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CLINICAL RESEARCH

Adult clonidine overdose: prolonged bradycardia and central nervous system depression, but not severe toxicity

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ABSTRACT

Context: There are limited reports of adult clonidine overdose. We aimed to describe the clinical effects and treatment of clonidine overdose in adults.

Methods: This was a retrospective review of a prospective cohort of poisoned patients who took clonidine overdoses (>200 µg). Demographic information, clinical effects, treatment, complications (central nervous system and cardiovascular effects) and length of stay (LOS) were extracted from a clinical database or medical records.

Results: From 133 admissions for clonidine poisoning (1988–2015), no medical record was available in 14 and 11 took staggered ingestions. Of 108 acute clonidine overdoses (median age 27 years; 14–65 years; 68 females), 40 were clonidine alone ingestions and 68 were clonidine with co-ingestants. Median dose taken was 2100 µg (interquartile range [IQR]: 400–15,000 µg). Median LOS was 21 h (IQR: 14–35 h) and there were no deaths. Glasgow coma score [GCS] <15 occurred in 73/108 (68%), and more patients taking co-ingestants (8/68; 12%) had coma (GCS <9) compared to clonidine alone (2/40; 5%). Miosis occurred in 31/108 (29%) cases. Median minimum HR was 48 bpm (IQR: 40–57 bpm), similar between clonidine alone and co-ingestant overdoses. There was a significant association between dose and minimum HR for clonidine alone overdoses ($p = 0.02$). 82/108 (76%) had bradycardia, median onset 2.5 h post-ingestion (IQR: 1.7–5.5 h) and median duration 20 h (2.5–83 h), similar for clonidine alone and co-ingestant overdoses. There were no arrhythmias. Three patients ingesting 8000–12,000 µg developed early hypertension. Median minimum systolic BP was 96 mmHg (IQR: 90–105 mmHg) and hypotension occurred in 26/108 (24%). 12/108 patients were intubated, but only 2 were clonidine alone cases. Treatments included activated charcoal (24), atropine (8) and naloxone (23). The median total naloxone dose was 2 mg (IQR: 1.2–2.4 mg), but only one patient given naloxone was documented to respond with partial improvement in GCS.

Discussion: Clonidine causes persistent but not life-threatening clinical effects. Most patients develop mild central nervous system depression and bradycardia. Naloxone was not associated with improved outcomes.

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Clonidine; poisoning; overdose; bradycardia; imidazoline

Introduction

Clonidine has been available since the 1970's, initially for the treatment of hypertension, then opioid and alcohol dependence, sedation and more recently for the treatment of attention deficit disorder in children [1,2]. Clonidine is a 2-imidazoline derivative that was discovered in the course of testing it for use as a topical nasal decongestant. It is a centrally acting alpha-2 adrenoreceptor agonist and an imidazoline receptor agonist, and these actions result in its central nervous system (CNS) depression and cardiovascular effects [1].

Clonidine overdose is characterized by CNS depression, bradycardia and miosis, and can mimic opioid poisoning [1,3]. Other clinical effects include early hypertension, followed by hypotension, hypothermia and respiratory depression [1,2,4–8]. Clonidine overdoses are uncommon, and the

toxicodromic triad of CNS depression, bradycardia and hypotension can often appear serious. In addition, the duration of some of the clinical effects may be prolonged, particularly the bradycardia. Case reports and reviews suggest clonidine may result in severe toxicity with ingestions of small amounts resulting in significant CNS depression and cardiovascular effects [1,7,9].

Despite numerous case reports and series of paediatric clonidine ingestions, there are few reports of poisoning in adults [9–11], and even fewer in the last 20 years since the widespread use of clonidine in addiction medicine. A lack of reported cases in adults and concerns about the potential severity of clonidine overdose has sometimes resulted in over-treatment, including both level of monitoring and use of antidotes in the authors' experience. It remains unclear whether the CNS depression and bradycardia are always of sufficient severity to require interventions with either

antidotes or intubation and ventilation. For this reason further information on the time course and severity of adult clonidine ingestions is required.

A number of antidotes have been used for the treatment of clonidine overdose, including naloxone and atropine with variable success. There continues to be controversy over the role of naloxone and whether it reverses coma or influences cardiovascular effects [3]. Atropine is often used to treat the bradycardia but again there is limited evidence to decide if this is required, considering the short duration of action of atropine compared to clonidine. It is important to determine whether specific treatments are beneficial in clonidine poisoning, or whether supportive care alone is sufficient [12].

This study aimed to determine the severity and duration of clinical effects resulting from clonidine overdose in adults. In addition we report the effect of various treatments in clonidine poisoning to attempt to improve our understanding of different interventions.

Methods

Study design and setting

We undertook a retrospective observational study of adult clonidine overdoses admitted to an inpatient toxicology unit. The toxicology unit admits all adult (>15 years age) poisoning and overdose presentations to the emergency department from a population of over 500,000 people. All admissions to the unit have demographic and clinical information collected using a standardized data collection form, which is part of the emergency department assessment. Further information on complications, outcomes and treatment is collected throughout the admission, and all cases are reviewed and additional information obtained from the admitting clinical toxicologist. Trained research assistants enter all the data into a relational database within a week of the presentation to hospital. Toxicology patients are seen daily by the toxicology unit and treatment is according to the attending clinical toxicologist. The use of the database and patient medical records for research has been granted by the Area Health Service Human Research Ethics Committee.

Patients

The toxicology database was searched from January 1987 to September 2015 for all adult (>15 years) clonidine overdose or poisoning admissions to the toxicology unit. Ingestion of clonidine was based on the history from the patient, collateral history from family and friends, and any information recorded by ambulance or emergency services. Overdoses were included with and without coingestants. Ingestions <200 µg were excluded. Staggered ingestions were included but reported separately to acute overdoses.

Data collection

All data for clonidine overdoses were extracted from the toxicology database. Medical records were reviewed for missing

data and for information on duration of the bradycardia and hypotension, and response to antidote treatment. Data extracted included: demographic information (sex, age), ingestion details (dose, time of ingestion, acute or staggered ingestion, and coingestants), medication history, clinical observations (heart rate [HR] – minimum, onset and duration of bradycardia; blood pressure [BP] – maximum, minimum and duration of hypotension; arrhythmias; Glasgow coma score [GCS]; miosis; temperature – minimum), treatment (charcoal, admission to intensive care unit [ICU]; intubation/mechanical ventilation; and antidotes – atropine, naloxone and inotropes) and length of stay (LOS). For each parameter the most extreme appropriate measurement (maximum or minimum) was recorded from the observations.

Outcomes

Pre-defined outcomes included: bradycardia (HR <60 beats per minute [bpm]), hypotension (systolic BP <90mmHg), hypertension (systolic BP >180mmHg), coma (GCS <9), hypothermia (temperature <35 °C), arrhythmia and death. The duration of bradycardia and hypotension was recorded from the time of onset (or first recording) until resolution or discharge. The administration of antidotes and reported response to antidotes was recorded as a treatment outcome.

Analysis

Dichotomous outcomes/variables were reported with 95% confidence intervals (CI) which were calculated using Wilson's procedure and continuity correction. Continuous variables were reported as medians, interquartile ranges (IQR) and ranges where appropriate. Linear regression of minimum HR, minimum BP and minimum GCS versus dose was used to determine if there were any associations. All statistical analysis was undertaken in Graphpad Prism, version 6.05 for Windows (GraphPad Software, La Jolla, CA; www.graphpad.com).

Results

There were 133 admissions for clonidine overdose or poisoning between January 1988 and September 2015. Medical records were not available for 14 cases and 11 took staggered ingestions, leaving 108 acute ingestions. In 40/108, clonidine was ingested alone. In the remaining 68 there were one to five co-ingestants. The commonest co-ingestants were benzodiazepines, antipsychotics, opioids, anticonvulsants and alcohol (Supplementary Table 1). Table 1 compares cases with clonidine alone to those with co-ingestants. Sixty-eight of the 108 (63%) were female, and the median age of patients was 27 years (range: 14 to 65 years). The source of the medication was the patient's in 78 cases, someone else's medication in 24 cases (children [12], other family member [6], other person [6]), and the source was unknown in six cases. The median dose taken was 2100 µg (400–15,000 µg) which did not differ between clonidine alone cases and those with coingestants. The median length of stay was 21 h

Table 1. Demographic information, clinical effects, outcomes and treatments for clonidine overdoses comparing clonidine alone to clonidine with coingestant overdoses.

Clinical effect	Alone (40)	%	Coingestant (68)	%
Female	23	58%	45	66%
Age, years; Median (IQR)	26 (14 to 55)		27 (16 to 65)	
Dose, μg ; Median (IQR)	2175 (1313–3500)		2000 (1025–3375)	
Cardiovascular effects				
Bradycardia (HR <60)	27	68%	55	81%
Median minimum HR; Median (IQR)	48 (40–62)		47 (40–55)	
Hypotension (Sys BP <90 mmHg)	10	25%	16	24%
Severe hypertension (Sys BP >180 mmHg)	0	0%	2	3%
Central nervous system effects				
GCS <15	22	55%	51	75%
Coma (GCS <9)	2	5%	8	12%
Miosis	10	25%	21	31%
Hospital admission				
Length of stay, h; Median (IQR)	21 (11 to 27)		20 (15 to 35)	
Intensive care	9	23%	17	25%
Intubated	2	5%	10	15%
Treatments				
Atropine	4	23%	4	6%
Naloxone	7	18%	16	24%
Activated charcoal	10	25%	14	21%

(interquartile range: 14 to 35 h) which did not differ for patients taking coingestants. There were no deaths.

Clinical effects

The median minimum GCS was 14 (IQR: 13 to 15). There was a decreased level of consciousness (GCS <15) in 73/108 (68%) of admissions, and coma in 10 (9%). There were more patients with severe CNS depression (coma or GCS <9) in the group co-ingesting medications (8/68; 12%) compared to those ingesting clonidine alone (2/40; 5%). All the eight patients with coma co-ingested a benzodiazepine: one with only a benzodiazepine, two with two different benzodiazepines, two with heroin, two with alcohol and one with chlorpromazine and methadone. There was no association between the dose in 40 clonidine alone overdoses and minimum GCS ($p=0.40$). Miosis occurred in 31 (29%) admissions and hypothermia in 11 patients.

The median minimum HR for all admissions was 48 bpm (IQR: 40 to 57 bpm; range: 32 to 88 bpm), which was similar between the clonidine alone group and the group co-ingesting other medications. There was a significant association between dose and minimum HR in the clonidine alone group and the data was fitted using linear regression (slope = -0.002 ± 0.001 bpm/ μg , $p=0.02$; Figure 1). 82 of 108 (76%) patients developed sinus bradycardia with a median onset of 2.5 h post-ingestion (IQR: 1.7 to 5.5 h; $N=76$). The onset of bradycardia was similar for clonidine alone and patients co-ingesting other medications (Figure 2(A)). Bradycardia persisted for a median of 20 h (2.5 to 83 h; $N=76$; Figure 2(A)) and was similar for clonidine alone and mixed ingestions. Figure 2(B) shows the proportion recovered to a normal HR over time showing no difference between clonidine alone and co-ingestants. 34 of the 82 patients (41%) with sinus bradycardia were discharged still bradycardic. No other arrhythmias were reported.

Three patients ingesting large amounts (8000, 10,000 and 12,000 μg) developed early hypertension. In two patients the

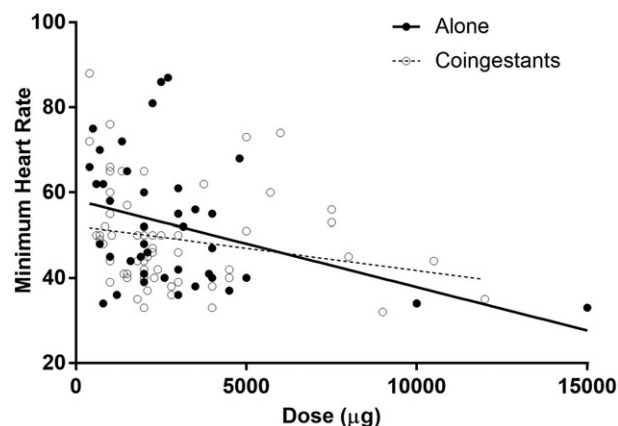


Figure 1. Relationship between the dose and minimum heart rate for clonidine alone overdoses (filled circles) and clonidine overdoses with co-ingestants (open circles) demonstrating a significant association between dose and decreasing heart rate for clonidine alone overdoses ($p=0.02$).

BP decreased over 2 h and they then developed mild hypotension (minimum systolic BP 78 mmHg and 84 mmHg).

The median minimum systolic BP was 96 mmHg (IQR: 90 to 105 mmHg; range: 70 to 154 mmHg), and there was no relationship between dose and minimum systolic BP for clonidine alone and co-ingestant overdoses. Hypotension occurred in 26 of 108 (24%) and had a median onset of 4.2 h (IQR: 2. to 7.8 h) in clonidine alone overdoses and a median onset of 8 h (IQR: 3.7 to 18 h) in clonidine overdoses with co-ingestants (Figure 3). The duration of hypotension was 11 h (IQR: 1.8 to 13 h) in clonidine alone overdoses and 2.8 h (IQR: 1.7 to 6 h) in clonidine overdoses with co-ingestants (Figure 3).

Treatments

Twenty-six patients were admitted to ICU and twelve were intubated and ventilated. Two patients who ingested clonidine alone were intubated. One patient was intubated for aggression. The second ingested 5000 μg and was intubated in a peripheral hospital for decreased level of consciousness

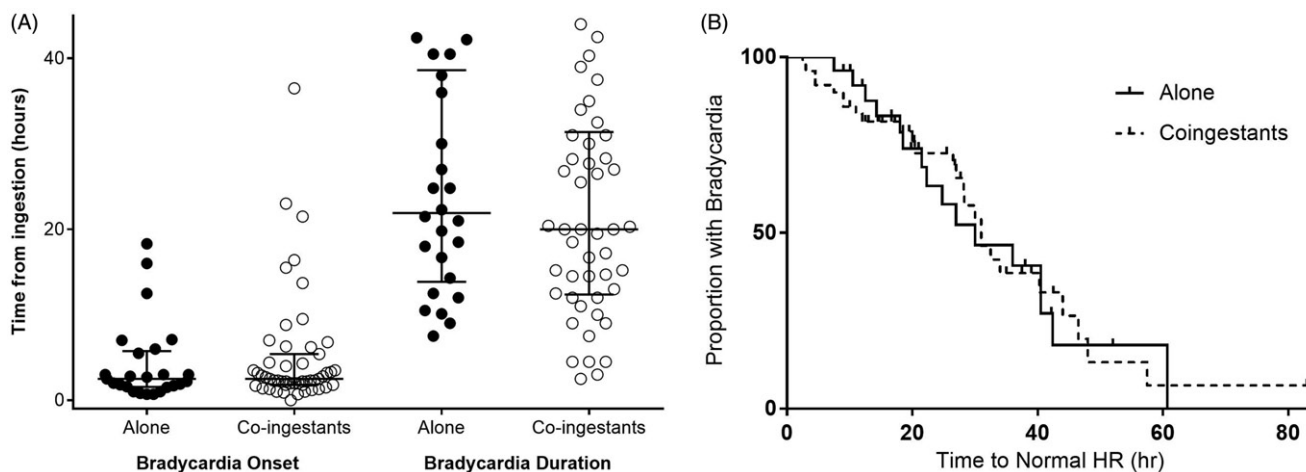


Figure 2. Scatter plots of the time of onset from ingestion to bradycardia for clonidine alone (median 2.5 h; IQR: 1.6 to 5.8 h) and co-ingestant overdoses (median 2.5 h; IQR: 1.8 to 5.5 h), and the duration of bradycardia for clonidine alone overdoses (median 22 h; IQR: 14 to 39 h) and clonidine with co-ingestant overdoses (median 20 h; IQR: 12 to 31 h) (A), and the time to recovery of heart rate to normal for clonidine alone and clonidine with co-ingestant overdoses (B).

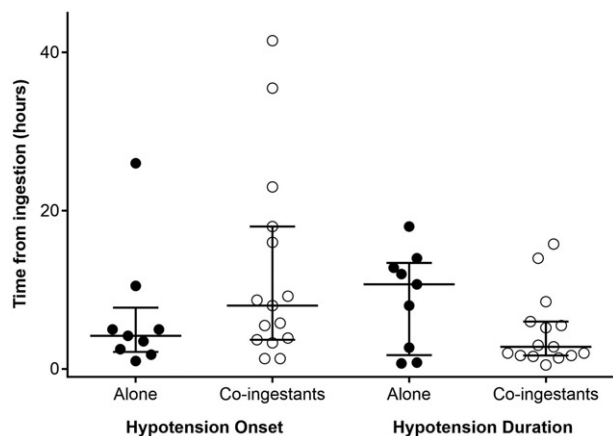


Figure 3. Scatter plots of the time of onset from ingestion to hypotension for clonidine alone (median 4.2 h; IQR: 2.2 to 7.8 h) and co-ingestant overdoses (median 8 h; IQR: 3.7 to 18 h) and duration of hypotension for clonidine alone (median 11 h; IQR: 1.8 to 13 h) and co-ingestant overdoses (median 2.8 h; IQR: 1.7 to 6 h).

prior to retrieval. The remaining 10 intubated patients ingested other sedative drugs and included six patients with coma (GCS <9).

Treatments included activated charcoal (24), atropine (8) and naloxone (23). The median total dose of naloxone administered was 2 mg (IQR: 1.2 to 2.4 mg; range: 0.1 to 14 mg). Twenty two of the 23 patients given naloxone were not reported to respond by the treating clinician (no change in GCS and no change in HR). One patient was documented to have a partial improvement in GCS, but had also recently injected heroin. Patients administered naloxone took a larger dose (median: 3900 µg; IQR: 2000 to 6000 µg) compared to patients not given naloxone (median: 2000 µg; IQR: 1000 to 3000 µg). Patients administered naloxone also had a lower minimum GCS [median 9 (IQR: 5 to 14) vs. 14 (IQR: 14 to 15)] and had a longer LOS [median 41 h (IQR: 19 to 60 h) vs. 19 h (IQR: 12 to 27 h)], compared to those not given naloxone.

Atropine was given on one or more occasions in eight patients. In five patients there was evidence on the observation chart of a transient increase in the HR, which only lasted for 1 h. In one patient the increase in HR was also associated

with an increase in BP. One patient was given adrenaline for hypotension by the retrieval team, which was associated paradoxically with worsening hypotension.

Staggered ingestions

There were eleven patients (seven males; median age 34 years [19 to 42 years]) who took staggered ingestions over a median period of 1 day (0.5 to 7 days). The median ingested dose was 3600 µg (1500 to 30,000 µg) and ten took co-ingestants, most commonly benzodiazepines. Ten developed bradycardia, three had hypotension, four had a GCS <15 and none had a GCS <9. The median LOS was 22 (IQR: 12 to 42 h) and one was admitted to ICU for cardiac monitoring only. Atropine was used in one and naloxone in two with no reported benefit.

Discussion

Our study confirms the previously reported clinical effects of clonidine poisoning in adults, but shows that these are not usually severe and complications are rare. Bradycardia appears to persist on average for almost a day and may have contributed to the longer LOS compared to the median LOS for all overdose admissions to the same unit [13]. Respiratory interventions for CNS depression were uncommon in clonidine alone overdoses and were more common in patients co-ingesting other medications. Both naloxone and atropine were used in a small number of cases but did not appear to result in major improvement in the patients' condition.

The study defines the severity, variability and duration of bradycardia and hypotension in clonidine poisoning. Bradycardia was significantly associated with the dose ingested in the clonidine alone overdoses (Figure 1), and developed within hours of ingestion in both clonidine alone and clonidine with co-ingestant overdoses (Figure 2(A)). Bradycardia lasted for 24 to 48 h (Figure 2(A)) and was the same for clonidine alone and clonidine with co-ingestant overdoses. In contrast, hypotension was not dose-related,

had a later and far more variable onset and variable duration (Figure 2). The onset and duration of hypotension was also different between clonidine alone and clonidine with co-ingestant overdoses. This possibly suggests that the bradycardia is a direct effect of clonidine (imidazoline or alpha-adrenoceptor agonism) compared to the hypotension, which is more likely to be multifactorial, including being secondary to bradycardia, and being influenced by co-ingestants. Only one patient was treated with inotropes for hypotension, which was associated with paradoxical worsening of the hypotension and bradycardia.

Two common questions asked in regards to clonidine overdose are (1) Do they require ICU or high dependency unit admission? and (2) How long should they be observed? Based on the fact that only two clonidine alone overdoses developed coma and only two required intubation, the majority of clonidine alone overdoses could be observed in an emergency short stay unit with standard HR and oxygen saturation monitoring. In patients co-ingesting clonidine with other medications, admission to ICU may be more dependent on the co-ingestants. Almost half of the bradycardic patients were discharged with bradycardia, which means that the duration is under-estimated in this study. In addition, the absence of other arrhythmias and much shorter duration of hypotension suggests that the bradycardia is relatively benign. The patients who are normotensive, alert and are not symptomatic (dizzy) after 24h are most likely safe for discharge.

There are few studies of adult clonidine overdose. The earliest and only relatively large case series is from Stein et al. who reported 37 adult overdoses from the National Poison Information Service in London [9]. The range of doses appeared to be similar to our study and they reported a similar constellation of clinical effects, with more CNS depression and less bradycardia [9]. Other smaller studies that include adult patients report similar effects but less information on duration and treatments [10,11,14]. These earlier studies all report more severe poisoning with higher rates of CNS depression, respiratory depression and cardiac conduction abnormalities. These studies also suggest that the frequency of CNS depression and bradycardia is less common in adults compared to children. However, in comparing our study and more recent paediatric studies, the frequency of clinical effects and severity appears to be similar [2].

Limitations to the study were the retrospective design, possible inaccuracies in the ingested dose and reported drugs not confirmed by laboratory analysis. The majority of the data used in the study was recorded prospectively within a week of the patient admission, with pre-defined outcomes based on the pre-formatted admission sheets. However, some of the data including the time course of the clinical effects and response to treatment were extracted from the medical record. These latter outcomes are limited by how well the physicians or nursing staff recorded information.

An important limitation of the study was that interventions were not randomized, but determined by the admitting clinical toxicologist or critical care physician. There are likely to be confounding influences on the patient groups given particular treatments. However, the almost complete absence

of reports of responses to naloxone provides some support that naloxone is not clinically effective. In addition, naloxone appeared to be administered to the more severely poisoned patients, who are most likely to benefit, based on these patients taking larger doses, having lower GCS and longer LOS; naloxone itself is unlikely to double the LOS.

Confirmation of whether clonidine was actually ingested could not be confirmed analytically and the clonidine dose was based on patient report. Although this is commonly thought to be a limitation, we have reported on numerous occasions the accuracy of the patient history, including the reported dose [15]. The association between dose and minimum HR supports this, similar to other studies from the same toxicology unit [16,17].

Our study found that clonidine causes persistent but not life-threatening clinical effects including bradycardia and CNS depression. Although these initially appear to be clinically significant, they are unlikely to predict a poor patient outcome. The majority of patients will develop mild CNS depression and bradycardia which could be safely observed in an emergency short stay ward. The study did not find support for the routine use of either naloxone or atropine, but atropine may be required in patients with bradycardia and significant hypotension.

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Disclosure statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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