0090-3493/90/1810-1124$02.00/0
CRITICAL CARE MEDICINE

Vol. 18, No. 10
Printed in U.S.A.

Critical care for clonidine poisoning in toddlers

DEBRA H. FISER, MD; M. MICHELE MOSS, MD; WANDA WALKER, RN

Clonidine may be a source of serious toxicity when ingested by toddlers. We describe 11 cases of clonidine ingestion by toddlers (mean dose 0.15 mg/kg; range 0.01 to 0.57). The source of the clonidine was a grandparent in six of 11 cases. Symptoms included altered level of consciousness (n = 11), miosis (n = 5), bradycardia (n = 8), hypotension (n = 5), apnea and respiratory depression (n = 6), hypothermia (n = 5) and hypertension (n = 3). Therapeutic interventions included naloxone (n = 8) and atropine (n = 4), dopamine (n = 1), fluid resuscitation (n = 4), and endotracheal intubation (n = 1). There were no deaths. Symptoms of clonidine ingestion were typically mild if the dose ingested was <0.01 mg/kg, while bradycardia and hypotension occurred usually with doses of ≥0.01 mg/kg. Apnea and respiratory depression were common when the dose exceeded 0.02 mg/kg. More effective measures are needed to prevent these potentially serious intoxications. (Crit Care Med 1990; 18:1124)

Clonidine is a synthetic imidazole derivative with central and peripheral α_1 and α_2 adrenergic receptor agonist activity with clinical usefulness as an antihypertensive agent. It has also been investigated for prophylaxis against migraine headaches, treatment of menopausal hot flashes, narcotic withdrawal, and as an aid to cessation of smoking (1, 2) and is being prescribed with increasing frequency. The purpose of this study was to determine the relative prevalence of clonidine ingestion compared with other types of toxic ingestion in patients admitted to the pediatric ICU (PICU), the source of the clonidine tablets ingested, and to describe the presentation, treatment, and hospital course of clonidine ingestion by toddlers.

PATIENTS AND METHODS

A retrospective chart review was conducted including all cases of clonidine ingestion admitted to our PICU between June 1983 and November 1989. Eleven of the total 278 toxicology patients admitted to the PICU during this time period involved clonidine ingestion.

From the Departments of Pediatrics and Anesthesiology, University of Arkansas for Medical Sciences, and Arkansas Children's Hospital, Little Rock, AR.
Address requests for reprints to: Debra H. Fiser, MD, Arkansas Children's Hospital, 800 Marshall, Little Rock, AR 72202-3591.

ILLUSTRATIVE CASES

Patient 1

A previously healthy 4 2/12-yr-old male was brought to the ED after his grandmother noted increasing unresponsiveness during a visit at the grandmother's home. He had ingested four 0.2-mg clonidine tablets 4 h earlier (0.06 mg/kg). On physical examination he was unresponsive to pain, cool, and clammy; pupils were 1 to 2 mm bilaterally, heart rate (HR) 51 beat/min, respiratory rate (RR) 8 breath/min, and BP 90/40 mm Hg. Naloxone 0.02 mg/kg was administered iv followed by 0.01 mg/kg im, and atropine 0.02 mg/kg, iv. Five minutes later, his HR had increased to 130 beat/min, BP had increased to 120/80 mm Hg, and he was more responsive. Ipecac was administered and he was transported to a tertiary care facility for pediatric intensive care. On arrival, 7 h after ingestion, ECG revealed sinus bradycardia with an HR of 57 beat/min, RR 18 breath/min, and BP 92/44 mm Hg. He was easily aroused. Another dose of atropine was administered iv, as well as a fluid bolus. He also received magnesium citrate and activated charcoal. His vital signs stabilized and he became alert and playful. He was discharged home from the PICU the next day.

Patient 2

A previously healthy 1 7/12-yr-old female ingested three of her grandmother's 0.1-mg clonidine tablets (0.03 mg/kg) while visiting in her grandmother's home. She was immediately taken to the ED where she was sleepy, but arousable. BP was 96/45 mm Hg. Gastric lavage was administered within 30 min of ingestion followed by a dose of activated charcoal. She was then transported for tertiary care to a PICU. On arrival 2.5 h after the ingestion, she was somnolent but in no distress. Temperature was 35.5°C axillary; HR was 78 beat/min and slightly irregular. RR was 20 breath/min, and BP was 106/59 mm Hg. Six hours after admission to the PICU, she experienced an episode of hypotension (BP 87/46 mm Hg). She received 120 ml normal saline, resulting in BP stabilization. She was discharged on day 2 after admission.

Patient 3

A previously healthy 2-yr-old male ingested an undetermined amount of clonidine that he found in a car

belonging to a friend of the family. He was initially asymptomatic and emesis was induced at home. On ED arrival, the child was diaphoretic, lethargic, and intermittently delirious. Vital signs were BP 140/104 mm Hg, HR 144 beat/min, RR 20 breath/min and regular. Diffuse rhonchi were noted in all lung fields. His deep tendon reflexes were 3+ bilaterally. Atropine 0.01 mg/kg was administered iv. He also received activated charcoal and magnesium citrate. Thirty minutes later, he was alert with BP 124/94 mm Hg, HR 112 beat/min, and RR 20 breath/min. He was monitored overnight in the PICU and, remaining stable, was discharged home the next day.

Patient 4

A previously healthy 1 5/12-yr-old male opened a newly refilled bottle of clonidine, 0.2-mg tablets, en route home from the pharmacy, despite the presence of a protective cap, and ingested one tablet (0.02 mg/kg). Shortly thereafter, his parents noted that he was somnolent with irregular respiration. At the ED 45 min after ingestion, he was lethargic, but arousable. BP was 113/64 mm Hg, HR 113 beat/min, and RR 30 breath/min. He was treated with ipecac followed by activated charcoal. Naloxone 0.03 mg/kg was administered im. Thirty minutes later, his BP had decreased to 94/58 mm Hg and his temperature was 36.6°C axillary. He was transported to a tertiary care PICU. On arrival, he was alert but irritable. HR was 95 beat/min, RR 16 breath/min, and BP 110/54 mm Hg. He was in the PICU overnight for observation. His vital signs remained stable and he was discharged the next day.

Patient 5

A previously healthy 1 8/12-month-old male wandered into his grandparents' trailer adjacent to his own home. He was found by a sibling with a mouthful of 0.1-mg clonidine tablets. He was thought to have swallowed one or two tablets (0.13 mg/kg). He was brought to the ED 30 min after ingestion at which time he was lethargic, but easily arousable. His HR was 112 beat/min, RR 28 breath/min, BP 98/35 mm Hg, and temperature 36.4°C axillary. Ipecac, activated charcoal, and magnesium citrate were administered. Two hours postingestion, he became obtunded, his HR decreased to 70 beat/min, and his BP decreased to 46/30 mm Hg. He was given naloxone 0.03 mg/kg and dopamine 5 μg/kg·min with good response. The dopamine infusion was discontinued after 30 min. Subsequently, his HR was 103 beat/min and his BP 100/70 mm Hg. He was monitored in the PICU and required some subsequent fluid resuscitation. His mental status improved rapidly and he was discharged home the next day.

Patient 6

A previously healthy 1 7/12-yr-old female ingested approximately 1¼ tablets of clonidine 0.1 mg (0.01 mg/kg) which her aunt, a renal patient, kept in a cardboard box. Soon thereafter, she was noted to be staggering and somnolent. At the ED she was pale and lethargic but arousable. Her BP was 101/60 mm Hg, HR 110 beat/min, and RR 24 breath/min. Her pupils were slightly constricted. Ipecac was administered, followed by activated charcoal and sorbitol. She was monitored overnight in the PICU where she remained stable and was discharged home the next day.

Patient 7

A previously healthy 1 3/12-yr-old male was noted to be lethargic and unusually somnolent during the day before ED admission that evening. On questioning, his father admitted that he had spilled an entire handful of clonidine tablets earlier and the child had helped him to put them back into the bottle. At the ED, the child was lethargic, somnolent, and irritable. His deep tendon reflexes were diminished. His temperature was 36.1°C axillary with HR 88 beat/min and RR 32 breath/min. His pupils were constricted to 1 mm. After a dose of naloxone 0.01 mg/kg, his pupil size increased to 3 mm, his HR increased to 120 beat/min, his RR decreased to 24 breath/min, and his BP increased to 133/57 mm Hg. He also became more alert. He was admitted to the PICU for observation overnight and was discharged home the next day.

Patient 8

A previously healthy 1 9/12-yr-old male was visiting his grandmother's home. A sibling reported having observed the child with his grandmother's medication (clonidine 0.3-mg tablets). The child fell asleep but awoke an hour later screaming. He was brought to the ED approximately 90 min postingestion with the chief complaint that "the child would not stop crying." Judging from tablets missing, the child was estimated to have ingested up to 7.2 mg of clonidine (0.57 mg/kg). On examination, he was noted to be screaming with intermittent obtundation, cyanosis, and episodes of apnea. His HR was 73 beat/min, RR 21 breath/min, and BP 127/84 mm Hg. He was treated with naloxone 0.01 mg/kg iv and gastric lavage. Fifteen minutes later his HR had increased to 110 beat/min. However, his BP soon decreased to 70/50 mm Hg. He was given atropine 0.02 mg/kg iv and another dose of naloxone 0.02 mg/kg. His episodes of apnea became more frequent, requiring endotracheal intubation and mechanical ventilation. He was admitted to the PICU where his vital signs finally stabilized over the next 6 h.

However, the following day, he became febrile and was treated with an empirical regimen of nafcillin and cefuroxime. *Haemophilus influenzae* was subsequently cultured from the tracheal aspirate. He was extubated on the second hospital day; however, progressive postextubation edema and stridor necessitated reintubation. His course was further complicated by atelectasis and deteriorating gas exchange. He was successfully extubated 5 days later. He was discharged from the PICU on hospital day 8 and was discharged home on day 12.

Patient 9

A previously healthy 1 7/12-yr-old male visiting in his grandmother's home ingested his grandfather's prepared doses of clonidine 0.2 mg (0.02 mg/kg) and KCl 600 mg. Soon after, he was noted to be somnolent and difficult to arouse. He arrived in the ED in a somnolent state 1.75 h postingestion. His HR was 115 beat/min, RR 30 breath/min, and BP 112/67 mm Hg. He received gastric lavage followed by activated charcoal. He experienced apnea approximately 3 h postingestion and received naloxone 0.01 mg/kg iv, with little effect on apnea or mental status. He received an additional three doses of 0.02 mg/kg naloxone iv over the next hour with a resultant decrease in apnea and slight improvement in his mental status. He was transferred to the PICU where his mental status rapidly improved and his vital signs remained stable. He was discharged home on hospital day 2.

Patient 10

A previously healthy 2 3/12-yr-old male ingested 22 tablets of clonidine 0.2 mg (0.35 mg/kg). He became lethargic and was taken to the ED where he was noted to have respiratory depression followed by periods of increased alertness and activity. Vigorous stimulation was needed to promote normal respiration. His HR was 64 beat/min. His stomach was lavaged and activated charcoal was instilled. He also received atropine 0.02 mg/kg and naloxone 0.04 mg/kg iv. He was transported to a tertiary care PICU 4 h postingestion. At this time his HR was 98 beat/min, RR was 20 breath/min, and BP 128/67 mm Hg. He was noted to be lethargic and received another dose of naloxone 0.02 mg/kg. His HR continued to decline (to 62 beat/min) with BP 120/64 mm Hg. He received a third dose of naloxone 0.01 mg/kg iv for lethargy. His HR increased to only 71 beat/min and his RR declined to 12 breath/min. His ECG revealed only sinus bradycardia. He was admitted to the PICU for observation. His vital signs stabilized and his alertness returned over the next 8 h. He was discharged home on the second hospital day.

Patient 11

A previously healthy 19-month-old female found an open bottle and ingested approximately ten of her grandmother's 0.2 mg (0.17 mg/kg) clonidine tablets while her grandmother answered the telephone. The child became lethargic and difficult to arouse. On arrival at the local ED within 1.5 h postingestion, she was noted to be lethargic and to have miosis. Her HR was 76 beat/min, RR was 16 breath/min and her systolic BP was 130 mm Hg. Her temperature was 36.2°C rectally. She received naloxone 0.02 mg/kg, activated charcoal, magnesium citrate, and fluids. Three hours postingestion, her HR dropped to 59 beat/min and she was responsive only to painful stimuli. She was transported to a tertiary care PICU for continued management where she experienced episodes of irritability alternating with drowsiness along with continued lability of her BP (hypertension) and temperature. Her vital signs stabilized approximately 8 h postingestion. She was discharged from the PICU the next day and from the hospital on day 2.

RESULTS

Admission data and therapeutic interventions are summarized in Table 1; 82% of the group were male and all but two were ≤2 yr of age. The source of the clonidine was a grandparent in six of 11 cases and belonged to someone in the child's immediate household in only two cases.

All patients had an altered level of consciousness. Eight patients had bradycardia, five had hypotension, three had hypertension, and six had apnea or respiratory depression. There were no deaths.

Eight children received naloxone (total dose range from 0.01 to 0.07 mg/kg). Four of the eight children receiving naloxone exhibited a positive response to the drug, with a questionable response in two others. No adverse effects of naloxone were identified (e.g., hypertension).

DISCUSSION

In the 1980s, clonidine joined the ranks of hydrocarbons, tricyclic antidepressants, salicylates, acetominophen, organophosphates, and iron as a common substance ingestion leading to need for subsequent critical care support. While no deaths have been reported secondary to clonidine ingestion by toddlers, most experience serious CNS, hemodynamic, or respiratory manifestations of toxicity.

Clonidine is rapidly and completely absorbed after oral administration (75% absorption within 30 min [3, 4]). Because of the rapid onset of hypotensive action,

TABLE 1. Admission data, therapeutic interventions, and response to therapy for clonidine intoxication

Patient No.	1	2	3	4	5	6	7	8	9	10	11
Age (yr)	4.2	1.6	2.0	1.4	1.7	1.8	1.3	1.8	1.6	2.3	1.6
Sex	M	F	M	M	M	F	M	M	M	M	F
Clonidine source	GM	GM	FR	MO	GM	AUNT	FA	GM	GM/GF	?	GM
Ingested dose (mg/kg)	.06	.03	?	.02	.13	.01	?	.57	.02	.35	.19
Altered LOC	+	+	+	+	+	+	+	+	+	+	+
Miosis	+	−	−	−	−	+	+	−	+	−	+
Bradycardia	+	+	+	−	+	−	+	+	−	+	+
Hypotension	+	+	−	+	+	−	−	+	−	−	−
Hypertension	−	−	+	−	−	−	−	−	+	−	+
Apnea or respiratory depression	+	−	−	+	−	−	−	+	+	+	+
Hypothermia	−	+	+	−	+	−	+	−	−	−	+
Ipecac	+	−	+	+	+	+	−	−	−	−	−
Gastric lavage	−	+	−	−	−	−	−	+	+	+	+
Activated charcoal	+	+	+	+	+	+	−	−	+	+	+
Cathartic	+	−	+	−	+	−	−	−	−	−	+
Narcan total dose (mg/kg)	.03	−	−	.03	.03	−	.01	.03	.07	.07	.02
Narcan response	+	NA	NA	?	+	NA	+	?	+	−	−
Atropine total dose (mg/kg)	.02	−	.01	−	−	−	−	.02	−	.02	−
Fluid resuscitation	+	+	−	−	+	−	−	−	−	−	+
Vasoactive drug infusion	−	−	−	−	+	−	−	−	−	−	−
Endotracheal intubation/mechanical ventilation	−	−	−	−	−	−	−	+	−	−	−
PICU LOS (days)	1	2	1	1	1	1	1	8	1	2	1
Hospital LOS (days)	1	2	1	1	1	1	1	12	1	2	2

GM, grandmother; FR, friend; MO, mother; FA, father; GF, grandfather; LOC, level of consciousness; LOS, length of stay.

children who have ingested overdoses of clonidine rapidly become symptomatic. Most of the therapeutic and toxic effects of clonidine are mediated by activation of postsynaptic α-adrenergic receptors in the medulla oblongata, resulting in decreased efferent sympathetic activity (5).

While the triad of CNS depression, respiratory depression, and miosis usually prompts suspicion of narcotic overdose, the possibility of clonidine ingestion must be considered. Although narcotic levels may be useful in establishing a diagnosis, clonidine levels have not been proven useful clinically (2). In actuality, clonidine ingestion is a more frequent cause for admission of a toddler to our ICU than is narcotic overdose.

Despite the typical early onset of hypotensive action, it should be noted that early manifestations may be limited to mental status changes with later onset of hemodynamic instability. Patient 2 did not become hypotensive until 6 h after PICU admission. For this reason, we believe that all patients with clonidine ingestion should be monitored closely, preferably in a PICU, for a minimum of 24 h.

Because of the paucity of series case reports involving toddler clonidine ingestions, a dose/symptom relationship has not previously been apparent. In our series we have found that symptoms of clonidine ingestion are typically mild in toddlers if the dose ingested is <0.01 mg/kg, while bradycardia and hypotension tend to occur with doses of 0.01 mg/kg and higher. Apnea and respiratory depression are common when the dose exceeds 0.02 mg/kg.

Early transient hypertension, secondary to a predominant α-agonist effect, is less common and was thought to occur in association with large overdoses (1, 6, 7). However, our patients did not demonstrate a dose-response relationship with hypertension. Hypertension has also been reported (8, 9) after treatment with naloxone, although we did not experience this problem in our series.

Treatment is supportive and includes GI decontamination. Because altered level of consciousness may occur within the first half hour after ingestion, ipecac is best avoided after clonidine ingestion in favor of gastric lavage, activated charcoal, and cathartics.

Coma, apnea and respiratory depression may variably respond to naloxone in larger than usual doses; hypotension and bradycardia also have a variable response to naloxone in both animal and human studies (10–14). The benefit of naloxone in this setting is probably related to the fact that clonidine's inhibition of central sympathetic outflow is thought to be mediated by the release of an endogenous opioid (15). Because of the reported risk of inducing hypertension with naloxone, it must be administered with caution, using repeated small incremental doses with constant BP monitoring (9). Naloxone should probably be re-

served for patients whose mental status and respiratory control are so depressed that endotracheal intubation would be considered for airway management if naloxone were not used. Since the response is variable and may not be dramatic, respiratory depression that does not reverse with naloxone will require endotracheal intubation and mechanical ventilation.

Other supportive care includes treatment of hemodynamically significant bradycardia with atropine. While hypotension usually responds to fluid resuscitation, dopamine may be needed as well. Hypertension, if threatening end-organ damage, should be treated with very short-acting agents, such as tolazoline or sodium nitroprusside, so that they may be discontinued if hypotension occurs. Diuresis is not recommended either for treatment of hypertension or for increasing excretion of the drug. Dialysis is also ineffective.

In a recent study of accidental ingestion of prescription drugs by children, 35% of the toxic drugs ingested in the child's home belonged to someone not in the child's immediate family, most often a grandparent (16). The seriousness of the toxic effects of clonidine overdose warrants extra precaution when prescribing the drug. Physicians and pharmacists should warn patients for whom the drug is prescribed of the hazard to small children. Double-barrel packaging may hinder toddlers from obtaining the tablets. However, not only tablets pose a danger. Patches have been reported to cause toxicity in a child co-sleeping with a treated adult and when disposed patches are chewed by toddlers (2, 17). Used patches may contain as much as 3 mg of residual clonidine after 7 days (18). Safe disposal technique should be discussed with patients if not printed on the patch itself.

Clonidine ingestions represent a significant proportion of the toxicology admissions to the PICU and an even greater proportion of the toxicology admissions requiring critical care intervention over and above GI decontamination and monitoring. In this latter group, clonidine ingestions are among the most frequent. More effective measures are needed to prevent these potentially serious intoxications.

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