric ward after a period of observation in the ED to ensure that no acute decompensation requiring critical management takes place. Most pediatric patients with clonidine and guanfacine poisoning have very short hospital lengths of stay and do not undergo critical care interventions.

Disclosure statement
This study received no funding and the authors have no conflicts of interest to disclose.

References
[1] Giovannitti JA, Thomis SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015;62(1):31–39.
[2] Garrett BN, Kaplan NM. Clonidine in the treatment of hypertension. J Cardiovasc Pharmacol. 1980;2(Suppl 1):S61–S71.
[3] Langley MS, Heel RC. Transdermal clonidine. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. Drugs. 1988;35(2):123–142.
[4] Gowing L, Farrell M, Ali R. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2016;(5):CD002024.
[5] Pringsheim T, Hirsch L, Gardner D, et al. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part I: psychostimulants, alpha-2 agonists, and atomoxetine. Can J Psychiatry. 2015;60(2):42–51.
[6] Amico K, Cabrera R, Ganti L. Outcomes following clonidine ingestions in children: an analysis of poison control center data. Int J Emerg Med. 2019;12(1):14.
[7] Gummin DD, Mowry JB, Spyker DA, et al. 2018 annual report of the American Association of Poison Control Centers’ national poison data system (NPDS): 36th annual report. Clin Toxicol (Phila). 2019;57(12):1220–1413.
[8] Wang GS, Le Lait M-C, Heard K. Unintentional pediatric exposures to central alpha-2 agonists reported to the National Poison Data System. J Pediatr. 2014;164(1):149–152.
[9] Seger DL, Loden JK. Naloxone reversal of clonidine toxicity: dose, dose, dose. Clin Toxicol (Phila). 2018;56(10):873–879.
[10] Toce MS, Freiman E, O’Donnell KA, et al. Clinical effects of pediatric clonidine exposure: a retrospective cohort study at a single tertiary care center. J Emerg Med. 2020; Online ahead of print.
[11] Liss DB, Phillips TM, Pizon AF, et al. Delayed seizures in bupropion overdose with concomitant ingestion of alpha-2 agonist: a case report. Toxicol Comm. 2017;1(1):15–17.
[12] Even KM, Armsby CC, Bateman ST. Poisonings requiring admission to the pediatric intensive care unit: a 5-year review. Clin Toxicol (Phila). 2014;52(5):519–524.
[13] Cairns R, Brown JA, Buckley NA. Clonidine exposures in children under 6 (2004–2017): a retrospective study. Arch Dis Child. 2019;104(3):287–291.
[14] Sagarin MJ, Chiang V, Sakles JC, et al. Rapid sequence intubation for pediatric emergency airway management. Pediatr Emerg Care. 2002;18(6):417–423.
[15] Tenenbein M. Do you really need that emergency drug screen? Clin Toxicol (Phila). 2009;47(4):286–291.
[16] Pohjola-Sintonen S, Kivisto KT, Vuori E, et al. Identification of drugs ingested in acute poisoning: correlation of patient history with drug analyses. Ther Drug Monit. 2000;22(6):749–752.