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Selected Topics: Toxicology

TOXICITY FROM UNINTENTIONAL PEDIATRIC INGESTION OF A PERFORMANCE-ENHANCING DRUG: A CASE REPORT WITH REVIEW OF CLENBUTEROL TOXICITY AND TREATMENT

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☐ **Abstract—Background: Clenbuterol is a long-acting β-adrenergic agonist that is not Food and Drug Administration–approved for use in the United States, but may be obtained without a prescription from various unregulated sellers. It has seen increasing use as a performance-enhancing drug for sports. Literature on pediatric toxicity and treatment is limited. Case Report: We report a case of a 2-year-old female presenting after an exploratory ingestion of clenbuterol. Why Should an Emergency Physician Be Aware of This?: Use of performance-enhancing agents is increasing and physicians should be aware of the potential toxicity of intentional and unintentional ingestions of β-adrenergic agonists. Patients may exhibit nausea, vomiting, tremor, tachycardia, and hypotension, along with laboratory abnormalities, including hyperglycemia, hypophosphatemia, hypokalemia, and hyperglycemia. Hypotension might not respond to adrenergic agents and may require administration of β-adrenergic antagonists to maintain adequate perfusion.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—clenbuterol; β-adrenergic agonist; performance-enhancing drugs**

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INTRODUCTION

Clenbuterol is a long-acting β_2- and β_3-selective adrenergic agonist used for reversal of bronchoconstriction for asthma and nutrition partitioning for athletic enhancement. Clenbuterol is not Food and Drug Administration (FDA)–approved for use in the United States, but is being misused or abused increasingly by athletes desiring enhancement of lean muscle mass to adipose tissue ratio. Agonism at β_2 and β_3 adrenergic receptors creates a hyperadrenergic state characterized by tachycardia with reflex hypotension exacerbated by smooth muscle relaxation. β_2 receptor activation causes skeletal muscle potassium uptake, creating a state of functional hypokalemia. Clenbuterol increases available glucose by upregulating glycogenolysis, gluconeogenesis, and glycolysis, while also stimulating insulin secretion to enhance skeletal muscle glucose utilization. β_3 stimulation by clenbuterol enhances adipose lipolysis. Clenbuterol toxicity in adults and children causes tachycardia, hypotension, nausea, vomiting, tremor, hyperglycemia, hypokalemia, and hypophosphatemia. As clenbuterol use in the United States increases, emergency physicians should be aware of how to recognize and treat clenbuterol toxicity.

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CASE REPORT

A previously healthy 2-year-old female (7.8 kg) was found by her mother ingesting the contents of a bottle containing clenbuterol 60-μg tablets. The patient's father had purchased the tablets from the Internet for enhancement of athletic performance. The mother estimated that between 1 and 10 tablets had been ingested, or 7.7–76.9 μg/kg. The poison center was contacted and the patient was referred to a local emergency department.

Emergency Department Course

On initial evaluation, the patient was normothermic with heart rate (HR) 170 beats/min, blood pressure (BP) 100/40 mm Hg, and had normal oxygen saturation on room air. Her examination was significant for flushed skin, dilated pupils, and a hyperactive sensorium. Laboratory evaluation was notable for hypokalemia (2.7 mmol/L) and hyperglycemia (315 mg/dL). A complete blood cell count was significant for a leukocytosis (white blood cell count 20 $\times$ $10^3/\mu$L). An electrocardiogram showed a QRS interval of 76 ms and prolonged corrected QT interval of 550 ms. She received 500 mL of 0.9% saline, 10 mEq of i.v. potassium chloride, 10 mEq of oral potassium chloride (with unclear absorption due to vomiting), and 1 mg of i.v. lorazepam. She was then transferred to a tertiary care pediatric intensive care unit (PICU).

PICU Course

On arrival to the PICU, 4 h after ingestion, temperature was 39.1°C, HR 194 beats/min, BP 79/37 mm Hg, respiratory rate 40 breaths/min, and 98% oxygen saturation on room air. Physical examination showed a well-developed but tremulous child, pupils were 6 mm and reactive, lungs were clear to auscultation, tachycardic to cardiac auscultation without appreciable murmur, abdomen was soft and nontender, extremities were warm with mild mottling and normal capillary refill, and skin was dry with mild facial flushing. Laboratory evaluation revealed the following: sodium 142 mmol/L, potassium 2.4 mmol/L, chloride 112 mmol/L, HCO_3 16 mmol/L, blood urea nitrogen 14 mg/dL, creatinine 0.25 mg/dL, glucose 212 mg/dL, calcium 7.5 mg/dL, ionized calcium 1.08 mmol/L, albumin 2.6 g/dL, magnesium 1.4 mg/dL, and phosphorous 0.7 mg/dL. Whole blood lactate was elevated at 4.4 mmol/L. Serum acetaminophen, salicylate, and ethanol were undetectable. A urine drug screen was negative for amphetamine, barbiturate, benzodiazepine, cannabinoid, cocaine metabolite, ecstasy, methadone, methamphetamine, opiate, oxycodone, and phencyclidine.

Soon after arrival, a norepinephrine infusion was started at 0.01 μg/kg/min and titrated to 0.1 μg/kg/min over the first hour. However, the patient remained tachycardic and hypotensive. Toxicology was consulted and recommended esmolol infusion, which was started about 90 min after the patient's arrival. Esmolol was titrated to 400 μg/kg/min over the next 10 h. Once the esmolol infusion reached this rate, the norepinephrine dose was rapidly down-titrated with a corresponding improvement and stabilization of BP (Figure 1). Norepineprhine was discontinued on the morning of hospital day 3 and esmolol was titrated down and discontinued that evening. Vital signs at that time included HR 102 beats/min and BP 110/48 mm Hg. She was given supplemental calcium gluconate and sodium phosphorus while continuing to receive i.v. fluids while in the PICU. On hospital day 3, all i.v. medications were discontinued and she was transferred to the hospital floor. On hospital day 4, she was discharged home.

DISCUSSION

A 2-year-old patient ingested clenbuterol and developed significant symptoms and laboratory abnormalities, including nausea, vomiting, tremor, tachycardia, hypotension, hypokalemia, and hypophosphatemia. She initially had poor response to norepinephrine but exhibited subsequent improvement of her hemodynamic status with the initiation of esmolol, a β-adrenergic antagonist.

Clenbuterol Pathophysiology and Pharmacokinetics

Clenbuterol is a β-adrenergic agonist selective for β_2 and β_3 receptors. β receptors are G-protein–coupled receptors that mediate adrenergic signaling and are involved in numerous autoregulatory physiologic functions. Activation of β_2-adrenergic receptors results in multiple effects, including vascular smooth muscle relaxation, bronchodilation, inhibition of uterine contractions, decreased gut motility, inhibition of mast cell degranulation, and increased potassium uptake by skeletal muscle. It also increases available glucose by stimulating skeletal muscle glycogenolysis, stimulating hepatic gluconeogenesis and glycolysis, and increasing insulin and glucagon secretion. Activation of β_3-adrenergic receptors increases adipose lipolysis and thermogenesis. Clinical effects of clenbuterol toxicity include tachycardia, hypotension, hypophosphatemia, hypomagnesemia, and hyperglycemia. Clenbuterol has also been reported to cause supraventricular tachycardia and atrial fibrillation (1).

At therapeutic oral dosing, clenbuterol reaches peak plasma concentration in 2.5 h and this concentration is maintained for over 6 h. The half-life in plasma is about

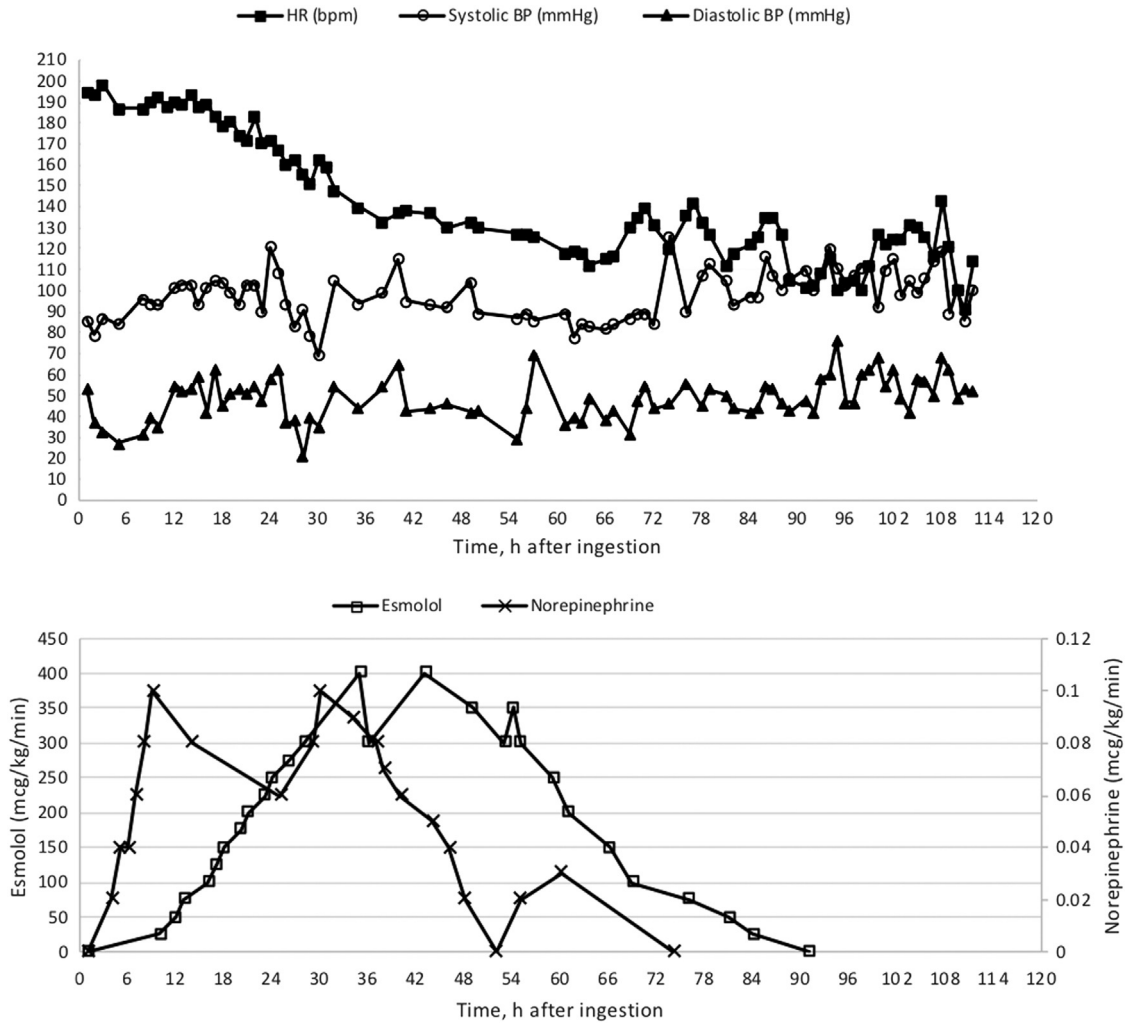

Figure 1. Blood pressure (BP), heart rate (HR), and rate of infusion of esmolol and norepinephrine during hospitalization.

35 h, which is significantly longer than other β_2 agonists and accounts for the patient's prolonged hospital course and symptoms. Clenbuterol is 89–98% protein-bound in plasma (2).

Exposures and Misuse

Clenbuterol is not approved for human use in the United States. In 1998, the FDA approved Ventipulmin Syrup (Boehringer Ingelheim Vetmedica, Inc, Duluth, GA) for the treatment of airway obstruction in horses. The anabolic properties of clenbuterol have been used by the cattle/meat industry to increase beef production, but it is banned from use in food or show animals in the United States. Outbreaks related to ingestion of contaminated liver have been reported in other countries (1).

Clenbuterol is approved for asthma in humans outside the United States and is available in 0.01- or 0.02-mg tablets and liquid preparations, with recommended dosage of 0.02–0.03 mg twice a day. Clenbuterol is a banned substance under World Anti-Doping Agency Guidelines and by the statutes of numerous specific sports. It is used by athletes as a nutrition partitioning agent to increase lean muscle mass and decrease adipose tissue. Surveillance of the European Medicines Agency EudraVigilance database showed increasing adverse drug reactions related to clenbuterol misuse/abuse over the 2006–2016 time period (3). Analysis of calls to the New South Wales Poisons Information Centre regarding clenbuterol exposure between 2004 and 2012 also showed an increase in calls over that time period, with the most common reasons for use being bodybuilding and slimming (4). This increased use poses a risk of more availability in the home, and unintentional pediatric exposures and misuse among the adolescent sports population. Abuse by bodybuilders has resulted in rhabdomyolysis, cardiac dysrhythmias, myocardial

infarction, and electrolyte disturbances (1,5). Inadvertent adult clenbuterol intoxication has also been reported from contaminated supplements marketed as anabolic steroids, and from heroin adulteration (6–11).

Treatment for Toxicity

The use of a β-adrenergic antagonist agent is paradoxical when treating hypotension, but is effective in interrupting the β-adrenergic stimulation, which results in tachycardia and hypotension. Although no clinical trials have compared β-agonists to other treatments, their successful use is documented in numerous adult cases (6,10,12–15). Esmolol is an ideal β-adrenergic antagonist due to its short duration of action, allowing rapid titration and discontinuation if necessary. A continuous esmolol infusion should be titrated to HR, BP, and perfusion examination. Patients may require esmolol infusion for 24–48 h due to the long duration of action of clenbuterol. Our patient's blood pressure responded well to the esmolol infusion, and her tachycardia persisted in part due to the clenbuterol and the continuation of norepinephrine.

Although adverse effects related to clenbuterol toxicity in adults are well described, few cases of unintentional pediatric clenbuterol ingestion have been reported. Woolum et al. report a case of a 4 ½-year-old male who ingested veterinary clenbuterol hydrochloride confirmed by laboratory analysis of the product. This patient exhibited tachycardia, hyperglycemia, hypokalemia, and hypophosphatemia, similar to the patient in our report (15). Ou-Yang et al. described a case series of 28 children aged 1–13 years hospitalized with acute clenbuterol poisoning in China, where clenbuterol is available for treatment of asthma. Patients exhibited symptoms of vomiting, palpitations, and limb shaking. Laboratory evaluation showed hypokalemia, hyperlactatemia with acidosis, and hyperglycemia. Patients were treated with β-antagonists, potassium supplementation, and supportive care, and symptoms resolved in 12–78 h. These findings are consistent with our case and suggest that pediatric clenbuterol toxicity is similar to adult toxicity and that treatment with β-antagonists in children is appropriate, as it is in adults (16).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Increased use of clenbuterol for enhancement of athletic performance may result in increased risk for unintentional pediatric exposures and adolescent misuse for sports performance. Clenbuterol is a long-acting β-adrenergic agonist, and affected patients will require prolonged and close monitoring and frequent laboratory evaluation. Clenbuterol toxicity can result in nausea, vomiting, tremor, tachycardia, and hypotension. Laboratory abnormalities may include hyperglycemia, hypophosphatemia, hypokalemia, and hyperglycemia. Recommended treatment for significant hemodynamic instability includes electrolyte repletion and initiation of β-adrenergic antagonists.

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