

ORIGINAL ARTICLE

Systematic review of the clinical consequences of butyrfentanyl and corresponding analogues

Alexander Dinh LE¹, Saeed Khaled ALZGHARI²

¹ School of Pharmacy, Texas Tech University Health Sciences Center, Abilene, Texas, USA

² Baylor Scott and White Medical Center, Waxahachie, Texas, USA

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ABSTRACT

Butyrfentanyl and its analogues are being increasingly used throughout the United States and Europe. Currently, lethal cases are emerging across the United States, England, and Europe without any end in sight. We therefore performed a systematic review of existing case reports on the literature of butyrfentanyl and similar analogs. We searched PubMed and Embase for articles (up until September 2018) using terms such as “butyrfentanyl” or “butyrylfentanyl.” In total, our search found 271 articles and identified 10 for inclusion in this review. A total of 33 cases were found with 61% of those being fatal. The most common route of administration was intravenous, but other routes of administration were readily used such as oral, intranasal, and inhalation. Most cases reported use of concomitant licit and illicit pharmacological agents. The toxidrome was consistent with other opioid overdoses, and naloxone was successfully used in nine of 10 patients. We encourage toxicology screenings of novel fentanyl analogs such as butyrfentanyl or 4-fluorobutyrfentanyl when an opioid overdose of unknown nature presents.

KEY WORDS: opioids; street drugs; drug overdose; butyrfentanyl

Introduction

Opioid overdose is a problem for many worldwide. In 2015, approximately 118,000 individuals died due to an opioid use disorder. Both prescription and non-prescription (e.g. illicit) opioids are responsible for these deaths (World Health Organization, 2018). Mechanistically, opioids produce their analgesic effect by interacting with one of three major opioid receptor subtypes (i.e. μ , δ , and κ) found in the central nervous system (Prekupec *et al.*, 2017). However, opioids affect the part of the brain that regulates breathing and an overdose can lead to respiratory depression and death (World Health Organization, 2018). An increase in the number of opioid prescriptions dispensed has occurred in many developed countries including the United States, Canada, Australia, Germany, Norway, and the United Kingdom (Shipton *et al.*, 2018). Novel synthetic opioids (NSOs) are gaining momentum in changing the landscape of opioid use disorders. NSOs

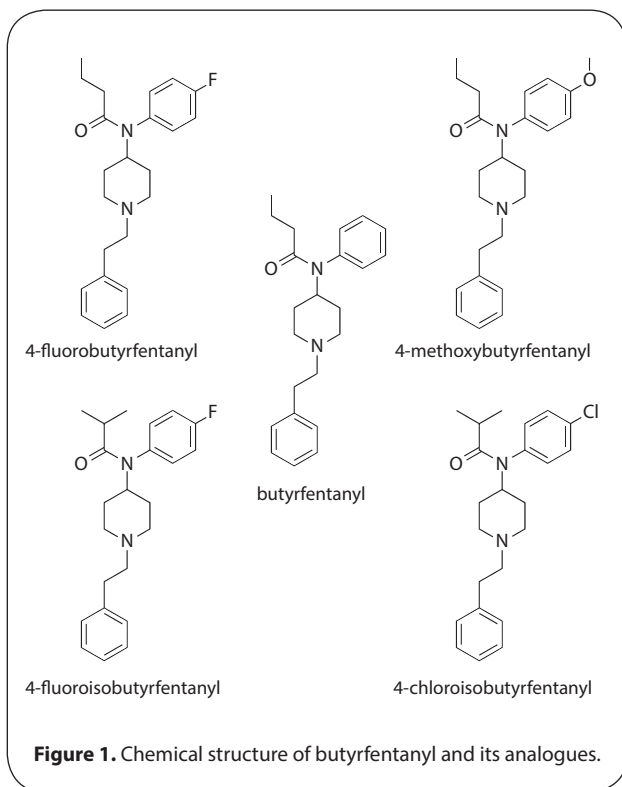
include a variety of fentanyl analogues and non-fentanyl agents (Prekupec *et al.*, 2017). Butyrfentanyl or butyrylfentanyl (BF), an analogue of fentanyl, is a NSO with growing use. BF’s potency is seven times that of morphine (Armenian *et al.*, 2018). A number of analogues of BF have also been synthesized (Figure 1). It is currently a schedule I agent in the United States where it has no accepted medical use (Drug Enforcement Administration, Department of Justice, 2018). The scheduling of BF was due to the increasing number of deaths associated with its use. We performed a systematic review of the literature regarding BF and its analogues to understand the clinical consequences associated with this illicit agent.

Methods

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was conducted on PubMed and Embase for case reports, published until September 10, 2018, using keywords such as “butyrfentanyl” or “fentanyl analog.” We utilized the following inclusion criteria for article selection: (1) involve humans using BF, or 4-fluorobutyrfentanyl, or

Correspondence address:

Saeed Khaled Alzghari, M.S., M.B.A. (HOM), Pharm.D., BCPS
Clinical Pharmacist, Baylor Scott and White Medical Center
2400 N. I-35E, Waxahachie, TX 75165, USA
TEL.: +1 469-843-4000 • E-MAIL: Saeed.Alzghari1@BSWHealth.org



4-methoxybutyrfentanyl, or 4-chloroisobutyrfentanyl, or 4-fluoroisobutyrfentanyl; (2) be either a randomized controlled trial, prospective trial, retrospective analysis, case series or case report; (3) include clinical findings at presentation. Alex D. Le (ADL) formulated the search strategy. Saeed K. Alzghari (SKA) identified relevant articles reporting clinical and analytical outcomes. ADL extracted data from all articles. The extracted data were cross-reviewed by SKA.

Results

Our database search retrieved 271 articles, where 54 were screened as potentially relevant articles with 10 articles meeting inclusion criteria with publication dates between 2015 and 2018 (Figure 2) (Bäckberg *et al.*, 2015; Cole *et al.*, 2015; Farkas *et al.*, 2018; Helander *et al.*, 2016, 2017; Hikin *et al.*, 2018; McIntyre *et al.*, 2016; Poklis *et al.*, 2016; Rojkiewicz *et al.*, 2017; Staeheli *et al.*, 2016). The patients' characteristics are summarized in Table 1. We identified 33 patients that used BF or a similar analog. Of those cases, 82% were male with 26 of the 33 patients being from Europe (13 England, 10 Sweden, 2 Poland, and 1 Switzerland) and seven from the United States. Four cases involved oral exposure, four involved inhalation, four intranasal, and 11 involved intravenous route. All the others were of unknown exposure. Of the 33 cases, 61% were postmortem cases, while the others concerned patients that had recovered. According to the available autopsies, one patient had edematous/congested lungs, another had edema of the brain, one had mild atherosclerosis with left

concentric ventricular myocardial hypertrophy, and one had mild left ventricular myocardial hypertrophy with mild nephrosclerosis.

Regarding the remaining patients who lived after exposure from BF and similar analogs, nine patients were from the Swedish STRIDA (Samverkansprojekt kring Toxicitetsutredning och Riskbedömning av InternetDroger baserat på laboratorieAnalyser) Project. Bäckberg and colleagues had four patients that were monitored in the emergency department or the intensive care unit (ICU), with all patients being discharged either the same or the following day (Bäckberg *et al.*, 2015). Helander and colleagues reported four patients that required an ICU stay for 1–2 days with one patient in particular needing ventilator support due to pulmonary aspiration (Helander *et al.*, 2016). In another set of case series by Helander and colleagues, one patient was observed for 1–2 days at the hospital and another patient required intensive care support for five days (Helander *et al.*, 2017). Cole and colleagues published a detailed case of one patient overdosing on BF with diffuse alveolar hemorrhage (Cole *et al.*, 2015). The patient was transferred to the pediatric ICU, required intubation until day 4, and was discharged on day 7.

All but one case obtained analytical findings from blood and/or urine samples. The other case used high-performance gas chromatography and mass spectroscopy to identify the opioid in question.

Discussion

BF and its analogues are gaining use that is rivaling other licit and illicit opioids. Many of the cases presented in this review mimicked those of opioid overdoses associated with licit opioids such as respiratory depression and central nervous system depression (Schiller & Mechanic, 2018). Many patients who consumed BF and similar analogs survived as opposed to those taking other NSOs such as AH-7921 or U-47700 (Rambaran *et al.*, 2018, 2017). It is proposed that BF has 1/30th efficacy of that of fentanyl and is 7 times more potent than morphine. It is expected that other fluorinated analogs are even less efficacious (Higashikawa & Suzuki, 2008).

Many of the patients that survived originated from the Swedish STRIDA project, a program that monitors the occurrence and health hazards of newly emerging drugs in Sweden (Bäckberg *et al.*, 2015; Helander *et al.*, 2016, 2017). These patients used a number of different routes of administration including intranasal, inhalation, oral, and intravenous. Fentanyl analogs are being purchased through novel psychoactive substance (NPS) suppliers that are readily available via the internet. Bäckberg and colleagues noted that a simple search found acetylfentanyl, BF, and 4-fluorobutyrfentanyl readily marketed online for illicit use (Bäckberg *et al.*, 2015). Other formulations are available online for rectal and sublingual administration.

All of the cases from England were fatal (Hikin *et al.*, 2018). Markers for heroin use such as morphine,

6-monoacetylmorphine, noscapine and papaverine were found. Additionally, serum levels of carfentanil were found in blood or urine in all cases. Hikin and colleagues noted that BF and similar analogs were used more often in the first 3 months of 2017; however, the last 3 months of 2017 included patients that presented solely with serum levels of carefentanil (Hikin *et al.*, 2018). This could be due to a change in supply of illicit fentanyl analogs that are readily available in the immediate patient population in England.

There were two lethal case of 4-fluorobutyrfentanyl overdoses from Poland and one lethal overdose of BF from Switzerland (Rojkiewicz *et al.*, 2017; Staeheli *et al.*, 2016). One of the patients from Poland in particular had used an e-cigarette with e-liquid as the route of administration. The other patient from Poland had 4-fluorobutyrfentanyl in powder form (Rojkiewicz *et al.*, 2017). Interestingly, 4-fluorobutyrfentanyl was found in the blood, urine, liver, kidney, and stomach contents of the patient who had the e-liquid. This could be due to abuse of 4-fluorobutyrfentanyl through multiple routes of administration (Rojkiewicz *et al.*, 2017).

Of the seven cases originating from the United States, four patients survived (Farkas *et al.*, 2018; McIntyre *et al.*, 2016; Poklis *et al.*, 2016). Detailed autopsy findings were available for the deceased. Two patients had edematous lungs with a total weight of 1705g and 1250g respectively, while the other had lungs weighing 960g (McIntyre *et al.*, 2016; Poklis *et al.*, 2016). Overall, the autopsy findings were unremarkable. It should be noted that patients from the United States are using a number of routes of administration of BF formulations including intravenous, oral, and inhalation. One patient in particular that survived was an 18-year-old male who had a past medical history of intravenous heroin abuse (Cole *et al.*, 2015). The patient's mother found him unconscious with labored breathing. Once emergency medical services arrived, the patient was found obtunded with gurgling respirations. Naloxone was administered and the patient's mental status improved. At the emergency department, the patient reported to have purchased illicit fentanyl analogs from the internet. The patient complained of dyspnea and coughed up blood. His chest radiograph showed bilateral "batwing"-shaped perihilar opacities with diffuse interstitial markings. The patient was transferred to the pediatric intensive care unit. The patient became progressively more dyspneic requiring intubation. A bronchoscopy and a serial decline in hemoglobin were consistent with diffuse alveolar hemorrhage. The patient could not be extubated until day 4 and was discharged on day 7 after being treated for ventilator-associated pneumonia (Cole *et al.*, 2015).

There are limitations to this review. All of the cases reported in this review are from case reports or case series that are mostly from European reports of BF and similar analogs. The applicability of this review may not be generalizable to the entire population. Additionally, almost every patient had concomitant drug abuse that could have attributed to his or her overdose. There is only pre-clinical data as to the efficacy of BF and similar

analogs. There is no way to ascertain BF's true effect from a clinical trial, only from observational cases. The route of administration varied between patients and specific doses were not stated.

Treating patients with BF or any similar analog should be similar to that of an opioid overdose. It is important to suspect a generalized opioid toxidrome such as respiratory depression, central nervous system depression, and pinpoint pupils. It is important to note that a majority of the patients who lived were transferred to the ICU, and intubation may be needed until patients have fully recovered (Lucyk & Nelson, 2017). Naloxone was successful in treating all but one patient in this review and should be considered when a patient is presenting with an opioid overdose. BF and similar analogs can show up as a false positive of fentanyl in urine and should be treated as such. Gas chromatography-mass spectrometry or liquid chromatography-mass spectrometry may be useful in identifying the opioid in question (Bäckberg *et al.*, 2015; Cole *et al.*, 2015; Farkas *et al.*, 2018; Helander *et al.*, 2016, 2017; Hikin *et al.*, 2018; McIntyre *et al.*, 2016; Poklis *et al.*, 2016; Rojkiewicz *et al.*, 2017; Staeheli *et al.*, 2016).

An emerging concern is that a number of NPSs are readily available online including BF, 4-methoxybutyrylfentanyl, acetylfentanyl, U-47770, and AH-7921 (Alzghari *et al.*, 2017; Cole *et al.*, 2015; Helander *et al.*, 2016; Rambaran *et al.*, 2018, 2017; Solimini *et al.*, 2018). Many dosage forms are available and anecdotal accounts of experiences related to these NSOs are posted on internet forums (Alzghari *et al.*, 2017; Fort *et al.*, 2016; Rambaran *et al.*, 2018, 2017). Since 2013, there have been 40 fatal BF overdoses in the United States, a majority originating from New York, and as many as 88 reports of BF between 2014 and 2015 from California, Florida, Illinois, Indiana, Kansas, Minnesota, North Dakota, New York, Ohio, Oregon, Pennsylvania, Tennessee, Virginia, and Wisconsin (Drug Enforcement Administration, Department of Justice, 2016). As more NSOs become available, a growing public health crisis is

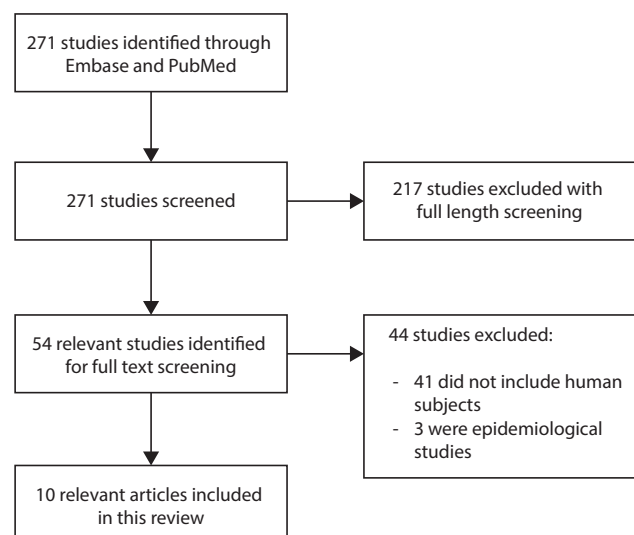


Figure 2. Search flow diagram.

Table 1. Case reports involving the use of butyrfentanyl and its analogues.

| Author (Year) | Agent | Country | Age | Sex | Peripheral blood concentration (ng/mL) | Heart blood concentration (ng/mL) | Route of administration | Presence of | | | | | Naloxone use | |
|-----------------|--------------|---------|-----|-----|--|-----------------------------------|-------------------------|----------------|-----|---------|----------------------|-------------|--------------|-----------------|
| | | | | | | | | Another opioid | BZD | Ethanol | Another illicit drug | Other drugs | | Lung weight (g) |
| Bäckberg (2015) | BF | Sweden | 23 | M | 0.9 | - | Inhalation | X | - | - | X | - | - | - |
| Bäckberg (2015) | BF | Sweden | 19 | M | - | - | Intranasal | X | - | - | - | - | - | X |
| Bäckberg (2015) | BF | Sweden | 23 | M | 0.6 | - | Intranasal | - | - | - | X | - | - | X |
| Bäckberg (2015) | 4-F-BF | Sweden | 25 | M | 15 | - | Oral | X | X | - | X | - | - | - |
| Cole (2015) | BF | USA | 18 | M | - | - | Inhalation | - | - | - | - | - | - | X |
| Farkas (2018) | 4-F-BF | USA | 39 | M | - | - | - | X | - | - | X | - | - | X |
| Farkas (2018) | 4-F-BF | USA | 37 | M | - | - | - | X | - | - | X | - | - | - |
| Farkas (2018) | 4-F-BF | USA | 38 | F | - | - | Intranasal | X | - | - | X | - | - | X |
| Helander (2016) | BF; 4-MeO-BF | Sweden | 29 | F | 1.3 | - | - | X | - | - | X | - | - | - |
| Helander (2016) | 4-MeO-BF | Sweden | 28 | M | 3.1 | - | - | X | X | - | X | - | - | X |
| Helander (2016) | 4-MeO-BF | Sweden | 34 | M | - | - | Oral | - | X | - | - | - | - | X |
| Helander (2016) | 4-MeO-BF | Sweden | 22 | M | 11 | - | Intranasal | X | X | - | - | - | - | X |
| Helander (2017) | 4-Cl-IBF | Sweden | 28 | M | 5.1 | - | Intravenous | X | - | - | - | - | - | X |
| Helander (2017) | 4-F-IBF | Sweden | 27 | M | 38 | - | Intravenous | - | - | - | - | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 39 | M | - | - | Intravenous | X | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 47 | M | - | - | Intravenous | X | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 41 | M | - | - | Intravenous | X | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 44 | M | - | - | Intravenous | X | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 47 | M | - | - | Intravenous | - | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 39 | M | - | - | - | X | X | - | X | - | - | X |
| Hiklin (2018) | BF | England | 40 | M | - | - | - | X | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 28 | F | - | - | - | X | X | - | X | - | - | X |
| Hiklin (2018) | BF; 4-F-BF | England | 25 | M | - | - | Intravenous | X | X | - | X | - | - | X |

Abbreviations: 4-Cl-IBF: 4-chloroisobutyrfentanyl; 4-F-BF: 4-fluorobutyrfentanyl; 4-F-IBF: 4-fluoroisobutyrfentanyl; 4-MeO-BF: 4-methoxybutyrfentanyl; BF: butyrfentanyl; BZD: benzodiazepine; F: female; M: male

Table 1. Continued ...

| Author (Year) | Agent | Country | Age | Sex | Peripheral blood concentration (ng/mL) | Heart blood concentration (ng/mL) | Route of administration | Presence of | | | | | Naloxone use | |
|-------------------|------------|-------------|-----|-----|--|-----------------------------------|-------------------------|----------------|-----|---------|----------------------|-------------|--------------|-----------------|
| | | | | | | | | Another opioid | BZD | Ethanol | Another illicit drug | Other drugs | | Lung weight (g) |
| Hikin (2018) | BF, 4-F-BF | England | 31 | M | - | - | Intravenous | X | X | - | X | - | - | X |
| Hikin (2018) | BF, 4-F-BF | England | 30 | M | - | - | - | - | X | - | X | - | - | X |
| Hikin (2018) | 4-F-BF | England | 53 | M | - | - | - | X | - | - | - | - | - | X |
| Hikin (2018) | BF, 4-F-BF | England | 51 | M | - | - | Intravenous | X | X | - | X | - | - | X |
| McIntyre (2016) | BF | USA | 44 | M | 58 | 97 | Intravenous | X | - | - | X | - | X | X |
| Poklis (2016) | BF | USA | 53 | F | 99 | 220 | Oral | - | - | - | - | - | X | X |
| Poklis (2016) | BF | USA | 45 | F | 3.7 | 9.2 | Oral | X | - | X | X | - | X | X |
| Rojkiewicz (2017) | 4-F-BF | Poland | 26 | M | 91 | - | Inhalation | - | - | - | - | - | - | X |
| Rojkiewicz (2017) | 4-F-BF | Poland | 25 | F | 112 | - | - | - | - | - | - | - | - | X |
| Staeheil (2016) | BF | Switzerland | 23 | M | 66 | 39 | Inhalation | X | - | - | - | - | X | X |

Abbreviations: 4-Cl-IBF: 4-chloroisobutyrylfentanyl; 4-F-BF: 4-fluorobutyrylfentanyl; 4-F-IBF: 4-fluoroisobutyrylfentanyl; 4-MeO-BF: 4-methoxybutyrylfentanyl; BF: butyrylfentanyl; BZD: benzodiazepine; F: female; M: male

unfolding. These NSOs are sold under the guise of “research chemicals” where one can easily purchase these substances online without fear of prosecution. Furthermore, detection of NSOs is limited to targeted spectrometry test because urine drug screens cannot detect the substance or the result shows up as a false positive for a different agent (Rambaran *et al.*, 2018, 2017). The ease of obtaining NSOs coupled with difficulty detecting these substances leads to the rising morbidity and mortality associated with this new class of drugs. Stricter regulation of “research chemicals”, development of urine drug screens that can detect NSOs, and educating clinicians as well as the public are necessary measures to curtail this widespread problem (Alzghari *et al.*, 2017).

In conclusion, our systematic review shows the morbidity and mortality associated with BF and similar analogs. The most common route was intravenous administration. Patients could reverse the effects of overdose with naloxone. BF and its analogues are readily available on the Internet and governments across the globe need to consider ways to combat the spread of these agents in the midst of a growing public health crisis.

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