Emerging Synthetic Fentanyl Analogs

Harold E. Schueler

ABSTRACT

Hundreds of synthetic substances have been introduced into the illicit drug market over the last ten years, but none of these drugs has had as poisonous a consequence as the emergence of the synthetic fentanyl analogs. Initially, pharmaceutical grade or illicit fentanyl was mixed with heroin, allegedly to boost the potency of the heroin. Then, the amounts of fentanyl spiked gradually increased until the proportion of fentanyl was greater than the proportion of heroin. Ultimately, many overdose cases began consisting of only fentanyl. The emergence of numerous synthetic fentanyl analogs, including acetylfentanyl, butyrylfentanyl, acrylfentanyl, furanylfentanyl and β -hydroxythiofentanyl, which are manufactured in China, were made available to the illicit drug traffickers over the Internet. In July of 2016, the most potent commercially available opioid, carfentanil, started appearing in illicit drug submissions and medical examiner death investigation cases in Northeast Ohio. Postmortem femoral blood carfentanil concentrations are in the picogram per milliliter (pg/mL) range, which is extremely low, and tests the limits of detection for most analytical forensic toxicology laboratories. The interpretation of these low carfentanil blood concentrations in antemortem and postmortem specimens is made difficult due to the overlap in the concentrations between these specimen types. The presence of these powerful synthetic fentanyl analogs presents a challenge to forensic toxicology laboratories preparing to analyze for these substances. *Acad Forensic Pathol.* 2017 7(1): 36-40

AUTHOR

Harold E. Schueler PhD, Cuyahoga County Medical Examiner's Office - Toxicology

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CORRESPONDENCE

Harold E. Schueler PhD, 11001 Cedar Avenue, Cleveland OH 44106-3043, hschueler@cuyahogacounty.us

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INTRODUCTION

During the past decade, several hundreds of synthetic compounds that are manufactured to mimic the pharmacology of various illegal drug classes (e.g., cannabinoids, cathinones, hallucinogens, opioids) have been introduced into the illicit drug market. None of these groups of substances have had as significant an impact on drug overdose deaths as the synthetic fentanyl analogs. In Cuyahoga County, Ohio, the heroin detected in drug paraphernalia and autopsy specimens was initially mixed with either pharmaceutical grade or illicit fentanyl, presumably in order to boost the potency of the heroin. Over time, the amount of fentanyl spiked gradually increased until the proportion of fentanyl became greater than the proportion of heroin. Eventually, many of the overdose death cases consisted only of fentanyl. Subsequently, numerous synthetic fentanyl analogs were being manufactured in China, and these highly potent drugs were made available to the illicit drug traffickers over the Internet. In 2016, one of the most potent commercially available opioids, carfentanil (Wildnil, a large animal general anesthetic agent) was being produced and started appearing in illicit drug submissions and medical examiner death investigation cases throughout Northeastern Ohio. The emergence of these powerful synthetic fentanyl analogs has directed attention to some deficiencies in laboratory drug testing that hinder forensic toxicology laboratories preparing to analyze for these compounds.

DISCUSSION

Fentanyl was first synthesized by Paul Janssen in 1960 and the extensive use of the drug prompted the production of the citrate salt (Sublimaze), which quickly gained popularity as a general anesthetic in medicine. Fentanyl being a strong mu-opioid receptor agonist with rapid onset and short duration of action, is used as a potent synthetic opioid analgesic for the treatment of moderate to severe chronic pain. The syntheses of other legitimate fentanyl analogs also possessing rapid onset and short duration of action, such as sufentanil in 1974 and alfentanil in 1976 by Janssen Pharmaceutica, and remifentanil in 1996 by Glaxo Wellcome, pro-

vided medical professionals with several options for potent, short-acting synthetic opioid analgesics that offer pain relief to patients during surgery and as an adjunct to anesthesia. Until the mid-1990s, only occasional fentanyl or fentanyl analog overdoses were reported. Most of these opioid overdose cases involved either medical misuse or the abuse of fentanyl or one of the potent synthetic analogs by medical professionals having access to these drugs. However, during a five-month period in 1988, at least 16 overdose deaths were attributed to the extremely potent 3-methylfentanyl analog ("China White"), which was synthesized by an industrial chemist in Pittsburgh (1, 2). The drug was only distributed locally and most of the deaths occurred during the several months of investigation by local and federal law enforcement agencies. The abuse of pharmaceutical grade fentanyl by the public increased after the drug was released in the 1990s as a transdermal patch for mild to severe chronic pain relief. Since then, thousands of overdose deaths have resulted from the illicit misuse by self-administering multiple patches simultaneously or using nontransdermal modes of administration compromising the contents of the fentanyl patch, such as intravenous, oral or transmucosal, rectal, or inhalation of the drug (3-8).

More recently, heroin laced with fentanyl was being distributed and was determined to be responsible for at least 700 deaths nationwide between 2013 and 2014 (9). To be more competitive, drug traffickers were adding either pharmaceutical grade or illicit fentanyl with the heroin in order to increase the potency or compensate for lower quality heroin. Routine postmortem toxicological analyses on blood specimens obtained from these deaths frequently detected the metabolites of heroin (i.e., morphine, codeine, and 6-acetylmorphine), fentanyl, N-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP), and N-(1-Phenethylpiperidin-4-yl)-N-phenylacetamide (acetylfentanyl). The 4-ANPP has been designated by the Drug Enforcement Administration (DEA) as an intermediate chemical precursor used in the synthesis process for the illicit production of the schedule II controlled substance, fentanyl, and other related opioids. Accordingly, the DEA approved the control of 4-ANPP also as a schedule II substance under the Controlled Sub-

stances Act (CSA). The presence of a small amount of 4-ANPP detected in a postmortem specimen may be an indication that the fentanyl taken was clandestinely manufactured in which trace amounts of 4-ANPP can remain as an impurity. Between 2005 and 2006, approximately 1000 fentanyl-related overdose deaths were the result of illicitly produced fentanyl (10). The 4-ANPP is also suspected to be involved in the production of other fentanyl analog compounds as well, such as acetylfentanyl, butyrylfentanyl, and furanylfentanyl. Some investigators believe 4-ANPP may also be a metabolite of fentanyl and these other analogs (11, 12). For certain enzyme-linked immunosorbent assay (ELISA) drug screens, the cross-reactivity for 4-ANPP with the fentanyl assay is very low and will not produce a positive result. Acetylfentanyl was ruled as a DEA Schedule I substance under the CSA, since the drug has no known approved medical or industrial applications and after 39 acetylfentanyl overdose deaths occurred in six states during 2013 and 2014 (13). Acetylfentanyl can be readily converted into fentanyl and is frequently detected as an impurity from the illicit manufacturing of fentanyl. The risk of an acetylfentanyl overdose is quite high due to the fact that the drug is about 15 times more potent than morphine. Postmortem blood acetylfentanyl concen-

trations ranged from 1.6 to 2.8 ng/mL from four cases ruled as multiple drug intoxications including fentanyl, heroin, cocaine, and phencyclidine. Acetylfentanyl is sold over the Internet, where the drug is sometimes posted as a “research chemical.” The cross-reactivity for acetylfentanyl with the fentanyl assay on most ELISA drug screens is high enough to produce a positive result.

Within the last two years, a barrage of many different fentanyl analogs has been introduced into the illicit drug market including: N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylfuran-2-carboxamide (furanylfentanyl); N-(3-methyl-1-phenethyl-4-piperidyl)-N-phenylpropanamide (3-methylfentanyl); N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]pentanamide (valerylfentanyl); N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylbutyramide (butyrylfentanyl); N-{1-[2-hydroxy-2-(thiophen-2-yl)ethyl]piperidin-4-yl}-N-phenylpropanamide (β -Hydroxythiofentanyl); N-Phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide (acrylfentanyl); and most recently, 4-((1-oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester (carfentanil) (**Figure 1**).

Figure 1: Structures of some fentanyl analogs.

These fentanyl analogs are manufactured in China, sold over the Internet, and enter into the United States through Canada or Mexico. Ohio was hit exceptionally hard in 2016 by the influx of carfentanil with emergency rooms and coroners reporting record-breaking overdose admissions and deaths, respectively (14). Most ELISA fentanyl immunoassays demonstrate positive cross-reactivity with several of the fentanyl derivatives, including furanylfentanyl, butyrylfentanyl and valerylfentanyl. Currently, no fentanyl immunoassay cross-reacts with carfentanil, which requires a specific assay. The relative potency of some of these analogs compared to morphine is shown in **Table 1**.

In Cuyahoga County, an 80-year-old male who died at the hospital of a 3-methylfentanyl overdose had an antemortem hospital blood concentration of 1.13 ng/mL 3-methylfentanyl; no other drugs were present. Postmortem femoral blood carfentanil concentrations for ten deaths in Cuyahoga County ranged from 10.7 to 535 pg/mL, with mean and median concentrations of 159 and 95 pg/mL, respectively. In four cases, carfentanil was not detected in the femoral blood; alternate matrices, such as urine or vitreous humor, were analyzed for the presence of the drug. The postmortem urine carfentanil concentration range for 14 cases was from 14.5 to 6842 pg/mL, with mean and median concentrations of 1098 and 367 pg/mL, respectively. The two cases involving vitreous humor had 25.2 and 96.8 pg/mL of carfentanil. These very low 3-methylfentanyl and carfentanil concentrations demonstrate the extreme potency of these fentanyl analogs. In some

instances, the determination of the cause of death was based solely on the presence of carfentanil in the urine or vitreous humor. Interestingly, six law enforcement “driving under the influence” cases have also been found positive for carfentanil, with antemortem blood concentrations of 11.8, 15.2, 48.4, 100, 220, and 293 pg/mL (mean 114 and median 74 pg/mL). This overlap of antemortem and postmortem carfentanil blood concentrations further complicates the interpretation of nontoxic and toxic carfentanil concentrations.

CONCLUSION

This latest epidemic of synthetic fentanyl analogs has added to the escalating pressure on forensic toxicology laboratories to increase the scope of analytes detected in routine comprehensive drug screens and to improve sensitivity by significantly lowering levels of detection. This comes on the heels of several other outbreaks of synthetic compounds including synthetic cannabinoids, synthetic cathinones, and synthetic phenethylamines that have already negatively impacted many forensic toxicology laboratories. Most standard ELISA drug screens do not adequately detect the majority of synthetic compounds being found in cases. By adding more specific ELISA assays to already large drug screening panels increases the amount of labor, time, and cost necessary to complete these drug-related cases. The limited availability of standard reference materials and the inability to quickly acquire instrumentation that is faster, more comprehensive, and sensitive, such as high performance liquid chromatography/time-of-flight mass spectrometry, are factors affecting the performance of these laboratories. Synthetic fentanyl analogs are the most potent substances to enter the illicit drug market. Only time will tell if these extremely toxic compounds will end drug users’ attraction with lethal highs or fuel the search for more potent, and ultimately deadly, synthetic drugs.

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Table 1: Fentanyl Analog Potencies Relative to Morphine

Fentanyl Analogs	Compared to Morphine
Fentanyl	80 to 100x
Acetylfentanyl	15x
Valerylfentanyl	< 20x
Furanylfentanyl	20x
Butyrylfentanyl	20 to 25x
Acrylfentanyl	100x
3-Methylfentanyl	400x trans and 6000x cis isomers
Carfentanil	10 000 to 100 000x

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