Fentanyl Overdose Increases Risk of Acute Lung Injury and Multiorgan Damage

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Introduction

► **Drug overdose mortality among adolescents** in the United States has increased significantly in recent years, and the primary mechanism of fatal overdose in opioid toxicity is **severe ventilatory depression**. Alarmingly, patients discharged after an overdose often die from subsequent opioid overdoses within just one month, despite the widespread availability of naloxone.

► There is a **higher incidence of Acute Lung Injury (ALI)** in patients who end up in an ICU on mechanical ventilators after a fentanyl overdose. The mechanisms linking opioid toxicity, ventilatory compromise, and naloxone reversal to pulmonary injury are poorly understood.

► We developed a **4-hour fentanyl overdose rat model**, with and without rescue naloxone, to investigate the individual and combined effects of fentanyl and naloxone in the development of Acute Lung Injury.

Methods

► **Fentanyl-only overdose:** Male Sprague–Dawley rats (7.5 weeks, 250–275 g; n=13) received a single intraperitoneal (IP) dose of fentanyl (0.72 mg/kg).

► **Fentanyl-overdose + Naloxone-reversal:** Male Sprague–Dawley rats (7.5 weeks, 250–275 g; n=8) were administered the same fentanyl dose (0.72 mg/kg) followed by intramuscular (IM) naloxone (0.4 mg/kg) 15 minutes later.

► **Measurements:** SpO2, Heart Rate, Respiratory Rate (RespR), Muscle Rigidity, Activity Score, Breathing Score, Laryngospasm and oral secretions.

► **Euthanasia & Necropsy** at 4 hours. Bronchoalveolar lavage fluid from right lung lobes, ABG, Clinical Chemistry, CBC, and full organ procurement of the left lung, liver, kidney, and heart for freezing and 4% PFA fixation - histopathology.

Results

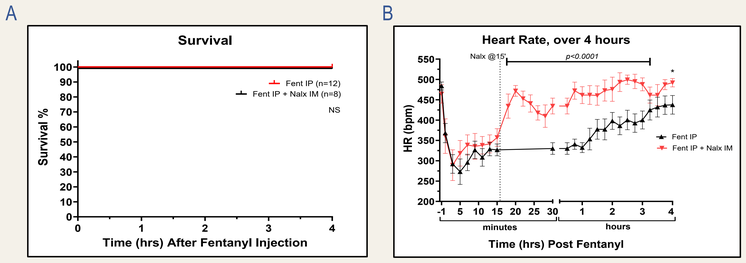


Figure 1. Survival and heart rate over a 4-hour fentanyl overdose and naloxone reversal in rats. (A) All rats survived following naloxone administration. (B) Fentanyl decreases HR; naloxone partially restores it, but recovery also occurs spontaneously over 4 hours.

Results

Respiratory Function

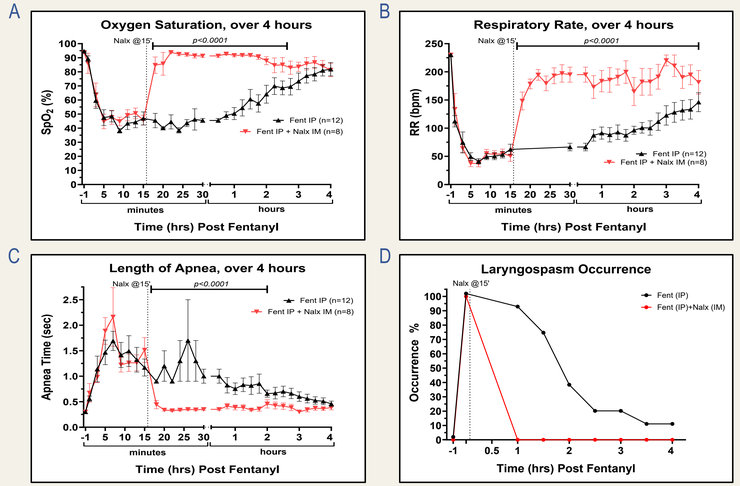
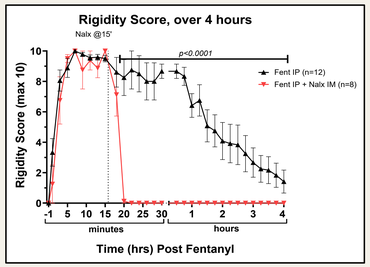


Figure 2. Oxygen saturation (SpO_2), respiratory rate, length of apnea, and laryngospasms during 4-hour fentanyl overdose and naloxone reversal in rats. (A) Fentanyl induced immediate hypoxemia, which was reversed within 5 minutes of naloxone administration; oxygen saturation then gradually declined. (B) Fentanyl reduced respiratory rate by approximately 75%, and naloxone partially restored it toward baseline. (C) Fentanyl increased apnea duration, and naloxone did not eliminate apneic episodes. (D) Fentanyl can cause laryngospasms.

Muscle Dystonia

Muscle Rigidity Scoring	
Anatomical Location	Point Value
Tail	1
Lower Limb	
Unilateral	1
Bilateral	2
Upper Limb	
Unilateral	1
Bilateral	2
Thorax / Trunk /Core	3
Neck / Head	2
TOTAL POSSIBLE SCORE	10



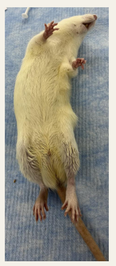


Figure 3. Muscle Rigidity during 4-hour fentanyl overdose and naloxone reversal. Fentanyl causes immediate full-body muscle rigidity. Naloxone can immediately reverse the muscle rigidity.

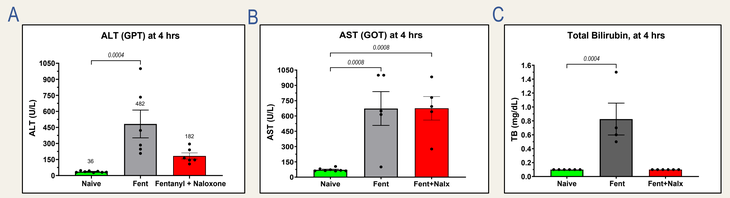


Figure 4. Effects of fentanyl on liver function. (A) Fentanyl increases ALT levels, and naloxone reduces this effect. (B) Fentanyl increased AST levels, which were not altered by naloxone. (C) Fentanyl increased total bilirubin levels, and naloxone reversed this elevation.

Results

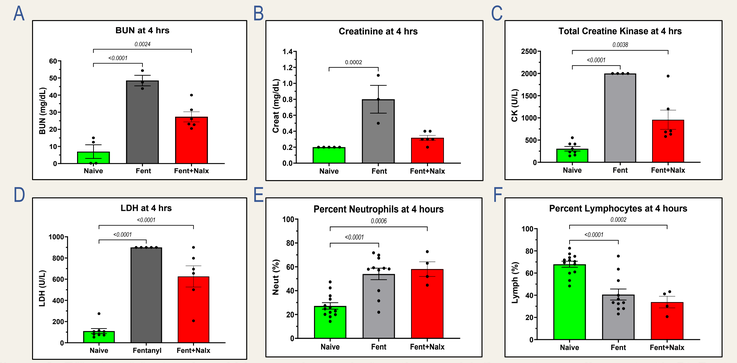


Figure 6. Effects of fentanyl on kidney and muscle function, and inflammatory cell counts (A–B) Fentanyl elevated BUN and creatinine, which were partially reversed by naloxone. (C–D) Fentanyl promoted muscle injury, reflected by increased Creatinine Kinase and LDH. (E–F) Fentanyl and naloxone induced neutropenic inflammation.

Left Lung Histology

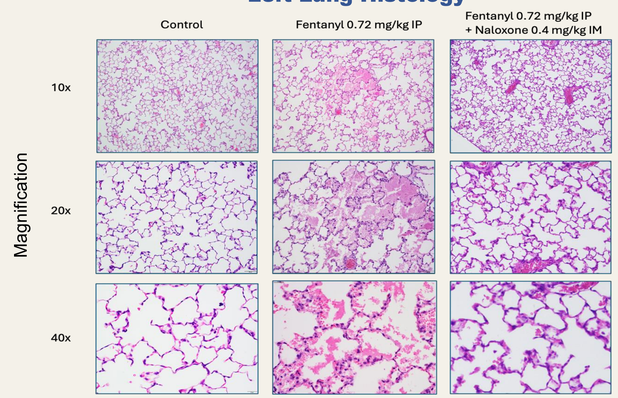


Figure 6. Histopathological Assessment of left middle lung lobe in rats. Lymphocytic infiltration and alveolar fluid inside the alveoli present in both Fentanyl-only and combined fentanyl & naloxone treatment.

Conclusions

- Fentanyl overdose caused hypoxemia, bradypnea, bradycardia, increased work of breathing, laryngospasm, and whole-body rigidity, contributing to impaired respiratory function that was reversible with naloxone treatment.
- ALI at 4 hours was present in multiple animals with the most severe form in fentanyl-only group. After naloxone, there is persistent pulmonary fluid, lymphocytic infiltrate, alveolar thickening, and alveolar collapse.
- **Naloxone only partially reverses fentanyl-induced lung, liver, kidney, and muscle injury.**

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