

Case Report

Detection of Clenbuterol in Heroin Users in Twelve Postmortem Cases at the Philadelphia Medical Examiner's Office

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Abstract

The presence of clenbuterol, a β_2 -adrenergic agonist banned for human use in the United States because of its serious side effects, is reported in a series of 12 postmortem cases in which the cause of death was attributed to illicit drug use. During the first three months of 2007, postmortem specimens from cases previously screening positive for opiates or fentanyl were screened specifically for clenbuterol using enzyme-linked immunosorbent assay. Confirmation of clenbuterol was performed using solid-phase extraction, derivatization with trimethylboroxine, and analysis utilizing a gas chromatograph–mass spectrometer (GC–MS) operated in the full-scan mode. The limits of detection and quantitation in blood were 2.5 and 5 ng/mL, respectively. Linearity was from 5 to 100 ng/mL. Clenbuterol was positive in 12/106 (11%) drug-related cases and in 12/575 (2.1%) of the total cases tested. In each of the 12 cases positive for clenbuterol, heroin use was either confirmed by the presence of 6-acetylmorphine or strongly suspected by the presence of morphine with a history of heroin abuse. Because the use of clenbuterol in the United States is restricted to veterinary medicine, its detection is an unexpected finding. Its presence in these cases serves as a caution to emergency room physicians and toxicologists to consider and test for clenbuterol when treating a suspected heroin user who presents atypically. This is the first known series of clenbuterol-positive cases of illicit drug users to be reported from a medical examiner's toxicology laboratory.

Introduction

Clenbuterol, 4-amino- α -tert-butylaminomethyl-3,5-dichlorobenzylalcohol, is a β_2 -adrenergic agonist capable of exerting a variety of neurological and cardiovascular effects. These include increases in aerobic capacity, oxygen transportation and blood pressure, CNS stimulation, and relaxation of smooth muscle. It has been shown to increase the rate at

which both fat and protein are metabolized while at the same time reducing the rate of glycogen storage (1,2). The primary usage of clenbuterol is in veterinary medicine as a bronchodilator (Ventipulmin[®]); it is banned for use in humans in the United States (1,3). Clenbuterol is the only member of its class to be approved by the U.S. Food and Drug Administration for use in horses. However, because of its positive effect on respiration and subsequently on racing performance, the Association of Official Racing Chemists lists it as a "doping agent"; its identification in postrace samples may lead to sanctions (4).

Because of its growth-promoting properties, clenbuterol can be added to animal feed to induce weight gain and increase muscle mass; its use is banned in the United States for this purpose. However, internationally, some countries have approved it for use in animals not used for food, and a small number of countries have approved it for therapeutic uses in food-producing animals. Despite concerted efforts by the USDA and FDA to enforce a ban in this country, there have been reports of clenbuterol in animals at stock shows in Ohio, Oklahoma, and Colorado (3). Outside the United States, there have been reports of food poisoning caused by clenbuterol in Italy in 1996 (5), in Portugal in 2005 (6), in Spain in 2005 (7) and more recently, in China in 2006.

Clenbuterol's attractive properties as a muscle-building, fat-burning agent have gained the attention of professional and amateur athletes as well as the general public. In 2006, former Major League baseball pitcher Jason Grimsley admitted to using clenbuterol in testimony before federal investigators, effectively ending his career. Professional tennis player Mariano Puerta was suspended for nine months in 2003 for using clenbuterol and more recently was given a second suspension for two years for using the cardiac stimulant etilefrine. Numerous articles promoting clenbuterol as the new weight-loss wonder drug have been reported in the written press and on the Internet. However, the drug also has serious, unpleasant side effects that have been well-documented. These include hypokalemia, hypophosphatemia, hyperglycemia, hypomagnesemia, tachycardia, headaches, muscle spasms, insomnia, and vertigo (2). These

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toxic effects of clenbuterol are similar to that of other beta-adrenergic agonists and may be quite serious. Polish cardiologists reported a case of myocardial infarction in a previously healthy 17-year-old body builder who used clenbuterol (8).

Confirmed reports of clenbuterol use are relatively rare. This is due, in part, to the low concentrations of clenbuterol found in blood or urine that often are below the detection limits of the methods used by clinical laboratories that test only human samples. A case of an accidental clenbuterol poisoning was previously reported by the New York City Poison Control Center (9). More recently there have been reports from five states, New Jersey, New York, North Carolina, South Carolina, and Connecticut, of atypical reactions associated with heroin use that were attributed to adulteration of the illicit drug with clenbuterol (10,11).

In January 2006, clenbuterol was detected unexpectedly in the broad-spectrum GC-MS urine drug screen in one of our cases. Shortly after this occurred, we received a communication from the Philadelphia Poison Control Center that clenbuterol was suspected in several patients, known heroin users, who were being treated at local emergency rooms. Subsequently the Philadelphia Medical Examiner's Office undertook a study to detect the presence of clenbuterol in cases that were presumed to be illicit drug users from either the case history or the initial drug screening results.

Materials and Methods

Specimens

All specimens that included fluoridated blood (1% NaF) from the cardiac area, urine, decomposition fluid, and spleen were collected during autopsies performed between January 1 and March 31, 2007. Aliquots were stored in glass tubes or glass jars at a temperature of -20°C until time of analysis.

Reagents

Solvents used for all analyses were HPLC-grade and obtained from Fisher or J.T. Baker. Columns used for extractions were CSDAU303 columns purchased from United Chemical Technologies (Bristol, PA). Clenbuterol powder used to prepare calibrators and trimethylboroxine (99%) used to prepare the derivatizing reagent for confirmation testing were obtained from Sigma-Aldrich. Clenbuterol powder used to prepare quality control samples was obtained from Alltech Associates.

Initial specimen testing

A broad-spectrum drug screen was performed initially using urine (when available), fluoride-preserved blood obtained from the cardiac area, decomposition fluid, or spleen or liver tissue from decomposed bodies. Samples were extracted by an in-house solid-phase extraction (SPE) method using a modified procedure from United Chemical Technologies (Bristol, PA). Acid/neutral and basic elutes from the SPE columns were collected separately and analyzed by electron impact gas chromatography-mass spectrometry (EI-GC-MS) in the full-scan mode.

Immunoassay procedure

Specimens from all cases were routinely analyzed by immunoassay with the Opiate and Fentanyl Microplate EIA kits from OraSure Technologies (Bethlehem, PA) using the procedure provided by the vendor. Target drug for the opiate procedure was morphine with a cutoff concentration of 50 ng/mL. Target drug for the fentanyl procedure was fentanyl with a cutoff concentration of 1 ng/mL. Specimens positive for either opiates or fentanyl by immunoassay were then screened for clenbuterol using the Clenbuterol Enzyme-Linked Immunosorbent Assay (ELISA) from Neogen (Lexington, KY). The Neogen test procedure was followed except that the in-house calibrators and case specimens were diluted 1:5 with deionized water prior to analysis. In-house calibrators were spiked at 5 ng/mL in both urine and fluoridated blood and used as the cutoffs. They typically had separation of 0.5 absorbance units from their respective negative calibrators. The calibrators were run in duplicate and were required to have absorbances agreeing $\pm 10\%$. All specimens positive by the clenbuterol immunoassay were then confirmed by GC-MS.

Clenbuterol extraction procedure

Confirmation of clenbuterol was performed (3 mL of blood or 5 mL of urine) using an SPE procedure similar to the in-house method referenced here with modifications of the elution solvent followed by derivatization with trimethylboroxine as described by Abukhalaf and colleagues (12). Reaction schemes for clenbuterol and internal standard, metoprolol, are shown in Figure 1. The basic SPE fraction was eluted with 78:20:2 methylene chloride/isopropanol/ammonium hydroxide, evaporated to dryness under nitrogen at 40°C , reconstituted in 50–100 μL trimethylboroxine reagent (23 μL trimethylboroxine in 10 mL ethyl acetate), heated at 70°C for 20 min, centrifuged to get the solvent to the bottom of tube, and transferred to an ALS vial for injection into the GC-MS.

Clenbuterol calibrators were prepared in negative whole blood at 2.5, 5, 10, 50, 100, 500, and 1000 ng/mL and analyzed in duplicate. Linearity was obtained from 5 to 100 ng/mL with a correlation coefficient of 0.999. Limit of detection (LOD), determined by the lowest calibrator demonstrating acceptable chromatography (symmetrical peak shape with baseline resolution greater than 90% from any co-eluting peaks) and having qualifier ions ratios within $\pm 20\%$ of corresponding ions ratios for the 10 ng/mL calibrator, was 2.5 ng/mL. Limit of quantitation (LOQ), determined by the lowest calibrator meeting criteria for the LOD and having a coefficient of variation (CV) $\leq 10\%$, was 5 ng/mL ($n = 10$, replicates of 5 on 2 separate runs). Precision for the 20 ng/mL control was calculated from total of 15 controls run on two separate days; CV was 7.9%. A 20 ng/mL control was run with each set of data, and the data were acceptable if the control was within $\pm 20\%$ of the target. Linearity was from 5 to 100 ng/mL.

Testing of evidence was done on syringes, spoons, or packets taken from each of the cases when available. Syringes and spoons were washed with 200 μL of methanol. A small amount of powder was removed from the packets using the end of a Pasteur pipette and dissolved in 200 μL of methanol. One microliter of the methanol washing was injected into the GC-MS.

GC-MS analytical method

GC-MS analysis of clenbuterol in postmortem samples and clenbuterol, heroin and cocaine in methanol washings from case evidence was done with HP 6890 GC with 7683B autosampler and 5975 MS. Chromatography was accomplished with a ZB5MS capillary column (15 m \times 0.25-mm i.d., 0.25- μ m film thickness) from Phenomenex. The initial oven temperature was set at 50°C, held for 1.5 min, then increased by 20°C/min to 300°C, and held for 4.0 min. Instrument conditions were as follows: injection port was 250°C; source was 230°C; detector was 150°C; and MS transfer line was 280°C. The split injection (1:1) mode was used with a solvent delay of 4.0 min. Quantitation of clenbuterol was carried out in the full-scan mode scanning ions m/z 160 to 400. Clenbuterol derivative ions were monitored at m/z 243, 285, and 245 (Figure 2A) and the internal standard (metoprolol, 50 ng/mL) derivative ions were monitored at m/z 276 and 291 (Figure 2B). The quantitation ions are underlined. The selection of ions was made after examining the full-scan mass spectra separately to ensure 1. the corresponding ions from the internal standard must not have occurred in the analyte and the corresponding ions from the analyte must not have occurred in the internal standard, 2. the largest mass-to-charge ratio ions were selected, and 3. high abundance and lack of baseline interference were required. Retention times of the clenbuterol derivative and metoprolol derivative were 10.32 and 10.04 min, respectively. Methanol washings of the evidence were analyzed using the same GC program described here. Heroin ions were monitored at m/z 327, 369, and 310. Cocaine ions were monitored at m/z 182, 303, and 272. Retention times of heroin and cocaine were 12.69 min and 10.82 min, respectively.

Case Histories

Case 1

The decedent was brought to the emergency room after being involved in a motor vehicle accident. Decedent was the

operator and sole occupant of a car that veered into another lane on a two-way street and struck several parked cars. An external examination by the medical examiner revealed that the decedent had suffered no serious injuries or trauma. There was reportedly minimal damage to the car. Cause of death was determined to be adverse drug reaction.

Case 2

The decedent was found unresponsive at home and was dead upon arrival at the local emergency room. A nurse in the emergency room reported the decedent had been treated at the hospital in the past for drug use. The autopsy report indicated dilated heart, hepatosplenomegaly, marked pulmonary edema, and congestion. Medical records indicated that the decedent had been treated at a methadone clinic the previous year. Cause of death was determined to be cardiomyopathy with adverse effect of drugs as a significant condition.

Case 3

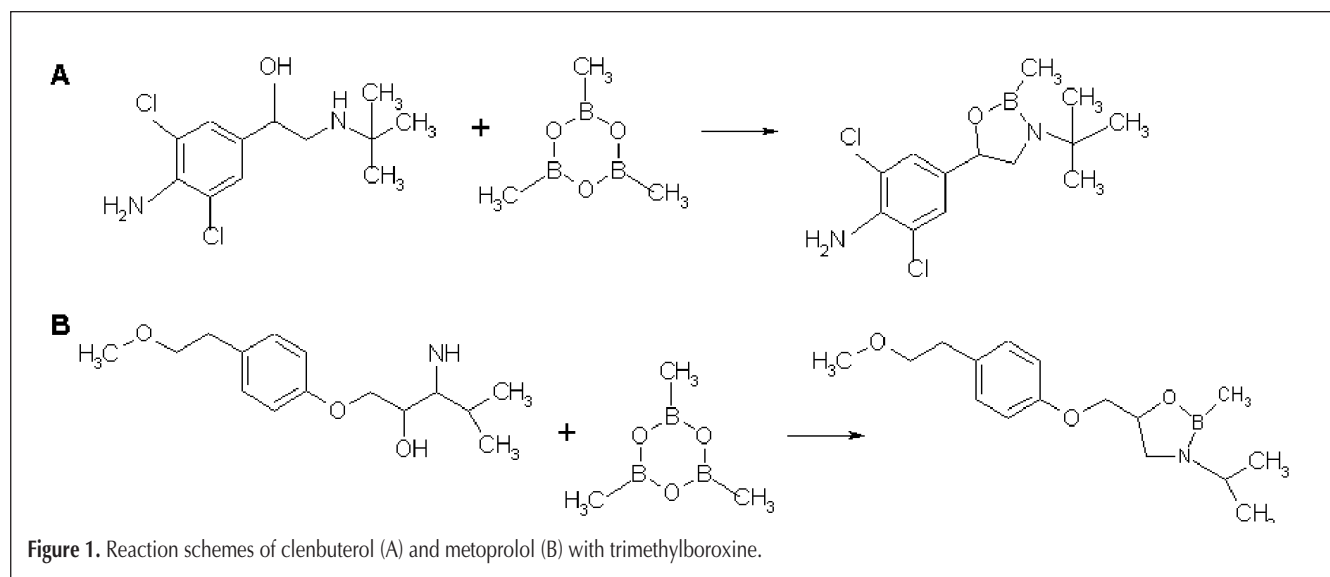
The decedent was assaulted during a robbery and sustained severe head trauma. Death occurred shortly thereafter at a local hospital. The autopsy report indicated severe contusions about the brain, and protuberant swelling of left forehead. Informants stated that the decedent had used drugs and had been in rehabilitation for heroin use. Cause of death was determined to be blunt head trauma and the manner of death homicide.

Case 4

The decedent was a homeless person found on an abandoned property. Drug paraphernalia was found near the body. The mother confirmed that the decedent had a drug problem. The autopsy report indicated pulmonary edema and splenomegaly. Cause of death was determined to be adverse effect of drugs.

Case 5

The decedent was found down in the residence. The medics found the decedent cold, cyanotic, and asystolic. Decedent was



dead on arrival at a local hospital. Drug paraphernalia, including a spoon and syringe, were found in decedent's pockets. Family members reported that the decedent had a history of IV heroin and alcohol use. The autopsy report indicated generalized organ congestion with no evidence of active disease or trauma. The cause of death was determined to be adverse drug reaction.

Case 6

The decedent was brought by car to the emergency room by friends and arrived unresponsive, cyanotic, pulseless and apneic. Death occurred shortly thereafter. Friends stated that the decedent had been riding in car and began complaining of shortness of breath and burning in his throat; they had been doing heroin earlier that night. The decedent may have had a history of seizures. The autopsy report indicated pulmonary edema, visceral congestion, and track marks on the antecubital fossa. The cause of death was determined to be adverse drug reaction.

Case 7

The decedent was found by landlord on the floor of the shower. A small plastic bag was found on the bed. The landlord stated that the decedent was a known drug user who had gone

into a methadone-treatment program. After a pregnancy, the decedent had left the methadone program and was back using drugs. The autopsy report indicated that the body showed bloating decomposition and that there were no visible needle punctures or tracks. The cause of death was determined to be adverse effect of drugs.

Case 8

The decedent was found in fetal position in bathroom by his fiancée. A syringe and spoon were found by the body. The decedent had a history of heroin use, and the fiancée reported that the decedent was going out to buy drugs just prior to the witnessed collapse. The autopsy report indicated generalized organ congestion, severely edematous lungs, and dusky brain. The cause of death was determined to be adverse drug reaction.

Case 9

Decedent was found with a needle in arm by a friend. Decedent had past history of heroin, alprazolam, cocaine, and methadone use and had been going to a methadone clinic for about a month. Autopsy report indicated mild pulmonary edema and congestion, dusky brain, and nephrosclerosis. The cause of death was determined to be adverse effect of drugs.

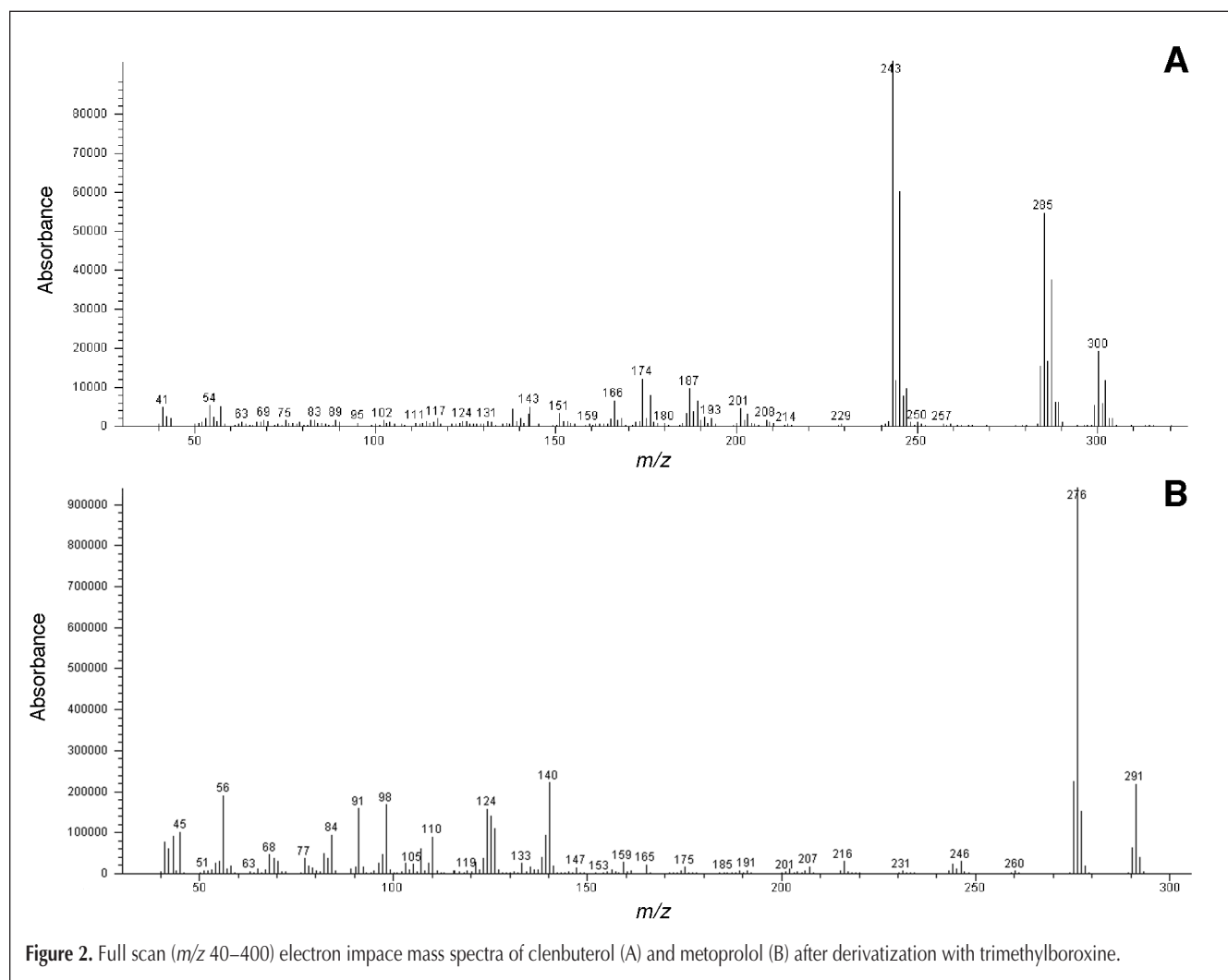


Figure 2. Full scan (m/z 40–400) electron impact mass spectra of clenbuterol (A) and metoprolol (B) after derivatization with trimethylboroxine.

Case 10

The decedent was found dead in bed by spouse and had a past history of emphysema and drug use. The autopsy report indicated generalized organ congestion, edematous lungs, and dusky brain. The cause of death was determined to be adverse drug reaction.

Case 11

The decedent was a known heroin addict who was found dead in prison cell after being admitted to prison two days before. The decedent was vomiting the night before and morning of death and had been going through detoxification but had refused to take medication. The autopsy report indicated generalized organ congestion, severely edematous lungs, and dusky brain. The cause of death was determined to be adverse drug reaction.

Case 12

The decedent was found at home in cardiac arrest by

paramedics and could not be revived at the emergency room. The decedent had been previously treated at the same hospital for asthma-related complications. The autopsy report indicated emphysema and a dusky brain. The cause of death was determined to be adverse effect of drugs with asthma and emphysema as other significant conditions.

Results

As part of our regular workload, a total of 575 cases were tested in the Toxicology laboratory during the first quarter of 2007. In 106 cases (18%), the cause of death was determined to be drug-related. Clenbuterol was present in specimens from 12 cases representing 11% of the drug-related cases. The cause of death in 11 of these clenbuterol positive cases was determined to be drug-related; in one case the decedent was victim of a homicide but had a history of heroin abuse. The group con-

Table 1. Results of Case Specimens

Case	Matrix	Clenbuterol	6-AM*	Morphine	Other
1	Urine Blood	Present 76 ng/mL	Present ND	Present 72 ng/mL	Methadone, Present Methadone, 668 ng/mL
2	Urine Blood	Present Trace	Present ND	Present ND	Fentanyl, Present; Alprazolam, Present; Diazepam, Present Fentanyl, 20 ng/mL; Benzodiazepines, NA
3	Urine Blood	Present 7.6 ng/mL	ND ND	Present ND	Hydromorphone, Present; Ethanol, 0.051 g/dL Hydromorphone, ND; Ethanol, 0.041 g/dL
4	Urine Blood	Present Trace	ND ND	Present ND	Fentanyl, Present; Cocaine, Present Fentanyl, 10 ng/mL; Cocaine, < 20 ng/mL; Benzoylcegonine, 960 ng/mL
5	Urine Blood	Present ND	Present ND	NA 169 ng/mL	
6	Blood	10 ng/mL	Present	625 ng/mL	Fentanyl, 10 ng/mL; Codeine, < 50 ng/mL
7	DF Spleen	5.5 ng/mL 12 ng/g	ND NA	426 ng/mL NA	Ethanol, 0.118 g/dL Cocaine, 500 ng/mL; Benzoylcegonine, 2100 ng/mL Ethanol, NA; Cocaine, NA; Benzoylcegonine, NA
8	Urine Blood	Present ND	Present Present	Present 463 ng/mL	Ethanol, 0.160 g/dL Ethanol, 0.103 g/dL
9	Urine Blood	Present Trace	Present Present	NA 425 ng/mL	Cocaine, Present Cocaine, 35 ng/mL; Benzoylcegonine, 2800 ng/mL
10	Urine Blood	Present ND	Present ND	NA < 50 ng/mL	Propoxyphene, Present; Alprazolam, Present; Codeine, Present Propoxyphene, 410 ng/mL; Alprazolam, NA; Codeine, ND
11	Urine Blood	Present 6.3 ng/mL	ND ND	Present ND	Codeine, Present Codeine, ND
12	Urine Blood	Present 20 ng/mL	Present ND	Present 87 ng/mL	Codeine, Present; Cocaine, Present Codeine, ND; Cocaine, 180 ng/mL; Benzoylcegonine, 350 ng/mL

* Abbreviations: 6-AM, 6-acetylmorphine; ND, not detected; NA, not analyzed; and DF, decomposition fluid.

sisted of six males and six females; nine were white, two African-American, and one Hispanic; and they ranged in age from 20 to 54 years.

Toxicology results for the specimens from all of the cases in which clenbuterol was detected are listed in Table I. Both urine and blood were tested when available. In case 6, only blood was available. In case 7, only decomposition fluid and spleen tissue were available. Clenbuterol was detected in all of the urine samples tested, in blood from eight of the cases, and in both decomposition fluid and spleen from one case. Blood concentrations ranged from not detectable to 76 ng/mL.

Five of the 12 cases had available evidence that was tested (Table II). In case 12, clenbuterol was present in the packet along with both heroin and cocaine. This was the only piece of evidence in which clenbuterol was detected. Heroin was present in one piece of evidence from each of these five cases, and cocaine was present in evidence from four of the five cases.

Discussion

The clenbuterol-positive cases cited in this study represent a series of illicit drug users. Heroin use was confirmed in post-mortem specimens from eight of the cases by the presence of 6-acetylmorphine. In each of the other four cases (cases 3, 4, 7, and 11), heroin use by the decedent is strongly supported by the presence of morphine with a documented history of heroin abuse. Multi-drug use was predominant with cocaine present in four cases, fentanyl present in three cases, ethanol and a benzodiazepine present in two cases, and methadone present in one case. With illicit drug users, many of whom use multiple drugs, it is often not possible to determine the contribution of each individual drug to the cause of death. This appears to be true in the series of cases presented here as well. The elimination half-life of clenbuterol is relatively long (25–39 h) compared with cocaine (0.7–1.5 h), heroin (2–6 min), and its metabolites 6-acetylmorphine (6–25 min) and morphine (2–3 h) (2). Consequently, the deleterious and potentially lethal effects of clenbuterol might be expected to last much longer

after ingestion than the effects of cocaine or heroin and many other drugs as well.

Clenbuterol is a potent, β -adrenergic agonist that has been restricted in the United States to veterinary use only; consequently, there are very limited data in the literature documenting human clenbuterol blood levels. Evidence of the drug's effectiveness after administration of very small doses is shown in clinical studies. Repeated dosing of subjects using therapeutic doses of 20, 40, or 80 μ g resulted in clenbuterol plasma concentrations of less than 1 ng/mL (13). One woman survived an accidental ingestion of a fingertip quantity of an unknown white powder that was later identified as clenbuterol by her boyfriend, who was using it for bodybuilding purposes (9). She had a reported serum concentration of 2.93 ng/mL 3 h after ingestion and remained symptomatic for 20 h, much longer than clenbuterol was detectable in her serum. Further evidence of the potency of clenbuterol is provided in the case of a 17-year-old Polish body builder who was a self-reported clenbuterol user and subsequently survived a myocardial infarction (8). The clinical symptoms, routine clinical laboratory results, and EKG were well-documented, but no clenbuterol serum levels were reported. Another report documents the cases of two people in Portugal who ingested clenbuterol-tainted calf liver and became ill with food poisoning with serum levels of 58 and 62 ng/mL (14). Details of how these two individuals were treated and managed to survive these very high clenbuterol levels were not available. A more recent report documents the case of a 55-year-old Hispanic male who survived a myocardial infarction (15). Initial laboratory testing revealed that he had used heroin, and further testing showed that he had also ingested clenbuterol, but no blood levels were documented.

Heroin has often been found to contain adulterants or additives used to increase its volume or to provide a desired pharmacological effect. In 2006, the Philadelphia Medical Examiner's Office reported over 250 drug-related deaths due to fentanyl-tainted heroin. Several other notable heroin adulterants recently detected include xylazine (16), an α 2-adrenergic agonist, and diphenhydramine, a mixture known as "cheese" (17). Clenbuterol is available for purchase in quantity over the internet from foreign countries. In this series of cases, it seems to be an unlikely additive because its fat-metabolism-enhancing or muscle-building properties would probably have little appeal for illicit drug users. However, clenbuterol is a bronchodilator and enhances respiratory function, so this is one possible explanation for its presence. Unfortunately the other, adverse effects of clenbuterol, including tachycardia, hypokalemia, hypophosphatemia, and hypomagnesemia, that accompany any potentially beneficial effects can be toxic and even lethal. However, if the presence of clenbuterol is recognized and treated in a timely fashion, the patient can recover successfully (8,9).

Evidence testing from these drug-related cases indicates that clenbuterol was mixed together with heroin and cocaine before ingestion in at least one instance (case 12). This is probably true in some, if not all, of the other cases as well, even though, in our study, the amount of clenbuterol left in the evidence to test may have been too small to detect. In addition,

Table II. Results of Evidence Testing

Case	Type of Evidence	Clenbuterol	Heroin	Cocaine
4	Packet	Not detected	Trace	Present
5	Syringe	Not detected	Present	Not detected
	Spoon	Not detected	Trace	Not detected
8	Syringe	Not detected	Present	Trace
	Spoon	Not detected	Present	Present
	Packet	Not detected	Present	Trace
9	Syringe	Not detected	Present	Present
12	Packet	Present	Present	Present

the presence of syringes and spoons indicates that the users probably injected the drug mixture.

Conclusions

To our knowledge, this represents the first such series of clenbuterol positive illicit drug users to be reported from a medical examiner's toxicology laboratory. Clenbuterol is a powerful, β -adrenergic agonist with potentially toxic and even lethal side effects. These adverse clinical effects may be treated successfully if they are recognized promptly. Clenbuterol's exact contribution to the cause of death in illicit drug users may be hard to determine and its presence in these cases may be difficult to detect because of its low concentration in postmortem specimens. However, this report serves as a caution to emergency room physicians and toxicologists to consider and to test for clenbuterol in heroin users who present atypically.

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