**ToxTalks: Substances of Abuse and Misuse**

***Highlights from the Field***

**Blue Ridge Poison Center | University of Virginia Health | March 2023**

# Fentanyl and Fentanyl Analogues

*This is a special edition dedicated to substance use & misuse. Look for more of these editions as we encounter emerging and growing concerns. Funding support provided by the CDC's Prescription Drug Overdose: Prevention for States program in partnership with the Virginia Department of Health.*

**Case Example**

A patient arrives unresponsive to the emergency department. On exam, the patient is noted to be comatose with a respiratory rate of 4 breaths per minute, cyanosis, and pinpoint pupils. Naloxone is given intravenous with immediate effect. Upon awakening, the patient recalls snorting a crushed "Perc 30." A standard urine drug screen is obtained and is negative for opiates.

**Epidemiology**

Deaths from illicitly produced synthetic opioids is on the rise. According to the CDC, there was a 56% increase in synthetic opioid-related deaths from 2019-2020. In 2020, there were 57,834 deaths from synthetic opioids increasing to 71,238 in 2021. Fentanyl is cheaper than heroin to produce and is the rapidly emerging opioid available on the street. Clandestine chemists continue to produce fentanyl analogues in efforts to stay ahead of law enforcement scheduling and detection methods.

**Pharmacology**

Fentanyl is a short acting synthetic opioid that is 50-100 times more potent than morphine. Like morphine and other opioids, it acts on the mu-opioid receptor to modulate pain signals, making it effective in the management of acute pain. Fentanyl causes respiratory depression by interfering with both hypercapnic and hypoxic respiratory drive leading to apnea. Stimulation of the parasympathetic nervous system causes miotic pupils. Opioids stimulate indirect release of dopamine, leading to their sought-after euphoric effects.

Fentanyl analogues exert clinical effects similar to fentanyl and vary in potency. Acetylfentanyl, para-fluorofentanyl, beta-hydroxyfentanyl, and carfentanil are just a few examples of analogues that have been found to contaminating the drug supply in our region.

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**Available Forms**

Medical fentanyl is supplied for intravenous administration, in transdermal patch, or as a sublingual spray. Fentanyl is a common contaminate in illicit drugs. Heroin is currently being replaced by fentanyl due to lower production costs. Counterfeit pill presses can press fentanyl to look like a variety of legitimate prescription medications.

**Clinical Manifestations**

Respiratory depression, pinpoint pupils, and sedation are the hallmark signs of an opioid overdose, such as fentanyl.

**Testing**

Typical health system urine drug screens are immunoassays, which use an antibody that binds to a substance to trigger a positive result. In the case example, the opiate screen was negative despite the patient presenting with an opioid toxidrome. Most immunoassays are testing for opiate metabolites, which are products of the opium poppy (e.g., morphine, codeine). Heroin is metabolized to morphine and therefore turns such opiate urine screens positive. Fentanyl, a synthetic substance, has a chemical structure different than morphine, therefore antibodies will not bind it. A urine screen specific to fentanyl must be used in order to produce a positive result. The same is true for other opioids like oxycodone, methadone, tramadol, and buprenorphine. Blood level testing for fentanyl and fentanyl analogue can be obtained from large commercial labs, but have a long turnaround time and are not useful in acute management.

**Management**

Respiratory depression from fentanyl exposure can be reversed with naloxone, a competitive opioid receptor antagonist. An observation period of 4 hours following naloxone administration (allowing for ~5 elimination half-lives of naloxone) is recommended to ensure no further episodes of re-sedation or respiratory depression occur. Patients requiring multiple doses of naloxone should be started on a naloxone infusion at 2/3 the dose required to reverse respiratory depression. Patients should be monitored for at least 4 hours once a naloxone infusion has been discontinued prior to discharging. Recall, naloxone is eliminated by the kidneys and anyone with renal dysfunction will require longer monitoring following naloxone administration.

**Pitfalls**

Intravenous naloxone should be administered and titrated to restore respiratory drive. Sedation alone is not an indication for naloxone. Overshooting naloxone administration may trigger acute withdrawal, leading to a catecholamine surge, which can subsequently lead to pulmonary edema. In the event that intubation is required, there is no longer a role for naloxone once the patient is intubated and on life support. Urine drug screens should not be relied upon to diagnose acute intoxication. A urine drug screen that is negative for opiates does not preclude the presence of a synthetic opioid like fentanyl or a fentanyl analogue. *References available upon request.*