Not Just Fentanyl: Severe Withdrawal and Prolonged QT from Para-Fluorofentanyl

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INTRODUCTION

- Fentanyl analogs, including para-fluorofentanyl, pose significant risks due to their potency, unpredictable pharmacologic effects, and high potential for overdose. These substances have been increasingly detected in illicit drug supplies, often mixed with other opioids, leading to heightened morbidity and mortality.
- Their impact on cardiac conduction, particularly QT prolongation, remains underrecognized but clinically significant. Patients with opioid use disorder who unknowingly use fentanyl analogs may experience severe withdrawal, precipitated withdrawal during medication-assisted treatment initiation, and cardiac complications.
- This case illustrates the clinical management of a patient with severe opioid withdrawal and QT prolongation secondary to p-fluorofentanyl use.

PATIENT PRESENTATION

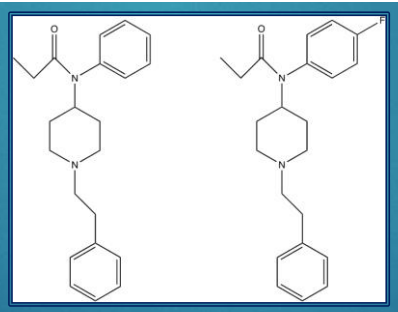
A 50-year-old woman presented to clinic with severe opioid withdrawal, including chills, myalgias, and anxiety, following a relapse on daily use of p-fluorofentanyl. She had a history of opioid use disorder, initially believing she was using heroin. Her symptoms persisted despite an attempted outpatient buprenorphine induction.

Vital Signs on Admission:

- Blood Pressure: 145/78 mmHg
- Pulse: 88 bpm
- Oxygen Saturation: 99% on room air
- QTc Interval: 525 ms on ECG
- Mild hypomagnesemia (1.9 mg/dL) was noted

PRE HOSPITAL COURSE

- Two weeks prior, she was hospitalized for complications arising from outpatient buprenorphine induction, which included severe withdrawal, possible seizure-like activity, and demand ischemia.
- At that time, ECG showed a QTc of 636 ms.
- She maintained sobriety for two weeks before relapsing on illicit opioids, later identified as p-fluorofentanyl.
- Confirmatory testing via extended liquid chromatography/mass spectrometry identified para-fluorofentanyl. Testing was qualitative and quantitative. Other opioids were not detected



Structures of fentanyl (left) and *p*-fluorofentanyl (right)

No other identifiable causes of QTc prolongation: Negative for methadone, cocaine, stimulants, or other medications known to prolong QT. Mild hypomagnesemia was identified later in the course but insufficient to explain profound QT prolongation, and patient had received magnesium even when her magnesium was normal to address the possibility of deficient ionized magnesium

HOSPITAL COURSE

Initial Management:

- Admitted to telemetry for continuous cardiac monitoring.
- Electrolyte repletion, particularly magnesium.
- Carvedilol 6.25 mg BID initiated to mitigate QT prolongation.

Buprenorphine Induction:

- Despite a low Clinical Opiate Withdrawal Scale (COWS) score of 8, clinical symptoms suggested significant withdrawal.
- Low-dose buprenorphine (2 mg) initiated and titrated up to 8 mg/day over 48 hours.
- ECG monitoring continued; QTc improved to 512 ms.

Symptom Improvement & Discharge Plan:

- Successfully managed without precipitated withdrawal.
- Discharged on buprenorphine 2 mg BID, magnesium oxide, famotidine (to reduce drug interactions), and carvedilol.
- Scheduled for close outpatient follow-up with addiction medicine and cardiology.

DISCUSSION

Para-Fluorofentanyl Risks: A potent fentanyl analog with high receptor affinity, p-fluorofentanyl can cause severe withdrawal and QT prolongation, increasing arrhythmia risk. Although Hypomagnesemia was briefly noted, correcting electrolytes alone didn't fully normalize the QTc. Additionally, QT-prolonging agents were avoided throughout her care. Emerging literature indicates that fentanyl analogs may carry arrhythmogenic and QT prolonging potential (Bitting et al., 2022; Canfield & Sprague, 2024), thus warranting consideration for confirmatory toxicology.

Confirmatory Toxicology Testing: Standard fentanyl screens may not differentiate fentanyl analogs; advanced testing (e.g., mass spectrometry) is necessary for accurate identification.

QT Prolongation Mechanisms: Fentanyl analogs may disrupt cardiac ion channels, leading to prolonged repolarization and increased arrhythmogenic risk.

Buprenorphine Induction in Synthetic Opioid Users: Standard protocols may be insufficient; individualized, slow titration strategies are needed to prevent precipitated withdrawal.