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SHORT COMMUNICATION

Two cases of intoxication with new synthetic opioid, U-47700

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ABSTRACT

Background: Novel substances often referred to as “designer drugs” have emerged as drugs of abuse, and recognition of these is difficult as routine blood and urine screening tests do not detect these agents. U-47700 is a synthetic selective μ-opioid agonist that can be bought online for as little as $40 per gram. We report two patients presenting after insufflation of U-47700, with subsequent confirmation of this substance in urine samples.

Case details: A 26-year-old man and 24-year-old woman insufflated a substance they believed to be “synthetic cocaine.” The man was found down with cyanosis and agonal respirations. He was intubated and taken to hospital where he recovered well with supportive care. The woman presented with anxiety, tremors and drowsiness and was admitted for observation. Urine samples from both patients were analyzed using GC/MS/MS and LC/QToF, and U-47700 was isolated in both cases. No other opioids were detected.

Discussion: These cases are concerning because U-47700 is a relatively new agent that is easy to obtain over the internet and has the potential to cause significant morbidity and mortality.

Background

Drug abuse is a continuing concern in the United States (US). Since 2000, the rate of deaths from drug overdoses has increased 137%, including a 200% increase in the rate of overdose deaths involving opioids.[1] By 2009, drug overdose deaths outnumbered deaths from motor vehicle crashes for the first time in the US.[2]

Novel substances often referred to as “designer drugs” have emerged as drugs of abuse. Psychoactive agents such as phenylethylamine variants including synthetic cathinones, synthetic cannabinoids, tryptamine variants, piperazines and piperidines have been used to mimic the effects of other controlled substances like methylenedioxymethamphetamine and marijuana.[3,4] Recognition of these novel substances is difficult as routine blood and urine screening tests do not detect these agents.

More recently, reports of novel opioids have surfaced. U-47700 (3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide) is a synthetic, selective μ-opioid agonist developed in the 1970s[5] that can be bought online for as little as $40 per gram.[6] We report two patients presenting after insufflation of U-47700. Urine samples from both patients were analyzed using GC/MS, LC/MS/MS, and LC/QToF, and U-47700 was isolated in both cases. No other opioids were detected.

Case details

A 26-year-old man and 24-year-old woman were celebrating their first apartment together. They consumed alcohol and alprazolam, then insufflated a powdered substance they believed to be “synthetic cocaine” named U-47700, purchased on the internet. This was the first time either of them had used the drug.

Patient one

The initial symptoms of the man after insufflation of the U-47700 are unclear. Approximately 3 h after use, the man was found face down on the lawn with agonal breathing and cyanosis. Emergency Medical Services (EMS) were called, and the providers reported the man to be cyanotic with oxygen saturation of 50% on ambient air. He was intubated in the field and placed in a c-collar for transport. Medications used during intubation were ketamine, lorazepam and rocuronium. Naloxone was not given as the initial report of substances ingested was alcohol and alprazolam. In the emergency department (ED), his GCS was 3 and pupils were pinpoint. Vital signs on arrival: HR 125 beats/min, BP 150/63 mmHg, RR 14 breaths/min, and T 97.4°F (36.3°C). His initial oxygen saturation was 84%, but it rapidly improved to 100% once on the ventilator. Arterial blood gas on arrival showed a pH 6.97, PCO₂ >90, PO₂ 80, HCO₃ 21.4. Chest X-ray showed bilateral pulmonary consolidation. Chest computed tomography performed to exclude pulmonary embolism showed patchy consolidation in the right upper lobe, and computed consolidation of bilateral lower lobes. Findings were reported as concerning for pneumonia or aspiration, with the lower lobe findings at least partially related to atelectasis. The ED urine drug
immunoassay screening for amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates and PCP was negative. The serum ethanol level was 55 mg/dL. Laboratory tests were remarkable only for mild acute kidney injury (creatinine 1.5 mg/dL) and elevated lactate of 4.4 mmol/L which both normalized after intravenous fluid administration. Electrolytes were normal. WBC was 11.2 K/µL, glucose was 94 mg/dL, and CK 130 U/L. Serum acetaminophen and salicylates were not detected. ECG showed sinus tachycardia at 125 bpm with normal intervals and nonspecific ST changes. Troponin levels were not tested. The patient was admitted to the intensive care unit (ICU), sedated on propofol and given antibiotics for presumed pneumonia. The patient self-extubated in the ICU and was discharged three days after presentation with a normal exam. He denied a history of prior illicit or pharmaceutical drug use but admitted to occasional alcohol consumption. The woman with him corroborated his reported drug history.

**Patient two**

After insufflation of the U-47700, the woman described feeling “cool and relaxed”, which surprised her as this was comparable to heroin and she was expecting a stimulant. She had used heroin in the distant past. She fell asleep after use of the U-47700, awoke approximately 3 h later and called EMS after finding the man outside as described above. She was also transported to the ED where she reported anxiety, nausea and abdominal pain. She also reported shivering. Her temperature on arrival was 97.8 °F (36.5 °C) and the temperature outside was 52 °F (11.1 °C). On physical exam she was drowsy but had no dyspnea. Pupils were normal sized and reactive. Vital signs: HR 97 beats/min, BP 111/77 mmHg, RR 18 breaths/min and oxygen saturation 100% on room air. She underwent the same ED urine drug immunoassay testing as the man, and her result was (+) for THC. Serum ethanol level was 11 mg/dL. Serum acetaminophen and salicylates were not detected. Chest x-ray was reported as normal. ECG showed normal sinus rhythm at 87 beats/min with normal intervals and no ST changes. Laboratory tests were unremarkable, with WBC 7.3 K/µL, normal electrolytes and normal renal function. Glucose was 107 mg/dL. Creatine Kinase and Troponin were not tested for.

The urine sample was treated with deuterated internal standard, beta-glucuronidase and sodium acetate buffer and were extracted using SPEware PSCX cartridges. The eluents were evaporated to dryness, reconstituted with methanol and aqueous mobile phase A (5 mM ammonium acetate and 0.01% formic acid). The extracts were subsequently analyzed by a 1260 Infinity LC coupled to a 6460 tandem mass spectrometer (Agilent Technologies, Santa Clara, CA) using positive electrospray ionization and operated in multiple reaction monitoring mode. Injections were separated within 8 min using a gradient profile of aqueous mobile phase A and 0.01% formic acid in methanol with a 0.5 mL/min flow rate on an Agilent Poroshell 120 EC-C18 (2.1 mm × 100 mm, 2.7 µm) column that was maintained at 50 °C. Fragmentation of the U-47700 reference standard that was used during development of the method is shown in Figure 1. The peaks shown represent the fragments that result when U-47700 was analyzed by the mass spectrometer.

Samples were sent to a second facility where a GC–MS (gas chromatography–mass spectrometry) screen for approximately 300 drugs and LC/QToF (liquid chromatography quadrupole time-of-flight) analysis were performed. For GC–MS analysis, one mL of the man’s urine was extracted under alkaline conditions using methylene chloride:cyclohexanes:isopropanol (4.5:4.5:1.0), concentrated to dryness and reconstituted using hexanes:ethanol (1:1). GC–MS analysis using an Agilent 7890A/5975 system equipped with a Phenomenex DB-1 column indicated the presence of acetaminophen and propofol. For LC/QToF analysis, a 50 µL aliquot of each patient’s urine and control sample was diluted with 250 µL pure water in a 2 mL HPLC injection vial and mixed well. Diluted samples were injected onto a Phenomenex Kinetics C18 (Phenomenex, Torrance, CA) (100 × 3.0 mm, 2.6 µm) column. Separation was accomplished using an 8 min linear gradient starting with 10% 2 mM ammonium acetate with 0.1% formic acid in methanol and finishing at 90%. Compounds were detected using an ABSciex 5600 TripleTOF mass spectrometer (SCIEX, Framingham, MA) set for Information Dependent Acquisition (IDA).

**Analytical results**

Initial ED immunoassay analysis of the man’s urine was negative, but a later urine collection of a 28 panel immunoassay test was positive for benzodiazepines, cannabinoids and ketamine. LC/MS/MS testing detected lorazepam, cotinine, ketamine, norketamine and U-47700. U-47700 was detected in the male patient’s urine at 0.1 ng/mL. Figure 2 shows the chromatography of the patient’s urine, and the detection of the U-47700 fragments noted in Figure 1.

GC–MS detected the presence of propofol and acetaminophen. LC/QToF qualitative analysis detected the presence of acetaminophen, ketamine, ketorolac, ofloxacin, piperacillin and U-47700. Consistent with the findings, this patient received lorazepam and ketamine during intubation and was sedated with propofol during admission.

GC–MS analysis was not performed on the woman’s urine due to insufficient sample volume. Both ED and later immunoassay tests of the woman’s urine were positive for cannabinoids. LC/MS/MS analysis detected only cotinine. LC/QToF analysis of the woman’s urine detected acetaminophen, ketorolac, piperacillin, thebomeline and U-47700.

Both urine samples were negative for other opioids, including fentanyl, hydrocodone, oxycodone, 6-monoacetylmorphine,
codeine and tramadol. No other sedative hypnotic agents or skeletal muscle relaxants were detected including alprazolam, carisoprodol and gabapentin.

**Discussion**

These cases are concerning because U-47700 is a new agent that has the potential to cause significant morbidity and mortality. In two recent reports, the drug has been found in post-mortem samples in Europe.[7,8] U-47700 is a synthetic opioid developed by a team at The Upjohn Company in the 1970s working to synthesize a non-addicting analgesic as potent as morphine.[5] It belongs to the trans-1,2-diamine class of analgesics [5] and is selective for the μ-opioid receptor,[9] showing 7.5 times the potency of morphine in animal models.[10] Upjohn posted several patents on related compounds and used U-47700 in their later work to synthesize κ-selective agents such as U-50488.[5] Prior studies on the pharmacologic profile of U-47700 and related compounds focused on opioid receptor binding and analgesic effects.
effects rather than duration of action [10,11] and essentially no pharmacokinetic data exist. U-47700 has not been studied in humans but produces morphine-like pharmacological effects in animals [10,11] and would be expected to produce typical opioid effects, including sedation, euphoria and respiratory depression in humans. It certainly yielded miosis and CNS and respiratory depression in our male patient. Also, the female patient described a euphoria that was similar to when she had used heroin in the past, "cool and relaxed".

U-47700 is easily found on the internet where it is marketed as a "research chemical". The first page of a Google search of "buy U-47700" done on June 22nd 2016 yielded four vendors claiming to ship to the USA, as well as two vendors shipping to Europe only. U-47700 is sold in powdered form in quantities starting at 1g, priced from $40, with discounts available if larger quantities are purchased. A liquid form labeled as containing 20 mg/mL is sold in 15 mL bottles priced at $35.99. The concept of purchasing drugs of abuse online is not new, but prior focus has been on synthetic cannabinoids and cathinones.[12]

U-47700 is not the only novel synthetic opioid available for abuse. Others include the fentanyl derivatives [13] and AH-7921.[14] AH-7921 is structurally similar to U-47700 and was developed in the 1970s by the British pharmaceutical manufacturer Allen and Hanbury’s. AH-7921 was also synthesized as a potential analgesic, but later abandoned due to its addictive properties.

Anecdotal reports found on online discussion forums [15,16] describe U-47700 being administered by ingestion, insufflation and intravenous injection. Internet forum threads discussing U-47700 use began to appear in 2014.[15] Most of the contributors to these discussions report obtaining the substance online. Users may not understand its effects or that it is an opioid, thus, increasing the risk of use. Our patients were expecting a cocaine-like intoxication but instead experienced varying degrees of sedation.

While the man presented with the opioid toxidrome, he was also tachycardic, which is not consistent with an opioid toxidrome. Reasons for the tachycardia could include inadequate sedation, discomfort from the ET tube, moderate hypoxia, acidosis, or the presence of a stimulant agent that was neither reported nor detected on routine urine drug immunoassay. A sedative hypnotic withdrawal syndrome is unlikely because his alcohol history was not extensive and he did have ethanol present. Of note, both patients reported using alprazolam, but this was not detected in either patient’s urine. We suspect the substance sold to the patients as alprazolam may have been ketorolac, which was detected in both patients’ urine despite neither using that medication.

In contrast to the man, the woman reported nausea, anxiety and mild drowsiness. One explanation for this is that the woman received a smaller dose of U-47700 and her opioid toxidrome had cleared prior to presentation. This idea is supported in that although U-47700 was detected qualitatively in both patients’ urine samples on LC/QToF analysis, levels in the woman’s urine were below the detection threshold on LC/MS/MS testing.

Use of U-47700 has been reported to the European Monitoring Center for Drugs and Drug Addiction, and Sweden made the drug illegal in January 2016.[17] As a result of our report, the Texas Department of State Health Services (TDSHS) started working to place U-47700 on the Texas scheduled substance list. The FDA is placing AH-7921 into Schedule I, and the TDSHS will do the same. Since U-47700 is derived from AH-7921, TDSHS will control it based upon it being an analog (personal communication, Karen Tannert, Texas Department of State Health Services, 12 May 2016).

This report has several limitations. The patients were not seen directly by the authors; however they were interviewed by telephone. While complete hospital records were obtained and reviewed, we were unable to obtain EMS records. The duration of opioid effects on the man are difficult to assess because he was intubated and propofol sedation was administered. The timing of his self-extubation is not clear in the records. The amount of urine we were able to obtain from the woman was small, thus limiting the degree of drug testing.

Conclusion

U-47700 is a novel selective μ-receptor agonist that produces opioid effects including severe respiratory depression requiring intubation. It is easy to obtain over the internet, and the authors anticipate a growing use of the drug.

Disclosure statement

The authors report they have no declarations of interest.

References


