

71. The ratio of serum fentanyl to norfentanyl is associated with the level of care needed after nonfatal opioid overdose

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Background: The ratio of fentanyl to norfentanyl may identify clinically distinct patterns of use as metabolic ratios do for semi-synthetic opioids. Previous studies found that the ratio of fentanyl:norfentanyl (F:NF) ranged between 0 and 0.4 in individuals who intended to take substances other than fentanyl and did not show signs of the opioid toxidrome. The distribution of F:NF has been described in postmortem samples, but not in antemortem samples from symptomatic patients. The goal of this analysis was to evaluate the association between F:NF ratio and initial level of care required in those who presented with an opioid toxidrome and required at least one administration of naloxone.

Methods: The Toxicology Investigators Consortium (ToxIC) Drug Overdose Toxicology Surveillance (DOTS) Reporting Program (Food and Drug Administration Contract #75F40122D00028/ 75F40123F19002) enrolls patients 13 and older who present to one of 17 Emergency Departments (EDs) in the United States after a severe/life-threatening opioid or stimulant overdose. It is an ongoing prospective observational study that captures patient characteristics, clinical information, contextual data, and whole-blood drug concentrations. We performed a subgroup analysis of all patients enrolled from April 2023 to March 2024 after a presumed opioid overdose who had detectable concentrations of fentanyl and norfentanyl as determined by liquid chromatography tandem-quadrupole mass spectrometry. We used Fisher's exact test to determine whether there was a statistically significant association between F:NF and admission characteristics and Pearson correlation to ascertain the influence of time of blood draw on F:NF. We grouped F:NF into tertiles to compare it with the categorical variable of disposition from the ED. Summary statistics are expressed as median [interquartile range]. Central/site IRBs approved this study, and patients provided informed consent.

Results: Among 119 (40.6%) patients with clinical presentations consistent with the opioid toxidrome and a fentanyl concentration $>1\text{ng/mL}$, the median age was 45 [35–54] years and 77% were male. The median time between presentation and blood draw was 2 [1–6] hours. The median concentration of fentanyl and norfentanyl was 6.6 [3.1–14] ng/mL and 3.6 [1.8–7.3] ng/mL, respectively (F:NF 1.8 [0.8–2.7]). Patients with F:NF ratios in the highest tertile were more frequently observed in the ED (23/40, 57%) than admitted to an intensive care unit (ICU, 4/40, 10%). Patients with F:NF ratios in the lowest tertile were observed in the ED or admitted to the ICU at comparable proportions (13/40, 33% vs. 10/40,

25%, respectively). There is an association between ED disposition and F:Nf (Fisher's exact test, $p=0.03$), and the correlation between F:Nf and the time to blood draw ($r=-0.27$, $p=0.02$).

Conclusion: In this study, patients with higher F:Nf ratios were more likely to be observed in the ED than admitted to the ICU. The F:Nf ratio decreases over time. Future research can determine the relationship between F:Nf, stated pattern of use, and its dependence on the amount consumed, time since consumption, and coingestants.