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BRIEF REPORT

Toxicology

Heroin or fentanyl: Prevalence of confirmed fentanyl in ED patients with suspected heroin overdose

Siri Shastry MD, MS[1] | Jonathan Lin MD, PhD[1] | Kim Aldy DO[2,3] | Jeffrey Brent MD, PhD[4] | Paul Wax MD[2,5] | Alex Krotulski PhD[6] | Sharan Campleman PhD[2] | Shao Li MPH[2] | Alison Meyn MPH[2] | Stephanie Abston RN[2] | Barry Logan PhD[6,7] | Alexandra Amaducci DO[8] | Bryan Judge MD[9] | Michael Levine MD[10] | Diane Calello MD[11] | Joshua Shulman MD[12] | Adrienne Hughes MD[13] | Rachel Culbreth PhD[2] | Evan Schwarz MD[14] | Alex F. Manini MDMS[15] | the Toxicology Investigators Consortium Fentalog Study Group

[1]Icahn School of Medicine at Mount Sinai, New York, New York, USA

[2]American College of Medical Toxicology, Phoenix, Arizona, USA

[3]Baylor University Medical Center, Dallas, Texas, USA

[4]University of Colorado School of Medicine, Aurora, Colorado, USA

[5]University of Texas Southwestern Medical Center, Dallas, Texas, USA

[6]Center for Forensic Science Research and Education, Fredric Rieders Family Foundation, Willow Grove, Pennsylvania, USA

[7]NMS Labs, Horsham, Pennsylvania, USA

[8]Lehigh Valley Health Network/USF Morsani College of Medicine, Allentown, Pennsylvania, USA

[9]Corewell Health, Michigan State University, Grand Rapids, Michigan, USA

[10]University of California-Los Angeles, Los Angeles, California, USA

[11]Rutgers New Jersey Medical School, Newark, New Jersey, USA

[12]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[13]Oregon Health and Science University, Portland, Oregon, USA

[14]Washington University School of Medicine, St Louis, Missouri, USA

[15]Icahn School of Medicine at Mount Sinai, Center for Research on Emerging Substances, Poisoning, Overdose, and New Discoveries (RESPOND), NYC Health + Hospitals/Elmhurst, New York, New York, USA

Correspondence
Jonathan Lin, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Email: jonathan.lin@mountsinai.org

Supervising Editor: Brittany Punches, PhD, RN

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Abstract

Background: United States drug overdose deaths are being driven by the increasing prevalence of fentanyl, but whether patients are knowingly using fentanyl is unclear. We examined the analytical confirmation of fentanyl in emergency department (ED) patients with documented heroin overdose.

Hypothesis: We hypothesized that the proportion of fentanyl and fentanyl analogs would be higher than that of confirmed heroin.

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Methods: This is a subgroup analysis from a prospective multicenter consecutive cohort of ED patients age 18+ with opioid overdose presenting to 10 US sites within the Toxicology Investigators Consortium from 2020 to 2021. Toxicology analysis was performed using liquid chromatography quadrupole time-of-flight mass spectrometry. De-identified toxicology results were paired with the clinical database. The primary outcome was the proportion of patients with fentanyl analytes detected in their serum.

Results: Of 1006 patients screened, 406 were eligible, and of 168 patients who reported that they had taken heroin or had a documented heroin overdose, 88% ($n = 147$) were in fact found to have fentanyl and/or a fentanyl analog present on serum analysis ($p < 0.0001$). In contrast, only 46 of the 168 patients with reported or documented heroin overdose (27%) were found to have heroin biomarkers present.

Conclusion: The prevalence of confirmed fentanyl in ED patients with suspected heroin overdose was extremely high, while the prevalence of heroin was very low. There was a high degree of mismatch between the opioids believed to be the overdose agent versus the actual opioids identified on serum toxicology. Clinicians in the United States should presume that fentanyl is involved in all illicit opioid overdoses and should counsel patients on harm reduction measures.

KEYWORDS

fentanyl, heroin, opioids, overdose

1 | INTRODUCTION

1.1 | Background

Drug overdose deaths in the United States continue to rise year after year. Provisional data from the Center for Disease Control's National Center for Health Statistics indicate that there were 107,622 drug overdose deaths in the United States during 2021. A total of 80,816 of these deaths were attributable to opioids, a 15% increase from 2020.[1]

1.2 | Importance

Whereas "heroin" has traditionally been used to refer to diacetylmorphine, the recent emergence of fentanyl and its analogues as adulterants in the heroin supply has resulted in the detachment of the term from any specific chemical compound. The increasing prevalence of fentanyl and fentanyl analogs in the "heroin" supply is a major contributory factor in the rise of opioid overdose deaths. Of the 80,816 opioid overdose deaths in 2021, 71,238 (88%) were attributable to synthetic opioids including fentanyl, a 23% increase, compared to the year prior. Fentanyl exposure is often inadvertent and the increased potency of fentanyl in comparison to heroin increases the risk of overdose. The majority of opioid users who do not deliberately seek out fentanyl nevertheless test positive for fentanyl.[2]

1.3 | Goals of this investigation

The prevalence of inadvertent synthetic opioid exposure in opioid overdoses has not been well studied. An improved understanding of the nature of synthetic opioid overdoses has important implications on public health intervention strategies to address the ongoing opioid crisis and is crucial with regard to harm reduction counseling and overdose prevention efforts. In this study, we examined the prevalence of confirmed fentanyl overdose in emergency department (ED) patients with self-reported or documented heroin overdose.

2 | METHODS

2.1 | Study design and setting

This was a subgroup analysis of the Toxicology Investigators Consortium (ToxIC) Fentalog Study, an ongoing, multicenter study across 10 hospital sites in the United States (Table S1 in the Supporting Information).[3] ED patients with a presumed acute opioid overdose and residual blood samples were included in this cohort study between 2020 and 2021. A chart review and comprehensive serum toxicology analysis were conducted for each patient. Patient characteristics and data on clinical course were collected, until discharge or death.

The Bottom Line

United States drug overdose deaths are increasingly driven by fentanyl but whether patients are knowingly using fentanyl is unclear. This study analyzed the presence of fentanyl in emergency department (ED) patients presenting with opioid overdose with self-reported heroin use. We hypothesized that fentanyl and its analogs would be more prevalent than heroin. From a multicenter cohort of 406 adult ED patients with opioid overdose, 168 self-reported heroin use. Of these, 88% had fentanyl or its analogs, while 27% had heroin biomarkers. Fentanyl prevalence is extremely high in suspected heroin overdoses and clinicians should assume fentanyl involvement and promote harm reduction.

The WCG Institutional Review Board (IRB) and all site IRBs provided approval for this study with a waiver of informed consent.

2.2 | Selection of participants

Adult patients were screened for inclusion in the Fentalog Study if they experienced a suspected opioid overdose and had waste blood leftover from specimens obtained during routine clinical care. Screening for suspected opioid overdose included the following methods: (1) opioid overdose as chief complaint or discharge diagnosis, (2) administration of naloxone for overdose reversal in the ED or prehospital setting, or (3) self-reported opioid use resulting in overdose. Patients in law enforcement custody, with co-occurring trauma or burns, or with nontoxicological diagnoses such as sepsis were excluded.

2.3 | Study protocol

Patients at participating sites were screened and assessed for eligibility by research staff (medical toxicology physicians, fellows, or trained research assistants) using the above methods. *A priori* data collection consisted of demographic variables (eg, age, sex, race/ethnicity), past medical and psychiatric history, suspected exposures to opioids and other substances, clinical characteristics (eg, relevant laboratory data, specific organ toxicity), treatments received (eg, naloxone treatment), and disposition. Heroin use prior to arrival at the hospital was determined utilizing any available evidence within the chart. This includes documentation of heroin use in available care team notes that were derived from patient self-report and/or interpretation of urine drug testing results performed during the hospital encounter.

Data were de-identified and entered into a secure, web-based software platform (Research Electronic Data Capture [REDCap]) by research staff at each site. De-identified clinical data were linked to toxicology blood analysis using a unique study ID code. Database quality assurance was maintained by ToxIC staff in accordance with current best practices including database logical checks, quality assurance personnel, automated data cleaning, data tracking, encryption, and data abstractor training.

Waste blood samples obtained as part of routine clinical care were transferred to deidentified cryogenic tubes and stored at temperatures between −4°C and −80°C until toxicology analysis. Toxicology analysis was performed quarterly by the Center for Forensic Science Research and Education. Qualitative molecular identification consisted of liquid chromatography quadrupole time-of-flight mass spectrometry, with secondary analysis by liquid chromatography tandem quadrupole mass spectrometry when necessary (eg, for resolution of molecular isomers). The drug library used contains over 1100 substances, including traditional illicit drugs, pharmaceuticals, novel psychoactive substances, adulterants, metabolites, and other compounds. Toxicological analysis was performed blinded to clinical outcomes. Samples were considered positive for heroin based on the presence of heroin biomarkers, including 6-acetylmorphine, and/or papaverine. Samples were positive for novel potent opioids based on the presence of nitazene analogs (eg, metonitazene) or brorphine. De-identified toxicology results were then paired with the clinical database for analysis.

2.4 | Outcomes

The primary outcome of this study was the proportion of patients with self-reported or documented heroin use who had confirmed the presence of fentanyl in their serum.

2.5 | Data analysis

Descriptive statistics describing patient demographics and clinical characteristics were tabulated. Chi-squared tests were used to compare categorical variables. Analyses were conducted using SAS University Edition v.9.4 (SAS Institute) and SPSS v. 24 (IBM).

3 | RESULTS

A total of 1006 patients who presented with suspected opioid overdose were screened (Figure 1). Four hundred and six of these patients met the study inclusion criteria. Of these patients, 69% were male and the median age was 43.3 (Table 1). Forty-nine percent of the patients identified as White and 33% as Black. Of the 406 patients with opioid overdose, 168 (41%) had self-reported heroin use or documented heroin overdose, and 89 (22%) did not report a specific substance used.

Of the 406 patients with opioid overdose, 315 patients (78%) were found to have fentanyl, norfentanyl, and/or a fentanyl analog in their serum; 62 (15%) had para-fluorofentanyl present, and nine (2%) had novel potent opioids present (Table 2). Notably, only 61 (15%) were found to have heroin present in their serum. Thirty patients did not

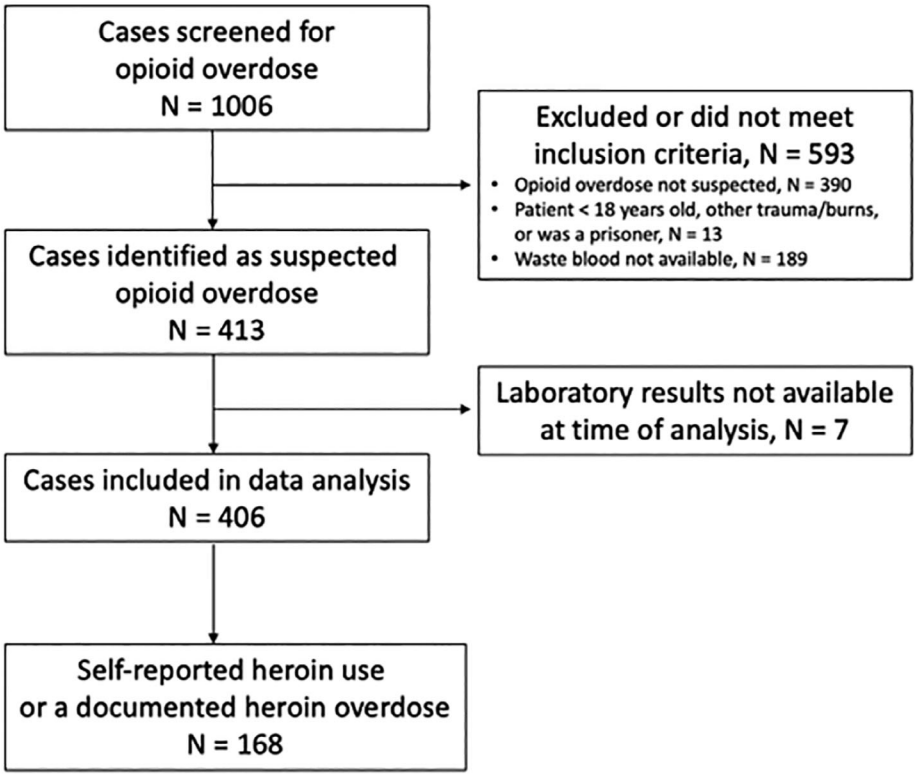

FIGURE 1 Cases of suspected opioid overdose identified during subgroup analysis of the Toxicology Investigators Consortium (ToxIC) Fentalog Study. Cases were further categorized by self-reported heroin use.

TABLE 1 Patient demographics.

Variable	*N* = 406
Age (mean, SD)	43.3 (SD: 14.6)
Sex (*n*, %)	Male: 280 (69%)
	Female: 126 (31%)
Race (*n*, %)	White: 197 (49%)
	Black: 133 (33%)
	Asian: 3 (0.7%)
	Other: 14 (3.4%)
	Unknown: 59 (15%)
Reported Heroin Use (*n*, %)	168 (41%)

TABLE 2 Summary of opioids found on serum analysis (*N* = 406).

Analyte	Frequency (*n*, %)
Heroin	61 (15%)
Fentanyl/fentanyl analogs	315 (78%)
Para-fluorofentanyl	62 (15%)
Novel psychoactive opioid	9 (2%)

have an opioid identified in their blood (7.4%). These cases may represent patients who received novel opioids not included in the drug library or patients who did not receive any opioids.

Of the 168 patients that had reported heroin use or a documented heroin overdose, 147 (88%) were found to have fentanyl or a fentanyl analog present in their serum. Furthermore, only 46 (27%) of these patients were found to have heroin in their serum (Figure 2, $p < 0.01$).

3.1 | Limitations

This study is limited by its observational design, geography, and its setting of primarily academic hospitals. Though the data were aggregated from 10 separate sites across the United States, the results seen here may not be generalizable to other geographic regions or care settings. Furthermore, chart reviews were utilized to obtain information about the substance the patient had used or the overdose substance suspected rather than via a standardized interview or patient survey.

4 | DISCUSSION

In this subgroup analysis, we found that among patients presenting to the ED with an opioid overdose, the majority (88%) of patients with self-reported heroin use or documented heroin overdose were found to have fentanyl or fentanyl analogs in their serum. This indicates a high prevalence of fentanyl/fentanyl analog use among patients that present to the ED with a suspected heroin overdose.

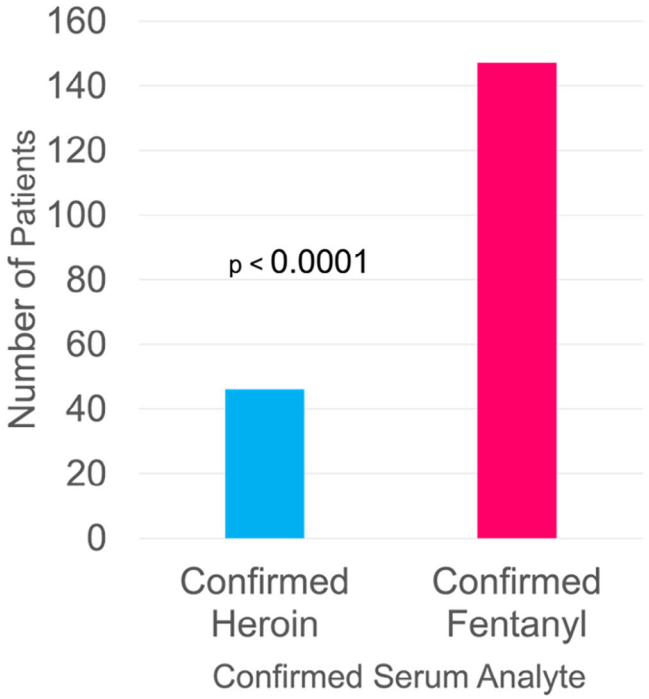

FIGURE 2 Confirmed serum analytes among patients with self-reported heroin use ($N = 168$).

In a recent study of people who inject drugs in New York City, 83% tested positive for fentanyl in urine testing though only 18% reported deliberate fentanyl use.[2,4] Similarly, a study in Dayton, OH, of people who self-reported heroin or nonpharmaceutical fentanyl-type drug use, showed that 90% of their participants tested positive for fentanyl or fentanyl analogs despite 60% reporting a preference for heroin.[5] These data match the observed high prevalence of inadvertent fentanyl or fentanyl analog exposure in our dataset. This indicates that the prevalence of unintentional fentanyl exposure extends to ED patients presenting with opioid overdose and suggests that fentanyl is playing a role in the rise in opioid overdoses nationwide.

Our study findings have important public health implications. Patients unknowingly taking a higher potency opioid may not engage in appropriate harm reduction measures. It has been shown previously that people who use drugs are open to and engage with harm reduction behaviors including abstinence, using drugs more slowly, or carrying naloxone.[6,7] Thus, bedside education regarding harm reduction measures including fentanyl test strips, test doses, not using alone, or safe injection sites may significantly benefit patients and reduce the likelihood of future opioid overdoses.[8] Furthermore, this finding has implications for the duration of ED observation as well as ED dosing strategies for naloxone and buprenorphine.[3]

This study demonstrates a high degree of mismatch between the opioids believed to be the overdose agent versus the opioids identified on subsequent comprehensive serum toxicology analysis. A large majority of patients with suspected heroin overdose had fentanyl or fentanyl analogs present in their serum and there was an overall high prevalence of fentanyl in all included patients. Based on this high prevalence of fentanyl, patients who intend to use heroin are far more likely to receive fentanyl. The high prevalence of fentanyl in the drug supply should be disseminated through harm reduction organizations, needle exchange sites, safe injection sites, and healthcare facilities. Clinicians should presume that fentanyl or fentanyl analogs are involved in all opioid overdose presentations and should provide counseling on harm reduction measures such as naloxone use and fentanyl test strips to any patient presenting with a presumed opioid overdose.

AUTHOR CONTRIBUTIONS

Siri Shastry has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Siri Shastry and Alex F. Manini. *Drafting of the manuscript*: Jonathan Lin, Siri Shastry, and Alex F. Manini. *Data acquisition, analysis, or interpretation and critical review of the manuscript for important intellectual content*: Siri Shastry, Jonathan Lin, Kim Aldy, Jeffrey Brent, Paul Wax, Alex Krotulski, Sharan Campleman, Shao Li, Alison Meyn, Stephanie Abston, Barry Logan, Alexandra Amaducci, Bryan Judge, Michael Levine, Diane Calello, Joshua Shulman, Adrienne Hughes, Rachel Culbreth, Evan Schwarz, and Alex F. Manini. *Statistical analysis*: Rachel Culbreth, Jonathan Lin, and Siri Shastry. *Obtained funding*: Alex F. Manini. *Administrative, technical, or material support*: Stephanie Abston, Alexandra Amaducci, Kim Aldy, Diane Calello, Sharan Campleman, Adrienne Hughes, Bryan Judge, Michael Levine, Shao Li, Alison Meyn, Alex Krotulski, Barry Logan, Evan Schwartz, Joshua Shulman, Paul Wax, and Alex F. Manini. *Project supervision*: Kim Aldy, Barry Logan, Paul Wax, Jeffrey Brent, and Alex F. Manini.

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CONFLICT OF INTEREST STATEMENT

The authors declare no commercial conflicts of interest.

ORCID

Jonathan Lin MD, PhD https://orcid.org/0000-0002-7484-2521

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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AUTHOR BIOGRAPHY

Siri Shastry, MD, MS, is an assistant professor in the Department of Emergency Medicine at Icahn School of Medicine at Mount Sinai in New York, NY.