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CLINICAL RESEARCH

Naloxone reversal of clonidine toxicity: dose, dose, dose

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ABSTRACT

Context: Following clonidine ingestion, naloxone is seldom administered as it is considered ineffective in reversing somnolence, bradycardia, or hypotension. However, this conclusion has been based on administration of small doses (2 mg or less) of naloxone. The somnolence is frequently treated with endotracheal intubation (ETI), a procedure with significant morbidity.

Objective: We aimed to determine if naloxone administration reversed the effects of clonidine or caused any adverse effects.

Methods: We performed a retrospective descriptive cohort (IRB approved) of hospital medical records for pediatric patients (6 months–16 years) with clonidine exposure. Demographics, history, co-ingestants, clinical data, treatments, and outcome were recorded in a de-identified database.

Results: The most common clinical findings in the 52 patients were sedation ($n = 51$), bradycardia ($n = 44$), and hypotension ($n = 11$). Of 51 somnolent patients, naloxone administration awoke 40 patients, five of which had co-ingestants. Nine patients experienced recurrent sedation that resolved with a repeat bolus of naloxone. Twenty somnolent bradycardic patients (11 less than 3 years old) received 10 mg naloxone via intravenous bolus. Thirteen awoke; bradycardia persisted in six of the awake patients. Of the remaining 31 patients, 22 awoke following 6 mg or less of naloxone. Naloxone reversed hypotension in 7 of 11 hypotensive patients. Only one hypotensive patient (with a coingestion) received vasopressors for hypotension. Three awake normotensive patients received vasopressors for bradycardia. Seven patients awoke and had normal vital signs following naloxone administration, but were chemically sedated and intubated for transport. There were no adverse events following the administration of any dose of naloxone.

Conclusions: Administration of naloxone to somnolent pediatric patients with clonidine toxicity awoke the majority (40/51) and resolved bradycardia and hypotension in some. Persistent bradycardia was benign. Hypotension was rare and clinically insignificant. No adverse effects occurred in any patient including the 21 patients who received 10 mg naloxone. Morbidity in this overdose may be due to ETI, a procedure that could be prevented if high-dose naloxone (10 mg) were administered. Administration of high-dose naloxone should be considered in all children with clonidine toxicity.

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Introduction

Although the clinical picture of clonidine overdose (OD) and opiate OD is similar, clonidine's lack of stimulation of opiate receptors has caused health care providers to assume that naloxone does not reverse the somnolence, bradycardia or hypotension caused by clonidine toxicity [1,2]. Case reports support this assumption [3–8]. The National Poison Data System (NPDS) reported 11,379 clonidine exposures from Jan 2013 until December 2015 in children less than 6 years of age. Naloxone was administered to only 1315 (11.4%) [9]. However, in cases reporting lack of efficacy only 2 mg or less of naloxone was administered, causing one to wonder why higher doses were not administered and if higher doses would have changed outcome [3–8]. Currently, endotracheal intubation (ETI) is performed for somnolence and/or transport, vasopressors are administered for bradycardia, and patients are admitted to the Pediatric Intensive Care Unit (PICU) [1,2]. Awakening the patient may prevent the high-risk, unnecessary procedure of ETI. This study aimed to evaluate the efficacy and potential adverse effects (AE) of naloxone administration to children with clonidine toxicity.

Methods

Study design

This retrospective descriptive cohort identified children (ages 6 months to 16 years) with a history of clonidine ingestion from the Vanderbilt Children's Hospital (VCH) toxicology consult log from January 2010 to December 2014. Poison Center database was searched to determine if there were any cases that did not have a toxicology consult. No missing cases were identified. Exclusion criteria was patients who remained asymptomatic. Patient management was at the discretion of the attending physician; all had consulted with the poison center. Tennessee Poison Center (TPC) consistently recommends naloxone for treatment of symptomatic clonidine exposures.) One non-blinded abstractor entered all the

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data from electronic medical records to a de-identified electronic database. Study protocol was approved by the IRB.

Data collection and measurements

Demographics (age, gender); ingested dose estimated by history, formulation, time, and co-ingestants (obtained from patient history); clinical data (symptoms, vital signs, physical examination); urine drug screen (UDS); and treatment modalities (naloxone, vasopressors, atropine, mechanical ventilation) were abstracted from the chart.

Mental status was defined as somnolent versus awake; bradycardia, hypotension, and hypertension were based on the pediatric vital sign table from Olsen; s Poisoning and Drug OD 6th edition [10]. High dose naloxone was defined as a 10 mg intravenous (IV) bolus.

Outcomes

Following the administration of naloxone, change in level of consciousness, heart rate (HR), blood pressure (BP), treatment (naloxone, sodium bicarbonate, vasopressors/inotropes, atropine, ETI), and outcome were recorded. Initial responses documented in the medical record were recorded as treatment outcome.

Analysis

Continuous variables were reported as medians, interquartile ranges (IQR), and ranges where appropriate.

Results

There were 53 clonidine exposures by history. One patient was excluded as she remained asymptomatic. The median age of patients was 3 years (6–16 years/IQR: 2.65); 34 (65%) were female. Twenty percent of ingestions were intentional and 80% were unintentional. Twelve (23%) had acute-on-chronic ingestions. The median dose ingested was 0.5 mg (0.1–7 mg/IQR: 0.2.2) which did not differ between patients with clonidine alone or those with coingestants. Eleven patients (21%) co-ingested one or more additional medications based on history: five benzodiazepines [two coingested only benzodiazepine; one trazodone; one tricyclics (TCA) and beta blocker; one citalopram, oxcarbazepine, and eszopiclone]; three patients coingested antipsychotics (one with buspirone); two coingested melatonin (one with citalopram), and one patient coingested levetiracetam. Only one patient received a specific treatment for a coingestant-sodium bicarbonate was administered for a tricyclic antidepressant (TCA) ingestion. The median length of stay (LOS) was one day for both clonidine alone and those with co-ingestants. (range 1–2 days). No patient tested positive for opiates on their UDS. There were no AE as a result of naloxone administration in either the clonidine alone or the clonidine with coingestant groups. There were no deaths in the study. All patients were followed until discharge.

Clinical effects

The most common clinical findings in the 52 patients included sedation ($n = 51$), bradycardia ($n = 44$), and hypotension ($n = 11$). One 13-year-old patient was awake, hypotensive, and bradycardic. Of the 51 somnolent patients, 44 were bradycardic (37 in clonidine alone group; 7 in the co-ingestant group) and 11 were hypotensive (6 in the clonidine alone group and 5 in the coingestant group). Two patients who received inotropes for bradycardia were transiently hypertensive (Table 1).

Treatment and outcomes

Naloxone

Following naloxone administration, mental status improved in 40 patients; 35 in the clonidine-alone group and 5 in the co-ingestant group. Although the dose of naloxone varied, all

Table 1. Demographics, clinical effects, and naloxone administration – comparing clonidine alone to clonidine with coingestants.

	Clonidine alone $n = 41$ (78.8%)	Coingestant $n = 11$ (21.2%)
Female	26 (63.4%)	8 (72.7%)
Age		
Median, years (IQR)	2 (2–5.5)	3 (2–14)
Dose (estimated)		
Median, mg (IQR)	0.5 (0.2–2.9)	0.65 (0.3–1.6)
Acute-on-chronic	9 (22.0%)	3 (27.3%)
Central nervous effects		
Not awake (Pre-N[a])	40 (97.6%)	11 (100.0%)
Sedation resolved	35 (87.5%) ($n = 40$)	5 (45.5%) ($n = 11$)
Cardiovascular effects		
Bradycardia (Pre-N[a])	37 (90.2%)	7 (63.6%)
Hypotension (Pre-N[a])	6 (14.6%)	5 (45.5%)
Hospital admission		
LOS, median (IQR)	1 (1–1)	1 (1–2)
Intubated	7 (17.1%)	4 (36.4%)
Naloxone administration		
Dose, median (IQR)	5 (4–10)	10 (3–10)
Dose, 10 mg	14 (34.1%)	7 (63.6%)
Maintenance drip	30 (73.2%)	5 (45.5%)
Adverse reaction	0 (0%)	0 (0%)

[a]Pre-N: prior to naloxone administration.

doses were administered as an IV bolus. One patient did not respond to an initial 5 mg bolus but awoke following a second five mg bolus (classified as responder). Six patients that initially awoke experienced recurrent sedation that resolved with a repeat boluses of the initial naloxone dose. A naloxone infusion was initiated on 35/52 patients; none became resedated. Mean dose of naloxone infusion was 5 mg/h (IQR 5–7; mean 6.5 mg/h; range 2–30). All infusions were discontinued by 12 h after presentation.

Naloxone (10 mg) IV bolus was administered to 21 patients; 11 were less than three years old. Of the 20 somnolent patients, 13 awoke, 6 of these 13 patients remained bradycardic; three of six hypotensive patients became normotensive. One awake, hypotensive bradycardic patient became normotensive but bradycardia persisted.

Variable doses of naloxone were administered to the remaining 31 patients; 22 awoke following 6 mg or less; one awoke following 18.4 mg; and one following 13 mg. There were no AE following the administration of any dose of naloxone. Of the 11 patients who had no change in mental status following naloxone, 9 awoke within 6 h of presentation.

In the clonidine alone group, 37 of the 40 somnolent patients were bradycardic. Following naloxone, 35 awoke, but 16 of these 35 remained bradycardic. Four of the five patients that did not awaken were bradycardic (not hypotensive) and remained bradycardic after naloxone (Table 2).

Five of six patients who ingested clonidine alone were somnolent and hypotensive. All five patients awoke; hypotension resolved in four, HR normalized in the three that were bradycardic. The one patient that remained minimally hypotensive had ingested 5 mg of clonidine (10 times more than the median dose). The awake, hypotensive, bradycardic patient became normotensive but remained bradycardic.

Two patients were transiently hypertensive. A 2-year-old hypotensive, bradycardic patient (pt29) awoke with normalization of HR and BP following naloxone (10 mg). A naloxone infusion (5 mg/h) was initiated. Fluctuating mental status with intermittent naloxone (totaling 60 mg) resulted in intubation for transport. She was transiently hypertensive while intubated and on the naloxone infusion. A 7-year-old female (pt 9) was unresponsive, bradycardic (50 bpm) and normotensive. She awoke following 10 mg naloxone but remained bradycardic. Upon resedation, a second dose of naloxone (15 mg) awoke her, but HR remained in the 50-s so dobutamine was initiated. Following transport, a naloxone drip was initiated which resulted in hypertension. The dobutamine drip was discontinued and hypertension resolved. She had coingested levetiracetam.

Atropine

Four patients received atropine at outside hospitals prior to ETI and transfer to VCH.

Vasopressors/inotropes

Three somnolent bradycardic patients were never hypotensive but received inotropes for bradycardia. A 15-year-old female awoke following naloxone (1 mg), but remained bradycardic. Dopamine was transiently administered in the ED.

A 2-year-old had no response to naloxone (5 mg) so the dose was repeated. The patient awoke and HR increased to 88 bpm. Dopamine was administered during transport but discontinued in the ED as the patient was never hypotensive.

A 7-year-old female (previously described) received dobutamine for bradycardia and was transiently hypertensive. Only one patient (with coingestants) received vasopressors for hypotension.

Endotracheal intubation (ETI)

Eleven patients underwent ETI. Seven had ingested clonidine alone; one had no response to naloxone (10 mg); three had fluctuating mental status following multiple small doses of naloxone and were intubated for transport; three awoke but were chemically sedated and intubated for transport.

Table 2. Comparison of somnolent patients who awoke following naloxone to those with no response.

	Awakened $n = 40$ (78.4%)	No CNS response $n = 11$ (21.6%)
Female	25 (62.5%)	8 (72.7%)
Age		
Median, years (IQR)	2.5 (2–6.5)	3 (2–6)
Dose (estimated)		
Median, mg (IQR)	0.50 (0.2–2.9)	0.55 (0.2–1.5)
Acute-on-chronic	10 (25.0%)	1 (9.1%)
Coingestant	5 (14.3%)	6 (54.5%)
Cardiovascular effects		
Bradycardia (Pre-N)	35 (87.5%)	8 (72.7%)
Bradycardia resolved	17 (48.6%) ($n = 35$)	0 (0%) ($n = 8$)
Hypotension (Pre-N)	7 (17.5%)	3 (27.3%)
Hypotension resolved	6 (85.7%) ($n = 7$)	0 (0%) ($n = 3$)
Hospital admission		
LOS, median (IQR)	1 (1–1)	1 (1–1)
Intubated	6 (15.0%)	4 (36.4%)
Naloxone administration		
Dose, median (IQR)	5.5 (3.5–10)	10 (5–10)
Dose, 10 mg	13 (32.5%)	7 (63.6%)
Maintenance drip	32 (80.0%)	2 (18.2%)
Adverse reaction	0 (0%)	0 (0%)

Pre-N: prior to naloxone administration; IQR: interquartile range.

Table 3. Patients intubated following clonidine ingestions (somnolent prior to naloxone).

Patient	Age	Coingestant	Pre-naloxone heart rate	BRADY	Pre-naloxone blood pressure	HYPO	Naloxone dose (MG)	Post-naloxone mental status	Post-naloxone heart rate	BRADY	Post-naloxone blood pressure	HYPO	Comments
1	7	No	54 bpm	Yes	80/50 mmHg	No	1	*Awake	69bpm	No	80/50mmHg	No	*ETI for transport
12	3	No	66	Yes	122/55	No	10	Not awake	60	Yes	120s/-	No	
24	2	No	93	Yes	104/55	No	4	Awake	167	No	124/91	No	ETI for transport
29	2	No	Bradycardia	Yes	Hypotensive	Yes	10	*Awake	Normal	No	Normal	No	*ETI for transport
34	6	No	61	Yes	118/88	No	10	Awake	108	No	110/81	No	ETI for transport
41	1	No	69	Yes	110/86	No	5	*Awake	84	Yes	139/89	No	*ETI for transport
42	2	No	61	Yes	63/52	Yes	4	Awake	96	No	110/56	No	ETI for transport
14	2	Melatonin	70	Yes	98/44	No	10	Not awake	82	Yes	105/45	No	
45	3	Metoprolol Alprazolam Amitriptyline	Bradycardia	Yes	Hypotensive	Yes	10	Not awake	Bradycardia	Yes	Hypotensive	Yes	
46	2	Clonazepam Trazodone	Bradycardia	Yes	Hypotensive	Yes	10	Not awake	Bradycardia	Yes	Hypotensive	Yes	
47	3	Clonazepam Citalopram Oxcarbazepine Eszopiclone	87	Yes	110/56	No	0.4	Awake	94	Yes	118/68	No	ETI for transport

ETI: endotracheal intubation.
*Awake but ETI for transport.

The one patient with coingestants that awoke was subsequently chemically sedated and intubated for transport. In summary, seven somnolent, bradycardic, normotensive patients awoke following naloxone. Two remained bradycardic. All seven awake normotensive patients were chemically sedated and intubated for transport (Table 3).

Discussion

Current morbidity of clonidine OD

The lack of reported deaths following clonidine OD may cause one to conclude that clonidine OD is innocuous and requires only supportive care. Yet morbidity (with the current management) may be significantly underestimated. Clonidine is one of the five single-drug ingestions that most frequently results in ETI. In fact, from 2000 to 2013, clonidine was the single drug ingested that most frequently resulted in ETI in children less than 6 years old. In children less than 6 years old, 865 children with single clonidine ingestion and 1052 children with multiple drug ingestions (including clonidine) were intubated. In the 6–12 age group, 77 children with single clonidine ingestion and 106 children with multiple ingestions (including clonidine) were intubated [11]. As clonidine ingestions are increasing, intubations will increase. The argument that it is not difficult to intubate a child without morbidity is not supported. Children are less frequently intubated than adults, desaturate more quickly during the procedure (as a result of age-related differences in oxyhemoglobin dissociation, oxygen consumption and pulmonary mechanics) and multiple attempts are more likely to cause peri-intubation AEs (especially esophageal intubation and hypoxia) [12–14]. (Personal communication of a death from clonidine OD due to inability to intubate a child in Maine.)

In a prospective study of 250 children intubated prior to admission to the PICU, technical problems occurred in 37%. The most frequent AE was mainstem intubation [14]. A prospective study in a tertiary care pediatric ED revealed AEs occurred in 25 (39%) of 66 patients undergoing intubation (hypotension in 21%; desaturation in 14%) [15]. A retrospective pediatric study of 77 emergent intubations described complications in 41% (desaturation in 29%; hypotension in 16%) [16]. It is clear that complications during intubation occur in pediatric tertiary referral centers as well as smaller community EDs [15]. As we saw in our study, chemical sedation and intubation are performed for transportation even if the patient is awake and normotensive following naloxone administration [2,5]. A better understanding of the clinical course of this OD may encourage naloxone administration to prevent the unnecessary high-risk procedure of ETI in awake patients to transport to a PICU (or even the need to transport), and administering vasopressors for bradycardia.

Clonidine mechanism of action relevant to OD

Clinical response to clonidine is different in hypertensive vs normotensive humans/animals. Three mechanisms of action (MOA) explain the clinical course of this OD. Firstly, clonidine binds to both alpha adrenergic and imidazoline receptors (in

the rostral ventrolateral medulla) which cooperatively regulate vasomotor tone. Stimulation of central presynaptic apha-2 adrenoceptors decreases sympathetic outflow which decreases the plasma norepinephrine concentration causing hypotension [17–19].

In therapeutic doses, clonidine has little effect on peripheral alpha2 receptors. However, high serum concentrations following IV administration (or a large OD), stimulate peripheral postsynaptic alpha2-adrenergic receptors which release norepinephrine in smooth muscle causing vasoconstriction and hypertension. The hypertension is transient because the centrally mediated sympathetic inhibition becomes the predominant effect and BP decreases [20].

Secondly, increased parasympathetic outflow increases vagal tone. In combination with decreased sympathetic outflow, HR decreases [21].

Thirdly, and most importantly, is the release of β-endorphin. In spontaneously hypertensive rats (SHR), but not normotensive rats, clonidine perfusion of brainstem slices causes release of β-endorphin. Antiserum to β-endorphin prevents the hypotension and bradycardia caused by IV clonidine [22,23]. In humans, clonidine increases the peak diurnal plasma β-endorphin concentration in hypertensive but not normotensive patients, and the increase correlates with the decrease in BP [24].

As there is no *in vivo* evidence that clonidine interacts with opiate receptors or that naloxone interacts with alpha adrenoceptors, naloxone likely reverses the effects of β-endorphin released in response to clonidine [25].

Research: naloxone reversal of clonidine cardiovascular effects-responders and nonresponders

Both animal and human studies document that there are "responders" [those in whom naloxone reverses the cardiovascular (CV) effects of clonidine] and "nonresponders" (those in whom naloxone does not reverse the CV effects).

Animal studies. In SHRs, clonidine reduces HR and BP, effects which are reversed by a single dose of naloxone (responders). In normotensive rats, clonidine decreases HR and BP, effects which are not reversed by naloxone (nonresponders) [25,26]. The effect of both clonidine and naloxone are dose-dependent.

Human studies. In 29 patients with essential hypertension, clonidine (0.3 mg/day) administration decreased HR and BP. Naloxone (0.4 mg) reversed the CV effects of clonidine in 17 patients (responders) but had no effect in the remaining 12 patients (nonresponders). Responders had higher control values for HR, mean arterial pressure, cardiac output, total peripheral resistance, stroke volume, and plasma epinephrine indicating hyperadrenergic hypertension with higher basal sympathetic tone. Naloxone increased norepinephrine and epinephrine in responders but not in nonresponders. The proposed mechanism of CV response to naloxone is responders (who have higher basal sympathetic tone) have a larger release of Beta endorphin following clonidine administration which is reversed by naloxone [27,28].

Vital sign abnormalities—the evidence and the assumptions

Our data is consistent with previous data reporting decreased sensorium and bradycardia as the most frequent presenting clinical signs [5,29]. But the interpretation of mental status and vital signs following clonidine ingestion needs further discussion to prevent the greatest morbidity of this OD, that of ETI.

Mental status

Children with clonidine ingestion usually arouse when stimulated and become unresponsive when left alone. Due to the fluctuation of mental status dependent on stimulation, Glasgow coma scores are frequently not reported with this ingestion. Awake and not awake (or somnolent) were the terms most frequently used to describe mental status in our study. Awakening children by administering naloxone would prevent ETI and its surrounding morbidity if clinicians understand the clinical course and that innocuous bradycardia may occur in awake normotensive children.

Bradycardia

A recent study of adult clonidine ingestion reported that HR did not correlate with BP and bradycardia was relatively benign persisting for a mean of 20 h [30]. In our study, bradycardia was also benign. We were unable to determine bradycardia duration due to the retrospective nature of the study, but it persisted in 20/37 patients (clonidine alone) who awoke and were normotensive. Although bradycardia is usually an ominous sign in pediatric patients, that is not true following clonidine ingestion as evidenced by normal mental status and BP in these bradycardic patients. Yet concern about bradycardia caused administration of vasopressors to awake normotensive children (as evidenced by three children in our study).

Hypotension/hypertension

Although 10 patients were hypotensive by definition, a vasopressor was administered to only one patient (with a coingestion), indicating that hypotension was not clinically significant. Blood pressure improved in some patients but they remained hypotensive for age by definition of the reference table.

Although hypertension has been attributed to naloxone administration [8], transient hypertension is more likely caused by a large clonidine dose. No reports describe sustained or emergent hypertension from clonidine ingestion alone [4,5,8,20]. In our study, two patients (previously described) became transiently hypertensive-one following administration of dobutamine to treat bradycardia (normal BP) and a second following intubation while on a naloxone drip.

Naloxone dose-some need more

Case reports clearly demonstrate naloxone reversal of clonidine somnolence and sometimes bradycardia [5,31–35]. Both animal and human studies demonstrate that response to naloxone may be dose-dependent [22,23,25,27]. Toxicologists recognized that higher than "normal" doses may be required in this OD, wondered why such low doses were administered, and suggested administering naloxone (10 mg) before deciding it is ineffective [35,36]. Yet recent reviews again reference cases demonstrating lack of efficacy of low-dose naloxone as a basis for concluding that naloxone is ineffective [1,2]. Why do we administer such small doses of naloxone?

In 1990, an American Academy of Pediatric Committee on Drugs published a letter recommending the following naloxone doses; 0.1 mg/kg for birth to 5 years; 2.0 mg if greater than 5 years and 20 kg. It was noted that doses up to 0.4 mg/kg did not cause AEs. Supporting references pertained to opiate addicted newborns. The lowest dose possible was recommended to prevent withdrawal. But these dosing recommendations cannot be extrapolated to naloxone dosing following clonidine ingestion. As long as clinicians continue to administer low dose naloxone, case reports will demonstrate and systematic reviews will conclude that naloxone is not effective [37].

Mostly efficacious but seldom administered

It is not surprising that there is so much confusion about the efficacy of naloxone. There are so many variables. Basal sympathetic tone (which we can't measure), dose of clonidine ingested and dose of naloxone administered determine response. Then there are the case reports and reviews proclaiming lack of efficacy following administration of small doses of naloxone. No wonder we are confused.

We are so convinced that naloxone does not reverse toxicity, that even when naloxone awakens patients and vital signs are normal, we chemically sedate and intubate them for transport. Our study and other studies demonstrate this practice [9]. Pediatric intubation is not without AE [12–15]. Currently, clinicians are following a 1990 Committee's consensus recommendations for low dose naloxone based on opiate-addicted newborns. These recommendations cannot be extrapolated to clonidine toxicity which has an entirely different pathophysiologic basis compared to opiate-addicted newborns. Scientific evidence reveals that that clonidine releases β-endorphin whose effects are reversed by naloxone [25–27].

Case reports which demonstrate naloxone reversal have largely been ignored. Our study reveals efficacy of naloxone in many patients and no AE. We must relook at the scientific evidence from the place of new understanding.

Limitations

A major limitation of the study is that treatments were not randomized. TPC has been recommending high-dose naloxone for years; therefore many patients received 10 mg of naloxone. Additionally, the retrospective nature incurs potential inaccuracies in history and there is the lack of analytical confirmation. Clinical data was extracted from the medical record, which is more complete than poison center records, but is not prospective. Immediate and continuous vital signs were not consistently recorded post naloxone administration. Although BP may have increased in some patients, it did not increase enough to be "normal" by the chart, so these patients were still listed as hypotensive. GCS was not reported on most patients. The abstractor was not blinded which could bias the process

Conclusion

There is variability in both CNS and CV response to naloxone in children with clonidine toxicity. Reversal is dependent on basal sympathetic tone, dose of clonidine ingested, and dose of naloxone administered. Wakening the patient prevents intubation. Bradycardia is innocuous. Hypotension is rare. Case reports demonstrating lack of efficacy following administration of low dose naloxone have caused the scientific community to erroneously conclude that naloxone is not efficacious in reversing clonidine toxicity. There are no AEs following high-dose (10 mg) naloxone administration in children with clonidine alone ingestions or clonidine with coingestants, but there is morbidity in intubating children. Administration of high dose naloxone (10 mg IVP) should be considered in all children with clonidine toxicity.

Disclosure statement

No potential conflict of interest was reported by the authors.

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