Case report

Clenbuterol: a new toxic substance in paediatrics

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SUMMARY

A 13-year-old girl presented to the emergency department with acute onset of chest pain, nausea and tremor. The patient denied drug ingestion, and urine toxicology was negative. ECG demonstrated sinus tachycardia, prolonged QTc (541 ms) and ST depression. Laboratory testing demonstrated metabolic acidosis, hypokalaemia, hypophosphataemia and hyperglycaemia. She was commenced on continuous cardiac monitoring and treated with intravenous fluids and electrolyte replacement. Presenting features and laboratory abnormalities resolved within 48 hours. The National Poisons Information Service and Clinical Biochemistry were integral to her management, advising the clinical team on the likeliest aetiology. Five weeks after discharge, urine toxicology, using mass spectrometry, identified clenbuterol. Clenbuterol is an oral β2-agonist with anabolic and lipolytic effects that is misused as a performance and image enhancing drug. Clinicians must be aware of the increasing availability of these drugs and their potential for causing harm in children and adolescents.

BACKGROUND

A multidisciplinary approach is crucial to managing paediatric patients with known or suspected substance ingestion. The National Poisons Information Service (NPIS), and their online information database 'TOXBASE', and Clinical Biochemists are an underused yet abundant source of toxicology knowledge.[1] They can assist in the investigation and management of suspected substance ingestion in children and adolescents.

We present a case of an adolescent female deliberately ingesting clenbuterol for self-harm. Despite suspicions of an ingested substance, it was only proven by extended urine toxicology, using mass spectrometry, at a specialist UK centre, 5 weeks after discharge. This case aims to highlight useful learning points in the investigation and management of an unknown ingested substance.

Clenbuterol is an oral β2-agonist with anabolic and lipolytic effects, used off-licence as a 'fat-busting' drug.[2] Adverse effects in adults are well documented, but there are limited data on effects in children or adolescents.[3 4] Serious adverse effects include arrhythmia, hypotension and myocardial infarction, even in the absence of concomitant cardiovascular risk factors.[5] Parents should be counselled as to the dangers these drugs pose and how to safeguard young people from accessing them.

CASE PRESENTATION

A 13-year-old girl was brought to the emergency department (ED), via ambulance, with sudden onset of chest pain, nausea, palpitations and tremor. She denied any breathlessness, loss of consciousness or limb pain. She disclosed a high caffeine intake, including energy drinks, fizzy drinks and coffee. She denied any substance ingestion, including legal substances. Multiple clinicians corroborated the history, including questioning her away from her parents. Her parents denied any additional substances kept in the home. She was previously fit and well and had no history of self-harm or mental illness. She took no daily medications and had no allergies. There was no family history of childhood illnesses or unexplained death. She was an only child and lived at home with her parents.

On examination, she was alert and orientated, but anxious. She had clear breath sounds but was tachypnoeic. She was flushed and tachycardic, with normal heart sounds and bounding pulses. She had fine tremors of her extremities. She was warm to touch and vomited during her examination. Vital signs demonstrated tachycardia (139 beats/min) and tachypnoea (22 breaths/min), with normal oxygen saturations (99% in air), blood pressure (110/79 mm Hg) and core temperature (37.0°C).

INVESTIGATIONS

ECG demonstrated sinus tachycardia (123 beats/min), with a significantly prolonged QTc (541 ms) (figure 1). There was T wave inversion in the inferior leads and ST depression in the anterior leads.

Laboratory testing demonstrated leucocytosis, with low levels of magnesium, phosphate and potassium (table 1). Venous blood gas highlighted a high anion gap metabolic acidosis, with hyperlactataemia. Serum troponin levels were negative. Serum paracetamol and salicylate levels were also negative. Urine dipstix testing was highly positive for glucose (glucose +++) but negative for ketones or infective markers. The urine tested negative for pregnancy. Urine toxicology was negative for common substances of abuse.

DIFFERENTIAL DIAGNOSIS

The primary differential was caffeine toxicity, given her substantial reported caffeine use. Her presenting features matched reports of caffeine toxicity.[6 7] Caffeine is a methylxanthine which, when ingested in toxic quantities, presents with anxiety, tachycardia and vomiting, hyperglycaemia and hypokalaemia on laboratory testing and ischaemic changes on the ECG; our patient had all of these features.[6] Given the presence of ischaemic

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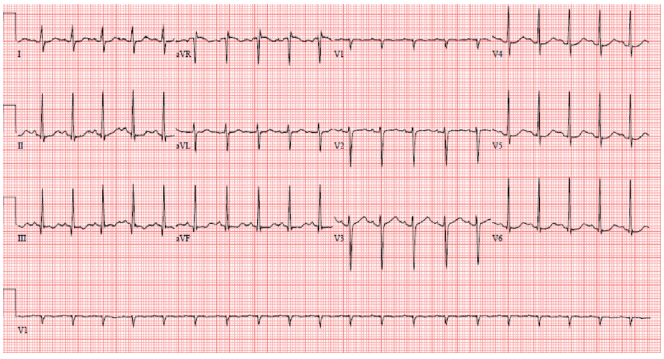

Figure 1 Admission ECG.

ECG changes, cardiology were consulted; they concurred that her clinical examination findings and ECG changes were most likely caffeine induced. A primary tachyarrhythmia was considered unlikely, given the deranged biochemistry and its spontaneous resolution. Recreational drug ingestion was considered less likely, given the lack of disclosure and negative urine testing. Her case was also discussed with the on-call NPIS team, who suggested β-agonist toxicity as a potential cause. Our local clinical biochemist suggested theophylline, also a methylxanthine, as a potential cause, having previously seen cases similar to this. The features of acute chest pain, palpitations and vomiting, with hypokalaemia, hypophosphataemia and hyperglycaemia on laboratory testing and the ECG demonstrating sinus tachycardia and ischaemic changes, matched reports of β-agonist toxicity.[2 8] However, β-agonist toxicity was considered unlikely, given the absence of comorbidities and daily medications, plus the family denied any β-agonist medications being kept in the household.

TREATMENT

The TOXBASE database was used to guide treatment. The patient was monitored with continuous cardiac monitoring, on the acute receiving ward. Her electrolytes were corrected with intravenous fluids, at maintenance rate, containing a high concentration of potassium (0.9% sodium chloride +5% glucose +40 mmol/L potassium chloride). Magnesium and phosphate deficiencies were also corrected with magnesium sulfate (1 g intravenous, $MgSO_4^{3-}$ 50%) and phosphate Sandoz (1 g oral, 32 mmol PO_4^{3-}).

OUTCOME AND FOLLOW-UP

Repeat electrolytes at 6 hours were improving and normalised after 48 hours. She remained tachycardic at 24 hours, but this fully resolved by 48 hours. The initial ischaemic changes on her ECG resolved by 48 hours. At this point, she was asymptomatic and discharged home, with a presumptive diagnosis of caffeine toxicity.

Following advice from the local clinical biochemist, the patient's admission urine sample was sent for extended testing at Leicester toxicology laboratory, which tested negative for caffeine. The urine was retested at Birmingham City Hospital, using qualitative mass spectrometry, and tested positive for clenbuterol and weakly positive for caffeine.

The toxicology results were communicated with the patient's family, who explained that she later disclosed ingesting a 'handful' of her father's 'fat-busting' tablets. Her father confirmed that these tablets were clenbuterol, which he used for his body-building regime. The patient admitted doing this deliberately for self-harm, so she was referred to the child and adolescent mental health services.

Since the urine result was only weakly positive for caffeine, it was felt that this substance was not the principal cause for her symptoms. However, since caffeine could have a contributory effect, it was agreed that the patient should abstain from caffeinated substances.

Table 1 Admission blood results

Blood results	White cell count 30×10^9/L ($4–11\times10^9$/L) Sodium 140 mmol/L (135–145 mmol/L) Potassium 2.3 mmol/L (3.5–5.0 mmol/L) Urea 4.5 mmol/L (2.5–6.5 mmol/L) Creatinine 77 µmol/L (35–70 µmol/L) Magnesium 0.69 mmol/L (0.7–1.0 mmol/L) Phosphate 0.38 mmol/L (0.9–1.8 mmol/L) Glucose 15.9 mmol/L (4–6 mmol/L)
Blood gas results	Hydrogen ions 48.8 nmol/L (35–45 nmol/L) Carbon dioxide 4.6 kPa (4.5–6.0 kPa) Bicarbonate 17.5 mmol/L (22–28 mmol/L) Base excess −7.7 mmol/L (±2 mmol/L) Lactate 7.5 mmol/L (1.0–2.5 mmol/L)

DISCUSSION

Clenbuterol is an oral, β-adrenergic agonist, which is relatively selective for β2 receptors.[5] It is a globally accessible drug, licensed for use in some European countries as a bronchodilator.[9] At significant concentrations, clenbuterol produces a toxidrome of nausea, vomiting, tremor, tachycardia and tachypnoea.[8 10] Peak serum effect is seen within 2–3 hours after ingestion. Clenbuterol has a long half-life (25–39 hours); as such, symptoms may persist for several days after ingestion.[11] ECG changes include sinus tachycardia, QT prolongation and arrhythmias.[10] Metabolic effects include hyperglycaemia, hypokalaemia,

Patient's perspective

Patient's perspective: I felt embarrassed at the time and also scared to let anyone know that I had taken the tablets. Things were getting too much with the other girls at school. I know it was silly and will not do anything like this again. Things are much better at school and with my friends now.
Parents' perspective: We were obviously extremely concerned and worried at the time, the doctors not knowing exactly what the cause had been and her heart murmur made it all the more frightening. The doctors seemed convinced that she had ingested some form of drug either medicinal or recreational. We knew she would never touch illegal drugs and we were convinced she was telling the truth regarding the clenbuterol as several doctors had questioned her in private and we spoke with her on separate occasions to let her know she was in no trouble and that she had to tell the truth as we were worried the condition might get worse if the doctors could not identify the cause. When she was allowed to return home we continued to have chats with her and she eventually admitted taking the drug after we told her the report from the toxicologist was due back and would tell the doctors everything. We have since spoken with a family councillor who met our daughter on several occasions; he told her about coping skills and other ways of dealing with problems and after only a few meetings was happy that she was in a better place and better placed to deal with issues going forward. We now have no performance enhancers or fat burning supplements at home.

Learning points

- β-Agonist toxicity presents with acute sympathomimetic features, ischaemic ECG changes, high anion gap metabolic acidosis and deranged biochemistry (hypokalaemia, hypophosphataemia, hypomagnesaemia).
- Methylxanthine and β-agonist toxicity present similarly, so be wary of attributing features to caffeine alone, without considering other causes.
- Thorough history taking is paramount, when substance ingestion is suspected—ask specifically about prescription and recreational drugs, over-the-counter medications and herbal supplements, which could have been accessed.
- National Poisons Information Services and clinical biochemists are a very useful, yet underused, source of clinical information to guide diagnosis and management in suspected toxic ingestion.

hypophosphataemia, hypomagnesaemia and a high anion gap metabolic acidosis.[5] These effects are transient, with complete resolution to baseline after drug elimination.[10]

In the UK, clenbuterol is a class C controlled substance and as such, illegal to acquire.[12] Clenbuterol can easily be purchased online, however, and is increasingly used without medical supervision, as a performance and image enhancing drug (PIED).[2] Typically, PIED users are reluctant to disclose use of these substances to medical professionals.[13] This makes identifying these substances particularly difficult, given the fear of judicial ramifications.

A small number of cases of clenbuterol ingestion have been described in children and adolescents.[5 8 14] Despite similarities in how children and adults present following clenbuterol ingestion, difficulties arise in paediatric patients being unable, or fearful of, admitting ingestion.[5] These patients may also be unable to accurately quantify the dose they have ingested. Among this cohort, ingestion may be accidental in younger children or for body-enhancing purposes, among vulnerable adolescents.[8 14] As in this case, they may also be used for deliberate self-harm. Despite being an inherently healthy cohort, myocardial injury may result, depending on the dose ingested.[14] Clenbuterol may induce temporary ischaemic changes or irreversible infarcted segments, even in the absence of traditional cardiovascular risk factors.[3]

This case highlights the need for a multidisciplinary approach in the management of children and adolescents with suspected and/or proven toxic ingestions. The TOXBASE database provides information on ~17 000 substances that can be deliberately or accidentally ingested.[15] Additionally, on-call NPIS can provide crucial information to assist in the diagnosis and management of toxic ingestions, especially when the cause is unclear. Our local clinical biochemist was a vital source of toxicology information and led to the eventual diagnosis of clenbuterol ingestion. With the increasing plethora of substances that may be ingested, it is crucial to consider ingestion of a toxic substance, even in the absence of positive urine toxicology. This was the first time this substance had been encountered in our department, but since then, we have seen another case of deliberate clenbuterol ingestion.

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