

## Case Report

# Low Dose Clenbuterol Toxicity: Case Report and Review of Literature

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### Abstract

#### Description

Clenbuterol is a long-acting  $\beta$ -agonist used in oral and inhaled form for asthma treatment outside the U.S. and in veterinary medicine within the U.S. It is also used off-label for anabolic effects worldwide. Toxicity with clenbuterol is increasingly seen in U.S. hospitals, primarily in younger individuals using the drug for competitive athletics or bodybuilding. We present a case of a young patient who presented after an intentional overdose and discuss the relevant literature. Presentations do not correlate with the dosage ingested. Signs and symptoms can range from simple nausea to myocardial ischemia, rhabdomyolysis and cardiogenic shock. Treatment of overdose is simple and should be promptly started using intravenous fluid hydration and potassium supplementation. Benzodiazepines may be utilized for agitation or delirium.  $\beta$ -blockers or phenylephrine may be used to give hemodynamic support. More research is needed to gain an understanding of the optimal treatment of clenbuterol toxicity, especially if it becomes a more frequent reason for medical encounters in the U.S.

#### Keywords

clenbuterol; clenbuterol/toxicity; beta agonist toxicity; cardiotoxins; prescription drug misuse; drug overdose/therapy; case report; review

### Background

Clenbuterol is a long-acting  $\beta$ 2-agonist used for asthma treatment outside the U.S. and in veterinary medicine within the U.S.<sup>1</sup> It is also used off-label (and illegally) for muscle-building anabolic effects by meat farmers, racehorse owners, and athletes, and as a lacing agent in street cocaine and heroin.<sup>1,2</sup>

Previously rare in U.S. medical settings, clenbuterol overdose has become familiar enough to be described in a magazine targeting emergency medicine physicians, in multiple case reports over the last 20 years, and in case series in Australia and Virginia.<sup>1,3-6</sup> The severity of the presentation varies widely. In one case, symptoms persisted even after the serum level had decreased to undetectable.<sup>7</sup> Multiple case series have described clenbuterol toxicity in patients taking heroin contaminated with clenbuterol.

In one retrospective observational study by the New South Wales Poisons Information Centre (equivalent to The American Association of Poison Control Centers), a total of 63 clenbuterol exposures were reported from 2004 to 2012, with only 3 cases in 2008 but 27 in 2012. Patients most commonly used the drug for bodybuilding and slimming. Of these patients, 84% required hospitalization, including a 21-year-old man who suffered a cardiac arrest. The study authors concluded that clenbuterol should be considered in any patient using bodybuilding/slimming products and presenting with sympathomimetic activity.<sup>5</sup>

Reported symptoms of clenbuterol overdose have included nausea, palpitations, chest pain and dyspnea. Signs on examination may include tachycardia, mydriasis, tremors, agitation, confusion, hypotension and tetany. Labs might show hyperglycemia, hypokalemia, hypophosphatemia, lactic acidosis and rhabdomyolysis.<sup>2,8</sup> However, these general symptoms and

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signs may be confounded by the simultaneous ingestion of other substances. For example, hypotension may be absent due to concurrent cocaine use, or heroin may cause miosis.<sup>2</sup>

Cardiac complications include not only chest pain but also supraventricular tachycardia (SVT) and atrial fibrillation (AF) with a rapid ventricular response (RVR).<sup>5</sup> This was first reported in 2007 in a 31-year-old male with an SVT of 254 bpm that did not respond to adenosine 6mg and 12mg but did decrease to 150 bpm with intravenous diltiazem 10mg and then converted to AF with RVR of 125-147 bpm. This patient was eventually successfully cardioverted after 48 hours of AF and then discharged with oral metoprolol.<sup>6</sup> Demand ischemia can be sufficient to cause significant non-ST-elevation myocardial infarction (NSTEMI) or even ST-elevation myocardial infarction (STEMI). One case of NSTEMI occurred in a 23-year-old male who took 5000 mcg of clenbuterol in an attempt to lose weight and presented with chest tightness, ST depressions, and troponin of 5.39 at a hospital in Canada.<sup>9</sup> The only published case report of STEMI thus far is a 55-year-old male in Connecticut who presented with inferior STEMI and rapid AF with a negative coronary catheterization, leukocytosis, hypokalemia, hyperglycemia, anion-gap metabolic acidosis, as well as an osmolal-gap.<sup>4</sup>

Other case reports of NSTEMI have raised suspicion of direct cardiac toxicity from clenbuterol. Two such cases were reported in Massachusetts in 2011 involving two male bodybuilders aged 18 and 21. Both presented with elevated troponins over 4.0 and negative coronary catheterization and echocardiogram. The 18-year-old patient additionally had a normal cardiac MRI.<sup>10</sup> Animal models have shown direct myocardial toxicity and inferior wall necrosis from clenbuterol, which would be consistent with the observed pattern that myocardial injury, when present, appears to affect the inferior wall most often.<sup>11</sup>

Typically, clenbuterol overdose is managed with supportive intravenous fluids and potassium supplementation, as well as benzodiazepines, as needed, for agitation. However, significant tachycardia or hypotension is handled in a seemingly counterintuitive manner.  $\beta$ -blockers such as metoprolol, labetalol or esmolol, which

ordinarily worsen hypotension, are used in this case to counteract the  $\beta$ -agonist effect of clenbuterol. Vasopressors with primary  $\alpha$ -agonist activity such as phenylephrine or norepinephrine are the preferred supportive treatment when  $\beta$ -blockers are insufficient to reverse hypotension.<sup>1</sup>

The majority of clenbuterol overdose cases involve young male bodybuilders or other athletes. Street cocaine/heroin and contaminated meat are other known causes. However, these are not the only types of patients who may present with clenbuterol overdose.

### Case Description

A 21-year-old female presented to ED at approximately 9 pm after ingesting seven of her boyfriend's 40 mcg clenbuterol pills (which were reportedly prescribed for his asthma) due to an argument. She then experienced eight episodes of non-bloody, non-bilious emesis.

On admission, she was in sinus tachycardia to the 140s and hypotensive to 80s/40s but alert and responding to questions appropriately. She was asymptomatic during the admission interview, feeling well, denied psychiatric history and stated she took the pills because she "needed to sleep" because she had to work the following day. She denied suicidal or homicidal ideation or intent to go to sleep without waking up. Pupils were dilated at 6-7 mm, but otherwise, the physical exam was normal.

Urine toxicology panel, serum salicylate level and serum ethanol level were all negative the night of admission. The serum potassium level was noted to be 2.2 mEq/L and magnesium 1.6 mEq/L. Both were supplemented. Blood glucose was initially 249 mg/dL, though this quickly resolved to the 60s-70s after treatment initiation. Significant leukocytosis on admission (white blood cell count  $26.9 \times 1000/\text{mm}^3$ ) improved without antibiotics to  $14.7 \times 1000/\text{mm}^3$  the following morning.

The case was discussed with a toxicologist at the Poison Control Hotline, who recommended a phenylephrine drip to raise systolic blood pressure (SBP) to  $>100$  mmHg with a concurrent esmolol drip to counteract the  $\beta$ -agonism of clenbuterol. The patient was thereupon

transferred to intensive care and started on phenylephrine at 60 mcg/min and esmolol at 50 mcg/kg/min. 60 mEq of potassium bicarbonate by mouth was also dosed. Initial sinus tachycardia without ST changes in the 120s rapidly resolved to normal sinus rhythm in the 90s. A further recommendation by the Poison Control hotline was to monitor pH by venous blood gas (VBG) and to administer bicarbonate for any VBG with a pH <7.25. However, the patient's VBGs never showed a pH less than 7.30.

The patient was downgraded from intensive care on hospital day two after maintaining stable vital signs for four hours after being weaned off both the phenylephrine and esmolol drips. The patient was monitored for an additional night on telemetry and then discharged home in stable condition.

## Discussion

There are no set guidelines for clenbuterol toxicity, but it is becoming familiar enough that it may be worth developing guidelines. Ongoing issues would include:

1. Must all cases be admitted to an intensive care unit (ICU) and receive esmolol drips and possible pressors?
2. Multiple cases in the literature have been treated with oral beta-blockers only, rather than IV, with excellent outcomes. Is there a role for shorter-acting oral beta-blockers?
3. Should clenbuterol level be an orderable test in the hospital for young patients presenting with chest pain or dyspnea (especially athletes/bodybuilders)?
4. Is there any safe dose of clenbuterol, given case reports of toxicity at low doses as well as high doses?

Our patient clinically appeared very stable and asymptomatic despite significant hypotension and two positive systemic inflammatory response syndrome criteria (tachycardia plus leukocytosis). She was transferred to ICU mainly out of an abundance of caution. The dose of clenbuterol she took (280 mcg) was significantly lower than those reported in most analogous prior cases. It appears plausible in hindsight that she might have recovered equally well had she been given only oral  $\beta$ -blockers and intravenous fluids on the telemetry unit, and that this could have saved the significant

expense of an ICU transfer. On the other hand, case reports have shown significant troponin leaks and myocardial injury even in young and healthy patients in whom hypotension was not reported. Given this, the expense of a short intensive care stay for closer monitoring and more aggressive correction of tachycardia and hypotension was arguably justified. It may even have prevented the development of cardiac symptoms or actual ischemia a few hours later.

Treatment with oral  $\beta$ -blockers would have required at least a few more hours to titrate dosing to the desired effect, as compared to minutes for the intravenous esmolol drip. Oral dosing would also have risked over-correction, if the initial oral  $\beta$ -blocker dose was too high, given the low initial clenbuterol dose in this case. Even though our patient presumably had a strong and healthy heart with sufficient reserve to withstand several hours of hypotension and tachycardia without any apparent permanent damage, prolonging the situation for a few more hours may have been an unacceptable risk.

Our facility cannot measure serum clenbuterol levels. Fortunately, this did not impact our case, as the patient's history was reliable, and there was no doubt regarding the identity of the toxin or the cause of her vital sign and lab abnormalities. Even a negative test may not have been helpful in this case since it appears that even low or undetectable levels of clenbuterol do not exclude ongoing toxicity in other case reports. However, we can envision two scenarios in which the ability to "rule in" clenbuterol, and therefore, need for intravenous  $\beta$ -blocker drips, could make a difference. For a more medically-complicated patient in whom other causes of hypotension or shock might be a concern (such as an older bodybuilder in whom clenbuterol toxicity needs to be distinguished from sepsis, heart failure or acute coronary syndromes), a positive clenbuterol test would favor the use of  $\beta$ -blockers over vasopressors. Meanwhile, in a "classic" clenbuterol patient presenting with myocardial infarction or significant troponin elevation, such as a young, healthy athlete with no cardiac history, confirming clenbuterol as a cause would obviate the need for cardiac catheterization that might otherwise be done despite the low likelihood of any findings.

Case reports of cardiac toxicity at relatively low doses of clenbuterol (as low as 20 mcg in one case) likely constitute an argument in favor of continuing to withhold FDA approval for this medication in the United States.<sup>12</sup>

## Conclusion

Though previously very rare, clenbuterol toxicity is being seen more frequently, especially in younger individuals involved in competitive athletics or bodybuilding. No minimum dosage has been identified as necessary to cause adverse effects. Therapies should be based on the patient's hemodynamic stability and symptomatology. Treatment of overdose is simple and should be promptly started using intravenous fluid hydration and potassium supplementation. Benzodiazepines may also be utilized for agitation or delirium. Lastly,  $\beta$ -blockers and/or phenylephrine may be used to give hemodynamic support.

More research is needed to gain an understanding of the optimal treatment of clenbuterol toxicity, especially as it continues to become more prevalent.

## Conflicts of Interest

The authors declare they have no conflicts of interest.

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