Fentanyl and a Novel Synthetic Opioid U-47700 Masquerading as Street "Norco" in Central California: A Case Report

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In 2013 and 2014, more than 700 deaths were attributed to fentanyl and fentanyl analogues in the United States. Of recent concern is the cluster of unintentional fentanyl overdoses because of tablets thought to be "Norco" purchased on the street in Northern California. U-47700 (*trans*-3,4-dichloro-*N*-[2-(dimethyl-amino)cyclohexyl]-*N*-methylbenz-amide) is a nonfentanyl-based synthetic opioid with 7.5 times the binding affinity of morphine to μ-opioid. We report a case of fentanyl and U-47700 intoxication from what was thought to be illicitly purchased Norco. A 41-year-old woman presented to the emergency department (ED) for altered mental status shortly after ingesting 3 beige Norco pills bearing a Watson imprint. She had pinpoint pupils and respiratory depression, which reversed after 0.4 mg naloxone administration intravenously. She had complete recovery and was discharged from the ED after a 4-hour observation period. Serum testing with liquid chromatography–quadrupole time-of-flight mass spectrometry (LC 1260 QTOF/MS 6550; Agilent, Santa Clara, CA) confirmed the presence of the medications the patient reported receiving, and additionally fentanyl (15.2 ng/mL) and U-47700 (7.6 ng/mL). In this case report, street Norco purchased in Central California resulted in altered mental status requiring naloxone reversal because of fentanyl and the novel synthetic opioid U-47700. Because these compounds are not detected by routine urine drug testing and physical examination findings are similar to those of a traditional opioid toxidrome, emergency providers should use the patient's history and other circumstantial details to aid in diagnosis. In cases with suspicion of opioid or opioid analogue cause, we recommend that emergency providers contact their local poison control center, medical toxicologist, or public health department to aid in the investigation. [Ann Emerg Med. 2017;69:87-90.]

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INTRODUCTION

Since 2008, poisonings have been the leading cause of injury death in the United States, with the majority of these cases caused by opioid analgesics.[1] As the use and misuse of prescription opioid analgesics have increased, so have outbreaks of morbidity and mortality from synthetic opioids.[2,3] Recent cases in California were attributed to pills with the street name of "Norco," containing fentanyl and various amounts of acetaminophen and hydrocodone. From March to April 2016, 12 fentanyl-related fatalities and 40 additional cases of toxicity were reported in Sacramento and Yolo Counties in Northern California because of different Norco pills containing fentanyl with and without hydrocodone.[4] Additional cases were identified in the San Francisco Bay Area.[5] One pill with an M367 imprint was analyzed in the San Francisco outbreak and contained acetaminophen, fentanyl, promethazine, and cocaine. Patient specimens from these cases also contained hydrocodone.[5] Although the pills in the California outbreak are being called Norco on the street, they may or may not contain the hydrocodone and acetaminophen found in brand-name Norco pills.

Many novel psychoactive substances are produced in China and then enter the US market for pill production and sale. Since more than 100 psychoactive substances, including 6 fentanyl analogues, were banned by China on October 1, 2015, novel synthetic opioids such as U-47700 and W-18 have entered the market, replacing more established and outlawed drugs.[6] Initially, these novel synthetic drugs are not scheduled as controlled substances for months until the Drug Enforcement Administration has enough abuse and overdose death cases to warrant legal action. We report a case of unintentional exposure to fentanyl and a novel synthetic opioid U-47700 in a woman presenting with opioid toxidrome after ingesting street-bought Norco in Central California.

CASE REPORT

A 41-year-old woman presented to the emergency department (ED) for a depressed level of consciousness. ED staff carried her out of a colleague's vehicle because they were carpooling to work when she became unresponsive. She had

pinpoint pupils and was minimally responsive to sternal rub. Two minutes after arrival, she received naloxone 0.4 mg intravenously, after which she woke up and was able to answer questions. The first set of vital signs, recorded 10 minutes after naloxone administration, was blood pressure 141/98 mm Hg, pulse 134 beats/min, respiratory rate 19 breaths/min, and SpO_2 100% on nonrebreather mask. Her physical examination result was otherwise unremarkable. Serum chemistry obtained 48 minutes after arrival was significant for acetaminophen level less than 10 μg/mL and glucose level of 64 mg/dL (reference 70 to 99 mg/dL), for which she was given a meal. No urine drug-of-abuse screen was performed. Pruritus and anxiety shortly after naloxone administration resolved with lorazepam 1 mg intravenously and diphenhydramine 50 mg intravenously. For 2 hours, she remained somnolent but was able to wake up and speak coherently. She tried to leave against medical advice multiple times and was discharged home 4 hours after arrival, completely recovered.

One and a half hours before ED arrival, on her way to work, she ingested 3 tabs of what she believed to be Norco that were illicitly purchased. She normally buys acetaminophen-hydrocodone combination pills on the street for chronic back pain and receives 2 to 3 at a time, 2 to 3 times a day. On this occasion, she felt sleepy fewer than 30 minutes after ingestion and next remembered waking up in the resuscitation room. The pills bore the usual Watson imprint but were beige instead of white. She voiced that concern to the emergency physicians immediately on awakening, which prompted this investigation. Despite receiving 3 pills at a time in the past, she had never become somnolent or required emergency care for opiate toxicity. She was not intending to harm herself and denied any other illicit drugs or ingesting any medications other than her prescription medications (baclofen, gabapentin, and sertraline). Social history included current alcohol use, with 3 to 4 beers consumed per day, cigarette smoking (6 to 8/day), and marijuana use, with history of methamphetamine abuse. Medical history included bipolar 2 disorder, asthma, L3/4 disc herniation, chronic pain, and anxiety.

Serum samples were analyzed with liquid chromatography–quadrupole time-of-flight mass spectrometry (LC 1260 QTOF/MS 6550; Agilent, Santa Clara, CA).[7] Results were significant for the presence of fentanyl and U-47700 (*trans*-3,4-dichloro-*N*-[2-(dimethyl-amino)cyclohexyl]-*N*-methylbenz-amide). All other detected compounds except for evidence of cocaine use (benzoylecgonine) were self-reported by the patient. Quantitative results are presented in the Table. No pill specimen was available for analysis. The LC-QTOF/MS analysis screened for 581 drugs, including 303 designer drugs. Suspect screening for 54 opioid analogues was also conducted, given the high probability of opioid or opioid analogue involvement. Quantitative analysis of detected drugs was conducted by the isotope dilution method, using 8-point calibration curves and deuterated reference standard of drugs as internal standards.

Table. Serum drug concentrations.

Drug	Serum Concentration, ng/mL		Therapeutic Concentration, ng/mL*
	13 Minutes Postarrival	44 Minutes Postarrival	
Acetaminophen	10,032.8	8,098.4	10,000–20,000
Benzoylecgonine	46.6	36.8	<100
Fentanyl	15.2	11.0	1–2
Gabapentin	350.9	254.4	5,900–21,000
Hydrocodone	107.6	90.1	2–24
Sertraline	15.7	12.7	50–250
U-47700	7.6	6.0	NA†

NA, not applicable.
*All reference ranges from Uges[17] except benzoylecgonine, which is from Schulz et al.[18]
†No reference range available.

DISCUSSION

Fentanyl has 50 to 100 times[3] and U-47700 7.5 times[8] the binding affinity of morphine to μ-opioid receptors. Even for an opioid-tolerant patient who is expecting to receive a certain concentration of hydrocodone, such as in this case, receiving additional concentrations of fentanyl or U-47700 could lead to unanticipated opioid toxicity. Although U-47700 exhibits some κ-opioid receptor agonism, it has far more activity at the μ-opioid receptors.[8] It was patented by the Upjohn Company in 1978 as an analgesic, but no human studies have been conducted, to our knowledge.[9] When rapidly swallowed, fentanyl bioavailability is approximately 30% because of extensive metabolism in the liver and intestinal wall.[10] In a recent *Morbidity and Mortality Weekly Report*, an analyzed pill contained 3.5 mg fentanyl, and patient serum fentanyl concentrations ranged from 1.6 to 10.1 ng/mL.[5] Although pill analysis was not available in this case, the initial serum fentanyl concentration of 15.2 ng/mL is consistent with the acute fentanyl intoxication observed in the *Morbidity and Mortality Weekly Report*. Pharmacologic information on U-47700 is limited and naloxone doses required to reverse toxicity are unknown. Although fentanyl should reverse with standard naloxone dosing, some reports have suggested that certain fentanyl analogues may require repeated doses of naloxone for opioid reversal.[11,12] Toxic effects of these compounds are similar to those of other