



# Multiplex detection of 14 fentanyl analogues and U-47700 in biological samples: Application to a panel of French hospitalized patients

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## ► To cite this version:

Jean Jung, Allan Kolodziej, Elise Pape, Michael Bisch, Lucie Javot, et al.. Multiplex detection of 14 fentanyl analogues and U-47700 in biological samples: Application to a panel of French hospitalized patients. *Forensic Science International*, 2020, 317, pp.110437. 10.1016/j.forsciint.2020.110437 . hal-03492148

**HAL Id: hal-03492148**

**<https://hal.science/hal-03492148>**

Submitted on 17 Oct 2022

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## Title

Multiplex detection of 14 fentanyl analogues and U-47700 in biological samples: application to a panel of French hospitalized patients.

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## Abstract

Synthetic opioids (SO) associated with the recent alarming increase of deaths and intoxications in United States of America and Europe are not detected by the usual first-line opiates drug screening assays. We developed a liquid chromatography tandem mass spectrometry analytical method for the multiplex detection of 14 fentanyl analogues (2-furanylfentanyl, 4-ANPP, 4-methoxybutyrylfentanyl, acrylfentanyl, alfentanil, carfentanil, despropionyl-2-fluorofentanyl, fentanyl, methoxyacetylfentanyl, norfentanyl, ocfentanil, remifentanil, sufentanil and valerylfentanyl) and U-47700 in whole blood and urine samples. The method was validated according to the requirements of ISO 15189. A simple and fast liquid-liquid extraction (LLE) with De-Tox Tube-A was performed leading to better recovery of molecules in urine than in blood samples. Depending on the compound, the limits of detection (LODs) ranged from 0.01 to 0.10 ng/mL and from 0.02 to 0.05 ng/mL in whole blood and urine, respectively. Calibration curves were linear in the range 0.5-50.0 ng/mL and the limit of quantification (LOQ) ranged from 0.10 to 0.40 ng/mL in blood. Internal quality controls at 1 and 40 ng/mL showed intra-day and between-day precision and accuracy bias below 10% in urine and 15% in blood. The method was applied to the screening of 211 urine samples from patients admitted in emergency or addiction departments. The presence of legal fentanyl analogues in 5 urine samples was justified by their therapeutic use as analgesics. Only one patient was concerned by fentanyl misuse and addiction whereas no illegal SO was detected. This study is not in favor of a huge misuse of SO in the Lorraine region.

**Keywords:** fentanyl analogues; U-47700; synthetic opioids; misuse; HPLC-MS/MS

## 1) Introduction

Fentanyl and its analogues are synthetic opioids (SO) (1)(2) classified as NPS “New psychoactive substances” (3)(4). Nowadays, more than 30 fentanyl analogues are globally identified as narcotics in the world (5), some of them, namely fentanyl, sufentanil, alfentanil and remifentanil being marketed for severe pain management (6).

However, the use of fentanyl analogues emerges as an international public health threat. Indeed, more than 72,000 people died from opioid overdose in 2017 in North America (7)(8) and fentanyl has become the first cause of overdose in the USA since 2018, exceeding those caused by heroin. The nonmedical use of fentanyl and its derivatives is also reported in Europe although at a lower frequency than in North America. Since the first misuse-related cases of fentanyl-related deaths reported in Sweden in 1997 (9), hundreds of people died from fentanyl overdose in Germany, Finland, United Kingdom, Greece (10)(11) and more generally across entire Europe (12). In France, some fentanyl-related deaths and intoxications were reported between 2010 and 2015 by the French Addictovigilance network (13) whereas illicitly manufactured fentanyl (IMF) were offending in few intoxications since 2016 (14)(15). One problem arising from the increased use of marketed or IMF and analogues is their inability to be detected by the first-line analytical methods used for the screening of opiates. As a consequence, their contribution to intoxications is likely underestimated due to both the lack of general knowledge regarding their possible use (especially if other drugs such as heroin, cocaine, amphetamines or benzodiazepines are already detected) and the technical challenge to detect them. To circumvent this limitation, several analytical methods have been developed to detect up to twenty-four IMF and analogues in biological fluids (16)(17). Whole blood is frequently used as a matrix, due to the search for IMF as the possible cause of deaths (18)(19)(20). However, urine is also a matrix of choice for documenting drug consumption in clinical or forensic toxicology due to the significant elimination of fentanyl analogues and metabolites in urine (16). Unconventional samples like vitreous humor or bile (21), hair (19) (22) or dried blood spot (23) have been proposed as alternate matrices. Mass spectrometry (MS) is the reference method to detect IMF and analogues with the coupling to liquid chromatography (LC) separation (18)(19)(20)(21)(23)(24)(25) being more frequently used than to gas chromatography (GC) (26). One plausible explanation could be the limitation of GC/MS to detect compounds such as carfentanil (27) although analytical performance can be comparable to LC-MS/MS for furanylfentanyl, ocfentanil, acetylfentanyl and butyrylfentanyl (26).

In the present study, we developed a new sensitive and specific LC-MS/MS method to detect and quantify 14 fentanyl analogues and U-47700 in whole blood and urines. We aimed to provide a fast, simple and sensitive analytical tool for addictologists and emergency physicians to estimate and/or follow the consumption of these emerging narcotics in our eastern French region sharing frontiers with 3 European countries. We validated its suitability by performing a retrospective screening of urine or blood samples of patients admitted either in one emergency or the addiction departments of our university hospital between March and September 2019.

## **1. Materials and method**

### **a. Chemicals and standards**

Fentanyl and its analogues were obtained as powder or solution from different suppliers: 4-methoxybutyrylfentanyl and valeryl fentanyl from Alsachim (Illkirch, France), acrylfentanyl, despropionyl-2-fluorofentanyl and methoxyacetylfentanyl from Cayman chemical (Ann Arbor, USA), alfentanil, carfentanil, 2-furanylfentanyl, ocfentanil, remifentanil, sufentanil and U-47700 from Cerilliant (Round Rock, USA), 4-ANPP from Chiron (Trondheim, Norway), fentanyl and norfentanyl from LGC (Luckenwalde, Germany). Five deuterated internal standards were also supplied: carfentanil-D5 (Cerilliant, Round Rock, USA), fentanyl-D5 and norfentanyl-D5 (LGC, Luckenwalde, Germany), alfentanil-D3 and remifentanil-C6 (TRC, North York, Canada). Methanol and ammonium formate were purchased from Honeywell (Charlotte, USA) and Sigma-Aldrich (Saint-Louis, USA), respectively. Acetonitrile, formic acid and DE-TOX TUBE A™ were purchased from VWR (Fontenay-sous-bois, France) and Dyna-Tek Industries (Lenexa, Kansas, USA), respectively. Standard solutions (0.1 mg/mL and 1 mg/mL) were prepared by diluting the drugs in methanol, according to the manufacturer's recommendations.

Blank human blood and urine were obtained from Ingen Biosciences (Chilly-Mazarin, France).

### **b. Instrumentation**

The study was performed with an ultra-high-performance liquid chromatography Nexera XR® (Shimadzu, Japan) linked to a 3200 QTRAP triple quadrupole mass spectrometer (Life

Sciences Holdings France SAS SCIEX, Villebon sur Yvette, France). Analyst<sup>®</sup> software (version 1.6) was used for quantification.

Chromatography was performed using a Restek Pinnacle<sup>®</sup> DB PFP Propyl column (2.1 $\mu$ m particle size, 2.1 mm x 50 mm) maintained at 50°C in a thermostatically controlled oven. The following gradient of elution was applied using 5 mmol/L ammonium formate + 0.1% formic acid (mobile phase A) and acetonitrile (mobile phase B): 0.00-2.00 min: 5 - 20% B; 2.00-6.00 min: 20 - 90% B; 6.00-8.00 min: 90 - 100% B; 8.00 - 8.20 min: 100 - 90% B; 8.20-8.40 min: 90 - 5% B; 8.40-13.0 min: 5% B. The flow rate was 0.5 ml/min. Retention times of the molecules are shown in Table 1.

The column effluent was analyzed using a Turbo V ionization source equipped with electrospray ionization (ESI+) probe. Sources conditions were the following: spray voltage at 5.5 kV; gas 1: nitrogen, 40 psi; gas 2: nitrogen, 60 psi; ion source temperature 500°C; curtain gas: nitrogen, 30 psi. MS parameter settings were optimized by infusing neat standards individually in methanol. Cone voltage (CV), collision energy (CE) and cell exit parameter (CXP) were adjusted to maximize the signal for the 2 most abundant product ion of each drug (Table 1). The instrument was operated in dynamic SRM (Selective Reaction Monitoring) mode.

### **c. Method validation**

The method was validated according to the ISO15189 guidelines (28)(29). For that goal, the following parameters were checked: recovery, selectivity, carryover, matrix effect (ME), limit of detection (LOD), precision (repeatability and intermediate precision) and stability for identification in both whole blood and urine matrices. Analysis of accuracy, calibration model and limit of quantification (LOQ) were performed additionally to allow quantitative analysis in whole blood samples.

#### **i. Recovery**

Samples were submitted to liquid-liquid extraction (LLE) procedure. Briefly, 25  $\mu$ L of IS (100 ng/mL) mixture of carfentanil-D5, fentanyl-D5, norfentanyl-D5, alfentanil-D3 and remifentanil-C6 were added to 500  $\mu$ L of blank whole blood or urine aliquots. After addition of 2.7 mL deionized water, the mixture was transferred into DE-TOX TUBE A<sup>™</sup> (DTI),

which allows extraction of basic and neutral drugs at pH 9.0 using a patented mixture of heptane/isopropyl alcohol/dichloromethane. After agitation on a rotating mechanism for 5 min and centrifugation at 2.500 g for 5 min, the organic layer was gently evaporated to dryness under a nitrogen stream then reconstituted with 200  $\mu$ L of mobile phase A. A volume of 20  $\mu$ L was subsequently injected into the LC-MS/MS system. The recovery was calculated as the ratio of the peak areas measured post extraction over those obtained without extraction on blood and urine samples spiked at 1 ng/mL (low level) or 40 ng/mL (high level). Recovery was expressed as mean percentage of 5 values for both levels.

#### ii. Matrix effect (ME)

ME was determined using the experimental design proposed by Matuszewski *et al.* (30). ME was determined by comparing the ratio of the mean peak area obtained for five different blank urine and whole blood samples fortified with all analytes at 1 ng/mL (low level) or 40 ng/mL (high level) after extraction to the mean peak area obtained with pure solutions of the same analytes. Matrix effect was expressed as mean percentage for both levels.

#### iii. Selectivity and carryover

Selectivity was assessed by analyzing six blank urine samples and six blank blood samples to check for interfering compounds. To evaluate carryover, an extracted blank sample was analyzed immediately after running three replicates of the highest calibration standard (50 ng/mL).

#### iv. Linearity

Six calibration standards including a blank sample and five spiked concentrations over a range from 0.5 to 50 ng/mL were analyzed over a six-day period. The peak area ratio of analyte over corresponding internal standard (IS) versus analyte concentration was plotted for each molecule. Linearity was determined by analyzing and processing calibrators with 1/x weighting.

#### v. Limits of detection (LOD) and of quantification (LOQ)

The LODs and LOQs were determined by spiking blank urine and whole blood samples which were then serially diluted. A signal-to-noise (S/N) ratio greater than 3 standard deviations defined the LOD as the lowest concentration. The LOQ was defined as the lowest



concentration of the linearity for which accuracy between 80 and 120% (bias < 20%) and precision (coefficient of variation, CV) of  $\pm 20\%$  or less were obtained over six measurements.

#### vi. Precision and accuracy

Precision and accuracy were measured on spiked blood samples and urine samples, used as internal quality control (QC), at two concentration levels: low (1 ng/mL) and high (40 ng/mL). Both concentration levels were analyzed in 6 replicates.

### **d. Sample preparation and storage**

Blood and urine samples were submitted to the LLE procedure described above. Aliquots of 500 $\mu$ L of whole blood or urine were used. Urine and blood samples were frozen within 24h after collection and stored at -20°C until synthetic opioids (SO) screening by mass spectrometry.

Influence of storage conditions on the detection of fentanyl analogues and U-47700 was studied by measuring repeatedly analytes levels over a 30 days period. Compounds were analyzed at two concentrations (1 ng/mL and 40 ng/mL) following two different storage conditions (+4°C and -20°C).

### **e. Patients population**

Using the presently described method, we performed a retrospective study on samples of patients admitted in the Addiction (AD) or Emergency Departments (ED) of our University Hospital from March to September 2019. ED included the intensive care unit and the emergency medical services. All patients underwent urine narcotics screening (UNS) by an enzyme immunoassay (EIA) which included the detection of cocaine (COC), opiates (OPI), cannabis (THC), amphetamine/methamphetamine (AMPH) and related compounds by cross-reactivity. The immunoassay screens were performed on a Beckman AU5800 chemistry analyzer using Syva Emit II Plus reagents (Siemens Healthcare Diagnostics; Newark, DE). EIA results were reported as negative or positive based on whether the detected level exceeded a specific threshold for a given substance. The compounds used for calibration in

the UNS were benzoylecgonine for COC (cut-off level 150 ng/mL), morphine for OPI (cut-off level 300 ng/mL), 11-nor-delta<sup>9</sup>-THC-9-COOH for THC (cut-off level 20 ng/mL) and d-Metamphetamine for AMPH (cut-off level 300 ng/mL).

This study was approved by the local research ethics committee (request N°354).

## 2. Results and Discussion

### a. Method validation

The analytical method was validated to detect (urine) and quantify (whole blood) 14 fentanyl analogues and U-47700. Additional compounds failed unfortunately to be provided by the suppliers. The fifteen compounds are separated in a single run of 13 min. A representative chromatogram of a urine sample spiked with 5 ng/mL of each analyte is shown in Figure 1. Almost all analytical methods described in the scientific and medical literature use mass spectrometry, especially in tandem with coupling to LC, for specificity and sensitivity reasons (5)(16)(17)(26)(31). The validation data for the determination of SO in whole blood and urine samples are summarized in Table 1 and 2, respectively.

For the different compounds, the matrix effect ranged from 71% to 118% and from 74% to 121% for whole blood and urines, respectively (Tables 2 and 3). The matrix effect was in the same range for most molecules except for furanylfentanyl and valerylfentanyl which were more easily detected from urines than from whole blood. These values are in the range of the data reported previously for multiplex detection methods (18)(20)(23)(26) and confirms the higher impact of the matrix on low analytes concentration. The lowest value observed for valerylfentanyl in blood samples remains unexplained but this molecule is one of the less frequently searched amongst fentanyl analogues (20)(22)(23)(24) and is rarely found in case of intoxications and/or during post-mortem analysis (18)(19)(32). The recovery was satisfactory for all compounds in urines (over 58%) but remained below 39% in blood samples for valerylfentanyl and sufentanil. Such result may be due to the LLE methodology used which is less efficient than cleaning-up methods such solid-phase extraction (18)(20)(32) or microextraction with packed sorbent (MEPS) (33) to concentrate analytes (27). However, as simple precipitation methods (24)(34) our LLE protocol allows a fast, simple and cheap extraction of fentanyl analogues (19)(35) from only 500µL of sample. The 13 min separation is consistent with previously published methods (18)(20)(34) and suitable for routine analysis,

even if shorter runs have been logically reported using ultra-high performance liquid chromatography (UPLC) systems (19)(22)(32).

Using five hundred microliters of biological samples, the LODs ranged from 0.02 to 0.05 ng/mL and 0.01 to 0.10 ng/mL in urines and blood, respectively. These values are lower than previously published data in urines (33)(35) and in the range of those reported in blood (18)(32)(35) with the exception of the extremely low levels (0.7 to 2 ng/L) reported recently for a UPLC-MS/MS method (19). In our experimental conditions, the LOQs values ranged from 0.1 to 0.4 ng/mL for whole blood samples. Once again, our data are in the range of previously reported methods (18)(32)(35). Of particular interest is the ability of any method to detect and/or quantify compounds in the context of intoxication or autopsy (27). In published post-mortem blood analysis, 4-ANPP (18)(19)(32), furanylfentanyl (18)(19)(20)(32), methoxyacetylfentanyl (19)(20), fentanyl (18)(19)(24), norfentanyl (18)(19), acrylfentanyl (20)(32), carfentanil (18)(24)(32) and U-47700 (20)(32) were amongst the most frequently retrieved molecules. When provided, the mean or median blood concentrations were found above 2.5 ng/mL (18)(19)(20)(24)(32), excepted for carfentanil and acrylfentanyl which were in the range 0.24 to 0.86 ng/mL (24)(32) and at 1.86 ng/mL (32), respectively. For all these molecules, we determine LODs ranging from 0.01 to 0.1 ng/mL and LOQs ranging from 0.10 to 0.40 ng/mL (0.20 for carfentanil). This means that our method is enough sensitive to detect them adequately in biological samples (36) and even to quantify them with an acceptable accuracy.

Except for remifentanil which was only stable for 5 days at +4°C, stability testing showed urine concentrations within the range of 80-120% for all the compounds after 30 days of storage at +4°C and -20°C, whatever analytes concentration (data not shown). In whole blood samples, remifentanil was stable at -20°C but very unstable during storage at +4°C. Indeed, a significant decrease of its concentration (> 50%) was observed after 1 day, which is consistent with a former study having shown a 20% decrease after 5 hours at +4°C in samples without acidification (37). Concerning alfentanil, methoxyacetylfentanyl, norfentanyl, ocfentanil and U-47700, whole blood concentrations remained stable after 30 days whatever storage conditions. At both low and high concentrations, other fentanyl analogues were stable for at least 2 days at +4°C and 8 days at -20°C, respectively. Taken together, these data support that urine samples can be analyzed for fentanyl analogues until 5 days after collection if stored refrigerated but that blood samples must be frozen at -20°C, as soon as possible after sampling, to avoid analytes degradation.

## **b. Retrospective study**

Population characteristics are summarized in Table 4. Within the 6-month period of the study, 1 whole blood sample and 211 urine samples were analyzed by LC-MS/MS for the presence of 15 SO. Among these samples, 66.5 % (n=141) and 33.5 % (n=71) came from Emergency (ED) and Addiction (AD) Departments, respectively. The number of males (49%) and females (51%) was roughly equal and mean age was  $31.5 \pm 16.6$  years. Fifteen infants (7.1%) were hospitalized in the neonatal intensive care unit for close monitoring of neonatal abstinence syndrome (NAS). All urine samples from the AD were from patients aged over 18 years.

211 individual screening immunoassays for narcotics were performed with an overall screen positive rate of 50.2% (n=106). There was a high percent of positive screens for OPI (31.3%), THC (17.1%) and COC (19.9%) but a very low one for AMPH (1.9%). Most of the 66 positive urine samples screened for opiates were found on heroin addicts, a population of interest for the detection of possible SO use. SO are in fact consumed voluntarily either as opioid substitutes or unwittingly as heroin, cocaine or even drugs like oxycodone adulterants at very low doses, in order to reduce production costs of these substances and to potentiate their effects (24)(26)(38)(39)(40)(41)(42). However, SO usually fail to be detected by immunoassays which are based on the cross-reactivity towards the morphinane backbone of the natural opiates (43).

In our retrospective study, there is a quite low percentage (2.8%) of patients positive for SO identification (Table 5). As expected from an analytical point of view, all cases that were positive for NSO were negative for opiates immunoassay screening. The total number of SO exposures is thus likely underreported and underrated, because routine toxicology screens fail to systematically detect these compounds (44). As proposed by Seither and Reid (45), this result demonstrates the need to complete routine toxicology analysis with a sensitive methodology that can detect synthetic opioids in situations where opioids use may be implicated.

In the present study, all SO detected were related to pharmaceutical fentanyl. In 4 cases sufentanil was the detected drug, while fentanyl and its metabolite norfentanyl were identified in 3 other cases. Among the 211 patients screened in our study, no consumption of illicit fentanyl or fentanyl analogues has been detected. This suggests that our eastern French region, despite its close vicinity with transit lanes like Belgium, Luxembourg or Germany,

might be preserved to date from the opioid crisis observed in North America. This result is in accordance with the recent observations of the French Addictovigilance Network which recorded only 16 intoxications related to the consumption of non-medicated fentanyl (n=8), namely ocfentanil (5 overdoses including 2 deaths), carfentanil (n=2) and butyrylfentanyl (n=1) in our country between 2012 and 2017 (46).

In our study, five of the six positive cases were admitted into intensive care and were administered sedation, explaining the presence of pharmaceutical fentanyl or analogues in their biological samples, whereas no consumption of illicit fentanyl was detected. These data are encouraging about the apparent low-rate consumption of SO even if our study has been performed on a limited number of addicted patients. However, one case of medical prescription-induced addiction to fentanyl was observed (case 6 in Table 5). The medical story of this patient began in 2012 when he was hospitalized for chronic pain of unknown origin and was given ketamine and morphine to relieve it. However, progressive failure of pain relief led prescriber to start a fentanyl-based treatment in early 2018 using intra-nasal and transdermal routes which appeared efficient. Since then, the patient was suspected to develop addiction to opiates due to withdrawal syndrome features (nausea, vomiting, abdominal chronic pain) recorded during a consultation 6 months later. A substitution therapy with methadone was initiated and the patient was supported by hospital addiction department which carried out toxicological screening. The patient claimed that he stopped taking fentanyl three weeks ago but his urines were still positive for fentanyl and norfentanyl, which is not consistent with the pharmacokinetics of this molecule. He refused any further urinary tests and ask for a blood screening, including SO which returned negative results two weeks later. One may underline that one limitation of this retrospective study is that it did not address patients suffering from rheumatic or oncologic diseases and consulting for pain management. These patients can also be exposed to fentanyl or sufentanil and are not routinely controlled by toxicology screening. This matter has to be put in regards to the opioid crisis in North America which found its origin in an evolution from the consumption of opiates to those of licit then illicit fentanyl analogues (8)(47)(48)(49). Fentanyl analogues are, in fact, potent, short-acting synthetic opioids commonly prescribed for pain relief (1), usually by transdermal delivery system (patch), but also by transmucosal (sublingual, buccal, nasal) and intravenous route of administration (2)(3) in rheumatology, cancerology or neurology. The intra-nasal route is fast-acting but may also be more addictive, as has been observed in our retrospective NSA screening.

### 3. Conclusion

We developed a simple and routine LC-MS/MS method for the analysis of 14 fentanyl analogues and U-47700 in urines and whole blood. The method was validated according to the requirements of ISO 15189 and successfully applied to the screening of clinical samples. Amongst 211 urine samples tested, 6 were found positive to pharmaceutical fentanyl analogues. Neither illicitly manufactured fentanyl analogues, nor heroin or cocaine adulteration was observed. The presence of fentanyl analogues in urine samples was the result of a medical prescription with one case of misuse. Although the emerging use of these SO seems more limited in Europe than in North America, a routine toxicological analysis with a sensitive methodology able to detect them in biological samples should be used systematically. Indeed, the consumption of fentanyl analogues is likely underestimated due to the analytical limitations of first-line opiates screening methods, all the more that patients suffering from rheumatic or oncologic diseases are also exposed. The method is sensitive enough to be usable on biological samples in postmortem toxicological casework.

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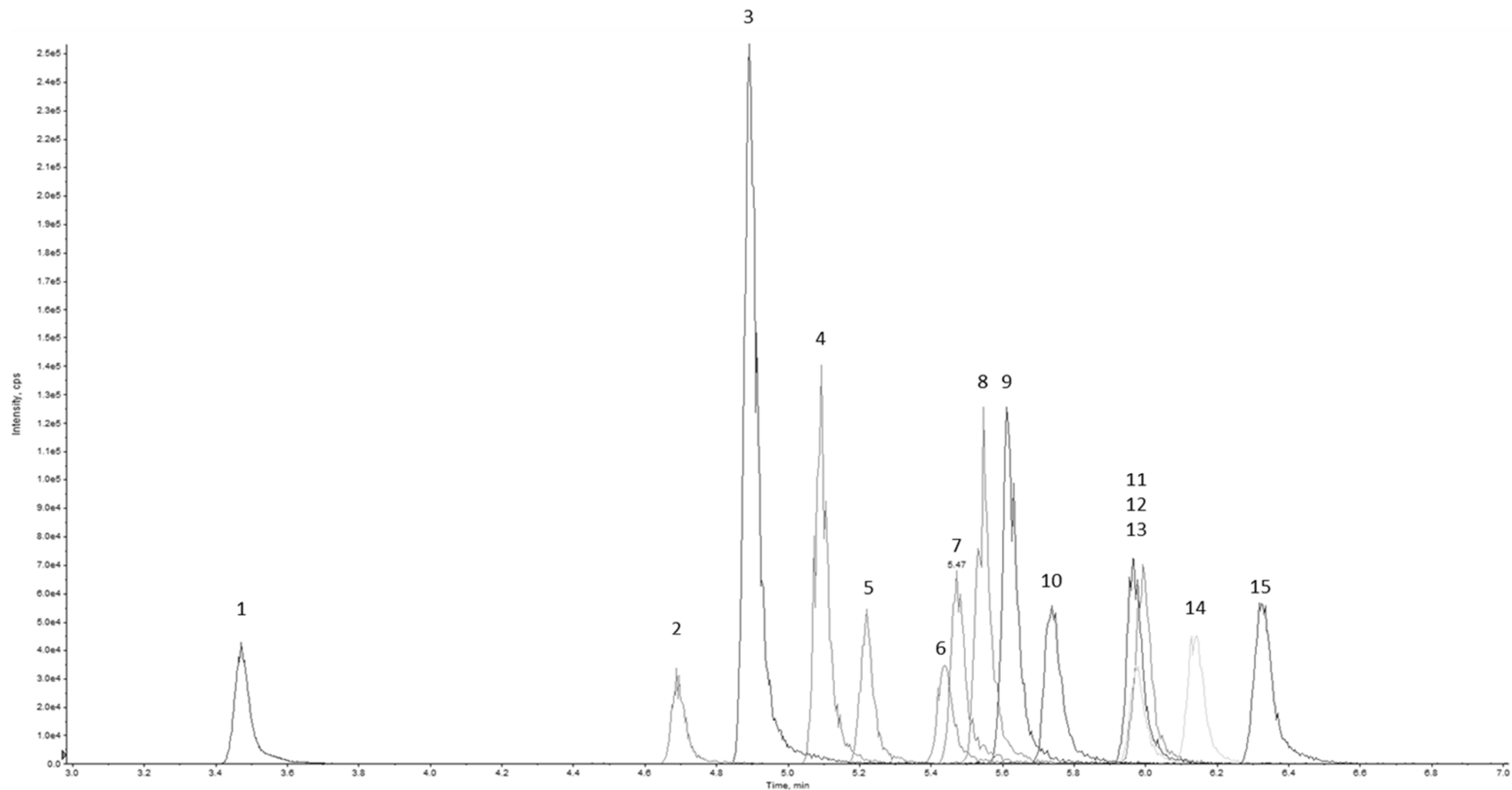
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**Figure 1.** LC-MS/MS chromatogram of a whole blood sample spiked with fentanyl and its analogs at 5ng/ml. **1:** Norfentanyl (RT=3.49). **2:** Remifentanyl (RT=4.70). **3:** Methoxyacetylfentanyl (RT=4.92). **4:** Ocfentanil (RT=5.11). **5:** Alfentanil (RT=5.25). **6:** U-47700 (RT=5.47). **7:** Acrylfentanyl (RT=5.52). **8:** Fentanyl (RT=5.65). **9:** Furanylfentanyl (RT=5.77). **10:** 4-ANPP (RT=5.85). **11:** 4-méthoxybutyrfentanyl (RT=6.01). **12:** Carfentanil (RT=6.01). **13:** Despropionyl-2-fluorofentanyl (RT=6.03). **14:** Sufentanil (RT=6.18). **15:** Valeryfentanyl (RT=6.38)

**Table 1.** Selective reactions monitoring (SRM) transitions and retention times for fentanyl analogues and U-47700 and corresponding internal standards (IS).

Compound	IS	Cone Voltage (V)	Q1 mass (m/z)	Quantification transition		Confirmation transition		RT (min)
				Q3 mass (m/z)	CE (eV)	Q3 mass (m/z)	CE (eV)	
4-methoxybutyrylfentanyl	Fentanyl-D5	56	381.2	188.1	33	105.1	53	6.01
Acrylfentanyl	Fentanyl-D5	51	335.1	188.1	29	105.1	47	5.47
Alfentanil	Alfentanil-D3	46	417.2	268.1	27	165.2	45	5.25
Carfentanil	Carfentanil-D5	46	395.2	335.1	27	113.1	41	6.01
Despropionyl-2-fluorofentanyl	Fentanyl-D5	41	299.1	188.2	25	105.1	39	6.03
4-ANPP	Fentanyl-D5	41	281.1	188.2	23	105.0	51	5.77
Fentanyl	Fentanyl-D5	56	337.1	188.1	31	105.2	47	5.52
Furanylfentanyl	Fentanyl-D5	66	375.1	188.2	29	105.1	51	5.65
Methoxyacetylfentanyl	Fentanyl-D5	51	353.2	188.1	29	105.2	49	4.92
Norfentanyl	Norfentanyl-D5	51	233.2	84.1	25	56.1	39	3.49
Ocfentanil	Fentanyl-D5	56	371.2	188.1	31	105.2	49	5.11
Remifentanil	Remifentanil-C6	41	377.1	116.1	37	113.1	41	4.70
Sufentanil	Fentanyl-D5	46	387.1	111.1	47	238.1	27	6.18
U-47700	Fentanyl-D5	41	329.0	284.1	23	173.0	41	4.70
Valerylfentanyl	Fentanyl-D5	56	365.2	188.1	31	105.1	53	6.38
Alfentanil-D3	/	41	420.2	165.1	45	/	/	5.25
Carfentanil-D5	/	46	400.2	105.2	59	/	/	6.01
Fentanyl-D5	/	51	342.2	105.0	49	/	/	5.52
Norfentanyl-D5	/	41	238.1	84.2	25	/	/	3.49
Remifentanil-C6	/	41	383.1	113.1	41	/	/	4.70

**V:** cone voltage in Volts ; **CE:** collision energy; **RT:** retention time; **D:** deuterium; **C:** carbon

**Table 2.** Validation parameters for fentanyl analogues and U-47700 in whole blood.

Substance	Accuracy (% bias)				Precision (% bias)				LOQ	LOD	Matrix effect		Recovery	
	Within-day		Between-day		Within-day		Between-day		(ng/mL)	(ng/mL)	(%)	(%)	(%)	(%)
	Low	High	Low	High	Low	High	Low	High			Low	High	Low	High
4-methoxybutyrylfentanyl	10.5	0.7	1.0	3.2	6.1	3.80	3.2	14.6	0.30	0.05	101	118	56	53
Acrylfentanyl	1.4	1.2	5.3	1.7	6.7	4.2	8.9	8.6	0.40	0.01	99	105	63	52
Alfentanil	0.7	2.5	4.3	1.6	4.3	4.2	6.6	4.5	0.10	0.05	90	103	75	65
Carfentanil	5.2	1.5	7.3	2.2	5.9	3.1	8.0	4.6	0.20	0.10	89	95	61	57
Despropionyl-2-fluorofentanyl	4.0	3.0	1.0	2.8	8.7	4.5	3.8	11.4	0.30	0.05	87	118	61	58
4-ANPP	12.3	1.9	0.5	0.1	5.7	4.8	10.3	9.8	0.20	0.10	87	99	55	50
Fentanyl	7.5	6.4	1.7	6.8	4.9	3.2	7.4	3.0	0.10	0.01	91	107	61	62
Furanylfentanyl	3.3	3.0	1.3	4.0	5.0	4.3	3.5	5.9	0.20	0.05	71	94	71	60
Methoxyacetylfentanyl	17.5	3.9	0.8	7.1	8.8	3.9	6.1	13.3	0.10	0.03	109	114	78	77
Norfentanyl	6.6	3.3	4.7	3.0	1.7	1.9	6.1	2.1	0.10	0.01	92	91	71	67
Ocfentanil	5.7	5.6	1.3	7.6	5.8	3.6	4.1	9.1	0.10	0.01	108	114	73	55
Remifentanil	2.1	2.7	2.3	7.2	5.3	3.4	6.0	8.3	0.10	0.05	92	95	65	66
Sufentanil	11.7	5.5	1.5	5.6	6.7	4.0	3.0	11.1	0.40	0.10	97	106	47	33
U-47700	8.3	4.7	3.2	9.5	7.3	4.3	8.0	9.1	0.40	0.05	97	113	67	56
Valerylfentanyl	9.8	1.4	3.0	5.4	4.8	4.4	3.7	5.4	0.20	0.03	69	83	49	39

**LOQ:** limit of quantification; **LOD:** limit of detection; **Low:** internal quality control 1 ng/mL; **High:** internal quality control 40 ng/mL

**Table 3.** Validation parameters for fentanyl analogues and U-47700 in urine.

Substance	Accuracy (% bias)				Precision (% bias)				LOD	Matrix effect		Recovery	
	Within-day		Between-day		Within-day		Between-day		(ng/mL)	(%)	(%)	(%)	(%)
	Low	High	Low	High	Low	High	Low	High		Low	High	Low	High
4-methoxybutyrylfentanyl	0.1	4.3	0.7	5.5	3.6	6.2	8.2	6.4	0.02	95	110	68	65
Acrylfentanyl	2.7	1.7	0.1	2.1	3.6	8.6	9.5	6.8	0.02	109	104	58	65
Alfentanil	1.0	4.5	4.5	3.8	5.7	3.8	5.0	8.3	0.02	94	91	72	73
Carfentanil	0.5	2.6	2.3	3.1	3.4	4.5	3.5	7.3	0.02	96	101	66	66
Despropionyl-2-fluorofentanyl	2.1	0.5	2.8	6.8	7.0	6.5	2.3	8.6	0.02	98	102	71	72
4-ANPP	5.0	0.3	5.6	2.5	2.6	6.4	9.8	9.7	0.03	87	98	80	68
Fentanyl	0.7	1.0	4.2	4.2	5.9	3.0	4.6	7.7	0.02	89	104	70	67
Furanylfentanyl	1.9	1.3	0.5	4.3	4.6	6.8	6.6	8.2	0.02	89	106	72	68
Methoxyacetylfentanyl	3.9	2.2	0.8	0.6	6.2	5.1	7.9	7.0	0.02	121	98	59	78
Norfentanyl	2.7	5.6	0.5	3.8	1.3	1.5	1.4	7.0	0.05	86	100	73	64
Ocfentanil	4.6	2.1	2.5	3.3	4.5	5.1	5.6	7.9	0.02	109	104	66	68
Remifentanil	3.1	2.3	0.8	1.6	4.7	3.2	5.5	6.5	0.02	87	97	72	72
Sufentanil	3.9	2.1	0.4	5.9	4.1	6.1	6.0	6.8	0.03	87	107	82	65
U-47700	5.5	2.5	2.7	2.2	4.8	6.5	9.1	8.9	0.03	74	86	66	74
Valerylfentanyl	1.4	0.5	1.3	3.7	2.3	4.9	3.9	9.5	0.02	86	109	72	62

**LOQ:** limit of quantification; **LOD:** limit of detection; **Low:** internal quality control 1 ng/mL; **High:** internal quality control 40 ng/mL

**Table 4.** Demographic characteristics of the population studied. Urine narcotics screening (UNS) and synthetic opioids (SO) identification in patients admitted in Nancy university hospital emergency departments (ED) and addiction departments (AD) from March to September 2019. Data are expressed as absolute number with corresponding percentage in brackets ().

Characteristics	ED + AD	ED	AD
<b>Number</b>	<b>211</b> (100)	<b>141</b> (66.8)	<b>70</b> (33.2)
<b>Gender</b>			
• Male	104 (49.3)	80 (37.9)	25 (11.8)
• Female	107 (50.7)	61 (28.9)	45 (21.3)
<b>Age group in years</b>			
• <2	15 (7.1)	15 (7.1)	0
• 2-11	6 (2.8)	6 (2.8)	0
• 12-17	27 (12.8)	27 (12.8)	0
• 18-75	163 (77.3)	93 (44.1)	70 (33.2)
<b>UNS –</b>	<b>105</b> (49.8)	<b>95</b> (45.1)	<b>10</b> (4.7)
<b>UNS +</b>	<b>106</b> (50.2)	<b>46</b> (21.8)	<b>60</b> (28.4)
• OPI +	66 (31.3)	23 (10.9)	43 (20.4)
• THC +	36 (17.1)	13 (6.2)	23 (10.9)
• COC +	42 (19.9)	12 (5.7)	30 (14.2)
• AMPH +	4 (1.9)	2 (0.9)	2 (0.9)
• SO +	6 (2.8)	5 (2.3)	1 (0.5)

**OPI:** Opiates; **THC:** Tetrahydrocannabinol; **COC:** Cocaine; **AMPH:** Amphetamines; **SO:** Synthetic Opioids, **UNS:** Urine narcotics screening.

**Table 5.** Characteristics of patients detected positive to fentanyl analogues in urine (n = 6).

Case	Age (years)	Gender	Department of admission	Medical history	UNS	SO	Indication of fentanyl and its analogs
#1	15	F	ICU	Head trauma following a fall from a height of 3 meters.	THC +	Fentanyl Norfentanyl Sufentanil	Sedation
#2	2	M	ICU	CRA following inhalation of a foreign body.	Negative	Sufentanil	Sedation
#3	38	F	ICU	CRA following occlusion of the AIV artery.	THC +	Sufentanil	Sedation
#4	49	F	ICU	Coma following hepatic encephalopathy.	Negative	Sufentanil	Sedation
#5	27	F	ICU	Coma following deliberate drug overdose	THC +	Fentanyl Norfentanyl	Sedation
#6	53	M	AD	Chronic chest pain without etiology initially treated by morphine. Methadone prescription by his GP because of morphine withdrawal symptoms. Introduction of Fentanyl (PO) and Instanyl™ (IN) by his GP for pain management. Then development of prescribed fentanyl addiction.	Negative	Fentanyl Norfentanyl	Pain management

**UNS:** urine narcotics screening; **SO:** synthetic opioids; **ICU:** intensive care unit; **AD:** addiction department; **CRA:** cardiorespiratory arrest; **AIV:** anterior inter-ventricular; **PO:** per os; **IN:** intranasal; **GP:** general practitioner; **THC:** tetrahydrocannabinol