FACT SHEET

U-47700

May 2017

For more information, please contact:
Dr. P. Blanckaert
Coordinator Belgian Early Warning System Drugs
Scientific Institute of Public Health
National Focal Point on Drugs
Jyliette Wytsmanstraat 14
B-1050 Brussels, Belgium
Tel : 02/642 5408
bewsd@wiv-isp.be
The information in this message is exclusively meant for the EWS-network, and was sent to you, as a member of this network, in a confidential way. Therefore the information in this message may not be copied, transferred or made public without the prior permission of the WIV-ISP. The WIV-ISP takes responsibility for the editing of a press release, if considered as necessary in the framework of its mission.

The information contained in this document is also available on the BEWSD-website (with corresponding pdf-files and analytical data). This part of the website is not accessible for the general public. A login can be requested by contacting ews.drugs@wiv-isps.be.
A. General information

Recent deaths in Belgium

Substance: U-47700
Date of analysis: March 2017
Product type: powder
Region: Antwerp

Substance: U-47700
Date of analysis: January 2016
Product type: powder
Colour: off-white
Region: Bruges

Updated
May 2017

Type
Narcotic drugs

Group
Opioids

Name
U-47700

Nature of substance
U-47700 is an opioid analgesic drug that was developed by Upjohn in the 1970s and was derived from the recently risk assessed opioid AH-7921. U-47700 was found to be selective for the μ-opioid receptor and considered to have a potency 7.5 times that of morphine. The substance is openly sold on the internet.

Systematic chemical name
3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide

B. Alerts

Alerts
Belgium, May 2017 and January 2016

Reports to EMCDDA

Croatia: On 7 April 2017 the Croatian FP reported a seizure of a plastic bag with 0,60 g of white powder seized on 29/12/2016 by the Police in Pula (Istria region).

Hungary: On 23 January 2017 the Hungarian FP reported a seizure of 4.80 g powder seized in October 2016 by the Police at Budapest (Airport).
**Ireland:** On 18 January 2017 the Irish FP reported that Forensic Science received a sample of white powder from a fatality in Cork. On analysis, the powder was found to indicate the presence of U-47700.

**Poland:** On 3 November 2016 the Polish FP reported a seizure of 0.03g white powder seized on 21.09.2016 by the Police at Kielce.

**Austria:** On 6 September 2016 the Austrian FP reported a seizure of 783.6g white powder seized on 01.04.2016 by the Police at Lower Austria.

**Lithuania:** On 24 August 2016 the Lithuania FP reported a seizure of 1,6677 g white powder seized on 11/07/2016 by the Customs at Vilnius. Package from China.

**Finland:** On 8 August 2016 the Finnish FP informed that two death cases in which U-47700 was detected occurred in Finland this year. Both of them were males in their 20’s and both had multiple other substances present in their blood. One of them had a relatively high blood alcohol concentration.

**Germany:** On 14 July 2016 the German FP reported a seizure of 49.9 gram white powder seized in February 2016 by the customs investigation unit in Essen.

**United Kingdom:** On 28 April 2016 the UK Focal Point reported a seizure of 761 tablets seized on 12/03/16 by the Police at Melvaig Place, Glasgow, Scotland.

**Sweden:** On 12 April 2016 the Swedish FP reported a death that occurred in February 2016.

**United Kingdom:** On 8 April 2016 the UK focal point reported 2 seizures:
- 854 white tablets seized on 28/01/16 by the Police at Main Street, Busby, East Renfrewshire, Scotland;
- 1014 yellow tablets seized on 11/02/16 by the Police at Slaemuir Avenue, Port Glasgow, Inverclyde, Scotland.

**Denmark:** On 4 March 2016 the Danish FP reported a seizure of 2g white powder seized on 26.01.2016 by the Customs at Copenhagen International Postoffice. Sent by airmail from Belgium to Denmark.

**France:** On 2 March 2016 the French FP reported a seizure of 10g white powder seized on 10/12/2015 by the Customs at Roissy airport (express freight). Parcel from China to France (in the same parcel, a 10g-bag of fentanyl pentanamide analogue). Analysed by the SCL (Paris).

**Sweden:** On 8 February 2016 the Swedish FP informed the number of seizures during 2015.

**Slovenia:** On 7 February 2016 the Slovenian FP reported a collected sample of 1 gram of white powder which was test-purchased on 09.12.2015 by the Slovenian National Forensic Laboratory as part of the EU co-funded project RESPONSE.
Belgium: On 28 January 2016 the Belgium FP reported a seizure of 10g off-white powder seized on 12.01.2016 by the Customs department DHL at Bierset, en route to Germany.

Belgium: On 28 January 2016 the Belgium FP reported a deceased case of a male, 27 years old, on 19.01.2016 at Bruges. In the room was also found a powder, which after analysis, was found to be a mixture of fentanyl and U-47700, together with some form of matrix (“hot melting powder”). U47700 and fentanyl found in blood and urine as well, toxicology report is clear that those drugs were the cause of death.

Spain: On 26 January 2016 the Spanish FP reported a seizure of 1.054 kg white powder seized on 18.01.2016 by the Spanish National Customs Surveillance Service at Adolfo Suárez-Barajas Airport (Madrid). It was a delivery from China but its final destination was supposed to be Barcelona.

Estonia: On 15 November 2015 the Estonian FP reported a seizure of 0,80g white powder with label “U-47700” seized on 12.10.2015 by the Customs at Tallinn, sent from UK.

Sweden: On 30 December 2014 the Swedish FP reported a seizure of 5.3 grams of white powder on 30 October 2014 by Swedish customs in Arlanda.

C. Pictures

White tablets seized by Scottish authorities, Forensic Services Gartcosh, Scotland

Yellow tablets seized by Scottish authorities, Forensic Services Gartcosh, Scotland
D. Clinical information

Usage: modes and scope of expected use
Very little, if any, information is available from scientific literature. Anecdotal evidence can be derived from user reports found on the internet. From these “trip reports”, it is obvious that this compound is being used as a (legal) substitute for other strong opioids, such as morphine, heroin or even fentanyl.

U-47700 is a strong \( \mu \)-opioid receptor agonist, and produces all (or most of the) effects common for opiates such as morphine: analgesia, pronounced euphoria, sedation, itching. It is presumed that side effects, including overdose reactions, will be very similar to other opiates/opioids as well: depressed respiration (slow breathing), miosis (pinpoint pupils), constipation. Prolonged use of U-47700 leads to development of tolerance to the effects, and possibly addiction. Very high dosages could result in coma and, ultimately, death.

Of interest is that the reported duration of action is quite short compared to the “classic” opiates; effects last around 60-90 minutes after a single administration. Oral and intravenous administration have been reported.

Health risks
See above. It is thought that the same health risks apply for U-47700 as for other strong opioids such as fentanyl and heroin, including respiratory arrest/depression, miosis, constipation, coma. Very high dosages might result in death, probably due to respiratory arrest and pulmonary oedema.

The antidote specific for opioid intoxications is naloxone. Careful monitoring is necessary, since multiple doses of naloxone may be required.

Other uses
None known.
E. Legal status

**Belgium**: not controlled

U-47700 is a controlled substance in Czech Republic, Estonia, Finland, Latvia, Sweden and USA.

F. Chemistry

**Systematic chemical name**
3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide

**Other chemical names and variants**
Unknown

**Chemical Abstracts Service (CAS) registry number**
121348-98-9

**Molecular information**
Molecular structure:

![Molecular structure diagram]

Molecular formula: C_{16}H_{22}Cl_{2}N_{2}O

Molecular weight: 329.26g/mol

Identification and analytical profile can be found at the end of this document and were kindly provided by Eurofins Forensics, Brugge, Belgium.
G. References


Dziadosz M et al. Postmortem concentration distribution in fatal cases involving the synthetic opioid U-47700. Int J Legal Med. 2017. doi: http://dx.doi.org/10.1007/s00414-017-1593-7


Elliott S.P., Brandt S.D. and Smith C., The first reported fatality associated with the synthetic opioid 3,4-dichloro-N-[2-(dimethylamino) cyclohexyl]-N-methylbenzamide (U-47700) and implications for forensic analysis, Drug Test. Analysis (2016), DOI 10.1002/dta.1984


A case of acute intoxication due to combined use of fentanyl and 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide (U-47700)

Vera Coopman a,*, Peter Blanckaert b, Geert Van Parys c, Serge Van Calenbergh d, Jan Cordonnier a,*

a Eurofins Forensics Belgium, Lieven Bauwenstraat 6, 8200 Brugge, Belgium
b Belgian Early Warning System on Drugs, Scientific Institute of Public Health, Juliette Wytsmanstraat 14, 1050 Brussel, Belgium
c Department of Pathology and Forensic Medicine, AZ Damiaan, Gouweloozestraat 100, 8400 Oostende, Belgium
d Laboratory for Medicinal Chemistry, Ghent University, Ottergemsesteenweg 460, 9000 Gent, Belgium

1. Introduction

Fentanyl and U-47700 are potent μ-opioid receptor agonists. Fentanyl (N-(1-phenethyl-4-piperidyl)-N-phenylpropanamide) is a synthetic narcotic analgesic which was first synthesized by Janssen in 1959 and is widely used for the management of chronic pain. In literature, a large number of fentanyl intoxications have been reported due to improper use of transdermal fentanyl patches; routes of administration included inhalation, intravenous injection after patch extraction, buccal or sublingual abuse [1–8].

U-47700 (3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide) is a novel compound with opioid properties, developed by Upjohn in the 1970s and derived from the earlier opioid analgesic AH-7921 (3,4-dichloro-N-[1-(dimethylamino)cyclohexyl]-N-methylbenzamide) [9–12]. The latter opioid with approximately the same potency as morphine, was extensively studied in vitro and in animals, but was never made commercially available for medical use. AH-7921 (referred to as ‘doxylam’) was first identified in 2012 in a seizure purchased over the internet and recently entered the recreational and illicit drug market in Japan, the USA and Europe. Fatalities and intoxications related with this psychoactive opioid are reported in literature [12,13]. U-47700 was never been studied in humans and is not registered for medical use in humans. Very little, if any, information is available in scientific literature [14]. Since the substance is not scheduled or controlled, it is openly sold on the internet as an opioid ‘legal high’. Anecdotal evidence from user reports on specialized internet drug fora reveals that U-47700 is actively being used as a legal substitute for...
other strong opioids, such as morphine, heroin or even fentanyl \[16\]. U-47700 is only controlled in Finland and Sweden (the latter since 26/01/2016). Fentanyl is 75–100 times more potent and U-47700 is approximately 7.5 times more potent than morphine.

This paper reports a fatality due to combined use of fentanyl and U-47700. A target analysis on U-47700 in blood and urine was performed using liquid–liquid extraction and ultra performance liquid chromatography tandem mass spectrometry operating in multiple reaction monitoring mode.

2. Case histories

In January 2016, a 30-year old man was found dead, on the ground of a small enclosed storage room in his house. The victim was dressed, lying on his left side with raised knees, the left arm in extension and his right arm in flexion. The right hand was lying on the left elbow and was holding a lighter. Next to the right leg, a piece of aluminum foil was present; the bottom side was blackened (caused by burning), and a brown residue was present on the top side, suggesting the use of a substance by vaporization on foil, as is common with heroin abuse. The victim was a well-muscled man of normal build. He weighted approximately 70 kg and was 179 cm tall. On careful examination, no injection sites or traumatic injuries were found. Pulmonary edema was observed. Drug paraphernalia were present on the table in the living room: a recently delivered envelope from China, a white powder (36 g), a digital scale and spoon. Questioning of friends by police revealed that the deceased was known to abuse illegal drugs, and experimented with substances purchased over the internet. On his mobile device a search history for the purchase of carfentanil and U-47700 over the internet was found.

3. Materials and methods

3.1. Materials

Reference U-47700 (molecular formula: C₁₈H₂₄C₂N₂O; molecular weight: 329.26 g/mol; chemical structure shown in Fig. 1) was kindly provided by the Belgian Early Warning System on Drugs (BEWSD, Scientific Institute of Public Health). The reference material of the internal standard fentanyl-d₅ (100 μg/mL in methanol) was obtained from Cerilliant (Round Rock, Texas). Standard compounds were diluted in methanol and stored at −18 °C. All other chemicals were of analytical grade.

3.2. Instrumentation

Target analysis on the presence of U-47700 was performed by UPLC–MS/MS, using a Acquity separations module coupled to a Acquity TQD mass detector equipped with ES interface (Waters, Milford, MA, USA). Chromatographic separation was achieved using a Acquity UPLC HSS C₁₈ column (150-mm length × 2.1 mm i.d., 1.8 μm particle size) with a HSS C₁₈ Vanguard column (5-mm length × 2.1 mm i.d., 1.8 μm particle size) as guard column at 50 °C. Mobile phases consisted of 0.15% formic acid (A) and 0.15% formic acid in acetonitrile (B). The following gradient elution was used (runtime 15.00 min). starting with 13% B held for 0.50 min, increased to 50% B in 9.50 min, changed to 95% B in 0.75 min and held for 1.50 min, and finally changed back to initial conditions in 0.25 min and held for 2.50 min. A flow rate of 0.400 mL/min was used. The electrospray source was operated in positive ionization mode. Product ions were obtained by collision-induced dissociation which allowed the MS/MS to be operated in the multiple reaction monitoring (MRM) mode. The MRM transitions and conditions for the measurement of U-47700 (retention time: 6.55 min): 330.20/285.20 (qualifier) and 330.20/173.20; cone voltage 28 V; collision energy 15 V and 28 V respectively; fentanyl-d₅ (retention time: 6.51 min): 345.42/188.25 (qualifier) and 342.42/105.10; cone voltage 40 V; collision energy 25 V and 28 V respectively. Quantitations were carried out using the first transition (qualifier). For confirmation, the percent ratio of the second transition to the qualifier was calculated and monitored. The source temperature and desolvation gas (nitrogen) temperature were set at 150 and 400 °C, respectively. The gas flow was delivered at a rate of 800 L/h. The capillary voltage was 3.00 kV.

![Fig. 1. Chemical structure of U-47700.](383x683 to 492x740)
Waters Mass-lynx system software Version 4.1 was used for instrument control and quantitation. Method validation was based on the document ‘Standard Practices of Method Validation in Forensic Toxicology’ published by the Scientific Working Group of Forensic Toxicology [15].

3.3. Samples

Only an external body examination was ordered by the magistrate during which subclavian blood (left) and urine were sampled by the medical examiner. Approximately 2 g of the powder found on the scene was submitted to the laboratory for analysis. Tissue samples were stored at -18 °C for 2 weeks before quantitation was performed.

4. Methods

4.1. Systematic toxicological analysis

Blood and urine were submitted to a comprehensive systematic analysis for the detection of alcohol and volatiles, CO and CN, medical and illegal drugs and new psychotropic substances (previously detected in ‘regional’ seizures) using different extraction procedures and analytical techniques including headspace gas
chromatography with flame ionization detector, liquid chromatography with diode array detector (HPLC/PDA), gas chromatography mass spectrometry in full scan mode (GC/MS), presumptive color testing and several methods applying ultra performance liquid chromatography mass spectrometry in multiple reaction monitoring mode (on blood and β-glucuronidase hydrolyzed urine).

The method for the quantitation of fentanyl and norfentanyl was previously described [1].

The white powder was subjected to the authors’ identification scheme (ISO/IEC 17025:2005 accredited) based on the analysis of a freshly prepared methanolic sample solution on HPLC/PDA and GC/MS. The U-47700 powder was found to be insoluble in methanol and other than the internal standard peak (diphenylamine), no peaks were detected in the chromatograms. Therefore HPLC/PDA and GC/MS analysis was performed on the alkaline extract: to a 5 ml aqueous suspension of an aliquot of the U-47700 powder, 1.0 ml 1 M potassium carbonate solution and 20 µL diphenylamine (1.0 mg/ml methanol) were added. Extraction was performed with 5.0 ml diethyl ether. After addition of 50 µL 10% (v/v) HCl in methanol to the organic phase, the extract was evaporated (40 °C, N2) and the residue was reconstituted in 200 µL methanol.

4.2. Sample preparation and extraction

Liquid–liquid extraction was applied for the quantitation of U-47700 in blood and urine: to a 0.5 ml aliquot of sample (blood or β-glucuronidase hydrolyzed urine), 5 µL of internal standard solution (fentanyl-d5 0.5 µg/ml in methanol) was added. After addition of the internal standard solution at a concentration level of 5 µg/L sample, the samples were vortexed and allowed to equilibrate 30 min prior to extraction. Alkalization was obtained by addition of 1.0 ml 1 M potassium carbonate solution followed by agitation on a vortex mixer. Extraction was performed with 5 ml of a mixture of n-hexane:ethanol acetate (7:3, v/v). After vortex mixing for 2 min and centrifugation at 3000 rpm for 5 min, the upper organic layer was separated and evaporated to dryness under a slow stream of nitrogen at 40 °C. The dried extracts were reconstituted in 0.25 ml of initial mobile phase. The reconstituted tissue extracts were centrifuged at 14,000 rpm for 5 min. A 10 µL aliquot was injected into the UPLC–MS/MS system. A blank was injected before every sample. Calibrators and quality controls were prepared by addition of standard solution to blank whole blood prior to extraction (see Table 1). Calibrators and controls were different preparations of the same drug standard lot. Samples were analyzed in triplicate and mean values are determined. Two aliquots of the powder (approximately 100 mg weighed in a 10 ml volumetric flask) were extracted with methanol. Three aliquots of each flask were quantitated by UPLC/MS–MS.

5. Toxicological results

Comprehensive systematic toxicological analysis demonstrated the presence of 10.9 µg/L fentanyl and a therapeutic level of 180 µg/L sertraline (HPLC/PDA) in subclavian blood. Fentanyl and sertraline were identified in the alkaline extract of the urine analyzed on GC/MS. The target analysis performed by UPLC–MS/MS revealed the presence of U-47700 at a concentration of 13.8 µg/L in blood and 71.0 µg/L in urine. An overview of the assessed validation parameters and validation data is shown in Table 1. No other compounds contributing to the death of the victim were detected. Fentanyl and U-47700 were identified in the alkaline extract of the powder analyzed by GC/MS, based on retention time and spectrum match with the reference. Quantitative results were obtained with UPLC–MS/MS: 0.0035% (m/m) for fentanyl and 0.0012% (m/m) for U-47700 by analysis of methanolic sample extracts (y = 1730.15x + 1807.62, r² = 0.999046).

6. Discussion

In opioid naive patients, the minimum effective analgesic serum concentrations of fentanyl range from 0.2 to 1.2 µg/L. With serum concentration greater than 2 µg/L, the risk of hypoventilation increases [17]. Due to this narrow therapeutic index, use of the substance in the recreational drug scene is exceptionally dangerous, in particular in opioid intolerant users. Considering its activity at the µ-opioid receptor, it seems plausible that comparable health risks apply for U-47700 as for other strong opioids such as fentanyl and heroin. These include respiratory arrest/depression, miosis, constipation and coma. Very high dosages might result in death due to respiratory arrest and pulmonary edema. In the reported case, the latter was observed during the external body examination.

Based on the crime scene findings, it was concluded that the route of administration was inhalation of the vaporized substances. The aluminum foil with brown residue from the scene was not available for analysis. No other packages or powders were found in the victims home. Due to the toxic concentration level of fentanyl and U-47700 in blood and urine, target analysis and hyphenated techniques needed to be applied for the identification and quantitation [18]. The recognition and analysis of highly potent, new psychotropic substances (NPS) in tissues are challenging in postmortem toxicology. A multidisciplinary approach with exchange of circumstantial evidence is vital, as experienced in this and previous cases.

The U-47700 powder was found to be insoluble in methanol and ultrapure water (native and alkaline). The powder needed to be extracted under alkaline conditions to obtain an identification by GC/MS and HPLC/PDA. Fentanyl was initially identified using GC/MS by means of computer based library search of the SWGDRUG Mass Spectral Library (Version 2.4) installed on Agilent Chemstation. Neither a library hit, nor a reference mass spectrum of U-47700 was found in literature. Fragmentation pattern analysis of the obtained mass spectra, coupled with information gained from the European RETOX EWS network, suggested the unknown to be U-47700, the identity of which was confirmed after purchase of a reference substance. The chromatogram of the alkaline extract of the powder, with mass spectra of both U-47700 from the powder and reference is shown in Fig. 2. The UV-spectrum of U-47700 from a reference solution is given in Fig. 3. No other substances were identified with the applied methods. The powder was labeled as ‘hot melt powder’.

Based on circumstantial evidence (police investigation, crime scene) and the results of the toxicological analysis, the medical examiner concluded that the cause of death was an acute intoxication and overdose with fentanyl and U-47700 immediately...
after inhaling the fumes of the vaporized powder. It was presumed the death was accidental due to excessive combined abuse of fentanyl and U-47700.

This case further illustrated the dangers associated with the sale of unknown (legal) compounds as NPS, especially when compounds with opioid activity are involved. Comparable opioid NPS compounds, AH-7921 and MT-45, were scheduled in 2015 by inclusion under schedule I of the 1961 United Nations Single Convention on Narcotic Drugs for AH-7921 [19] and an EU Council decision for MT-45 [20].

References