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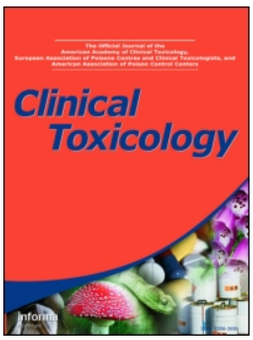

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SHORT COMMUNICATION

Near death from a novel synthetic opioid labeled U-47700: emergence of a new opioid class

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ABSTRACT

Background: In the last decade there has been a worldwide surge in the recreational abuse of novel psychoactive substances, particularly amphetamine derivatives and synthetic cannabinoids. Synthetic opioids such as AH-7921, MT-45, and U-47700, with structures distinct from those ever used therapeutically or described recreationally, have also recently emerged.

Case details: We report a patient who suffered respiratory failure and depressed level of consciousness after recreationally using a novel synthetic opioid labeled U-47700. A single dose of naloxone administered by paramedics completely reversed his opioid poisoning. Comprehensive laboratory analysis confirmed the presence of a novel synthetic opioid and excluded other drugs. The drug used appeared to have caused a false positive benzodiazepine result on the initial urine drugs of abuse panel.

Conclusion: The case we describe of toxicity from the synthetic opioid labeled U-47700 highlights the emerging trend of novel synthetic opioid abuse.

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U-47700; synthetic opioid; novel opioid; opioid poisoning; novel psychoactive substance

Introduction

In the last decade there has been a worldwide surge in the recreational abuse of novel psychoactive substances. Although the most popular of these have been synthetic amphetamine derivatives and synthetic cannabinoids,[1–3] novel synthetic opioids have also surfaced.[4–11] Traditionally, many novel synthetic opioids have been derivatives of therapeutically used drugs, primarily fentanyl and meperidine.[12] The recent identification of acetylfentanyl, butyrfentanyl, and 4-fluorobutyrfentanyl as drugs of abuse represent a continuation of this trend.[4,7,8] However, novel synthetic opioids with structures distinct from those ever used therapeutically or described recreationally have also recently emerged, including AH-7921 [3,4-dichloro-*N*-[(1 dimethylamino) cyclohexylmethyl] benzamide] (*trans*-1,2-diamine structure), MT-45 [1-cyclohexyl-4-(1,2-diphenylethyl)] (piperazine structure) and U-47700 [*trans*-3,4-dichloro-*N*-(2-(dimethylamino) cyclohexyl)-*N*-methylbenzamide] (*trans*-1,2-diamine structure).[5,6,9–11] We report a patient who nearly died after recreationally abusing a novel synthetic opioid labeled U-47700.

Case details

A 22-year-old male with a history of heroin abuse was found unconscious and apneic by his mother. His mother contacted emergency medical services and began to perform cardiopulmonary resuscitation (CPR) (rescue breaths and chest compressions) which she continued for four to five minutes until paramedics arrived. Paramedics found the patient to be cyanotic, having agonal respirations they estimated at 4 per minute and to have a room air pulse oximetry reading of 60%. The patient's initial blood pressure was 138/88 mmHg, pulse 134 per minute, and he was comatose with a Glasgow Coma Scale of 3. An oral pharyngeal airway was placed and the patient's respirations were assisted with a bag-valve mask that improved his oxygen saturation to 90%. Two milligrams of naloxone were administered intravenously which completely reversed his coma and bradypnea, and the patient was transported to the emergency department (ED). Upon presentation to the ED the patient's only complaint was a sore chest where chest compressions had been done and that his head was feeling "foggy". His initial vital signs in the ED were: blood pressure 112/71 mmHg, pulse 92 per minute, temperature 97.6 °F (36.4 °C), normal respirations, and pulse oximetry 97% on room air. Physical examination revealed the patient to be alert and oriented, to have normal sized and reactive pupils, clear lungs, the absence of track marks, and the presence of abrasions and tenderness over his sternum where chest compressions had been performed. The patient reported that just before being found by his mother, for recreational purposes, he had used the opioid agonist U-47700 he had acquired over the internet. He described having purchased what he interpreted as 250 mg of the drug in powder form which he divided into five separate doses. He described having used the drug two times previously without adverse effect. Each time he described placing the drug in a syringe, mixing it with water and applying it to his nostrils. He was

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not on any prescribed medications and denied the recent use of any other drugs.

A chest radiograph was normal, and an electrocardiogram was unremarkable demonstrating a normal QRS width and a QTc of 442 ms. A routine chemistry was normal as was a complete blood count except for a leukocytosis of 16,000/mm^3 (reference range 4–10,000 mm^3); differential with 88% neutrophils, 8% lymphocytes, 2% monocytes, 1% eosinophils. The patient was observed in the ED for approximately five hours during which he had no respiratory depression or sedation. No further naloxone was administered. A urine drugs of abuse panel by immunoassay (Roche ONLINE DAT Plus performed on a Cobas 6000 analyzer, Roche Diagnostics International Ltd. Switzerland) was positive for benzodiazepines as a class, but negative for amphetamines as a class, barbiturates as a class, benzoylecgonine (cocaine metabolite), methadone, opiates as a class, oxycodone, phencyclidine, and tetrahydrocannabinoids. He was discharged home and when contacted approximately a week later denied any symptoms.

The urine drugs of abuse panel by immunoassay uses nordiazepam at 100 ng/mL as a cutoff calibrator, but reacts with a variety of other benzodiazepines. Confirmatory testing for benzodiazepines in the urine by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using a limit detection of 20 ng/mL did not detect any of the following benzodiazepines and/or their major metabolites: alprazolam, clonazepam, diazepam, flurazepam, lorazepam, midazolam, oxazepam or temazepam. Further analysis of urine was performed using a broad spectrum liquid chromatography time-of-flight (LC-TOF) high-resolution mass spectrometry assay as previously described by Chindarkar et al.[13] The urine specimen was negative for sixty-one compounds that have been validated for this assay, and further excluded the following opioids: buprenorphine, dextromethorphan, fentanyl, hydrocodone, hydromorphone, meperidine, oxymorphone, propoxyphene, tapentadol, and tramadol.

The LC-TOF results confirmed the presence of a compound with the molecular formula $C_{16}H_{22}Cl_2N_2O$ in the patient's urine, which matches that of U-47700. The extracted ion chromatogram from the urine sample of the patient had identical retention time and mass spectra with that of the powder he provided for testing. Figure 1(A) shows an example chromatogram of the powder used which had predominant peaks at 5.25 and 5.36 min. The mass spectrum of the peak at 5.36 min (Figure 1(B)) was within 3 ppm of the expected protonated mass of U-47700 (329.1187). The mass spectrum of peak at 5.25 min (Figure 1(C)) was within 3 ppm of the elemental formula $C_{15}H_{20}Cl_2N_2O$ consistent with a demethylated version of U-47700 (protonated expected mass of 315.1031). The isotopic pattern of the molecular ions demonstrates that the compounds contain two chlorines with A + 2 abundance of about 66%. These compounds were also identified by LC-TOF analysis of drug the patient provided. The powder supplied by the patient had identical retention time and mass spectra of the compounds found in the patient's urine. We were unable to obtain an authentic reference standard for U-47700 from a reliable source, but we were able to do so for AH-7921 (Cayman Chemical, Ann Arbor, MI), which shares the same molecular formula (but different structure). The presence of AH-7921 in the patient's urine was excluded using the LC-TOF platform because the authentic compound had a different retention time (Figure 1(A)) and spectra (Figure 1(D)).

To determine if the drug our patient used could have caused the false positive on the benzodiazepine immunoassay used, the powder the patient provided was added to drug free urine at increasing amounts (from 1 μg/mL up to 25 mg/mL) and tested using the benzodiazepine immunoassay. Table 1 shows the cross-reactivity of the substance the patient used at varying concentrations. There was a dose dependent increase in the signal with increasing concentrations, but a positive immunoassay for benzodiazepines occurred only at a very high concentration of 10 mg/mL (10,000 mcg/mL). Given the high-concentration needed for the parent drug to cause a positive benzodiazepine positive result, and by history the relatively small amount of drug used, it appears likely that an unknown metabolite of U-47700 with more cross-reactivity than the parent drug may have caused the false positive benzodiazepine result. It also remains possible that the patient used a benzodiazepine not tested for on our analysis.

Discussion

The patient described nearly died after recreationally abusing a synthetic opioid sold as U-47700. He fortunately was resuscitated quickly and appears to have suffered no permanent sequelae. The toxicity he manifested (depressed level of consciousness and respiratory depression) and its reversal with naloxone administration is consistent with the known *in vitro* and *in vivo* opioid agonism of U-47700.[14,15] We are not aware of any metabolic or pharmacokinetic data on U-47700, nor any literature detailing any therapeutic effects of U-47700 in humans. Two recently published cases detail the identification of U-47700 postmortem and implicate its use in the deaths.[10,11] We are also unaware of any pharmacokinetic data on the similarly structured AH-7921. The short length of time the patient experienced opioid toxicity suggests the drug has a relatively short half-life. U-47700 is a μ opioid agonist that is one of many synthetic opioids in the *trans*-1,2-diamine class that were developed in the 1970s at the Upjohn Company by a chemist Jacob Szmuszkovicz.[16] The "U" in U-47700 refers to Upjohn. Drugs in this *trans*-1,2-diamine class have a distinct structure from other opioid agonists (Figure 2). Similar to other synthetic opioid agonists such as fentanyl, fentanyl derivatives, and meperidine, the structure is distinct from morphine which is used as the basis for opiate detection on most urine drugs of abuse panels.[17]

The laboratory technique we used (LC-TOF), enabled determination of the molecular formula of the drug used, which matched U-47700. However, to conclusively identify an unknown drug without the use of nuclear magnetic resonance (NMR) analysis, a reference standard is required. For novel psychoactive substances this is challenging as reference standards may be unavailable, as was the situation in this case.[18] AH-7921 is a drug in the same structural class as U-47700, shares the identical molecular formula, and has been previously described as an opioid of abuse.[5] By

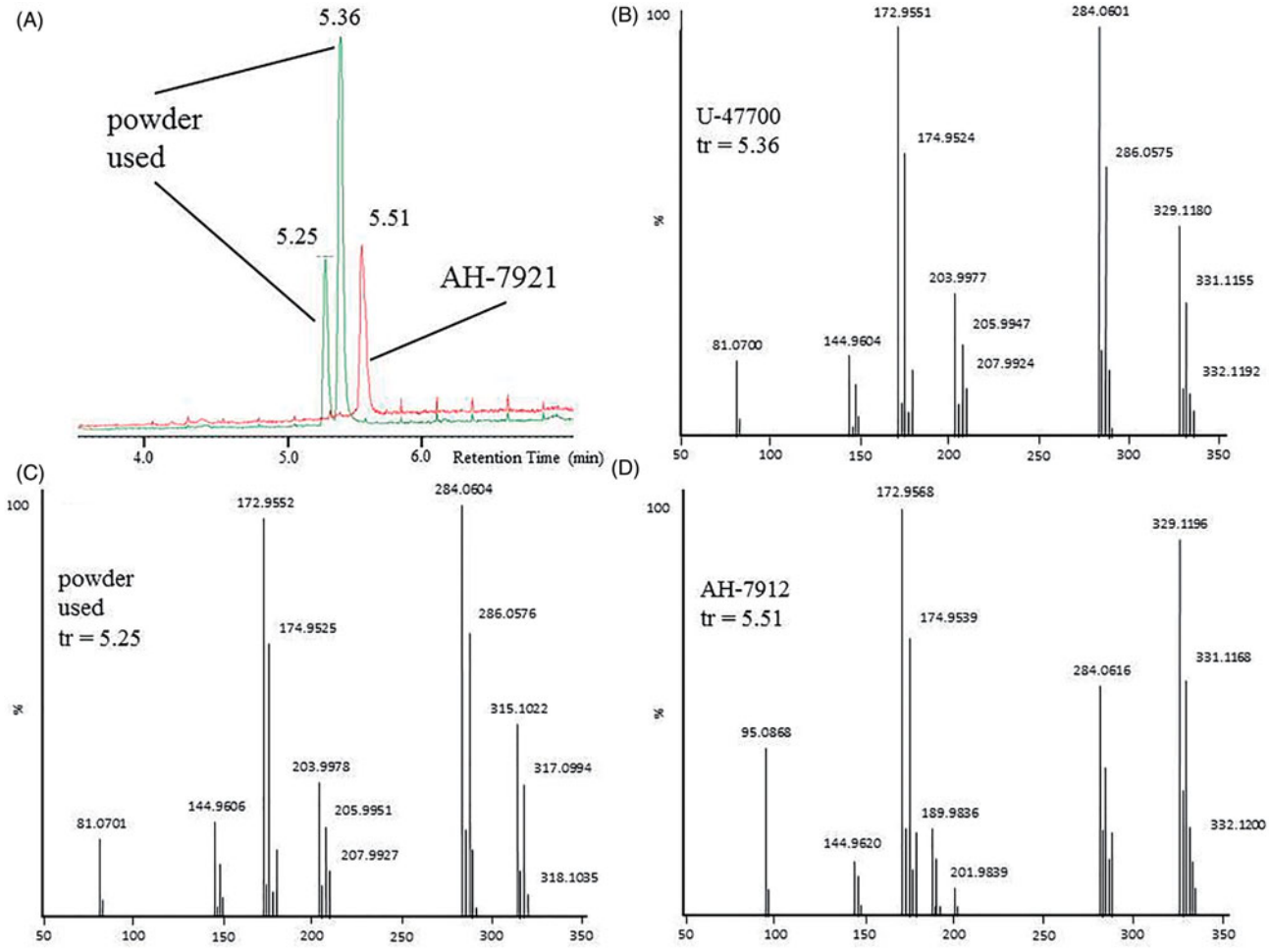

Figure 1. (A–D) Ultra performance liquid chromatography (UPLC) and mass spectra for powder used by the patient (labeled U-47700) and AH-7912. (A) UPLC spectrum of two independent runs overlaid showing elution powder used (U-47700 with tr = 5.36 and another peak at 5.25 min) which was purchased from the internet and AH-7912 (tr = 5.51). (B) High energy spectrum for the elution peak with tr = 5.36 corresponding to U-47700. (C) High energy spectrum for the elution peak with tr = 5.25 corresponding to U-47700 minus 14 Da. (D) High energy spectrum for the elution peak with tr = 5.51 corresponding to AH-7912.

Table 1. U-47700 Interference with benzodiazepine immunoassay.

U-47700 powder concentration (μg/mL)	COBAS 6000 benzodiazepine signal
Blank	805
1	802
10	804
100	844
1000	963
10,000	1110
25,000	1109

Benzodiazepine absorbance value greater than 1000 triggers positive.

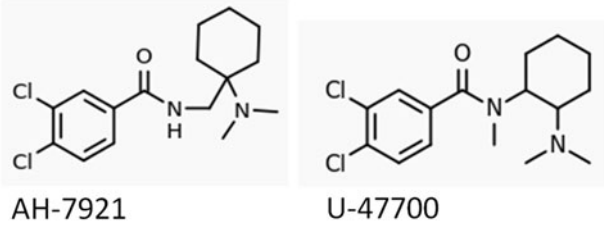

Figure 2. Chemical structures of AH-7921 and U-47700.

purchasing a reference standard for AH-7921 and testing it on our LC-TOF platform, we were able to exclude that it was the drug used. Although it seems very likely that the drug identified was U-47700, it is possible that another opioid, likely in the same structural class, may have been the one identified. NMR analysis was not utilized for identification. In our experience it is necessary to have pure compounds for NMR analysis, and the material supplied by the patient had a significant amount of a demethylated analog.

The only previous reports of toxicity related to U-47700 appear to be the two recently published forensic cases in which U-47700 was identified.[10,11] The similarly structured AH-7921, appears to have emerged prior to U-47700 as a drug of abuse. Similar to U-47700, AH-7921 was synthesized in the 1970s but has never been used medically. "AH" refers to "Allen and Hanburys", the company that patented the drug.[19] It was first detected in the United Kingdom in July of 2012 in a sample obtained via the internet.[20] In 2013, it was identified as a co-ingredient in synthetic cannabinoid and cathinone products in Japan.[21] The first death associated with its use was reported in Norway in December of 2012 and subsequently other cases of fatal and non-fatal

toxicities have been described in other countries in Europe.[20,22,23] To date, it has been described once in the United States. In that case, a 19-year old was found dead after using AH-7921, and its presence was confirmed in the vial he had used it from and in postmortem samples.[24]

Recreational abuse of opioids remains a serious problem. Synthetic opioids have not accounted for a significant percentage of the recent worldwide surge in abuse of novel psychoactive substances. However, the recent reports of abuse of AH-7921, MT-45, and U-47700 highlight the emerging trend of novel synthetic opioid abuse.

Disclosure statement

Authors report no conflicts of interest.

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