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First Polish case of fatal single-substance poisoning with cyclopropylfentanyl, a new synthetic opioid

Ewelina Pieprzyca[1], Rafał Skowronek[1], Małgorzata Korczyńska[1], Joanna Kulikowska[1], Piotr Czekaj[2]

[1] Department of Forensic Medicine and Forensic Toxicology, Medical University of Silesia in Katowice, Katowice, Poland
[2] Department of Cytophysiology, Chair of Histology and Embryology, Medical University of Silesia in Katowice, Katowice, Poland

SOUHRN

The article presents the first Polish case of fatal single-substance poisoning with cyclopropylfentanyl, a representative of fentanyl derivatives, whose victim was a 37-year-old man. This opioid was detected in biological material collected during medicolegal autopsy and in the syringe found near the deceased. Blood and urine samples were analyzed using liquid chromatography with mass spectrometry. The concentration of cyclopropylfentanyl was 24 ng/mL in blood and 73 ng/mL in urine.

Keywords: opioids – fentanyl analogs – cyclopropylfentanyl – new psychoactive substances (NPS)

První polský případ smrtelné intoxikace cyklopropylfentanylem, novým syntetickým opioidem

SUMMARY

Prezentovaná práce popisuje první případ smrtelné intoxikace derivátem fentanylu, konkrétně cyclopropylfentanylem v Polské republice, jehož obětí byl 37letý muž. Tento opioid byl prokázán v biologickém materiálu odebraném během soudně lékařské pitvy a ve stříkačce nalezené poblíž zemřelého. Krev a moč zemřelého byly analyzovány metodou kapalinové chromatografie s hmotnostní spektrometrií. V krvi zemřelého byla zjištěna koncentrace cyklopropylfentanylu 24 ng/ml a v jeho moči 73 ng/ml. Případ úmrtí byl uzavřen jako smrtelná intoxikace jedinou látkou - cyklopropylfentanylem s náhlým udušením ucpáním dýchacích cest. Z popsaného případu vyplývá, že cyklopropylfentanyl je další syntetický opioid, který ohrožuje životy jeho uživatelů, a proto vyžaduje neustálé sledování a další studie.

Klíčová slova: opioidy – analogy fentanylu – cyklopropylfentanyl – nové psychoaktivní látky (NPS)

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In the last decade, there has been a worldwide surge in the recreational abuse of new psychoactive substances (NPSs). By the end of 2018, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring more than 730 NPSs that had appeared on the European drug market over the previous 20 years. NPSs are classified into several groups with different modes of action, such as synthetic cannabinoids, stimulants, benzodiazepines, hallucinogens, and central nervous system depressants, such as opioids. In recent years, there has been a large increase in the availability of new synthetic opioids (NSOs) on the drug market. They are currently one of the fastest-growing groups monitored by EMCDDA, with the main role being played by fentanyl derivatives. Since 2009, 49 NSOs have been detected in the European drug market, including 34 new fentanyls, of which 10 were first reported in 2017 and six in 2018 (1). New fentanyls are highly potent. A few grams of the substances is enough to produce thousands of doses, making these substances easier to hide and smuggle. They are often sold as heroin or other illicit opioids, and even as falsified medicines. Only few opioids (fentanyl, alfentanil, sufentanil) have been used in medicine (2).

Cyclopropylfentanyl (IUPAC name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] cyclopropanecarboxamide; street names: "cyclopropyl," "synthetic heroin," "4-me-MAF," "MAF") is a representative of synthetic opioids which is structurally closely related to fentanyl - a potent opioid used for pain treatment in human and veterinary medicine or in combination with other medications for anesthesia (Fig. 1). Structurally, cyclopropylfentanyl (CPF) belongs to the 4-anilidopiperidine class and differs from fentanyl by replacement of the propionamide group with a cyclopropanecarboxamide group (4). CPF is also structurally related to crotonylfentanyl (isomer) and to butyrfentanyl (5). The synthesis of CPF was described in the literature in 1965, but it has not been introduced to clinical use (6,7). On the illegal drug market, CPF was first noted in July 2017 in Latvia and

✉ ***Correspondence address:***
Rafał Skowronek, M.D., Ph.D.
Department of Forensic Medicine and Forensic Toxicology
Medical University of Silesia in Katowice
18 Medyków Street, 40-752 Katowice, Poland
Phone number: +48-032-208-8374
Fax number: +48-032-252-7591
E-mail: rafal-skowronek@wp.pl

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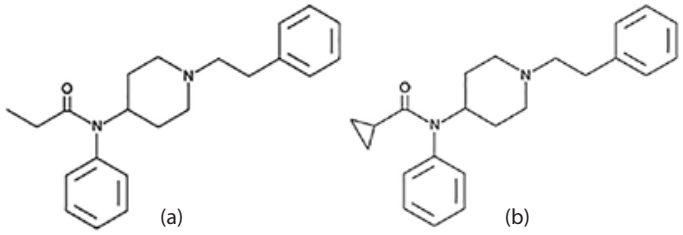

Figure 1. Chemical structures of fentanyl (**a**) and cyclopropylfentanyl (**b**).

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was reported to the EMCDDA in August 2017. CPF has also been identified in Austria, Bulgaria, Canada, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Lithuania, the Netherlands, Portugal, Slovenia, Spain, Sweden, and the Republic of Serbia (6,8).

CPF and other fentanyls are commonly sold as powders, tablets, ready-to-use nasal sprays, liquids, or blotting paper. Although less common, fentanyls has also been seized as green "herbal" material and are additionally sold as e-liquids for vaping in e-cigarettes. They are generally odorless and tasteless or have an unpleasant chemical odor and taste. Fentanyl and its analogs, including CPF, may be consumed by several routes, including injections, by oral or transdermal routes, by smoking, and intranasally or sublingually through a spray or vaporization (2,3,9). Synthetic opioids are often sold to users who believe they are receiving heroin, oxycodone, or other drugs of abuse, including stimulants such as MDMA and cocaine (6,10).

CPF is a highly selective μ-opioid receptor agonist (K_i = 0.088 nM) (6). The psychological effects of CPF may be similar to fentanyl and other opioids. These effects include relaxation, euphoria, analgesia, sedation, slowing of the heart, hypothermia, and respiratory depression (2,6,9). The same users compared the effects of CPF to those induced by U-47700, which is a more euphoric substance but with many more side effects (11). The action of CPF is similar to that of furanylfentanyl (12). Typical dosages of CPF cannot be defined because they depend on such factors as the administration route, user tolerance, and use of other drugs. The doses of CPF recommended by online forum users are in the range of 0.25–2 mg. CPF begins to act about 20 min after ingestion and its effects typically last for about 2–3 hours (however, they can last up to several hours) (2,6,9,13). Overdosing on NSOs can cause serious toxicity, including respiratory depression, which may lead to coma and, ultimately, death.

The aim of this study was to describe the first Polish case (to the best knowledge of the authors) of CPF identification in biological material obtained from a deceased person, together with the method of its analytical determination.

CASE REPORT

In August 2017, a 37-year-old man with a history of ethyl alcohol and NPS abuse was found dead in a hotel bathroom. The man was last seen alive 24 hours earlier. A syringe with brown residue was found on the floor near the deceased.

The time from death to autopsy was 5 days. The medicolegal autopsy revealed acute aspiration of gastric contents into the respiratory tract, acute lung distension, subconjunctival and subpleural petechiae, edema and hyperemia of the brain, and blood fluidity and hyperemia of the other internal organs. Traumatic lesions showed numerous injection marks on the left elbow and on both lower extremities. Anatomopathological changes showed mild generalized atherosclerosis, stenosis of the ascending aorta, a marked dilatation of the left ventricle of the heart, pneumoconiosis, liver steatosis, and erosive gastritis.

Histopathological examination confirmed the macroscopic diagnosis. In addition, it showed fragmentation of muscle fibers and small intracardiac hemorrhages, steatosis affecting about 10% of hepatocytes, and moderate lymphocytic inflammatory infiltration in the liver.

Biological material (femoral blood and urine) was collected from a corpse during medicolegal autopsy. The samples were stored at −20°C until further toxicological analysis, with no added preservatives. No ethyl alcohol in routine analysis was found, but a new fentanyl derivative, CPF, was detected in both syringe content and biological material (blood and urine), using new analytical method described below.

The syringe was flushed with methanol and mixed for 60 min. The methanol solution was transferred to Eppendorf vials and centrifuged at 13,000 rpm for 5 min. Then the solution was diluted and analyzed by GC-MS. The analysis was performed using a gas chromatograph (Trace 1300) coupled to a mass spectrometer (ISQ LT) equipped with a quadrupole mass analyzer (Thermo Scientific, USA). The injector was maintained at 280°C. Sample injection (1 μL) was in spitless mode. Sample separation was carried out on an RTX-5 capillary column (Restek, USA; length 30 m, inner diameter 0.25 mm, film thickness 0.25 μm). The carrier gas was helium with the flow rate of 1.0 mL/min. The temperature program consisted of three segments: the initial column temperature (75°C) was maintained for 1 min, then increased linearly at a rate of 25°C/min to 280°C, and finally maintained for 20 min. The mass detector was set to positive electron impact (EI) mode, and the electron beam energy was 70 eV. The mass detector operated in a full scan mode in the range of 40–450 amu range.

Analysis of the brown residue from the syringe found only CPF. The target compounds in the GC-MS method were identified by matching their retention times and spectra with reference libraries and the authors' own library. For CPF, under the obtained conditions, the peak eluted at 13.04 min. The EI-GC-MS spectra of the studied sample are shown in Fig. 2.

The analyses of biological material were performed on a Thermo Scientific TSQ Quantum Access Max mass spectrometer. The separation was performed on a Thermo Scientific C18 column (150 column length, 2.1 mm inner diameter, 5 μm particle size), thermostated at 25°C. The phase A was water, which contained 0.2% formic acid and 0.002 M of ammonium formate. The phase B was acetonitrile with 0.2% formic acid and 0.002 M of ammonium formate. All analyses used the following gradient mode (shown in relation to phase B content): 0 min, 5%; 6 min, 100%; 7 min, 5%; and 13 min, 5%. The total analysis time was 13 min. The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode with transitions at 349.3 → 188.3 (quantification) and 349.3 → 105.1 (qualification) for CPF and at 342.2 → 105.1 (quantification) and 342.2 → 188.1 (qualification) for fentanyl-D_5. The optimized collision energies were 22 eV for transitions at m/z 349.3/188.3 (CPF), 38 eV at m/z 349.3/105.1 (CPF), 40 eV at 342.2/105.1 (fentanyl-D_5), and 24 eV at m/z 342.2/188.1 (fentanyl-D_5). The mass detector parameters were as follow: capillary voltage, 2500 V; gas flow (nitrogen), 10 L/min; gas temperature, 325°C; and nebulizer pressure, 40 psi. The fragmentor voltages were set at 34 V for CPF and at 20 V for fentanyl-D_5.

The LC-MS method was validated for quantification of CPF in blood and urine. The limit of detection (LOD) of the method for CPF was 0.25 ng/mL. The limit of quantification (LOQ) was 0.5 ng/mL. Accuracy and precision data of the developed method are shown in Table 1.

CPF was measured in blood and urine in concentrations of 24 ng/mL and 73 ng/mL, respectively. MRM chromatograms of CPF and fentanyl-D_5 isolated from the blood sample are shown in Fig. 3.

Finally, forensic medical examiners established the following causes of death: initial—single-substance CPF intoxication, indirect—acute aspiration of gastric contents into the respiratory tract, and direct—sudden suffocation by clogging up of the respiratory tract.

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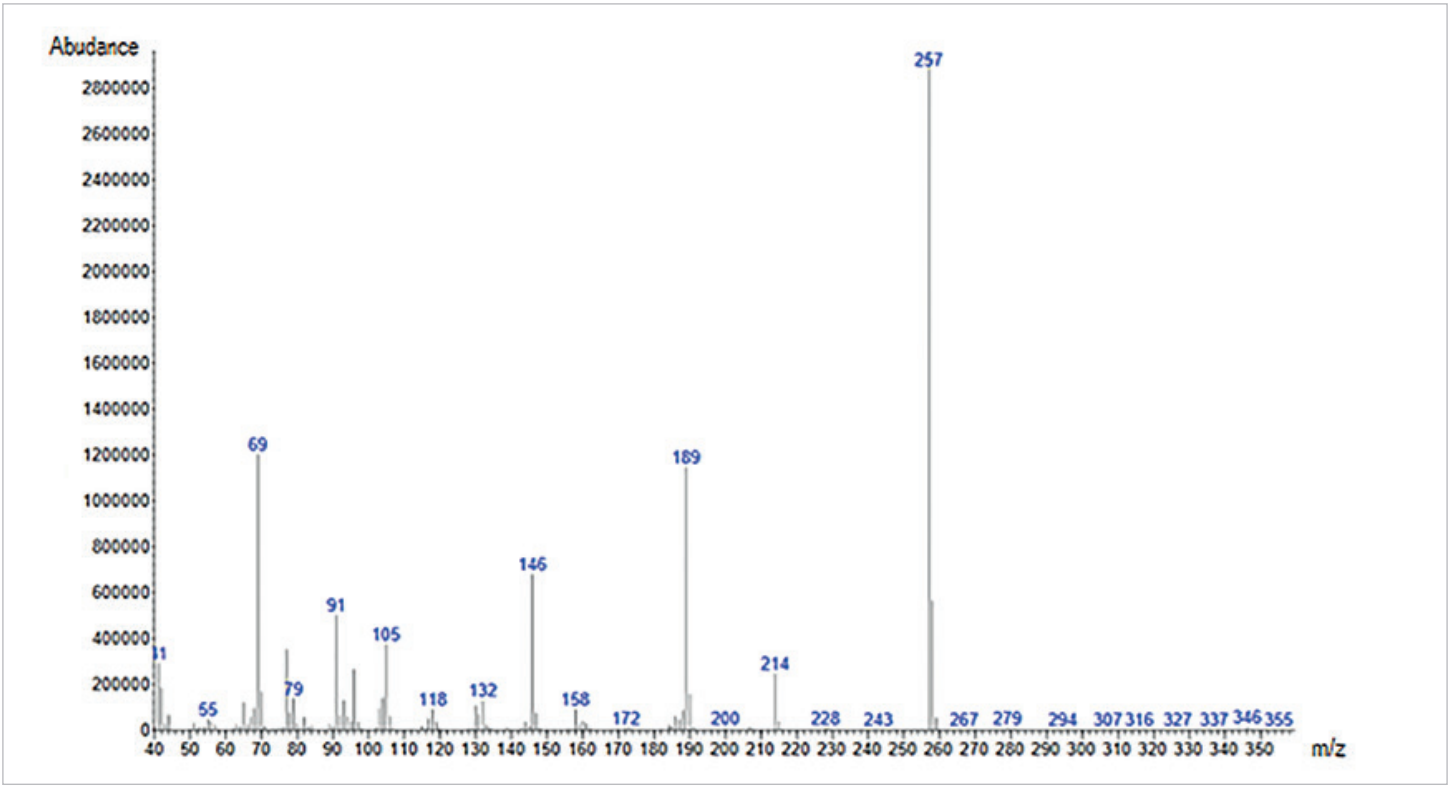

Figure 2. The EI-GC-MS spectra of the syringe content identified as cyclopropylfentanyl in the m/z range of 40–350. This compound has the exact mass of 348.22, and a prominent GC-MS base peak at m/z of 257. The EI mass spectrum of the study sample shows the major ions most abundant at m/z 189, m/z 69, and m/z 69.

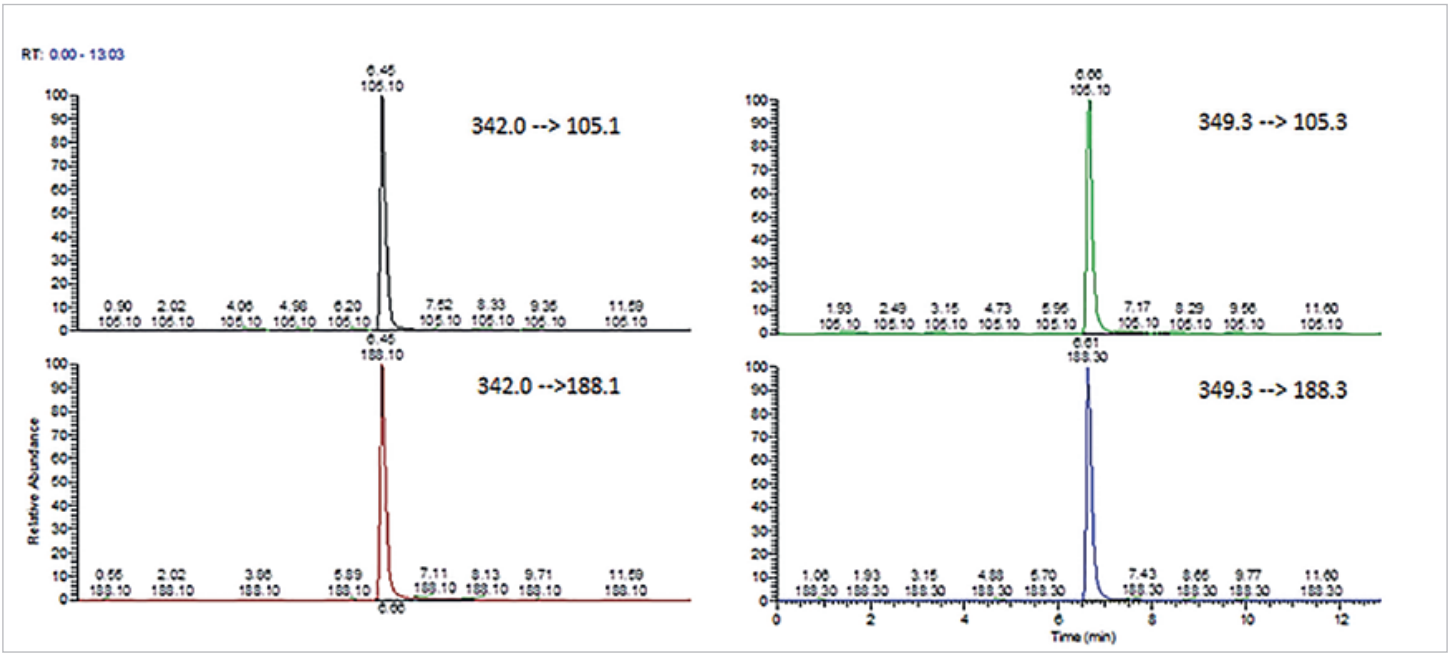

Figure 3. Multiple reaction monitoring (MRM) chromatograms obtained after analysis of forensic blood samples: fentanyl-D5 (internal standard)—left side; cyclopropylfentanyl—right side. The retention times of cyclopropylfentanyl and fentanyl-D5 were 6.66 and 6.45, respectively. The chromatograms obtained after analysis of forensic urine samples were similar; the only difference was in the signal intensity.

Table 1. Accuracy and precision data of the developed method.

Concentration of cyclopropylfentanyl (ng/mL)	Intra-assay (n = 5) blood		Intra-assay (n = 5) urine		Inter-assay (n = 15) blood		Inter-assay (n = 15) urine	
	Accuracy (%)	Precision (% RSD)	Accuracy (%)	Precision (% RSD)	Accuracy (%)	Precision (% RSD)	Accuracy (%)	Precision (% RSD)
0.5	12.5	13.1	16.7	14.6	10.9	10.2	12.7	11.2
50	-0.3	5.6	0.5	5.8	-0.1	3.8	0.8	8.9
100	1.2	3.6	0.9	6.7	2.6	7.1	1.3	6.8

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DISCUSSION

CPF is a new psychoactive substance that has appeared on the drug market only recently. It is difficult to pinpoint the popularity of CPF. Information on the prevalence of new psychoactive substances is limited mainly to online stores, surveys, and user reports posted on online discussion forums. Currently, new psychoactive substances are mainly sold as "research chemicals," and are called "RCs." Another source of distribution is street-level drug dealers, and a recent study has shown that they are the main source of supply for many users (6).

In Poland, CPF was first detected in illegal products in 2017. Unfortunately, there is no nationwide Polish forensic database of poisonings with new psychoactive substances that could be used to track changes in the availability of CPF. The first case of its detection in biological material was reported in our department at the end of August 2017, as described above. This compound was present in the blood sample collected from a 37-old-man, who probably took it intravenously. A screening analysis for NPSs showed the presence of CPF in blood and urine in concentrations of 24 ng/mL and 73 ng/mL, respectively. Importantly, this case is an example of single-substance poisoning not associated with the simultaneous use of other drugs, so it confirms high toxicity of CPF.

Information on the effects of the novel non-pharmaceutical fentanyls, especially in humans, is currently very limited (14). Like other synthetic opioids, CPF is a highly selective μ-opioid receptor agonist (15). Only a few scientific papers on CPF have been published, and they mainly comprised identification issues (16, 17, 18, 19, 20, 21). To date, there are almost no literature data on the pharmacokinetics or pharmacodynamics, human or animal toxicity, addiction or acute overdose potential, or long-term effects of CPF (22). The information is limited to self-reported use described on online forums. Even if the users think they have bought a pure substance, e.g. CPF, there is always a possibility they have been sold a different compound.

The acute toxicity of CPF has not yet been sufficiently studied. The available data suggest that its effects share some similarities with opioid analgesics such as morphine and fentanyl due to similar structure and mechanism of action. Cases of acute intoxication suspected to be due to CPF showed clinical features generally consistent with opioid-like toxicity (i.e. loss of consciousness, respiratory depression, pupillary miosis, hypothermia) (23). The most serious acute risk is respiratory depression, which can lead to apnea, respiratory arrest, and death. The administration of naloxone should reverse opioid toxidrome symptoms. Toxicological data on these deaths where CPF was detected suggest that the drug was the cause of death or was likely to have contributed to death (even in presence of other substances, i.e. polydrug use) (6).

In 2017, a total of 74 CPF-related deaths analytically confirmed in postmortem samples were reported in Europe (8). Another 115 deaths involving CPF were reported from the USA in 2017 (24). In most fatalities, there were other substances detected in addition to CPF, including cannabinoids, benzodiazepines, cocaine, antidepressants, ethanol, and other opioids (8, 24). So far, about 40 cases of analytically verified fatal intoxications have been published where the concentrations of CPF in biological material have been presented (10, 25, 26). Analysis result of our case against the background of other studies on CPF determination in biological material is shown in Table 2.

Table 2. Concentrations of cyclopropylfentanyl in biological material of presented case and another published fatal intoxications.

Source	Cyclopropylfentanyl concentration in postmortem blood samples
Our case	24 ng/mL
Fogarty et al. (10)	1.4 - 43.3 ng/mL
Fagiola et al. (26)	5.6 - 82 ng/mL
Maher et al. (4)	16.6 - 28.9 ng/mL
Brockbals et al. (25)	19.8 ng/mL

Fogarty et al. reported the concentrations of CPF found in the blood of 32 individuals. The range of CPF blood concentrations varied from 1.4 to 43.3 ng/mL (mean 15.3 ng/mL, median 12.3 ng/mL). All CPF cases were positive for other drugs. In addition to CPF, the researchers found morphine, 6-monoacetylmorphine, cocaine, benzoylecgonine, fentanyl, furanylfentanyl, and benzodiazepines (10). Fagiola et al. described five fatal intoxications of CPF, where its concentration in postmortem blood ranged from 5.6 to 82 ng/mL. Other significant findings included alprazolam, ethanol, and despropionyl fentanyl (4-ANPP, considered a precursor or impurity of fentanyl) (26). Maher et al. described five fatal intoxications of CPF, where its concentration in postmortem blood ranged from 16.6 to 28.9 ng/mL. CPF was deemed to have contributed to death in all five cases, even in the presence of other drugs (4). Brockbals et al. described one fatal case where CPF was determined in femoral blood in the concentration of 19.8 ng/mL. They also found that the central-to-peripheral blood ratio was 2.6, which suggests that postmortem CPF concentration should be interpreted with caution (25). In the case described by us, the blood concentration of CPF was 24 ng/mL, so it was similar to the mean concentration in Fogarty's study. We did not analyze the postmortem redistribution.

CONCLUSIONS

CPF is an analog of fentanyl that has no medical, veterinary, or industrial use. It has entered the illegal drug market and trade in recent years. It has been sold in Europe, including Poland, since 2017. Our knowledge of this substance is limited and is based partly on subjective accounts given by the users on online forums. It is a very potent substance that has opioid-like effects and high toxicity. Even milirogram doses can be fatal. The acute effects of CPF include sedation, bradycardia, hypothermia, and respiratory depression. It has an abuse liability and dependence potential. In conclusion, CPF is another synthetic opioid that threatens the lives of its users and thus requires constant monitoring and further studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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