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CASE REPORT

An Emerging Synthetic Opioid in the Drug Supply: A Case of Opioid Overdose with Biological Confirmation of Cychlorphine

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Abstract

Introduction Cychlorphine (also referred to as N-propionitrile chlorphine) is a non-fentanyl synthetic opioid that has been linked to the illicit drug supply and fatal overdoses in the United States since 2024.

Case Report A female in her 20s presented to the emergency department (ED) following ingestion of what the patient reported was alprazolam. Unresponsiveness and respiratory depression prompted 6 mg of intranasal naloxone administration by emergency medical services prior to arrival to the ED. Comprehensive toxicological testing of serum revealed the presence of cychlorphine. Additional substances found were bromazolam, carboxy-THC, acetaminophen, caffeine, citalopram, cotinine, naloxone, naproxen, nicotine, and trazodone and its metabolite.

Discussion This rare case of clinical signs of opioid overdose with cychlorphine detected is the first to provide direct evidence linking a non-fatal overdose to cychlorphine exposure. A naloxone responsive opioid toxidrome is described with an opiate and fentanyl negative initial urine drug screen. Advanced analytical techniques were required to identify the presence of cychlorphine.

Keywords Orphine · Cychlorphine · N-propionitrile chlorphine · Opioid · Overdose

Introduction

Orphines are a subclass of non-fentanyl synthetic opioids that have been detected in the illicit drug supply since 2019 [1–5]. Cychlorphine (or N-propionitrile chlorphine) is a piperidine benzimidazolone derivative with high affinity for the mu-opioid receptor and potency estimated as about ten times more than fentanyl [6, 7]. Cychlorphine has been linked to fatal overdoses, however the clinical effects in non-fatal overdose with confirmed cychlorphine exposure in the United States has not been reported to date [7]. We present a case of non-fatal opioid overdose with cychlorphine identified through the Toxicology Investigators Consortium (ToxIC) Fentalog Study, an ongoing multicenter prospective observational project that includes adult patients presenting to the emergency department (ED) with suspected opioid overdose [8]. For all patients in the study, clinical data are collected, and residual blood specimens remaining after routine ED clinical testing are sent to the Center for Forensic Science Research and Education (CFSRE) for comprehensive toxicological analysis.

Case Description

A female in her 20's with a past medical history of polysubstance use was found unresponsive with respiratory depression. Emergency medical services administered 6 mg of

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naloxone intranasally with reported improved level of consciousness, and transported the patient to an ED. She did not require any further naloxone in the hospital. The patient noted taking alprazolam prior to the overdose and denied any known opioid use associated with this episode.

A hospital urine drug screen was positive for benzodiazepines and cannabinoids, and negative for amphetamine, barbiturates, cocaine, fentanyl, methadone, opiates, oxycodone, and phencyclidine.

Comprehensive toxicological testing of serum was performed at CFSRE. Drug identification occurred via non-target liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) after basic and acidic liquid-liquid extractions. Acquired datafiles were processed against an in-house library database built upon analysis of standard reference materials and contained retention time, library fragmentation spectra, and other key chemical features. Testing revealed the presence of acetaminophen, bromazolam, carboxy-THC, caffeine, citalopram, cotinine, meta-chlorophenylpiperazine (trazodone metabolite), cychlorphine (N-propionitrile chlorphine), naloxone, naproxen, nicotine, and trazodone.

Discussion

This case describes the clinical toxicity with a naloxone-responsive opioid toxidrome after confirmed exposure to the novel potent opioid cychlorphine. As of January 2026, cychlorphine associated fatalities have been reported in 8 states and it has been found in the drug supply in 10 states [6, 7]. Our patient presented to a state in the Midwest in January 2026 within the same time frame the other cases were reported [6, 7].

Cychlorphine is structurally similar to chlorphine and brorphine, other members of the orphine class of novel opioids built on a piperidine benzimidazole scaffold [3]. Although the addition of a propionitrile group to the benzimidazole nitrogen may alter the pharmacologic properties of cychlorphine, insights may be drawn from its structural similarity to chlorphine which has been characterized in animal models.

Of the known and evaluated orphine analogs, chlorphine was found to have the highest affinity for the mu-opioid receptor, and has been proposed to be 2 times less potent than fentanyl [3]. Chlorphine's effects downstream of the mu opioid receptor have found a ratio of recruitment of the arrestin versus G protein pathways to be similar to that of hydromorphone [3]. In experimental models of antinociception testing, chlorphine was able induce maximum antinociception in one test, and significantly increased pain tolerance in another, with a sustained effect of several hours reported. These effects were attenuated by naloxone, though in one of two tests there was only limited impact of naloxone on pain tolerance when treated with chlorphine. Chlorphine also caused respiratory depression, an effect that was also attenuated by the administration of naloxone [3]. Because these were animal data, limited clinical inferences can be made from them. Further, clinical conclusions about cychlorphine that can be drawn from data on chlorphine are limited by the additional functional group added to the former.

Human reports of clinical effects of cychlorphine include a user in France who described it as having "opioid-like effects similar to oxycodone and fentanyl" and further characterized the effect as intense, but no additional clinical details after exposure were provided [4]. Reports gathered from online forums claim rapid onset of euphoria for a few hours followed by long lasting opioid-like effects, with some users claiming a duration of up to 48 h [4].

A previously published case report described a 36-year-old male who was found unresponsive and apneic and was administered a total of 5 mg of naloxone by first responders resulting in a partial response. He was bradycardic, hypothermic, and arousable on presentation to the ED [9]. Unfortunately, he declined further evaluation, limiting the assessment of clinical effects associated with his exposure. Although powder recovered from the scene identified cychlorphine, fentanyl, and xylazine, no biological testing was performed for these substances [9]. Therefore, direct evidence linking the reported non-fatal overdose to cychlorphine exposure is lacking.

Cychlorphine is currently not detected by standard assays used clinically, likely contributing to the sparseness of non-fatal exposures and clinical data. Due to its molecular structure, which is distinctly different than fentanyl and heroin (Fig. 1), cychlorphine is not expected to be detected by fentanyl or nitazene test strips, posing a particular danger to users [5]. In spite of our patient receiving a urine drug screen for multiple opioids, including both semi-synthetic and synthetic, it was notably negative for any opioid. The elimination half-lives of brorphine,

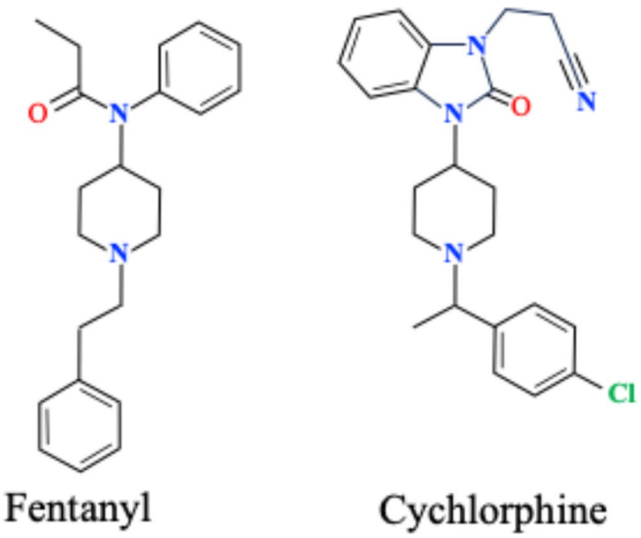

Fig. 1 Structure of fentanyl and cychlorphine

chlorphine, and cychlorphine have not been established, thus the duration of detectability after use remains unknown. However, because the confirmatory testing was performed on serum rather than urine, the detection of cychlorphine likely reflects relatively recent exposure, as serum typically has a shorter detection window than urine for most drugs. It is notable that the patient described in this report denied opioid use and intended to use alprazolam, which was likely a counterfeit pill with cychlorphine and bromazolam, holding with previously reported combinations found in cychlorphine fatalities [6]. The patient's reported improvement after administration of naloxone is suggestive that a significant portion of the clinical effects were secondary to an opioid, with cychlorphine being the only opioid detected in her blood. For non-opioid users, their lack of tolerance leaves them particularly vulnerable to opioid overdose and thus at high risk of mortality.

Conclusion

This report describes a case of clinical signs of opioid overdose with the sole opioid, cychlorphine, identified through advanced analytical testing for novel psychoactive substances. The case demonstrates an opioid toxidrome responsive to naloxone despite an opioid negative hospital urine drug screen, reinforcing the importance of empiric naloxone administration and maintaining clinical suspicion for opioid toxicity when the presentation is consistent. It also highlights the rapidly evolving illicit drug supply and the need for continued surveillance of emerging synthetic opioids.

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Author Contributions RK drafted the original manuscript. DL, SH, SH, AK, and KA critically reviewed and revised the manuscript. The corresponding author, RK, takes responsibility for the integrity of this manuscript.

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Declarations

Compliance with Ethical standards Consent was not available, but this case was anonymized according to JMT guidelines and publication was approved after review by members of the editorial board because the manuscript primarily focuses on the laboratory result and public health implications identified during this clinical event.

Previous presentations None.

Conflicts of interest None to declare.

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