**Selected Topics:**
**Toxicology**

**ARE ONE OR TWO DANGEROUS? CLONIDINE AND TOPICAL IMIDAZOLINES EXPOSURE IN TODDLERS**

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**Abstract**—Clonidine and the imidazolines, commonly found in topical ophthalmic and nasal decongestants, are chemically related drugs that have been responsible for many pediatric poisonings. These medications can cause significant morbidity in small doses. A review of the available literature reveals that young children have exhibited severe signs and symptoms after ingesting as little as one to two clonidine tablets or 2.5 ml of a topical imidazoline product. Central nervous system depression, respiratory depression, and cardiovascular instability are the most common features of poisoning. Signs and symptoms develop rapidly, within 4–6 h. Care is supportive. Death is rare, but many poisoned patients require monitoring in an intensive care setting. © 2003 Elsevier Inc.

**Keywords**— clonidine; topical imidazolines; pediatrics; toxicity; overdose

**INTRODUCTION**

Clonidine is an imidazoline derivative initially developed in the 1960s as a nasal decongestant. During clinical testing, clonidine caused hypotension and bradycardia, which led to its use as an antihypertensive agent (1). The therapeutic applications of clonidine more recently have expanded to narcotic and alcohol withdrawal, tobacco cessation and peri-menopausal hot flashes (2–5). Clonidine also has been used in children for behavioral problems such as attention-deficit hyperactivity disorder (ADHD) and Tourette’s syndrome (6).

Clonidine poisoning in young children is a significant problem in the United States. The American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS) documented 1438 clonidine exposures in children less than 6 years of age in 2001 (7). The number of clonidine poisonings appears to be increasing in frequency. Klein-Schwartz reports a 2-fold increase in the number of clonidine exposures reported to Poison Control Centers over the period from 1993 to 1999 (8). Expanded therapeutic applications of clonidine among children (e.g., ADHD) may have changed the epidemiology of pediatric clonidine poisoning. In 1990, Bamshad described a series of pediatric clonidine intoxications in which the medication belonged to a grandparent in 13 of 15 cases (9). In contrast, eight years later in 1998, Kappagoda et al. found that only 2 of 16 exposures involved medication belonging to an older relative, whereas the remaining 14 cases involved medications prescribed for children (10). In the largest series to date, Klein-Schwartz reviewed 10,600 pediatric clonidine exposure cases occurring between 1993 and 1999. In that period, the proportion of poisoning cases due to a child’s own medication rose from 2.6% to 13.1% for children under 6 years old (8).

Clonidine is available in the United States in tablets in
0.1 mg, 0.2 mg, and 0.3 mg strengths and in a transdermal patch (Catapress TTS®). The clonidine patch is applied to the skin and changed every 7 days. The patches contain either 2.5, 5, or 7.5 mg of clonidine and are designed to release 0.1, 0.2, or 0.3 mg of clonidine per day (11).

The topical imidazolines are found in many over-the-counter topical eye and nose decongestants. They can produce toxic effects similar to clonidine. Products with imidazoline components are numerous and include: Visine® (tetrahydrozoline), Naphcon® (naphazoline), Afrin Nasal Spray/Pump® (oxymetazoline), and Otrivin Pediatric Nasal® (xylometazoline).

As reported in the AAPCC TESS data, there were 891 children under 6 years old with exposures to ophthalmic tetrahydrozoline in 2001 (7). The number of cases may be so high because these products are accessible to children. Many of these products are available without prescription and most are not packaged with childproof safety caps (12). Furthermore, parents and caregivers may not perceive the potential harm of these products and may not store them safely.

### Table 1. Summary of Symptoms from Case Series of Children with Clonidine Exposure

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>133</td>
<td>10</td>
<td>6</td>
<td>25</td>
<td>11</td>
<td>14</td>
<td>47</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>Dose range mg</td>
<td>0.025–0.5</td>
<td>0.3–3 mg</td>
<td>0.2–4.6 mg</td>
<td>25</td>
<td>0.01–0.57</td>
<td>0.013–2 mg</td>
<td>0.2–10.2 mg</td>
<td>NR</td>
<td>0.008–0.12 mg</td>
</tr>
<tr>
<td>Altered mental status mg/kg</td>
<td>113 (85%)</td>
<td>10 (100%)</td>
<td>5 (83%)</td>
<td>24 (96%)</td>
<td>11 (100%)</td>
<td>14 (100%)</td>
<td>44 (94%)</td>
<td>77 (96%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Bradycardia mg/kg</td>
<td>32 (24%)</td>
<td>6 (80%)</td>
<td>5 (83%)</td>
<td>NR</td>
<td>8 (73%)</td>
<td>11 (79%)</td>
<td>25 (53%)</td>
<td>33 (41%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Hypotension mg/kg</td>
<td>28 (21%)</td>
<td>5 (50%)</td>
<td>3 (50%)</td>
<td>3 (12%)</td>
<td>5 (45%)</td>
<td>7 (50%)</td>
<td>18 (38%)</td>
<td>16 (20%)</td>
<td>4 (28%)</td>
</tr>
<tr>
<td>Respiratory depression or Apnea</td>
<td>23 (17%)</td>
<td>2 (20%)</td>
<td>5 (83%)</td>
<td>12 (48%)</td>
<td>6 (55%)</td>
<td>5 (36%)</td>
<td>18 (38%)</td>
<td>6 (8%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Hypothermia mg/kg</td>
<td>NR</td>
<td>2 (20%)</td>
<td>3 (50%)</td>
<td>4 (16%)</td>
<td>5 (45%)</td>
<td>6 (43%)</td>
<td>8 (17%)</td>
<td>18 (23%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Miosis mg/kg</td>
<td>18 (14%)</td>
<td>4 (40%)</td>
<td>5 (83%)</td>
<td>14 (56%)</td>
<td>5 (45%)</td>
<td>7 (50%)</td>
<td>12 (26%)</td>
<td>38 (48%)</td>
<td>NR</td>
</tr>
<tr>
<td>Hypertension mg/kg</td>
<td>3 (2%)</td>
<td>0</td>
<td>NR</td>
<td>11 (44%)</td>
<td>3 (27%)</td>
<td>6 (43%)</td>
<td>10 (21%)</td>
<td>27 (34%)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>NR</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

NR = not reported.

The exact mechanism behind the hypotensive effect of clonidine is not completely understood. In fact, clonidine can cause a transient rise in blood pressure by activating alpha 2 receptors on peripheral vascular smooth muscle. However, this is usually followed by a decrease in blood pressure and heart rate due to the activation of alpha 2 receptors in the brainstem. This causes decreased sympathetic nervous system output, decreased plasma concentrations of norepinephrine, and decreased peripheral vascular tone (1).

The topical imidazolines also have alpha 2 agonist activity. In contrast to clonidine, the topical imidazolines are designed to stimulate peripheral alpha 2 receptors on local vessels to achieve the intended clinical effect of vasoconstriction. Toxicity may manifest as hypertension, tachycardia, agitation, and generalized peripheral vasoconstriction exhibited as pallor, cyanosis, and diaphoresis (13,14). However, the topical imidazolines can also stimulate centrally located alpha 2 receptors, resulting in clonidine-like effects such as somnolence, hypotension, and bradycardia (15).

### PATHOPHYSIOLOGY

The exact mechanism behind the hypotensive effect of clonidine is not completely understood. In fact, clonidine can cause a transient rise in blood pressure by activating alpha 2 receptors on peripheral vascular smooth muscle. However, this is usually followed by a decrease in blood pressure and heart rate due to the activation of alpha 2 receptors in the brainstem. This causes decreased sympathetic nervous system output, decreased plasma concentrations of norepinephrine, and decreased peripheral vascular tone (1).

CLINICAL MANIFESTATIONS

There is no established minimum toxic dose of clonidine. Significant side effects have been reported after ingestions of one to two tablets. Clonidine toxicity is manifested as central nervous system depression, respiratory depression, and cardiovascular compromise. Clonidine toxicity may be confused with opiate intoxication because lethargy, miosis, and respiratory depression are prominent features. Frequently reported signs include altered mental status, miosis, hypothermia, respiratory depression, bradycardia, hypotension, or hypertension (Table 1). All of these signs have been found in children ingesting as few as 1–2 tablets (Table 2).

Central nervous system effects vary, but some degree of lethargy is common. Fiser et al reported a series of 11 cases of clonidine overdose in which one 21-month-old girl ingested 1¼ clonidine 0.1 mg tablets (0.01 mg/kg) and became somnolent but arousable. They also reported three other toddlers who ingested 0.1–0.3 mg (0.02–0.13 mg/kg) who also were noted to be lethargic but arousable (16). Wedin et al reported a 3-year-old child who ingested one 0.2 mg tablet and became responsive only to painful stimuli (17). Seizures have been reported rarely, and in these reports the exact amounts of clonidine ingested were unknown (18,19).
Respiratory depression is less common but may include apnea (20). Olsson et al. reported on a series of 6 children with clonidine exposure including a 14-month-old girl who ingested one 0.2 mg tablet and developed respiratory depression with apnea (21). There are a number of reports of patients with clonidine overdose requiring endotracheal intubation, however, these children had ingestions of unknown amounts or doses larger than 1–2 tablets (7,16,22–24). There have been no reports of ingestions of 1–2 tablets resulting in symptoms severe enough to require endotracheal intubation. However, the combination of decreased mental status and respiratory depression in very young children theoretically increases the risk of significant complications (e.g., aspiration).

Cardiovascular effects are variable. Bradycardia and hypotension are most commonly reported, but hypertension can also occur. Neuvonen et al. described a 21-month-old girl who developed hypertension and bradycardia after ingesting one 0.3 mg clonidine tablet (25). Olsson described a 14-month-old girl who ingested one 0.2-mg tablet of clonidine and presented with a blood pressure of 170/50 mm Hg and a heart rate of 72 beats/min (21). Cardiac dysrythmias other than sinus bradycardia, including sinus dysrythmia and premature atrial contractions, also have been noted, but the dose of clonidine ingested was not specifically reported in these patients (21,26).

Fiser et al. described a dose-response relationship between amount ingested and clinical manifestations among 11 children with clonidine intoxication (16). There were minimal symptoms in patients ingesting less than 0.01 mg/kg, bradycardia and hypotension in those ingesting 0.01–0.02 mg/kg, and respiratory depression in those in whom the dose exceeded 0.02 mg/kg. However, as illustrated in Table 2, severe symptoms can occur with doses as small as 0.009 mg/kg.

Symptoms of clonidine intoxication usually develop quickly because it is rapidly absorbed. Wiley et al. reported onset of symptoms within 4 h for all 47 patients reviewed (24). Rarely, serious symptoms may be delayed. Fiser et al. described a 19-month-old girl who ingested one 0.3 mg tablet of clonidine and developed hypotension 6 h after admission to the PICU (16). Symptoms usually resolve within 24–48 h (20,27).

Ingestion of a single clonidine patch may pose a significant risk to small children, as each patch contains a large amount of drug. Twenty to 75% of residual drug may remain even after the patch has been used for several days (22,28). There are several reports of patches that had been worn and discarded, but subsequently caused serious symptoms when ingested by young children (28,29).

Like clonidine, the topical imidazolines can stimulate centrally located alpha 2 receptors, resulting in somnolence, hypotension and bradycardia (15) (Table 3). Like clonidine as well, symptoms generally develop rapidly, within 15 min to 4 h after ingestion, and resolve within 24 h (12,14).

Altered mental status is the most frequent sign reported in topical imidazoline toxicity. Mahieu et al. reported a series of 19 children with naphazoline exposure in which 14 of the 19 had sleepiness, whereas 2 had agitation (14). The intoxicated child may exhibit both agitation and lethargy (30). Seizures have been reported rarely (31).

Table 2. Summary of Reported Cases of Children Ingesting 1–2 Tablets of Clonidine

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Amount ingested (mg/kg)</th>
<th>Altered mental status</th>
<th>Bradycardia</th>
<th>Hypotension</th>
<th>Respiratory depression</th>
<th>Hypothermia</th>
<th>Miosis</th>
<th>Hypertension</th>
<th>Naloxone administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamshad 1990 (9)</td>
<td>0.1 mg * (0.009)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fiser 1990 (16)</td>
<td>0.2 mg (0.02)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fiser 1990 (16)</td>
<td>0.1–0.2 mg (0.13)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fiser 1990 (16)</td>
<td>0.1 mg (0.01)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fiser 1990 (16)</td>
<td>0.2 mg ** (0.02)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Neuvonen 1979 (25)</td>
<td>0.3 mg (0.03)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Olsson 1983 (21)</td>
<td>0.2 mg (NR)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wedin 1990 (17)</td>
<td>0.2 mg (NR)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

NR = Not reported.
* Included a reported co-ingestant of HCTZ 50 mg.
** Included a reported co-ingestant of KCl 600 mg (sic).
† Temperature 36.4°C.
Visine® (tetrahydrozoline 0.05%) and had intermittent episodes of apnea (13).

As with clonidine, the topical imidazolines can cause either hypertension or hypotension, and bradycardia or tachycardia (15,32).

A minimum toxic dose of the topical imidazolines for children also has not been established. As little as 2.5–5 ml has caused serious symptoms, as illustrated in the case of a 1-year-old girl who became drowsy, pale, bradycardic with respiratory depression, cool extremities and miotic pupils after ingesting 2.5–5 ml of 0.05% tetrahydrozoline (33). However, it seems that exposure to topical imidazoline may be well tolerated by most children. In a review of Maryland Poison Center data over a period of 31 1/2 years, out of 64 cases of children exposed to tetrahydrozoline, 57 (86%) were managed at home, and only 7 (11%) had symptoms that could be attributed to the exposure (30).

Fatalities are unusual for clonidine and have not been reported for the topical imidazolines. In reviewing the AAPCC TESS data from 1983–2001, there was one clonidine-associated death in a child under 6 years old (7,34–51). The case was a 23-month-old who ingested an unreported amount of clonidine and developed bradycardia followed by cardiac arrest during intubation (50). Likewise, there have been few reported deaths in the literature. One involved a 3-year-old girl who ingested 20–30 tablets (52). There have been several reports of sudden death in older children who were taking clonidine and methylphenidate concurrently (53).

**TREATMENT**

The majority of studies referenced here are either case studies or case series. Consequently, therapeutic recommendations are based on the authors’ evaluation of the published data with strength of evidence less than that provided by randomized clinical trials, case control studies, and meta-analyses.

All children with suspected clonidine ingestion above the therapeutic dose (0.002–0.005 mg/kg) should be evaluated by a physician, preferably in a setting where hemodynamic monitoring is available (54). Children who remain asymptomatic for 6 h postingestion can be sent home with close supervision for the following 24 h. All others should be admitted. Most admitted children should go to an ICU setting because they are at risk for bradycardia and hypotension.

Children who have been exposed to topical imidazolines may be managed less conservatively. As demonstrated in the Maryland Poison Control series, asymptomatic children can be safely managed at home in the care of a responsible adult (30). A physician should evaluate children with symptoms (e.g., altered mental status).

Supportive treatment is appropriate for clonidine and topical imidazoline intoxications. Do not give ipecac syrup because central nervous system depression may develop rapidly. Administer activated charcoal for clonidine ingestion if there are no contraindications. Due to the rapid rate of absorption for the topical imidazolines, charcoal should be administered early, within 1 h of ingestion.

Administer supplemental oxygen to maintain a pulse oximetry reading at or above 95%. Endotracheal intubation is required rarely for symptomatic children. Children with bradycardia respond well to atropine. Hypotension often responds to crystalloid, although some patients may require vasopressors such as dopamine. Hypertension may be transient and followed by severe hypotension (55). Elevated blood pressure with evidence of

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (months)</th>
<th>Drug ingested</th>
<th>Amount ingested (mg/kg)</th>
<th>Altered mental status</th>
<th>Bradycardia</th>
<th>Hypotension</th>
<th>Respiratory depression</th>
<th>Hypothermia</th>
<th>Miosis</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahieu 1993 (14)</td>
<td>&lt;6 years</td>
<td>Naphthyliimidazoline</td>
<td>NR 1–6 drops</td>
<td>14 (74%)</td>
<td>12 (63%)</td>
<td>1 (5%)</td>
<td>10 (52%)</td>
<td>5 (26%)</td>
<td>1 (5%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Söderman 1984 (31)</td>
<td>&lt;6 years</td>
<td>Oxymetazoline 0.05%</td>
<td>Unknown 7.5–15 ml</td>
<td>2 (22%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Higgins 1991 (13)</td>
<td>&lt;24 months</td>
<td>Tetrahydrozoline 0.05%</td>
<td>24 months 2–17 months</td>
<td>2 (100%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Klein-Schwartz 1984 (30)</td>
<td>≤24 months Tetrahydrozoline 0.05%</td>
<td>5–17 months 7.5–15 ml</td>
<td>2 (100%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Jensen 1989 (15)</td>
<td>≥17 months</td>
<td>Tetrahydrozoline 0.1%</td>
<td>4–5 ml</td>
<td>1 (100%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mindlen 1986 (33)</td>
<td>12 months</td>
<td>Tetrahydrozoline 0.05%</td>
<td>2.5–5 ml 1/2 dropper</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thompson 1970 (32)</td>
<td>1 month</td>
<td>Xylometazoline</td>
<td>3 doses</td>
<td>1 (100%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NR = not reported.
end-organ compromise should be treated aggressively. Antihypertensive agents with a rapid onset of action and short half-life (e.g., nitroprusside) are appropriate in this situation (56).

There are reports of naloxone reversing symptoms of clonidine intoxication, including mental status depression, respiratory depression, and hypotension, but its use as an antidote remains controversial (8,57,58). Although naloxone is well tolerated by most children, there have been a number of clonidine-poisoned children in whom severe hypertension developed after naloxone administration (59,60). Naloxone is recommended in cases of clonidine poisoning causing severe respiratory depression where intubation may be needed. The use of naloxone should be considered in cases of severe mental status depression and cardiovascular compromise. Because naloxone has a half-life of 1 h, whereas that of clonidine is 12–16 h, patients who respond to the initial dose of naloxone may have recurrent symptoms requiring repeated dosing or a continuous infusion (11).

The only published report of the use of naloxone in topical imidazoline poisoning involves a 15-month-old girl who was exposed to naphazoline and was treated with 0.3 mg naloxone and 0.5 mg flumazenil without any clinical effect (14). Given the paucity of clinical data, naloxone is not recommended for routine use in topical imidazoline poisoning.

**CONCLUSIONS**

Clonidine and the topical imidazolines can cause serious toxicity in young children in doses as small as 1–2 tablets of clonidine and 2.5–5 ml of topical imidazoline. The expanded therapeutic application of clonidine, particularly among children, may lead to increased numbers of pediatric poisonings. Topical imidazolines are available in over-the-counter eye and nose preparations without childhood safety caps; this may give adults the impression that they are harmless, and makes these products potentially more accessible to young children.

Children under 6 years old who have ingested clonidine above the therapeutic dose should be examined by a physician. Symptomatic children exposed to the topical imidazolines also should be examined by a physician. All others can be watched at home as long as the history is reliable, close supervision is available, and the time of day allows for proper supervision. Symptom onset occurs within 4–6 h for most children. Observe children for at least 6 h after exposure.

Treatment is supportive, including activated charcoal, supplemental oxygen, and airway protection if indicated. More serious intoxications may require intravenous fluids and vasopressor agents. Consider naloxone if endotracheal intubation is imminent. Very few children die as a result of these exposures, but many require hospital admission and intensive care monitoring.

**REFERENCES**
