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Opioid intoxications involving butyrfentanyl, 4-fluorobutyrfentanyl, and fentanyl from the Swedish STRIDA project

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Background. The supply of unregulated “new psychoactive substances” (NPS) has shown a steady increase over the past six years. This report from the Swedish STRIDA project describes analytically confirmed non-fatal intoxications involving butyrfentanyl (butyrylfentanyl) or 4-fluorobutyrfentanyl (para-fluorobutyrfentanyl), two fentanyl analogues recently introduced as NPS opioids. Study design. Observational case series of consecutive patients with suspected acute NPS exposure and requiring hospital care from all over Sweden. Patients and methods. From May 2014 to January 2015, blood and urine samples were obtained from four intoxication cases involving butyrfentanyl and one case involving 4-fluorobutyrfentanyl (men, 19–30 years) presenting in emergency departments (ED) or intensive care units (ICU). Laboratory analysis of serum and/or urine samples was performed by multi-component liquid chromatography–mass spectrometry methods. Data on clinical features were collected during consultations with the Poisons Information Centre and retrieved from medical records. Case details. Of the five patients, two were discharged home from the ED and three were admitted to the ICU, of whom two required intubation and mechanical ventilation. Clinical features included typical opioid symptoms such as unconsciousness, respiratory depression, and apnea. In one case, naloxone successfully countered the effects. All patients were discharged the same or the following day. Butyrfentanyl was detected in two serum (0.6 and 0.9 ng/mL) and three urine (2.0–65.6 ng/mL) samples from three of four cases; three cases also contained fentanyl. In the 4-fluorobutyrfentanyl case, the substance was detected in serum (~15 ng/mL) and urine (~10 ng/mL). In four cases, other NPS and/or classical drugs were also detected. Analysis of two “butyrfentanyl” NPS products (nasal spray and powder) brought to hospital by patients showed that the 10-fold more potent fentanyl was the main active ingredient (~7.5–10-fold higher amount) in both. Conclusion. Typical and potentially life-threatening opioid toxicity was seen in acute intoxications involving butyrfentanyl, 4F-butyrfentanyl, and fentanyl. The incorrect labelling of butyrfentanyl NPS products which instead mainly contained fentanyl is alarming, given the narrow range between a safe and a lethal dose for opioids.

Keywords Butyrfentanyl; Butyrylfentanyl; Fentanyl analogue; Internet drugs; Mass spectrometry methods; New psychoactive substances; NPS; Opioid analgesic drug; para-Fluorobutyrfentanyl

Background

The supply of unregulated drugs of abuse has shown a dramatic increase since 2008, with hundreds of powerful and potentially harmful “new psychoactive substances” (NPS) introduced by open web-based sale.1 In 2014, an average of two NPS per week were launched on the European drug market.2 Many of these are structural variants synthesized as legal replacements of banned substances (“legal highs”);3 hence the process of controlling NPS may partly have driven this development. While the panel of NPS has largely been dominated by stimulants and synthetic cannabinoids, there is currently a growing diversity of drug classes. Today the NPS panel also includes potent novel opioids such as MT-45, AH-7921, and fentanyl analogues, substances associated with severe adverse effects and fatalities.4–6 Dealing with acute NPS poisoning and overdose has thus become a common task issue at emergency departments (ED) and intensive care units (ICU).3,7

Fentanyl (N-[1-(2-phenylethyl)-4-piperidinyl]-N-phenylpropanamide) (Fig. 1) is a synthetic opioid analgesic acting as a strong full agonist at μ-opioid receptors that was developed in the early 1960s.8 Due to its high potency (~50–100 times that of morphine), rapid onset of action, and short half-life, fentanyl was introduced into clinical practice as a narcotic analgesic.9 Nowadays common therapeutic applications are
4-Fluorobutyrfentanyl (also named butyrylfentanyl), and 4-fluorobutyrfentanyl (also named para-fluorobutyrfentanyl). Fentanyl and its analogues are metabolized by N-dealkylation, yielding the corresponding nor-metabolites as main products. 

Fig. 1. Chemical structures of fentanyl, butyrfentanyl (also named butyrylfentanyl), and 4-fluorobutyrfentanyl (also named para-fluorobutyrfentanyl). Fentanyl and its analogues are metabolized by N-dealkylation, yielding the corresponding nor-metabolites as main products. 

Methods

STRIDA (an acronym of the project name in Swedish) is a collaborative project between the Karolinska University Laboratory, the Karolinska Institutet, and the Swedish Poisons Information Centre (Stockholm) that monitors the occurrence and health hazards of newly emerging drugs of abuse in Sweden. Results of blood (serum) and urine drug testing are compared with associated clinical features, among cases of suspected NPS intoxication presenting to ED and ICU. Data on clinical features are collected from consultations to the Poisons Information Centre (a nationwide 24/7 phone service to hospital caregivers and the public) and reviewed retrospectively from medical records. The severity of intoxication was graded using the Poisoning Severity Score (PSS), and the level of consciousness by the Reaction Level Scale (RLS).

As for the wide spectrum of NPS, the identification and quantification of butyrfentanyl, 4F-butyrfentanyl, and fentanyl in serum (parent compounds) and urine (parent compounds and their N-dealkylated nor-metabolites) samples was performed by flexible multi-component liquid chromatography–tandem mass spectrometry (LC–MS/MS) and LC–high-resolution MS (LC–HRMS) (Fig. 2) methods. The methods are updated with new substances as they appear through web-based NPS sale and reference material becomes available. The quantification limit for the fentanyl analogues in serum and urine was 0.5 ng/mL and the routine measuring range 0.5–1000 ng/mL.

At the time of the investigation, a certified reference material was available for butyrfentanyl (Cayman Chemical) but not for 4F-butyrfentanyl; therefore, a test purchase of a 4F-butyrfentanyl product (nasal spray) was made from a Swedish web-based NPS vendor. Analysis of the purchased product, and of two butyrfentanyl products brought to hospital by two of the patients (Fig. 3), was performed by LR–quadrupole-time-of-flight–MS/MS (LC–QTOF–MS/MS) and nuclear magnetic resonance (NMR) spectroscopy at the Swedish Medical Products Agency (Uppsala).

The STRIDA project is conducted in accordance with the Helsinki Declaration and has been approved by the regional ethical review board (Nr. 2013/116–31/2).

Results

Poisons information centre calls on fentanyl analogues

During 2014, the Swedish Poisons Information Centre was consulted regarding cases of suspected butyrfentanyl
intoxication on three occasions in May and one in December (in total there were 1580 consultations regarding suspected NPS intoxications in 2014). The first and so far only consultation related to 4F-butyrfentanyl appeared in January 2015.

Results of laboratory investigations

Serum and/or urine samples for NPS analysis within the STRIDA project were obtained from four cases of suspected butyrfentanyl or 4F-butyrfentanyl intoxication that had consulted the Poisons Information Centre. Sampling was done ∼1–7 h after arrival at hospital. In two of the butyrfentanyl cases and the single 4F-butyrfentanyl case, the corresponding substance was detected in both serum and urine samples (Table 1). In addition, butyrfentanyl was detected in urine of another STRIDA case from mid-April 2014 (case #1 in Table 1). Samples from three of the butyrfentanyl cases also contained fentanyl, in two cases along with butyrfentanyl, and in one alone. Furthermore, in all four cases where a urine specimen had been collected, several other NPS (N-ethylbuphedrone, flubromazepam, 3- and 4-MeO-PCP, α-PBP, α-PPP, and 4F-PVP) and/or conventional drugs (cannabis, pregabalin, and tramadol) were detected (Table 1).

LC–QTOF–MS/MS and NMR analysis of the two butyrfentanyl-labelled products (one white powder and one nasal spray) brought to hospital with two of the patients (one originating from case #3 in Table 1 that tested negative for butyrfentanyl but positive for fentanyl) showed that both items indeed contained butyrfentanyl, but that fentanyl was the main active ingredient. The molar ratio between butyrfentanyl and fentanyl was ∼1:7.5 for the powder and ∼1:10 for the nasal spray. Both products also contained traces of despropionylfentanyl and acetylfentanyl, which are known fentanyl degradants and process impurities. In contrast, the analysis of the purchased 4F-butyrfentanyl nasal spray showed no presence of other psychoactive substances (Fig. 4).

Clinical information related to the intoxication cases

All five patients were men aged 19–30 (mean and median: 24) years that arrived to ED or ICU in different parts of the country on different days (i.e. cases were apparently unrelated). Two of the patients testing positive for butyrfentanyl reported use of a nasal spray and one of a powder. The 4F-butyrfentanyl positive patient reported intake of “one pill” ∼9 h prior to blood and urine sampling in the ED.

Of the five patients, two were only monitored in the ED, while the other three, retrospectively graded as PSS 3, were transferred to the ICU; however, they were all discharged later the same or the following day. The clinical features included typical opioid symptoms such as a decreased level of consciousness, respiratory depression, and apnea.

Fig. 2. Results from LC–HRMS [M+H⁺] analysis of (A) butyrfentanyl (65.5 ng/mL; monoisotopic exact mass: 350.23581) and (C) fentanyl (118 ng/mL; monoisotopic exact mass: 336.22016), and the corresponding N-dealkylated nor-metabolites (B and D; used as qualifiers), in urine samples collected from cases #2 (butyrfentanyl) and #4 (fentanyl) in Table 1. Identification and quantification of compounds were based on HRMS full scan accurate mass data (5-ppm mass tolerance) acquired with the resolving power set to 70,000. RT, retention time; AA, peak area.
(Table 1). The opioid-receptor antagonist naloxone was administered to two patients; a sufficient improvement of the level of consciousness and respiration was reported in one case, while the other only received a “minimal” dose and without effects. In three cases with analytically confirmed recent poly-substance use, the clinical signs were more diverse. Case details for two of the butyrfentanyl-positive patients are presented below.

Case histories

Case #2 in Table 1
A 24-year-old man was transferred to a psychiatric ward after recovery from a suspected heroin-induced respiratory arrest four days prior. At midnight, shortly after complaining of insomnia, he suddenly collapsed and became deeply cyanotic and cardiopulmonary resuscitation was initiated. He had a stable circulation with adequate mean arterial pressure but was deeply unconscious (RLS varied between 4 and 8) and in need of ventilator support. During transport to the ICU, propofol was administered and on arrival his pupils were miotic and the core temperature was 35.8°C. A computed tomography of the brain was unremarkable, as were laboratory investigations including electrolytes, liver function tests, cardiac enzymes, and blood gas analysis. The patient was treated with therapeutic hypothermia at 36°C for 24 h and made a complete recovery.

In the ICU, a zip-locked transparent plastic bag, labelled “N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylbutyramide” (i.e. butyrfentanyl) (Fig. 3) and containing a white powder, was found on the patient. After a consultation contact with the Poisons Information Centre, blood and urine samples were collected and sent for analysis within the STRIDA project, together with the drug product.

Laboratory analysis demonstrated that the main active ingredients in the white powder were butyrfentanyl and fentanyl in a molar ratio of ∼1:7.5. Butyrfentanyl and fentanyl were both detected in serum (butyrfentanyl:fentanyl ratio ∼1:5) and urine (∼1:16) (Table 1). The urine sample also tested positive for cannabis (i.e. THC-COOH) and pregabalin, and for substances administered at intubation.

Case #3 in Table 1
A 19-year-old man was found unconscious ∼8 h after starting to use a butyrfentanyl nasal spray. On arrival of the ambulance, he was deeply unconscious (RLS 1), anxious, and with a moderately elevated body temperature (38.7°C). He was intubated with a face mask and administered naloxone (0.4 mg intramuscular + 0.2 mg intravenous) with return of consciousness and respiration. On arrival to the ED, he was fully awake (RLS 1), anxious, and with a moderately elevated body temperature (38.7°C). Initially he had tachycardia (109/min), a blood pressure of 140/80 mmHg, a respiratory rate of 14/min, and 100% oxygen saturation level on room air. He had a mild metabolic acidosis with pH 7.44, pCO₂ 4.1 kPa (31 mmHg), pO₂ 13 kPa (98 mmHg), base excess −2 mmol/L, and lactate 4.2 mmol/L. He was admitted to the ICU for further observation but was discharged later the same day when his condition had been stable for more than 6 h. He required no further naloxone administration during the stay.

A blood sample was collected ∼6 h after admission to the ED and sent for analysis within the STRIDA project (urine was not collected), together with a nasal spray bottle labelled “BF 25 mg, N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylbutyranamide” (Fig. 3) which was brought to the ED.
<table>
<thead>
<tr>
<th>Sex/age (date)</th>
<th>Reported or suspected substance(s)</th>
<th>Sampling time after admission (h)</th>
<th>Substance concentration in</th>
<th>Other substances detected in urine (probably hospital care related)</th>
<th>Hospital days in ICU</th>
<th>Symptoms before admission</th>
<th>Main clinical symptoms on admission (PSS)</th>
<th>Naloxone treatment (total dose, subdoses)</th>
<th>Laboratory abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Butyrfentanyl</td>
<td>Fentanyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1 M/30 (April 2014)</td>
<td>MT-45, flubromazepam</td>
<td>–</td>
<td>ND</td>
<td>8</td>
<td>0.3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>N-Ethylbuphedrone, flubromazepam, 3-MeO-PCP, methiopropamine, MT-45, α-PBP, α-PPP, 4F-PVP</td>
</tr>
<tr>
<td>Case 2 M/24 (May 2014)</td>
<td>Butyrfentanyl (powder)</td>
<td>–7</td>
<td>0.9</td>
<td>65.6</td>
<td>6.9</td>
<td>4.3</td>
<td>993</td>
<td>105</td>
<td>Cannabis, pregabalin, (atropine, pentobarbital, thiopental)</td>
</tr>
<tr>
<td>Case 3 M/19 (May 2014)</td>
<td>Butyrfentanyl (nasal spray)</td>
<td>–6</td>
<td>ND</td>
<td>–</td>
<td>–</td>
<td>1.5</td>
<td>–</td>
<td>–</td>
<td>ND</td>
</tr>
<tr>
<td>Case 4 M/23 (May 2014)</td>
<td>Butyrfentanyl (nasal spray), AB-FUBINACA</td>
<td>~1.5</td>
<td>0.6</td>
<td>2.0</td>
<td>2.0</td>
<td>10.2</td>
<td>118</td>
<td>118</td>
<td>N-Ethylbuphedrone, 3-MeO-PCP, 4-MeO-PCP, α-PBP, pregabalin (pentobarbital, thiopental)</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Sex/age (date)</th>
<th>Reported or suspected substance(s)</th>
<th>Sampling time after admission (h)</th>
<th>Other substances detected in urine (probably hospital care related)</th>
<th>Hospital days in ICU</th>
<th>Symptoms before admission</th>
<th>Main clinical symptoms on admission (PSS)</th>
<th>Other substances detected</th>
<th>Laboratory abnormalities</th>
<th>Naloxone treatment (total dose, subdoses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/25 (January 2015)</td>
<td>4F-butyrfentanyl (pill), pregabalin, clonazepam</td>
<td>∼1</td>
<td>Disorientation, unsteadiness, slurred speech, hypotension (90/60 mmHg)</td>
<td>0</td>
<td>Disoriented, miotic pupils (PSS 1)</td>
<td>Awake, miosis</td>
<td>Pregabalin, tramadol, O-desmethyltramadol, 4-hydroxyalprazolam, oxazepam</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

Based on information from friends, the butyrfentanyl nasal spray had been purchased from a Swedish web-based NPS vendor. Although it was unknown how much of the content he had consumed, the bottle was previously unopened and about two-thirds of the liquid remained on arrival in the ED. According to the labelling, each spray yielded 0.25 mg and the content was sufficient for 95–105 puffs.

Laboratory analysis demonstrated that the main active ingredients in the liquid nasal spray were butyrfentanyl and fentanyl in a molar ratio of ∼1:10. The serum sample (urine was not collected) tested negative for butyrfentanyl but contained a low concentration of fentanyl (Table 1).

**Discussion**

From the start in January 2010 until February 2015 (i.e. over ∼5 years), more than 2000 mainly non-fatal drug related intoxications presenting at ED and ICU all over Sweden have been enrolled in the STRIDA project. Although these cases have involved a wide range of substance classes, Sweden has largely been spared from poisonings by designer opioids causing fatal outbreaks in other countries, according to the Poisons Information Centre call statistics on drugs of abuse-related consultations. The danger inherent to opioids is their high potency and rapid onset of action, implying a narrow range between a safe and a lethal dose and blood concentration.

Besides, there is a risk of less common or previously unknown adverse reactions, such as alveolar hemorrhage reported for butyrfentanyl and ototoxicity for MT-45.4

The recent trend of an increasing number of harmful NPS opioids (e.g. MT-45, AH-7921, and fentanyl analogues) made available by web-based vendors, together with the often unknown drug content of NPS products, is therefore worrying. Internet searches carried out in mid-March 2015 revealed that three unregulated designer fentanylys (butyrfentanyl, 4-fluorobutyrfentanyl/para-fluorobutyrfentanyl, and acetylfentanyl) were marketed by Swedish NPS suppliers. Cases of serious medical complications and deaths associated with designer opioids were therefore expected. Accordingly, expanded access to the effective opioid antidote naloxone to reverse potentially fatal poisoning is becoming increasingly important.

In May 2014, the Swedish Poisons Information Centre was consulted in three cases of severe NPS intoxications with typical opioid-like clinical features assumed to involve butyrfentanyl. The availability of butyrfentanyl as blotters was first announced on a Swedish Internet drug forum in September 2012, although by then it was already known from international forums. According to user experiences posted on the forums, rectal, nasal, and intravenous routes of butyrfentanyl administration were mainly used, and blotters and sublingual administration also occurred.

During 2014, butyrfentanyl nasal spray was available from two Swedish web-based NPS retailers. Reported doses on drug forums ranged from ∼0.5 mg for opioid-naïve to >3 mg for opioid-tolerant subjects, and re-dosing appeared to be common.
The suspicion of butyrfentanyl involvement in cases of NPS intoxication within the STRIDA project stemmed from self-report information, the labelling of two drug products brought to hospital by patients, and the presence of opioid-like clinical features, and it was subsequently confirmed by laboratory analysis of blood and urine specimens. However, along with butyrfentanyl, several other psychoactive substances were also detected in the body fluids, in three cases including fentanyl itself. The analysis of two drug products which were sold and labelled as butyrfentanyl (one nasal spray and one powder) demonstrated that fentanyl was actually the main active ingredient (∼7.5–10 times the amount of butyrfentanyl) in both. This explained the ∼5-fold higher serum and ∼16-fold higher urine fentanyl concentrations relative to butyrfentanyl in case #2, and that only a low concentration of fentanyl was detected in the serum of case #3 (Table 1). Accordingly, because fentanyl is ∼10 times more potent than butyrfentanyl, some of the “butyrfentanyl” poisonings appear rather to be accidental fentanyl overdoses. No fentanyl was, however, detected in case #1 (Table 1), indicating involvement of a different butyrfentanyl preparation.

The incorrect labelling of two butyrfentanyl NPS products, and sale of an unlabelled 4-fluorobutyrfentanyl nasal spray, is in line with previous observations from the NPS market. The true psychoactive drug content of NPS products is sometimes not given on the package label, and the content of one product can also vary over time. For that reason, NPS users may be unaware of which substance they take, leading to increased risk for overdose and fatalities. Another example of this is the street drugs offered as “ecstasy” (i.e. MDMA), but instead containing para-methoxymethamphetamine (PMMA), that has resulted in several outbreaks of fatal poisonings throughout the world, the latest in early 2015.

As shown in this and previous publications from the STRIDA project, intentional co-ingestion of several substances of different or the same drug classes is common among Swedish NPS users. As already mentioned, this may also occur unintentionally because drug preparations contain two or more active ingredients, as demonstrated here for two “butyrfentanyl” products. A mixture of several psychoactive substances acting on the same or different neuronal signalling systems may cause more severe and complex clinical effects. The simultaneous presence of multiple drugs also makes it difficult to link the clinical features to a single out of several detected substances, although fentanyl

![Figure 4](image-url)
detected along with butyrfentanyl in the present case series has the same mechanism of action.

Other limitations of this investigation, that are, however, inherent in the method used to collect clinical samples and data from cases of acute intoxication, are the sometimes lack of recorded clinical findings and non-standardized time of sampling. It should also be noted that the total number of fentanyl analogue exposures is likely underreported and underestimated. Besides only part of all NPS-related consultations to the Poisons Information Centre result in STRIDA cases (i.e. both biological samples and clinical data are available), probably only the most severe intoxications are covered as all cases originated from ED or ICU.

Conclusion
As for common opioids such as heroin and morphine, induction of potentially life-threatening respiratory depression and loss of consciousness were seen in cases of acute intoxication involving butyrfentanyl, 4F-butyrfentanyl, and fentanyl. In this respect, incorrect labelling of NPS opioids is especially alarming, as demonstrated for two products which were sold and labelled as butyrfentanyl but mainly contained the –10 times more potent fentanyl. Consequently, if NPS users adapt the amount of substance (i.e. according to the product label) they take from dosage recommendations provided in Internet drug forums, this may cause serious adverse effects and deaths due to unintended overdose.

Declaration of interest
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References