Trends and Toxic Effects From Pediatric Clonidine Exposures

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Objective: To analyze the trends, demographics, and toxic effects associated with pediatric clonidine hydrochloride exposures reported to poison centers.

Design: Retrospective.

Setting and Patients: Clonidine-only exposures followed up to known outcome in children younger than 19 years reported to the American Association of Poison Control Center’s database from January 1, 1993, through December 31, 1999.

Main Outcome Measures: Frequency of exposures over time, acuity, reason, symptoms, management site, treatment, and outcome.

Results: There were 10060 reported exposures with 57% reported for children younger than 6 years, 34% for children between 6 and 12 years old, and 9% for adolescents between 13 and 18 years old. In 1999 there were 2.5 times as many exposures as in 1993. In 6- through 12-year-olds, clonidine was the child’s medication in 35% of the exposures, compared with 10% in children younger than 6 years and 26% in adolescents. The proportion of cases involving the child’s medication increased over 7 years. While unintentional overdose was most common in children younger than 6 years, therapeutic errors and suicide attempts predominated in 6- through 12-year-olds and adolescents, respectively. In 6042 symptomatic children (60%), the most common symptoms were lethargy (80%), bradycardia (17%), hypotension (15%), and respiratory depression (5%). Most exposures resulted in no effect (40%) or minor effects (39%). Moderate effects occurred in 1907 children (19%), major effects in 230 children (2%); there was 1 fatality in a 23-month-old.

Conclusions: While most of the clonidine exposures resulted in minimal toxic effects, serious toxic effects and death can occur. The trend toward increasing the number of exposures in children, especially with evidence of toxic effects in children receiving clonidine therapeutically, is cause for concern.

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CLONIDINE hydrochloride, an imidazoline-derived agent, has stimulatory effects on central α₂-adrenergic receptors resulting in a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. The only approved indication for clonidine is management of hypertension. Clonidine is also used for several unlabeled indications including ethanol and opioid withdrawal, smoking cessation, and mania and psychosis. Off-label uses in children include the management of attention-deficit/hyperactivity disorder (ADHD) and Tourette syndrome. The prevalence of pediatric clonidine use has been increasing. Zito et al.10 reported an up to 28-fold increase in clonidine use in preschoolers from January 1, 1995, through December 31, 1995, compared with January 1, 1991, through December 31, 1991. As clonidine’s therapeuic use increases in the pediatric population, the potential exists for an associated increase in adverse effects and poisonings. This study assessed the trends and evaluated the demographics and toxic effects associated with pediatric clonidine exposures reported to poison centers nationally.

RESULTS

The study population consisted of 10060 children younger than 19 years who were followed up until their outcome was known. Most exposures (56.6%) occurred in children younger than 6 years, accounting for 5696 cases. There were 3470 exposures (34.5%) in 6- through 12-year-old children, and 894 exposures (8.9%) in adolescents (aged 13-18 years). Exposures occurred more often in boys, accounting for 6579 cases (65.4%). The
METHODS

The American Association of Poison Control Center Toxic Exposure Surveillance System (AAPCC TESS) was analyzed for pediatric clonidine exposures followed up to known outcome in children younger than 19 years reported from January 1, 1993, through December 31, 1999. The number of poison centers submitting cases to TESS remained stable over the study period (64–67 centers); however, the proportion of the population of the United States served by these centers increased from 70% in 1993 to 96% in 1999. Data were analyzed for age group, acuity, reasons for the exposure, clinical effects, management site, therapy and medical outcome. The term “unintentional general” was used for accidental exposures. Ages were categorized as younger than 6 years, from 6 through 12 years, and from 13 through 18 years. In “acute-on-chronic” (acute exposure in a child receiving long-term clonidine therapy) and “chronic” exposures, clonidine was assumed to be the child’s medication. Clinical effects coded as related to the clonidine exposure were included; clinical effects coded as unrelated or unknown if related were excluded. Known medical outcomes as defined by AAPCC TESS were no effect (no signs or symptoms as a result of the exposure), minor effect (signs or symptoms that were minimally bothersome and resolved rapidly), moderate effect (signs or symptoms that were more pronounced, more prolonged, or more systemic in nature than minor, usually requiring treatment but not life-threatening), major effect (signs or symptoms that were life-threatening or resulted in significant residual disability), or death (death resulted from the exposure or a direct complication of the exposure). The total number of pediatric poisonings reported to poison centers in 1993 and 1999 was obtained from published AAPCC TESS annual reports as was case detail on fatalities.

Data were analyzed using Access (Microsoft Corp, Seattle, Wash) and Excel (Microsoft Corp). Summary statistics were generated and χ² tests performed to compare findings in the 3 age groups. The study was reviewed by the institutional review board of the University of Maryland, Baltimore, and determined to be exempt from the institutional review board approval process.

The number of exposures increased each year, with the greatest increase occurring between 1993 and 1995 (Figure 1). While the total number of cases involving children younger than 19 years reported to AAPCC TESS increased by 21% between 1993 and 1999, total clonidine exposures increased more than 2.5-fold in 1999 compared with 1993. After adjusting for the higher proportion of the US population served by reporting poison centers in 1999 compared with 1993, total clonidine exposures increased 1.9-fold.

Clonidine was the child’s own medication in 2011 exposures (34.5%). For children younger than 6 years and for the 13- through 18-year-old age group, 581 (10.2%) and 232 (26.0%) of the exposures, respectively, were to the child’s medication. The proportion of cases in which clonidine was the child’s medication increased in all 3 age groups during the study period. Comparing data for 1993 and 1999, exposures involving the child’s medication increased from 2.6% to 13.1% of the cases in children younger than 6 years, 22.1% to 40.4% in 6- through 12-year-olds, and 16.7% to 25.5% in adolescents (13- through 18-year-olds).

The reason for exposure varied depending on age. In children younger than 13 years, the exposures were usually unintentional. Unintentional general was the primary reason for exposure in children younger than 6 years accounting for 4325 cases (86.5%) followed by therapeutic errors in 686 (12.0%). In children from 6 through 12 years old, therapeutic error in 1975 cases (56.9%) was the most frequent reason for the exposure followed by unintentional general in 966 (28.7%), suicide attempt in 163 (4.7%), and intentional misuse or abuse in 132 (3.8%). In adolescents older than 12 years, 395 (44.2%) of the exposures were suspected suicide attempts, 204 (22.8%) were therapeutic errors, 146 (16.3%) were unintentional general, and 97 (10.9%) were intentional misuse or abuse. In all age groups, the remaining reasons included a small percentage coded as adverse drug reaction or other/unknown reason.

In 4018 children and adolescents (40%), no symptoms were reported. Table 1 lists the clinical effects in the 6042 symptomatic cases (60%). Twenty-three children experienced respiratory arrest. The exposure was managed on-site (home or another nonhealth care facility) for 2605 children (25.9%) and at a health care facility for 7111 children (70.7%) (Figure 2). For children younger than 6 years, 16.5% (940) were managed on site compared with 42.7% (1481) of the 6- through 12-year-olds, and 20.6% (184) of the adolescents (x² = 841, P < .001). For children younger than 6 years, 49.0% (2256) of those seen in the health care facility were admitted for medical care compared with 32.8% (610) of the 6- through 12-year-olds and 48.5% (317) of the adolescents (x² = 147, P < .001). In addition, 28 children from 6 through 12 years old and 60 adolescents were admitted for psychiatric care.

Gastrointestinal (GI) tract decontamination included activated charcoal in 4272 children (42.5%), ca-
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There was 1 fatality—a 23-month-old girl with an acute unintentional overdose of an unknown number of 0.3-mg clonidine hydrochloride tablets. In the emergency department the child’s stupor and bradycardia responded to a combined treatment of naloxone and atropine. Bradycardia recurred during intubation, progressing to pulseless electrical activity; resuscitative efforts were unsuccessful. Autopsy showed lung edema and a post-mortem plasma clonidine concentration of 47 ng/mL.

Comment

Clonidine poisoning in children has been described in numerous case reports and small case series dating back to the 1970s. These poisonings all involve young children.
To our knowledge, the 10,060 pediatric clonidine exposures described herein represent the largest series to date as well as the only series that includes children whose exposures were managed in both a nonhealth care facility and a health care facility. The 7-year time frame allows for an assessment of trends in pediatric clonidine exposures.

The most common off-label indication for clonidine in children is the management of ADHD, which occurs in 3% to 6% of the school-aged children. Although stimulant drugs are the first-line therapy for ADHD, other drugs are used in children who are either unresponsive to or intolerant of stimulants. Clonidine may be beneficial in children who have hyperarousal, hyperactivity, impulsiveness, and defiance. Clonidine can be used in conjunction with stimulants or may be useful for sleep disturbances associated with ADHD or its treatment.

Meta-analysis of 11 reports of clonidine for ADHD concluded that clonidine is less effective than stimulants but may be an effective second-line treatment.

As the prevalence of pediatric clonidine use for childhood behavioral disorders increases, children may be at greater risk of toxic exposures. A review of 14 hospital admissions in 13 children between 1985 and 1995 found that 8 admissions occurred in 1994 and 1995. Similarly, a medical record review of emergency department visits between 1990 and 1997 reported that all but 1 of 16 pediatric overdoses occurred between 1994 and 1997. These medical record reviews concluded that the incidence of pediatric clonidine poisoning has increased. These findings are supported by poison center data that show that total pediatric clonidine exposures increased from 693 in 1993 to 1762 in 1999. After adjusting for differences in population served by these poison centers in 1999 compared with 1993, there was close to a 2-fold increase in exposures. Possible explanations for this increase include an increase in pediatric use for ADHD and Tourette syndrome as well as an increase in off-label uses in adults. These trends in therapeutic use increase the likelihood of therapeutic errors in children as well as overdoses caused by greater availability in homes.

Recent studies suggest a changing pattern in the source of clonidine in clonidine poisonings. Several studies of unintentional pediatric clonidine poisonings implicate grandparents as the primary source of the drug. Two recent studies found that 14 of 16 poisonings and 8 of 14 poisonings resulted from exposures to clonidine belonging either to the child, a sibling, or another child. Although only 20% of poison center cases in the current study involved the child’s medication, over the 7-year study period the proportion of cases in which clonidine was the child’s medication increased in all pediatric age groups. The increase in proportion was 50% for adolescents compared with a 2-fold increase in the 6- through 12-year-olds and a 5-fold increase in children younger than 6 years. Presumably some of the other clonidine exposures were to medication belonging to another child or sibling. Given the increasing therapeutic use of clonidine in children, it is likely that in the future even higher proportions of clonidine exposure cases reported to poison centers will involve a child’s medication. In cases involving the child’s medication, the child was more likely to experience symptoms than in cases of single acute ingestions. This finding may reflect the fact that for single acute ingestions, the poison center was called as soon as the ingestion was discovered prior to symptom development whereas for children with either acute-on-chronic or chronic exposures the impetus for the call was the development of adverse effects.

Most cases were managed in a health care facility. For children younger than 6 years and adolescents, 80.8% and 73.0%, respectively, were treated in a health care facility while only 53.5% of the 6- through 12-year-olds received this level of care. Since as little as 0.1 to 0.3 mg (1 tablet) of clonidine hydrochloride can cause significant central nervous system depression in young children, some poison centers refer young children with a history of ingesting any amount to the emergency department. Similarly, intentional adolescent overdoses are referred to a health care facility rather than attempting home management. On the other hand, many of the exposures in 6- through 12-year-olds resulted from therapeutic errors where presumably the exact dose was known (eg, an extra dose administered), or the dose ingested was lower and hence the chance of a serious toxic effect was lower. Therefore, a higher proportion of these children could be managed outside a health care facility.

No specific treatment was provided in 38.1% of the children. For those children receiving treatment, the primary treatment modality was GI tract decontamination and children who received GI tract decontamination were more likely to experience a moderate or major outcome. This is most likely explained by the fact that children with a higher dose by history and/or symptomatic patients are more likely to receive GI tract decontamination. Although 62% of children received some type of treatment, only 19% experienced a moderate toxic effect and 2% developed a severe toxic effect. This disparity between a clinical toxic effect and treatment suggests that either treatment minimizes toxic effects or that concern regarding clonidine’s potential for toxic effect results in more children being treated than actually require treatment.

Study limitations should be considered in interpreting and generalizing the results of this study. The retrospective design of the study has its inherent limits. Factors such as the voluntary nature of reporting to poison centers and the change in the proportion of the US population served by poison centers during the study period may have introduced some reporting bias. Since some data entry systems default to acute in the acuity field and the specialist in poison information may not always change the default, use of acute-on-chronic and chronic as surrogates for child’s medication may have resulted in an undercount of cases in which the clonidine was the child’s medication. During the years of this study there was no dose or laboratory information available in AAPCCT ESS data. However, laboratory confirmation of clonidine is usually impossible because plasma clonidine concentrations are not routinely available.
The clinical manifestations of pediatric clonidine poisoning have been well described in numerous case reports and small case series. These poisonings all involve a small number of young children who are asymptomatic and whose conditions are managed in a hospital setting. The 10060 pediatric clonidine exposures described herein represent the largest series to date as well as the only series that includes children whose exposures were managed in both nonhealth care facility and health care facility. The 7-year time frame demonstrates a trend toward increasing numbers of clonidine exposures annually as well as a growing proportion of cases involving the child’s medication. Although most children (79%) exhibited no toxic effects or mild effects, moderate and major toxic effects occurred in 19% and 2% of the children, respectively.

In 1990 Bamshad and Wasserman warned that clonidine intoxications would become more common as the market for antihypertensive drugs expands. That warning is even more applicable today as clonidine use in children leads to greater availability and an ever-increasing number of clonidine exposures. Strategies for prevention will vary depending on the age group. For children younger than 6 years, child-resistant packaging and improved storage are potential methods of decreasing poisonings. For all children receiving clonidine therapeutically, especially those from 6 through 12 years old, prevention should focus on education directed at children and their parents regarding correct dosing and storage. Recognition and management of depression and substance abuse in adolescents and limiting access to large quantities of drugs would be potential avenues for preventing or minimizing the potential for toxic effects in this age group.

Most pediatric patients in this study exhibited minimal toxic effects following exposure to clonidine alone. However, in overdose clonidine can cause a serious toxic effect. With the expanding therapeutic role of clonidine in the pediatric population and associated greater in-home accessibility, the number of pediatric clonidine exposures reported to the AAPCC has dramatically increased over the years. This trend toward increasing number of exposures in children, toxic effects in children receiving clonidine therapeutically, and the serious nature of some of these cases are causes for concern.

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REFERENCES


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