The Elephant in the Room: Outbreak of Carfentanil Deaths in Minnesota and the Importance of Multiagency Collaboration

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ABSTRACT

Over a three-month period in early 2017, the Hennepin County Medical Examiner's Office investigated nine apparent opioid toxicity deaths that occurred in three separate urban, suburban, and rural counties in our jurisdiction. All decedents were known substance abusers and had reportedly recently used heroin; most were found with drug paraphernalia. Complete autopsies variably showed classic stigmata of opioid overdose with no significant injury or natural disease to explain death. Initial toxicology screens failed to identify heroin or other narcotic substances. Several cases were presumptively positive for fentanyl by immunoassay, yet failed to confirm positive for fentanyl. Following American Board of Forensic Toxicology reporting standards, these cases were reported as negative for fentanyl by the laboratory. Due to the discrepant scene and toxicology findings suggestive of an opioid toxicity death, further discussion between the medical examiners and toxicologists prompted additional testing at a referral laboratory. This resulted in quantifiable blood carfentanil in all cases (mean 0.26 ng/mL, range 0.12 – 0.64 ng/mL). Cointoxicants included ethanol (n=2), methamphetamine (n=3), benzodiazepines (n=3), and cocaine (n=1). No case had definitive evidence of acute heroin intoxication, but two cases had low concentrations of morphine present (0.03 and 0.06 ng/mL), and two others had 6-monoacetyl morphine in the urine without morphine in the blood, suggesting recent use. All deaths were certified as accidental acute or mixed carfentanil toxicity. These cases present additional information about carfentanil-related deaths and highlight the importance of collaboration between forensic pathologists and toxicologists. *Acad Forensic Pathol.* 2018 8(3): 729-737

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ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Carfentanil, Outbreak, Toxicology, Multiagency collaboration

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.1177/1925362118797746>

Submitted for consideration on 14 May 2018. Accepted for publication on 21 Jun 2018

INTRODUCTION

The United States is in the midst of an opioid epidemic: drug overdose deaths are currently the leading cause of deaths related to injury and a reported 33 091 people died of an opioid overdose in 2015 (1), which increased to 42 249 in 2016 (2). Complicating the opioid epidemic is the fact that, while there is an increasing rate of heroin-related deaths, the recent rapid increase in death rates is being driven by synthetic opioids (2), such as illicitly-manufactured fentanyl and related analogs (3).

Carfentanil is one such fentanyl analog that has only recently been implicated in opioid-related deaths in the United States, including 23 deaths in Ohio in 2016 (4). An ultra-potent mu-opioid receptor agonist, carfentanil has a potency much greater than that of morphine (approximately 10 000 to 100 000 times) and even fentanyl (approximately 100 times) (5). It was developed as a veterinary medication (Wildnil) approved for use in tranquilizing large animals for procedures (6). Although it is not approved for use in humans, there are reports of human exposure in the literature (5-8). This includes evidence suggesting it was mixed with remifentanyl and used as part of an aerosolized chemical agent attack by the Russian Special Forces on October 26, 2002 against a Chechen terrorist hostage siege, and resulted in 125 deaths (7). It has been reported to cause human toxicity following accidental mucous membrane exposure to the veterinary compound Wildnil (6).

Due to its extremely high potency, carfentanil is present at extremely low concentrations in specimens of users (pg/mL) (8), making detection very difficult. There have been reports of carfentanil being identified in specimens of individuals involved in “driving under the influence” cases who survived with concentrations ranging from 11.8 pg/mL to 293 pg/mL (0.0118 to 0.293 ng/mL) (5, 8). Additionally, there is significant overlap with postmortem blood concentrations in reported overdose deaths (range 0.0107 – 0.535 ng/mL) (5). Further complicating testing for carfentanil is the fact that it is thought that most current opiate immunoassays do not cross react with carfentanil (5).

In this article, we describe our experience with an outbreak of carfentanil deaths in our jurisdiction, including initial difficulty in detecting this novel drug and the subsequent changes to our toxicology testing algorithm, death investigation policies, and procedures. We also discuss our role in the multiagency public health response to this crisis and the preliminary results.

DISCUSSION

In the first three months of 2017, the Hennepin County Medical Examiner’s Office investigated nine apparent opioid-related deaths in which toxicology testing initially failed to identify a causative opioid substance. Most deaths occurred in individuals who had a history of substance abuse and who had reportedly recently used heroin. Drug or drug paraphernalia were identified at a majority of the death scenes. Autopsies revealed some nonspecific findings suggestive of opioid toxicity such as pulmonary edema, foam in the airways, and/or urinary retention; evidence of acute or chronic intravenous drug use was found in a few cases. A majority of the cases did not have significant natural disease to cause death. The following two cases highlight the types of cases that presented to our office during this time period; the accompanying **Table 1** is a summary of all of the cases of carfentanil-related deaths identified by our office from January through March of 2017 (cases 1-9) with two subsequent cases identified in April 2017 (cases 10-11). Our standard screening included a hybrid approach including both immunoassay (by enzyme-linked immunosorbent assay or homogeneous enzyme immunoassay) and mass spectrometry (targeted gas chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry) in blood and urine.

Case Examples

The first case example (case 2 in **Table 1**) was a 33-year-old female with a history of heroin use who was last seen alive highly intoxicated while reportedly mixing heroin and fentanyl. She was found deceased semi-prone on a mattress on the floor of her residence with abundant paraphernalia nearby (i.e.,

Table 1: Summary of Carfentanil-Related Deaths

	Date of Death	Demographics	History and Scene Findings	Autopsy Findings	Drug Screen	Drug Concentration	Carfentanil (ng/mL)	Cause of Death
1	1/30/17	31 W/M	History of heroin abuse; last known alive asking for money to buy drugs; found deceased with drug paraphernalia including white powder and rock-like substance	Pulmonary edema, urinary retention, acute needle puncture mark; no significant natural disease	IA negative; MS cocaine, cocaine metabolites, mirtazapine, nicotine, cotinine (urine); IA benzodiazepine; MS mirtazapine, quinine/quinidine (blood)	Ethanol 0.226 g/dL; cocaine - ND	0.13	Mixed carfentanil and ethanol toxicity
2	2/4/17	33 W/F	History of heroin abuse reportedly injecting heroin and fentanyl; found deceased on bed with drug paraphernalia	Pulmonary edema and airway foam, urinary retention; no significant natural disease	IA negative; MS morphine, quinine/quinidine, nicotine, cotinine (urine); IA negative; MS quinine/quinidine (blood)	Ethanol 0.177 g/dL; opiates - ND; 6-MAM (vitreous and urine) ND; quinine 430 ng/mL	0.64	Acute carfentanil and ethanol toxicity
3	2/8/17	26 W/F	History of substance abuse; found unresponsive after reportedly insufflating heroin with drug paraphernalia present	Foam in airway; no significant natural disease	IA amphetamine, benzodiazepine, and opiate; MS 6-MAM, morphine, amphetamine, methamphetamine, diphenhydramine, quinine/quinidine (urine)	Methamphetamine 0.09 mg/L; alprazolam 14 ng/mL; diazepam 57 ng/mL with nordiazepam 100 ng/mL; opiate - ND	0.12	Mixed carfentanil, methamphetamine, alprazolam and diazepam toxicity; OSC recent heroin use
4	2/14/17	43 W/F	History of recent drug overdose found deceased with tourniquet on arm, drug paraphernalia and white powder present	Pulmonary edema; obesity; focally severe atherosclerosis of left circumflex artery	IA amphetamine, benzodiazepine, fentanyl, opiate; MS alprazolam, amphetamine, methamphetamine, amitriptyline, nortriptyline, morphine, quinine/quinidine, ranitidine, nicotine, cotinine (urine)	Morphine 0.03 mg/L; fentanyl (blood and liver) - ND; methamphetamine 0.02 mg/L; alprazolam 15 ng/mL	0.27	Recommendation to coroner: mixed drug toxicity (carfentanil, methamphetamine, alprazolam, opiate)
5	2/16/17	34 W/F	History of heroin and drug abuse found deceased in a shed with syringes nearby	Drug bundle in the axilla; track marks, pulmonary edema with foam; no significant natural disease	IA amphetamine, benzodiazepine, cocaine, fentanyl, opiate; MS amphetamine, methamphetamine, clonazepam metabolite, cocaine, cocaine metabolites, morphine, ibuprofen, gabapentin, levamisole, quinine/quinidine, nicotine, cotinine (urine)	Morphine 0.06 mg/L; methamphetamine 0.18 mg/L; benzoylcegonine 0.15 mg/L; cocaine - ND; fentanyl (liver and blood) - ND; 6-MAM (vit) - ND; clonazepam 2.7 ng/mL 7-amino clonazepam 160 ng/mL	0.44	Mixed drug toxicity (carfentanil, opiate, methamphetamine); OSC recent cocaine and clonazepam use
6	2/17/17	23 W/M	History of heroin abuse with possible recent use found deceased slumped in bathroom grasping a syringe	Pulmonary edema; acute needle puncture mark	IA negative; MS quinine/quinidine (urine and blood)	Urine 6-MAM 0.006 mg/L; opiate - ND; syringe analysis diacetylmorphine, 6-MAM, morphine, 6-diacetylcodeine, codeine, fentanyl, methamphetamine, noscapine, papaverine, quinine/quinidine	0.14	Acute carfentanil toxicity; OSC recent heroin use

Table 1: Continued

	Date of Death	Demographics	History and Scene Findings	Autopsy Findings	Drug Screen	Drug Concentration	Carfentanil (ng/mL)	Cause of Death
7	3/8/17	43 W/M	History of opiate dependence for chronic pain; found deceased with syringe in antecubital fossa; family denies history of drug abuse (syringe reportedly for testosterone)	Acute and chronic needle punctures; pulmonary edema with microscopy consistent with intravenous drug use; cardiomegaly and left ventricular hypertrophy	IA benzodiazepine; MS alprazolam, citalopram and metabolite, diphenhydramine (urine); additional referral lab screen positive for mitragynine	Alprazolam 27 ng/mL; mitragynine 160 ng/mL; citalopram 400 ng/mL; diphenhydramine - ND	0.26	Mixed carfentanil and mitragynine toxicity
8	3/21/17	39 B/M	History of heroin dependency on methadone therapy; found in an alleyway and responded to Narcan, but later pronounced deceased in a hospital	Pulmonary edema, anoxic brain injury	IA cocaine metabolite; MS tramadol, cocaine and metabolites, quinine (admit urine), and naloxone (blood)	Cocaine 0.03 mg/L; benzoylecgonine 0.58 mg/L; tramadol - ND	0.19	Anoxic brain injury due to resuscitated cardiopulmonary arrest due to mixed carfentanil and cocaine toxicity
9	3/30/17	23 W/M	History of heroin abuse reportedly insufflating cocaine; found slumped in the bathroom with a spoon and a syringe in pants pockets	Acute needle puncture; no significant natural disease	IA amphetamine, opiate; MS methamphetamine, morphine, quinine/quinidine (urine)	Opiate - ND; 6-MAM (vit) - ND; amphetamine/methamphetamine - ND	0.16	Acute carfentanil toxicity
10	4/17/17	32 W/M	History of heroin dependence; found deceased prone with drug paraphernalia present (needles); linked to case 8 through police investigation	Pulmonary edema; no significant natural disease	IA amphetamine, benzodiazepine, fentanyl and opiate; MS alprazolam, amphetamine, methamphetamine, fentanyl, norfentanyl, morphine and paroxetine present (urine)	Amphetamine 0.08 mg/L; methamphetamine 0.41 mg/L; fentanyl (liver) 7.4 µg/kg; opiates - ND; 6-MAM (vit) - ND; 6-MAM (urine) 0.007 mg/L; 7-amino clonazepam 13 ng/mL	0.12	Mixed drug toxicity (carfentanil, fentanyl and methamphetamine)
11	4/26/17	63 NA/M	History of heroin abuse; reportedly insufflating heroin with another individual and both found unresponsive (other individual revived with Narcan)	Pulmonary edema with mucus plugging	IA cocaine; MS cocaine metabolites, naloxone and trazodone (admit blood)	Cocaine - ND; benzoylecgonine 0.03 mg/L; trazodone 0.21 µg/mL	0.10 (serum)	Mixed drug toxicity (carfentanil and trazodone)

W - White; B - Black; NA - Native American; M - Male; F - Female; IA - Immunoassay; MS - Mass spectrometry; ND - none detected; 6-MAM - 6-monoacetyl morphine; OSC - other significant conditions ; vit - vitreous

syringes, needles, cotton tips, and a large spoon with white substance). Autopsy revealed chronic injection sites (“track marks”), pulmonary edema with foam in the airways, and urinary retention with minimal atherosclerosis of the left anterior descending coronary artery (40% stenosis). Toxicology showed a blood ethanol of 0.177 g/dL; urine drug screen immunoassay was negative with mass spectrometry presumptive positive for morphine, quinine/quinidine, nicotine, and cotinine; blood drug screen had a negative immunoassay with only quinine/quinidine present by mass spectrometry. Blood opiate and liver fentanyl quantitations were negative; blood quinine quantitation was unremarkable (430 ng/mL). After this portion of investigation, there was nothing significant enough to explain her death.

The second case example (case 6 in **Table 1**) is that of a 23-year-old male with history of heroin abuse, reportedly sober following chemical dependency treatment (with methadone therapy), who had been “partying” with a friend and was found slumped partially prone in his bathroom with a vial containing clear liquid nearby and a syringe clutched in his hand. Autopsy showed an acute needle puncture in the distal aspect of the left arm and mild pulmonary edema with no significant natural disease or injury to explain death. Toxicology showed a blood ethanol of 0.023 g/dL with blood and urine drug screens showing only quinine/quinidine by mass spectrometry. A urine 6-monoacetyl morphine quantitation showed a concentration of 0.006 mg/L; blood opiate and blood quinine/quinidine were absent or below the limit of quantification. Syringe analysis detected diacetyl morphine, 6-monoacetyl morphine, 6-acetyl codeine, morphine, codeine, fentanyl, methamphetamine, noscapine, papaverine, and quinine/quinidine by mass spectrometry. After this portion of investigation, there was nothing significant enough to explain his death.

Collaboration Between Medical Examiners and Toxicologists

Based on these cases, we suspected that a new type of opioid had been introduced in the drug-using population of our jurisdiction; unfortunately, our routine

toxicology testing failed to identify an appropriate causative substance. Like many other offices, our office has weekly toxicology rounds where we collaborate with the toxicologists at our local laboratory to discuss our cases, especially ones that are challenging. We are fortunate in that our toxicology rounds are additionally attended by emergency room physicians, clinical chemists, and local poison control specialists. The various attendees provide us with invaluable feedback on what they experience in overdose patients in the emergency rooms and in cases reported to poison control. In this setting, we discussed our cases, including scene findings, autopsy findings, and initial toxicology testing. At that time, none of the attendees had knowingly seen or suspected carfentanil in their line of work, but still suspected some kind of fentanyl analogue in these deaths.

As a result of our discussions, we felt these deaths likely represented drug-related deaths and we were suspicious for opioids. Therefore, the toxicologists retrospectively reviewed select identified cases and looked for gaps or out of scope findings; comprehensive review included the raw data from blood and urine screening, including both immunoassay and mass spectrometry tests completed. They found that some of the cases were presumptively positive for fentanyl by immunoassay but failed to show fentanyl by mass spectrometry and upon fentanyl confirmation testing. These positive fentanyl immunoassay results were reported as negative upon confirmation testing in accordance with the American Board of Forensic Toxicology (ABFT) accreditation requirements which specify:

positive results from non-specific screening tests must be confirmed by another, more specific method, such as mass spectrometry

and that:

reporting the possible presence of drugs of abuse or other drugs in forensically significant circumstances, based on immunoassay screening results, is discouraged... (9).

Furthermore, the toxicologists informed us that they couldn't detect many of the new fentanyl analogues by mass spectrometry as these novel compounds were not included within the screening spectral library and, additionally, no method for confirmation was available in-house. Based on this new, stronger suspicion of an undetectable-to-us fentanyl analog, we sought testing from our referral laboratory, NMS Labs. We initially requested the Novel Psychoactive Substance Screen-1, which uses a high-performance liquid chromatography/time of flight-mass spectrometry that had shown previous success in identifying compounds beyond the scope of our typical screen. After carfentanil was identified in one of our cases by this method, we switched testing to their more directed Designer Opioid (2017 scope) test, which specifically detects and quantifies opioids like carfentanil.

Although we assumed that all results would be reported within the bounds of an individual assay's limits and understood that a qualitative immunoassay screen required secondary, quantitative or more specific testing, it confounded the examination for a potential cause of death to have screen results reported as negative, despite a presumptive positive, ultimately unconfirmed result. Through extensive discussions, we established the protocol with the toxicology laboratory that unconfirmed, presumptively positive immunoassay results would be verbally communicated to the ordering medical examiner, which allowed for further workup while maintaining the ABFT standards. Additionally, our office developed a procedure for investigating these cases so that if we had a case with history and scene findings suggestive of an opioid-related death, absence of anatomic findings at autopsy, and negative screening toxicology or communication from the toxicology laboratory that there was an initial positive fentanyl immunoassay that failed to confirm by mass spectrometry, then we would order an NMS Designer Opioid test. In doing so, our office was able to identify nine cases of carfentanil-related deaths that occurred in the first three months of 2017. The carfentanil concentrations detected in these deaths are found in **Table 1**.

Results

Through these procedures, over the first three months of 2017, nine carfentanil-related deaths were confirmed. Their case details and carfentanil concentrations are presented in **Table 1**. These deaths occurred from January 30 to March 30, involved five males and four females ages 23 to 43, and involved three different counties we served, encompassing urban, suburban, and rural areas. All or most decedents had a history of substance abuse (n=9), recent heroin use (n=8), and had drug paraphernalia present at the scene (n=8). In these cases, autopsies showed pulmonary edema or airway foam (n=8), needle punctures (n=5), urinary retention (n=2), and minimal significant natural disease (n=2). Toxicology testing in these cases was significant for only two cases showing fentanyl positivity on immunoassay with negative mass spectrometry findings; eight of the nine cases were positive for quinine/quinidine, a known cutting agent for illicit drugs. Two cases were positive only for carfentanil with an additional two cases showing carfentanil mixed only with ethanol. The remaining five cases had additional coin-toxicants, consisting of methamphetamine (n=3), benzodiazepines (n=3), and cocaine (n=1). Interestingly, no cases actually involved fentanyl or heroin, the substances most decedents reportedly thought they were using. Although, two cases had very low concentrations of morphine (without evidence of 6-monoacetyl morphine), suggesting recent opiate use, and two other cases had evidence of 6-monoacetyl morphine in the vitreous or urine (without detectable morphine in the blood), suggesting recent heroin use. Overall, our cases had a mean postmortem carfentanil concentration of 0.26 ng/mL, with a range 0.12 to 0.64 ng/mL.

The Public Health Response

Multiagency Collaboration

After the first five cases of carfentanil had been confirmed and another four cases were suspected (with pending confirmatory testing), the Hennepin County Medical Examiner's Office reached out to the three different police jurisdictions involved, the local Drug Enforcement Agency office, the state Department of

Health, local emergency rooms and first responders, poison control, and other regional medical examiner's offices. Our office informed them of the identification of the novel synthetic fentanyl analogue carfentanil in a number of our drug-related deaths to make them aware that this compound is now present in the drug supply in the region. The purpose of this was manifold. Because of the extreme potency of carfentanil, first responders and emergency medical professionals needed to be made aware that any suspected opioid overdoses may now require a larger and more sustained dosage of reversal agents (naloxone) (10). Police officers and medical examiner personnel investigating drug-related deaths needed to be made aware so they knew both that they may need to consider special toxicology testing to detect this substance and practice a great deal of caution at drug-related death scenes, as inadvertent exposure to carfentanil can occur through mucus membranes and can have catastrophic consequences (1).

The sheriffs' offices pressed for a public release of this information, for the reasons previously mentioned, and to warn users not to use alone and to have naloxone on hand, in case of inadvertent overdose. However, the Drug Enforcement Agency was concerned that media publicity of a powerful new opioid present in the presumed heroin supply might cause current drug users to specifically seek out carfentanil, resulting in even more carfentanil-related overdoses and deaths, a correlation that had occurred previously (11). Nevertheless, on March 30, 2017, two months after the first death occurred in our jurisdiction, a press conference was held, involving the Chief Medical Examiner, the Medical Director of poison control (an emergency room physician and toxicologist), the superintendent of the state Bureau of Criminal Apprehension, police Chiefs from two of the affected cities, and a special agent from the state branch of the Drug Enforcement Agency (12). They confirmed that five carfentanil-related deaths had been identified to date, with four additional suspected cases with toxicology confirmation pending. They stressed the importance of utmost caution in dealing with this drug, both from a user perspective and as a first responder/police officer/death investigator.

Results

After the press conference, two additional deaths were reported in our jurisdiction in April that eventually were confirmed to be related to carfentanil. One of those cases was only identified due to its relation to a previous carfentanil death by astute police investigation linking both decedents to the same drug dealer. We remain vigilant in detecting additional carfentanil-related deaths in our jurisdiction, and a handful have been confirmed since those described in this report.

Policy Development

The carfentanil outbreak also resulted in a policy change at the Hennepin County Medical Examiner's Office with the way all suspicious drug cases are investigated and processed in order to prevent inadvertent employee exposure to potential high potency opioids. Previously, for all presumed drug-related cases where paraphernalia and possible drugs were present at the scene, medical examiner investigators would process the material by photographing at the scene and securing the substance(s) within evidence bags for transportation back to the office. At the office, the physicians would photograph and document the material in the autopsy suite during the course of post-mortem examination. Following examination by the medical examiner, the material would be maintained at our office unless requested by investigating agencies for testing. After the identification of carfentanil-related deaths, it became our office's policy that the investigators do not handle any unknown suspicious substances at the scene. It is our policy that the investigators are to use appropriate personal protective equipment (e.g., gloves and masks at a minimum) and are to photograph suspected drugs and paraphernalia *in situ* at the scene and then release it to the investigating police agency, who will then take custody of all material, including any possible items on the body.

CONCLUSION

These cases highlight the challenges that medical examiner offices face in identifying causative agents in presumed drug-related deaths in this age of rapid

designer drug development. We presented our experience, challenges, and solutions in investigating these types of deaths, and highlight the importance of collaboration with forensic toxicology colleagues. Additionally, we presented 11 cases of carfentanil-related deaths with higher concentrations than previously reported postmortem carfentanil concentrations. We also described our approach to communicating the importance of the identification of a new, highly-potent fentanyl analogue in our drug-using population to other public health agencies and the public as a whole. While there wasn't a large number of carfentanil cases, deaths related to carfentanil appeared to drop off sharply following our concerted multiagency collaboration and public education campaign.

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