Domestic Abuse of the European Rave Drug Prolintane

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Abstract
Prolintane is a sympathomimetic amine with pharmacologic properties similar to d-amphetamine. Side effects include insomnia, nervousness, and irritability. Overdoses of prolintane may cause hallucinations, psychosis, and death. The drug is commonly prescribed in Africa, Australia, and Europe but is not available in the United States. This manuscript reports the first medically documented cases of prolintane abuse in the United States. In the first, a 34-year-old male presented to the emergency department confused, agitated, and unable to follow commands. Initial drug and alcohol screens were negative, but analysis by gas chromatography–mass spectrometry (GC-MS) indicated the presence of amitriptyline, nortriptyline, nicotine, and prolintane. The second patient, a healthy 26-year-old female, presented to the emergency department after intrauterine fetal death and spontaneous delivery. GC-MS revealed the presence of multiple drugs, including cannabinoids, cocaine, nicotine, hydrocodone, and prolintane. The medical and scientific communities should be aware of the potential for prolintane abuse because it may cause symptoms similar to those of the amphetamines but is not likely to be detected by a routine urine drug screen.

Case Histories

Case 1
A 34-year-old Caucasian male arrived at the emergency department after being found lying on the floor. The patient presented with confusion, agitation, and unintelligible speech;
he was responsive to painful stimuli but unable to follow commands. His vital signs were temperature 37.8°C, pulse rate 127 bpm, respiratory rate 18/min, and BP 141/101. The patient's skin was dry and warm. His pupils were 3-4 mm diameter and sluggish. He scored 10 (eyes 4, verbal 2, motor 4) out of 15 on the Glasgow Coma Scale. An electrocardiogram indicated sinus tachycardia. Naloxone was administered with no effect. The patient was also administered activated charcoal, sorbitol, cetriaxone, lorazepam, and intravenous (I.V.) saline. He was restrained after repeated attempts to remove his I.V. lines and to strike healthcare workers. An initial urine drug screen was negative. Analysis of the patient's urine by gas chromatography-mass spectrometry (GC-MS) revealed the presence of amitriptyline, nicotine, nortriptyline, and relatively high concentrations of prolintane and metabolites (quantification not available). After regaining his faculties, the patient reported using drugs at his girlfriend's house the previous evening.

Case 2
A healthy 26-year-old African-American female presented to the emergency department after intrauterine fetal death and spontaneous delivery. Initial physical exam showed an otherwise healthy patient with an intact placenta. Her blood pressure and heart rate were elevated (BP 172/106, HR 92 bpm), but the emergency department after intrauterine fetal death and available. After regaining his faculties, the patient reported using drugs at his girlfriend's house the previous evening.

Materials and Methods

Reagents
Type I water was acquired via a Millipore water filtration system (Billerica, MA). All other solvents were purchased from Fisher Scientific (Fair Lawn, NJ) and were of high-performance liquid chromatography (HPLC) grade or higher.

Sodium phosphate, proadifen hydrochloride (SKF-525A), and 2-amino-5-chlorobenzophenone were each 95% or higher purity as purchased from Sigma-Aldrich Corp. (St. Louis, MO). Prolintane (purity > 96% by HPLC) was received as a gift from Dr. Stefan Toennes (University of Frankfurt, Frankfurt, Germany).

Immunooassay screening
The urine samples of both patients were screened for drugs of abuse using Dade Behring Flex® reagents (Dade Behring, Deerfield, IL) on a Dade Behring Dimension® RxL. The cutoff limits for each assay were as follows: 500 ng/mL for amphetamines, 200 ng/mL for barbiturates, 200 ng/mL for benzodiazepines, 150 ng/mL for benzoylcegonine, 50 ng/mL for cannabinoids, 300 ng/mL for opiates, and 25 ng/mL for phencyclidine.

Subsequent experimentation involved the addition of prolintane HCl to drug-free urine. Immunooassay screens were performed on known concentrations of prolintane in urine using the Dade Behring Flex amphetamine reagent (cutoff 500 ng/mL) and the Syva® EMIT® II Plus amphetamine reagent (cutoff 300 ng/mL) to determine the cross-reactivity of the reagents to the drug.

GC-MS
Urine samples were extracted over Bond Elute Certify solid-phase extraction columns (Varian, Palo Alto, CA) according to the method of Chen et al. (9) with modifications. Essentially, 5 mL 0.1M monobasic phosphate buffer (pH 6) and 50 µL of internal standard (SKF-525A 50 µg/mL) were added to 5 mL urine. The extraction columns were conditioned with methanol and water. The sample mixture was added to the column and slowly aspirated. Columns were washed with water and 0.1M acetic acid before being dried with vacuum. Analytes were eluted using acetone/chloroform (1:1) and then 2% ammonium hydroxide in ethyl acetate. Sample eluate was evaporated to 50 µL on a heating block set at 40°C using a steady stream of nitrogen before the addition of the internal standard aminochlorobenzophenone and injection onto the instrument.

Analysis was performed using a Thermouquest GCQ™ (Thermo Fisher Scientific, Waltham, MA) GC–MS system. One microliter of each sample extract was injected into the injection port set to 225°C. Analyte separation was achieved using a Restek RTx®-5MS (Restek Corp., Bellefonte, PA). The oven temperature was held at 60°C for 1 min and then ramped at 20°C/min to 280°C, where it remained for the remainder of each analytical run. Compounds were ionized via electron impact ionization. The filament was switched on 4 min after injection and set to 70 eV. The detector was set to positive ion and full scan mode. Scans were acquired from m/z 40 to 500 each second. Peaks were compared to the Pfleger/Maurer/Weber library for identification.

Quantification of prolintane in the patient sample was performed against a standard curve (0.5–50 µg/mL, R² = 0.992) created by adding known quantities of prolintane to drug-free human urine. Each point in the calibration curve was generated by comparing the total response of the drug to the total response of the internal standard SKF-525A. The combined concentration of the metabolites was estimated using the standard curve of the parent drug.

Results
The amphetamine screens of both patients were negative. However, prolintane and metabolites of prolintane were identified in the urine of both patients after solid-phase extraction and analysis by GC–MS. Prolintane and two metabolites were retained on the column for 9.98, 18.44, and 18.77 min, respectively (Figure 2); the relative retention times of prolintane and the metabolites to the internal standard SKF-525A were 0.771, 1.425, and 1.450, respectively. Mass spectral
Analysis of prolintane resulted in a base peak at m/z 126 and other significant ions at m/z 55, 91, and 174 (Figure 3). The spectra of each metabolite also included a base peak at m/z 126 and other significant ions at m/z 107 and 96 (data not shown). Negative immunoassay results were obtained at up to 250 µg/mL prolintane with both of the amphetamine reagents.

Discussion

The medical and scientific communities should be made aware of the domestic presence of prolintane because of the adverse effects associated with overdose and lack of detectability during routine drug screening. The detection of prolintane in both patients’ urine by GC–MS emphasizes the importance of comprehensive toxicology analyses in situations of unknown ingestion. Other analytical methods noted to be effective in the detection of prolintane include GC and HPLC with ultraviolet detection at 252, 258, and 264 nm (10). The specific and comprehensive nature of GC–MS is advantageous over immunoassay in cases of unknown ingestion (11,12). The National Academy of Clinical Biochemists recommends that GC–MS capability be maintained on a regional level (13), but it is expensive and likely to be available only at major medical centers. Therefore, the diagnostic skills of the primary care physician are essential to the recognition of prolintane overdose.

Symptoms of prolintane overdose include those associated with sympathomimetic syndrome such as tachycardia, hypertension, hyperreflexia, mydriasis, and hyperthermia. Overdose with prolintane can result in hallucinations, cardiac arrhythmias, respiratory depression, and death (14). Symptomatic and supportive care should be provided to all patients suspected of prolintane ingestion. Decontamination with activated charcoal may be effective if administered early after ingestion.

References


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