Unintentional Pediatric Exposures to Central Alpha-2 Agonists Reported to the National Poison Data System

George Sam Wang, MD, Marie-Claire Le Lait, MS, and Kennon Heard, MD

Objective To investigate national trends in unintentional pediatric exposures to 3 common alpha-2 agonists: clonidine, guanfacine, and tizanidine. Secondary objectives were to describe outcomes, symptoms, treatments, and death.

Study design Retrospective chart review from the American Association of Poison Control Centers National Poison Data System from January 2000 to December 2011 for unintentional exposure to clonidine, guanfacine, and tizanidine in children ≤12 years of age.

Results From 2000-2011, there was a significant increase (5.9% per year, CI 3.6, 8.2) in unintentional pediatric exposures to National Poison Data System for central alpha-2 agonists. There were 27,825 clonidine exposures (67.3% male, median age: 4 years), 6,143 guanfacine exposures (69.8% male, median age: 6 years), and 856 tizanidine exposures (51.9% male, median age: 2 years). Guanfacine had the greatest proportional increase among the medications. Clonidine was associated with the most respiratory (799, 2.9%) and central nervous system symptoms (12,612, 45.3%), as well as the most episodes of bradycardia (2,847, 10.2%) and hypotension (2,365, 8.5%). Seven-hundred twenty-eight (2.0%) patients were intubated, and 141 patients (0.5%) were administered vasopressors. There were 7 cardiac arrests and 3 deaths from clonidine.

Conclusions The number of unintentional pediatric exposures to alpha-2 agonists increased from 2000-2011. Clonidine exposures were the most commonly reported, more symptomatic, and associated with 3 deaths. Despite central nervous system depression, bradycardia, and hypotension being common, the need for intubation and vasopressors was rare. (J Pediatr 2014;164:149-52).

Alpha-2 adrenergic agonists exert their effects by stimulating presynaptic alpha-2 adrenergic receptors in the brain. This results in decreased norepinephrine release and decreased sympathetic outflow. Three commonly used oral central alpha-2 adrenergic agonist medications are clonidine, guanfacine, and tizanidine. They are used both in pediatric and adult populations for on- and off-label indications, which include attention deficit hyperactivity disorder (ADHD), hypertension, muscle spasticity, opioid withdrawal, Tourette syndrome, headache, acute pain, nicotine dependence, restless leg syndrome, and tic disorders. Toxicity from overdoses of central alpha-2 adrenergic agonists have been well described in numerous case series and case reports, mostly for guanfacine and clonidine. Their action on central alpha-2 adrenergic receptors can result in central nervous system (CNS) depression, bradycardia, hypotension, miosis, and hypothermia. They have also been suggested to be a “one-pill can kill” pharmaceutical when children ingest single adult doses unintentionally.

As the diagnosis of ADHD has increased, the use of clonidine and, more recently, guanfacine as therapies have also increased. Our objective was to describe trends in unintentional pediatric exposures to clonidine, guanfacine, and tizanidine, 3 commonly prescribed alpha-2 adrenergic agonists, and investigate outcomes, symptoms, treatments, and death.

Methods

We performed a retrospective chart review to examine cases from the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) January 2000-December 2011. NPDS is the data collection system for all of the poison centers in the US and collects information regarding poison center calls in near real-time. Information is systematically collected into a formatted form by trained specialists. Cases are followed until the outcome can be determined. Data captured include demographic information along with circumstances surrounding the exposure such as location, dose, product, patch/non-patch formulation, treatment course, symptoms, and medical outcome. All poison centers have internal quality assurance programs to ensure data validity.
We searched NPDS using the generic codes for clonidine (201081), guanfacine (77773, 0077920), and tizanidine (177000). Only cases that were single substance, unintentional exposure calls for children ≤12 years of age were included in the search. Unintentional exposure was defined as an exposure resulting from an unforeseen or unplanned event. This includes general accidental exposures, therapeutic errors, and unintentional misuse. The cases were abstracted into a standardized data set and included demographic data (age, sex), management site (healthcare facility), symptoms (respiratory arrest, depression, cyanosis, drowsiness, lethargy, coma, bradycardia, hypotension, cardiac arrest, death), treatments (charcoal, atropine, intravenous [IV] fluids, intubation, naloxone, vasopressors, whole bowel irrigation), and severity of clinical effects (none, mild, moderate, severe). Treatments were considered given if they were documented as performed, or recommended and performed. Detailed definitions on NPDS data fields, including medical outcome, are available in the appendix of the AAPCC 2011 Annual Report of the NPDS. Major effect is defined as a patient who exhibits signs or symptoms as a result of the exposure that are life-threatening or result in significant residual disability or disfigurement. Moderate effect is defined as a patient who exhibits signs or symptoms as a result of the exposure that are more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Patch and non-patch formulations were separated for analysis. Death reports were provided to AAPCC NPDS if available. This study had local institutional review board approval.

Descriptive statistics were performed on demographic data, management site, symptoms, determined using a negative binomial linear model in SAS v. 9.3 (SAS Institute, Cary, North Carolina). The total number of human exposure calls to NPDS for children <12 years old was included in the model as an offset to account for the growth in annual poison center calls. This model examined the change in the percentage of calls (of all pediatric exposures) that were coded as exposure to alpha-2 adrenergic agonist medications.

Results

There were 27,825 clonidine exposures (67.3% male, median age: 4 years), 6143 guanfacine exposures (69.8% male, median age: 6 years), and 856 tizanidine exposures (51.9% male, median age: 2 years) of non-patch formulations during the 11-year period. There was a significant increase in poison center calls for all alpha-2 agonist medications over the 11 years (5.9% per year, CI 3.6, 8.2). Individually, the percentages of exposures from 2000–2011 have significantly increased for guanfacine and tizanidine. The majority of exposures were managed at a health care facility: 18,288 clonidine exposures (65.7%), 3376 guanfacine exposures (55%), and 499 tizanidine exposures (58.3%; Figure). There were 5558 major or moderate effects documented for clonidine (19.9% for clonidine exposures), 841 for guanfacine (13.7% of guanfacine exposures), and 34 for tizanidine (3.9% of tizanidine exposures). Clonidine exposures reported the most respiratory symptoms (799, 2.9% of clonidine exposures), CNS depression (12,612, 45.3%), bradycardia (2847, 10.2%), and hypotension (2365, 8.5%). In all exposures, there were 7 cardiac arrests and 3 deaths, all attributable to clonidine (Table I).

Several treatments were administered to patients with alpha-2 adrenergic agonist exposures. Clonidine exposures received the most and widest variety of interventions. This included 5217 (18.8%) patients treated with single-dose activated charcoal, 494 (1.8%) patients treated with atropine, 4620 (16.6%) patients treated with IV fluids, 710 (2.6%) intubations, 2301 (8.2%) patients treated with naloxone, and 132 (0.4%) patients requiring vasopressors (Table II). There were 220 clonidine patch exposures (58% male, median age 2 years). Of these, 141 (64%) were for reported ingestion. The majority of exposures (70.5%) were managed in a healthcare facility. Sixty-three (28.7%) patients were determined to have a major or moderate effect. There were 7 (3.2%) reports of respiratory symptoms, 105 (48.6%) with CNS depression, 38 (17.3%) with bradycardia, and 21 (9.5%) with hypotension. There were no cardiac arrests or deaths reported for patch exposures. Three (1.4%) exposures were treated with (performed, or recommended and performed) atropine, 47 (21.4%) IV fluids, 26 (11.8%) with naloxone, 5 (2.3%) required intubation, and 3 (1.4%) required vasopressors. Of the patch ingestions, 14 (6%) patients received single dose activated charcoal, 1 (0.4%) patient received multiple doses of activated charcoal, and 6 (3%) received whole bowel irrigation. The number of clonidine patch calls had a nonsignificant increase over time, 2.3%/y (P = .66).

Figure. Trends for alpha-2 agonist medication exposures from 2000–2011. There was a significant trend over time for the overall increase of alpha-2 agonist calls to NPDS at 5% per year, CI 3.6–8.2. (P < .001). Guanfacine and tizanidine had significant increases (P < .0001). Tizanidine calls increased by about 21.3% per year, clonidine by 3.3% per year, and guanfacine by 14.7% per year. The difference in the slope compared with tizanidine is significant for clonidine (P = .0007), but not for guanfacine (P = .2514).
Unintentional Pediatric Exposures to Central Alpha-2 Agonists Reported to the National Poison Data System

Over the 11-year time period, there has been an increase in unintentional pediatric exposures to central alpha-2 adrenergic agonists reported to US poison centers, with guanfacine showing the largest percentage increase in exposures over the time period. Patients with clonidine exposures were more likely to report symptoms and more likely to receive interventions. CNS depression, more specifically drowsiness and lethargy, and bradycardia were the most common effects. Respiratory arrest was uncommon. Very few patients required critical care interventions such as intubation, atropine, or vasopressors. Overall mortality was very low. There were few clonidine patch exposures, but the proportion with CNS depression, bradycardia, and hypotension was higher for patch than non-patch formulations of clonidine.

The increase of alpha-2 agonist unintentional pediatric exposure calls revealed a continued and marked increase from previous reports. Poison center data 1993-1999 showed an increasing trend, but there were less than 1000 clonidine from previous reports. Poison center data 1993-1999 showed the largest percentage increase in exposures over the time period. Patients with clonidine exposures were more likely to report symptoms and more likely to receive interventions. CNS depression, more specifically drowsiness and lethargy, and bradycardia were the most common effects. Respiratory arrest was uncommon. Very few patients required critical care interventions such as intubation, atropine, or vasopressors. Overall mortality was very low. There were few clonidine patch exposures, but the proportion with CNS depression, bradycardia, and hypotension was higher for patch than non-patch formulations of clonidine.

The increase of alpha-2 agonist unintentional pediatric exposure calls revealed a continued and marked increase from previous reports. Poison center data 1993-1999 showed an increasing trend, but there were less than 1000 clonidine exposures and 200 guanfacine exposures/y.16-20 This stands in contrast to the 2011 data, which shows that there were almost 3000 clonidine exposures and over 1500 guanfacine exposures. This parallels the increase in both the diagnosis of ADHD and the prescribing of ADHD medications. Specifically, with the addition of extended release guanfacine in 2010, the prescribed use of clonidine and guanfacine has almost tripled between 2009 and 2010.13 Other reasons may be the use of alpha-2 agonists by people in the home for other indications such as hypertension, however, this information was not examined.

Despite the high percentage of symptomatic exposures, the number of treatments and interventions besides IV fluids remained low. The majority of cases reported CNS depression. However, intubation was a rare event (2%), which suggests that CNS depression was minimal or not associated with respiratory depression. Bradycardia and hypotension were common events, but the need for atropine (2.3%) or vasopressors (0.5%) was very low. This may be related to the mechanisms of action of these medications. By inhibiting release of catecholamines, they expose underlying vagal tone, but do not directly decrease heart rate or blood pressure.

There was a variation and inconsistency in treatment patterns for these exposures with moderate to severe outcomes: 1%-6% received atropine, 2%-24% IV fluids, 5%-30% naloxone, and 0.5%-5% vasopressors. This suggests that not only clinical effects vary but also that one specific therapy was not highly effective. There are also mixed reports on the efficacy of naloxone and reversing alpha-2 adrenergic toxicity, which may reflect why only 8% of clonidine exposures received naloxone and even less with guanfacine and tizanidine.21-24

There have been several reports of toxicity in the literature resulting from either ingestion or prolonged dermal contact from clonidine patch exposures.25-29 In our review, exposure to clonidine patch formulations were much less common than non-patch formulations, but these exposures were more likely to produce moderate/major effects and symptoms. This may be due to the larger amount of clonidine in a patch formulation (a patch can carry up to 9 mg), prolonged release of medication from patches in the gastrointestinal tract, prolonged dermal exposure, or physician inexperience with management of patch ingestion (compared with pills) leading to increased reporting. However, there were no deaths with clonidine patch ingestions. With patch ingestions, if not chewed or torn, exposure doses may be lower over a prolonged period of time resulting in decreased absorption compared with immediate high-dose exposures and more rapid absorption from pill or liquid formulations. Activated charcoal and/or whole bowel irrigation also has been suggested to prevent absorption when a patch formulation has been ingested.25-27 Of the 141 patch ingestions, very few received gastric decontamination. Only 14 patients received single dose activated charcoal, 1 patient received multidose activated charcoal, and 6 received whole bowel irrigation. There were no serious outcomes or deaths from patch exposures.

We found no evidence to support the inclusion of clonidine as a pharmaceutical where “one pill can kill.” Mortality was very low (3 cases reported to NPDS) and all were exceptional cases. The first fatality was a 2-year-old female and her twin who ingested an unknown amount of clonidine with a suspicion of up to 55 tablets of unknown strength between the 2 siblings. She was found unresponsive and appeared to

### Table I. Symptoms reported to NPDS for central alpha-2 agonist exposures

<table>
<thead>
<tr>
<th></th>
<th>Clonidine</th>
<th>Guanfacine</th>
<th>Tizanidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(27 825)</td>
<td>(6143)</td>
<td>(856)</td>
</tr>
<tr>
<td>Moderate or major effects</td>
<td>5558 (19.9%)</td>
<td>841 (13.7%)</td>
<td>34 (3.9%)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>799 (2.9%)</td>
<td>24 (0.4%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>68 (0.2%)</td>
<td>3 (&lt;0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>717 (2.6%)</td>
<td>20 (0.3%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>14 (0.1%)</td>
<td>2 (&lt;0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>CNS depression</td>
<td>12 612 (45.3%)</td>
<td>1775 (28.9%)</td>
<td>187 (21.8%)</td>
</tr>
<tr>
<td>Drowsiness/lethargy</td>
<td>12 303 (44.2%)</td>
<td>1763 (28.7%)</td>
<td>185 (21.6%)</td>
</tr>
<tr>
<td>Coma</td>
<td>309 (1.1%)</td>
<td>12 (0.2%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2847 (10.2%)</td>
<td>497 (8.1%)</td>
<td>11 (1.3%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2365 (8.5%)</td>
<td>355 (5.8%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>7 (0.0003%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (0.0001%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table II. Treatments reported to NPDS for central alpha-2 agonist exposures. These were either performed or recommended and performed

<table>
<thead>
<tr>
<th></th>
<th>Clonidine</th>
<th>Guanfacine</th>
<th>Tizanidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(27 825)</td>
<td>(6143)</td>
<td>(856)</td>
</tr>
<tr>
<td>Single dose activated charcoal</td>
<td>5217 (18.8%)</td>
<td>723 (11.7%)</td>
<td>113 (13.2%)</td>
</tr>
<tr>
<td>Atropine</td>
<td>494 (1.8%)</td>
<td>28 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IV fluids</td>
<td>4620 (16.6%)</td>
<td>576 (9.2%)</td>
<td>36 (4.3%)</td>
</tr>
<tr>
<td>Intubation</td>
<td>710 (2.6%)</td>
<td>15 (0.3%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Naloxone</td>
<td>2301 (8.2%)</td>
<td>116 (1.8%)</td>
<td>6 (0.8%)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>132 (0.4%)</td>
<td>9 (0.1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
have aspirated. She was intubated and given epinephrine and atropine. She required dopamine and epinephrine infusions, but continued to deteriorate and died 48 hours into her hospital course. Her twin recovered after requiring intubation and vasoppressor support. The other fatality occurred to a 6-year-old who received a supratherapeutic dose of liquid clonidine because of a compounding error. This patient was unresponsive, apneic, bradycardic, and hypotensive. The patient was intubated and developed cerebral edema with worsening hemodynamic instability. The patient died 78 hours into his hospital stay. No fatality abstract was available for the third death.

The major limitation to our study is that not all cases are reported to the NPDS. There can be a reporting bias, as cases reported to poison centers may be more likely to be ill or have more clinical effects, and deaths may not be reported.\textsuperscript{30,51} Information is collected over the phone by specialists in poison information. Although the specialists are trained and collect a specified data set, they are limited to recording the information provided by the caller. Although categories of data are standard, the amount of information available or documented can be variable. For example, the exact dose is often unknown and laboratory confirmation of the exposure is rarely obtained. Therefore, it is impossible to validate exposure histories in many cases, and there is likely a proportion of cases where the dose is inaccurate or the exposure is suspected but did not actually occur.

In conclusion, there was a significant increase of unintentional pediatric exposure calls to central alpha-2 adrenergic agonists over the last decade. Clonidine exposures were most common and most likely to develop symptoms. There were 3 deaths all due to clonidine. Guanfacine exposures increased after it was approved for treatment of ADHD. For all exposures, CNS depression was frequently reported and bradycardia was the most common cardiovascular symptom. Despite CNS depression, bradycardia and hypotension being common, coma and respiratory depression were infrequent. The need for intubation, atropine, and vasopressors was rare and deaths appear to only occur in extreme cases.

Submitted for publication May 2, 2013; last revision received Jun 28, 2013; accepted Aug 20, 2013.

Reprint requests: George Sam Wang, MD, Rocky Mountain Poison and Drug Center, 777 Bannock St #0180, Denver, CO 80204. E-mail: George.wang@childrenscolorado.org

References