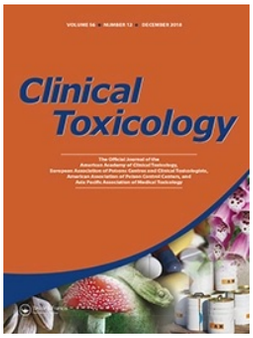

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

Death associated with brorphine, an emerging novel synthetic opioid

V. Vohra , A. M. King , E. Jacobs & C. Aaron

To cite this article: V. Vohra , A. M. King , E. Jacobs & C. Aaron (2021): Death associated with brorphine, an emerging novel synthetic opioid, Clinical Toxicology

To link to this article: https://doi.org/10.1080/15563650.2021.1879111

Published online: 01 Feb 2021.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2021.1879111

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Death associated with brorphine, an emerging novel synthetic opioid

To the Editor,

Novel psychoactive substances (NPS), specifically novel synthetic opioids, continue to fuel death rates in the United States' (US) opioid epidemic, posing an ongoing public health threat [1]. Non-pharmaceutical fentanyl (NPF) and fentanyl analogs ("fentalogs") have been significant drivers of synthetic opioid-related mortality this past decade [1–4]. Recent toxicosurveillance from the US Centers for Disease Control and Prevention and Drug Enforcement Administration (DEA) High Intensity Drug Trafficking Areas program have identified the emergence of synthetic opioids other than NPF and fentalogs [1,5]. One such opioid—brorphine—was recently found in Michigan as part of a mixture of substances called "purple heroin" [6]. Statewide, brorphine has been associated with at least three acute overdoses, one fatality, and a fourth under investigation since May 2020 [6]. We report the first brorphine-related fatality in Michigan with a detected post-mortem concentration.

A 61-year-old female with history of obesity, tobacco use, hypertension, chronic obstructive pulmonary disease, schizophrenia, hyperlipidemia, and no documented history of substance use, was found deceased at home following overdose. She lived alone and was found five days after last seen alive; advanced corporeal decomposition was evident. Post-mortem blood toxicology testing was conducted (Table 1). The medical examiner report stated the cause of death due to toxic effects of multiple substances, including brorphine and fentanyl, and manner of death as accidental.

According to the DEA National Forensic Laboratory Information System, brorphine appeared in the US in mid-2019 and has been found in combination with other opioids (e.g., fentanyl) or on its own [2,7]. "Purple heroin", seized and tested by our State Police Laboratory, revealed a mixture of fentanyl, niacinamide, acetaminophen, flualprazolam, buspirone, and brorphine. The term "purple heroin" is misleading since heroin may be absent and the powder may be white or gray or contain purple crystals.

Brorphine (chemical name 1-(1-(1-(4-bromophenyl(ethyl)piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one))) is a novel, non-fentanyl synthetic opioid with a substituted piperidine benzimidazolone structure, recently temporarily categorized as a Schedule I substance [2,7]. *In vitro* studies have demonstrated a similar mechanism and potency to fentanyl [2,7,8]. It can be used *via* injection, ingestion, and smoking [7]. Six brorphine metabolites have been identified in *in vitro* studies; only two have appeared *in vivo* and it remains unclear if they have opioid activity [2]. As of this communication, federal, state, and local forensic laboratories have found more than 100 cases with positive brorphine screens between June 2020 and October 2020 [2]. A series of 20 forensic cases involving brorphine exposure demonstrated post-mortem blood and urine concentrations ranging from 0.10 to 10 ng/mL and 0.20 to 23 ng/mL, respectively. Following personal correspondence with the case series authors for verification, subsequent testing of 28 additional forensic samples confirmed a post-mortem brorphine blood concentration of 27 ng/mL, the highest among all tested samples (range 0.43–27 ng/mL) [2]. An international report from Belgium documented a living patient's serum concentration of 69.4 ng/mL collected in the emergency department [8]. Brorphine currently remains unscheduled in Europe and does not fall under the purview of legislation targeting emerging NPS [9].

With no formal data or characterization of brorphine's post-mortem metabolism and redistribution, we are uncertain of the extent of influence advanced decomposition had on the concentration in our case. Although only one case series reported a range of post-mortem brorphine concentrations among tested samples, no established toxic reference range exists in living patients, precluding adequate interpretation of post-mortem concentrations. Further, despite a presumptive positive urine drug screen for benzodiazepines and amphetamines, with cross-reactivity of putrefactive/biogenic amines as a plausible explanation for the latter, these compounds, related analogs, and metabolites were undetected

Table 1. Decedent post-mortem blood and urine toxicology results.

Source	Compound	Result	Methodology	Reporting Limit
Cardiac blood	Ethanol	27 mg/dL	Gas chromatography	
	4-ANPP (despropionyl fentanyl)	Screen positive	Liquid chromatography/time-of-flight-mass spectrometry	0.10 ng/mL
	Brorphine	2.0 ng/mL	Liquid chromatography-tandem mass spectrometry	0.10 ng/mL
	Gabapentin	6.8 mcg/mL	Liquid chromatography-tandem mass spectrometry	1 mcg/mL
	Chlorpromazine	82 ng/mL	Gas chromatography	20 ng/mL
	Fentanyl	0.32 ng/mL	Liquid chromatography-tandem mass spectrometry	0.10 ng/mL
Urine	Benzodiazepines	Presumptive positive	Immunoassay	
	Amphetamines	Presumptive positive	Immunoassay	

upon confirmatory testing of post-mortem cardiac blood [10].

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Synthetic opioid overdose data. Last reviewed March 19, 2020; [cited 2020 Nov 1]. Available from: https://www.cdc.gov/drugoverdose/data/fentanyl.html.

[2] Krotulski AJ, Papsun DM, Noble C, et al. Brorphine—Investigation and quantitation of a new potent synthetic opioid in forensic toxicology casework using liquid chromatography-mass spectrometry. J Forensic Sci. 2020;00:1–13.

[3] Vohra V, Hodgman MJ, Marraffa JM, Barba K, et al. Fentanyl- and fentanyl analog-related deaths across five counties in Central New York between 2013 and 2017. Clin Toxicol. 2020;58(2):112–116.

[4] Gladden RM, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths – 27 States, 2013–2014. MMWR Morb Mortal Wkly Rep. 2016;65(33):837–843.

[5] Gulf Coast High Intensity Drug Trafficking Area Investigative Support Network Bulletin. Purple Heroin (Unclassified); [cited 2020 Dec 21]. Available from: https://www.gchidta.org/.

[6] Michigan State Police. Situational Awareness: purple rock like substance found in Upper Peninsula (Unclassified-Law Enforcement Sensitive). MSR-05-2020. June 2020.

[7] Drug Enforcement Administration, Diversion Control Division – Drug and Chemical Evaluation Section. Brorphine (chemical name:1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one). August 2020. Accessed December 4, 2020.

[8] Verougstraete N, Vandeputte MM, Lyphout C, et al. First report on brorphine: the next opioidon the deadly new psychoactive substances' horizon? J Anal Toxicol. 2020, 1–10. DOI:10.1093/jat/bkaa094

[9] Vandeputte MM, Cannaert A, Stove CP. *In vitro* functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Arch Toxicol. 2020;94(11):3819–3830.

[10] Apollonio LG, Whittall IR, Pianca DJ, et al. Matrix effect and cross-reactivity of select amphetamine-type substances, designer analogues, and putrefactive amines using the Bio-Quant direct ELISA presumptive assays for amphetamine and methamphetamine. J Anal Toxicol. 2007;31(4):208–213.

V. Vohra
Michigan Poison Center, Wayne State University School of Medicine, Detroit, Michigan, USA
varun.vohra@wayne.edu

A. M. King
Michigan Poison Center, Wayne State University School of Medicine, Detroit, Michigan, USA
Detroit Medical Center, Department of Emergency Medicine, Detroit, Michigan, USA

E. Jacobs
Detroit Medical Center, Department of Emergency Medicine, Detroit, Michigan, USA

C. Aaron
Michigan Poison Center, Wayne State University School of Medicine, Detroit, Michigan, USA

Received 6 December 2020; revised 14 January 2021; Accepted 16 January 2021