A Comparative Examination of Morphine and Fentanyl: Unraveling the Differential Impacts on Breathing and Airway Stability

Nicholas J. Burgraff[1], Nathan A. Baertsch[1,2], Jan-Marino Ramirez[1,3]
[1]Center for Integrative Brain Research, Seattle Children's Research Institute
[2]Department of Pediatrics, University of Washington
[3]Department of Neurological Surgery, University of Washington

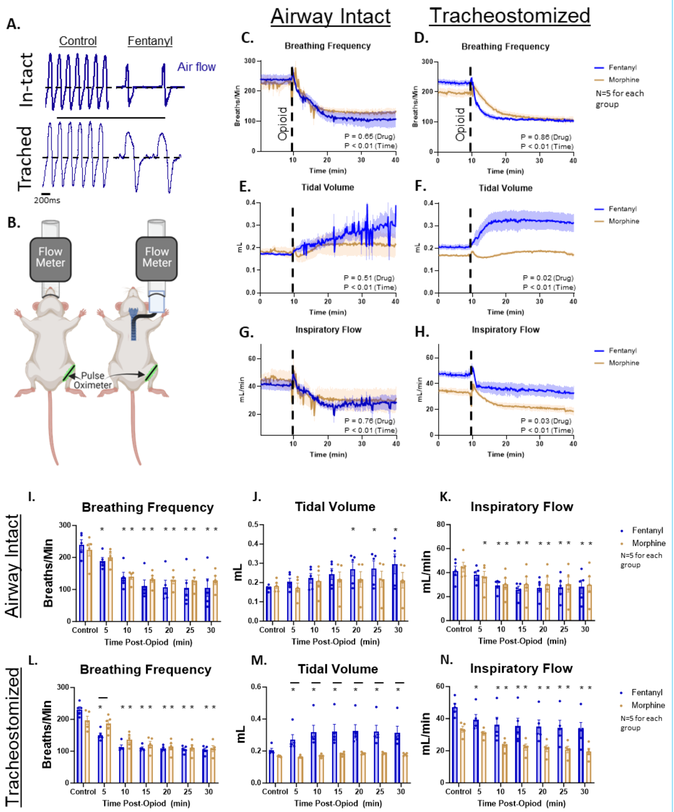
Seattle Children's HOSPITAL · RESEARCH · FOUNDATION
Center for Integrative Brain Research

UNIVERSITY of WASHINGTON

Introduction

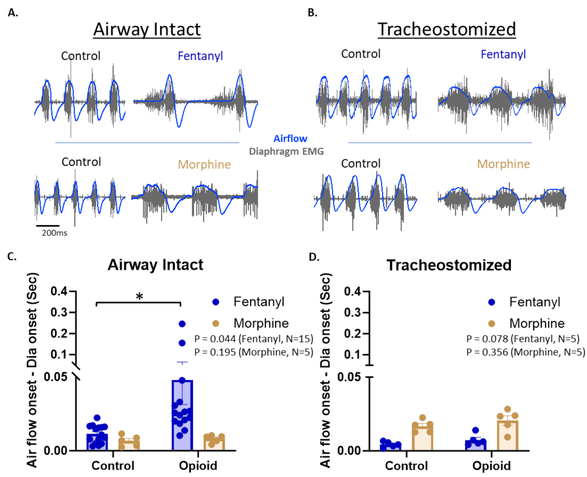
This study provides an in-depth analysis of the distinct consequences of the opioid drugs morphine and fentanyl during opioid-induced respiratory depression (OIRD). We explored the physiological implications of both drugs on ventilation and airway patency in anaesthetized mice. Our results revealed a similar reduction in respiratory frequency with equivalent scaled dosages of fentanyl and morphine, though the onset of suppression was more rapid with fentanyl. Additionally, fentanyl resulted in transient airflow obstructions during the inspiratory cycle, which were absent following morphine administration. Notably, these fentanyl-specific obstructions were eliminated with tracheostomy, implicating the upper airways as a major factor contributing to fentanyl-induced respiratory depression. We further demonstrate that bronchodilators salbutamol and adrenaline effectively reversed these obstructions, highlighting the bronchi's contribution to fentanyl-induced airflow obstruction. Our study also uncovered a significant reduction in sighs during OIRD, which were eliminated by fentanyl and markedly reduced by morphine. Finally, we found that fentanyl-exposed mice had reduced survival under hypoxic conditions compared to mice given morphine, demonstrating that fentanyl becomes more lethal in the context of hypoxemia. Our findings shed light on the distinct and profound impacts of these opioids on respiration and airway stability and lay the foundation for improved opioid use guidelines and more effective OIRD prevention strategies.

Figure 1. Respiration analysis following morphine and fentanyl administration in mice



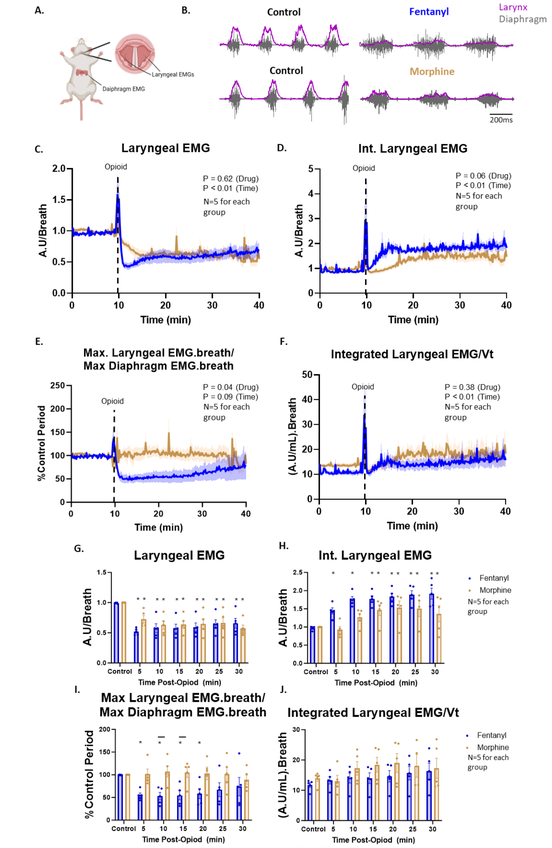
In both airway intact and tracheostomized, urethane anesthetized mice breathing 100% InO2, scaled dosages of morphine (150mg/kg) and fentanyl (500µg/kg) suppressed respiratory frequency by ~50% (C, D, I, L), with fentanyl acting faster, especially in tracheostomized mice (D, L). Both opioids substantially increased tidal volume irrespective of airway status (E, F, J, M), with a larger increase in tracheostomized mice by fentanyl (F, M). This led to similar reductions in inspiratory flow across both drugs and mouse preparations (G, H, K, N). * and black bar indicate statistical significance.

Figure 2. Fentanyl induces transient obstructions to airflow that are not present with morphine



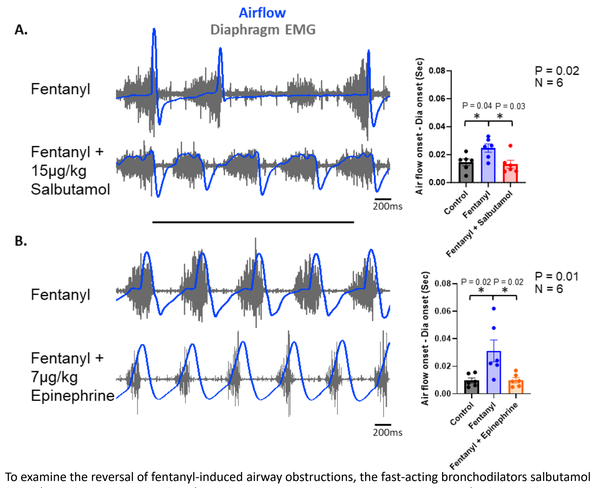
Fentanyl, unlike morphine, causes transient airflow obstructions in mice breathing 100% O2 (A,C). Under control, negligible delay between diaphragmatic EMG activation and inspiratory airflow was observed in both airway intact and tracheostomized mice (C,D). Post 500µg/kg fentanyl administration in airway intact mice, a 220±35% delay increase marked airflow obstruction at inspiratory cycle start (C), an effect unique to fentanyl and not seen with 150mg/kg morphine. In tracheostomized mice, neither opioid altered the diaphragm activation to inspiratory airflow delay (D). * Indicates P<0.05.

Figure 3. Reduction of laryngeal complex EMG activity by morphine and fentanyl



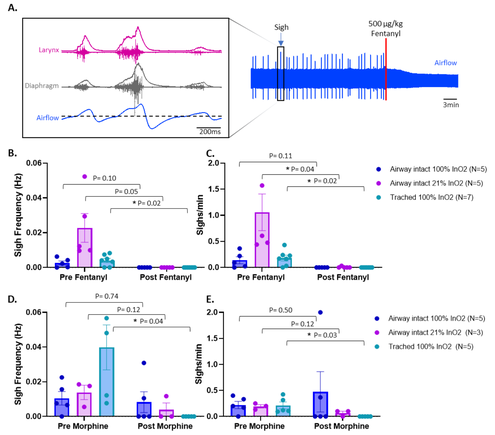
EMG wires were implanted in tracheostomized mice breathing 100% O2 to assess laryngeal activity. Both opioids resulted in around 50% reduction in peak laryngeal EMG activation during inspiration (B,C), with a quicker onset in fentanyl-treated mice. However, total integrated laryngeal activity nearly doubled post administration (D,F), tied to a larger tidal volume observed. Notably, fentanyl uniquely caused about a 50% reduction in relative maximum laryngeal EMG activation compared to maximum diaphragmatic activation (E), indicating a loss of diaphragm-laryngeal coordination. * and black bar indicate statistical significance.

Figure 4. Fentanyl-induced airway obstructions reversed by salbutamol and epinephrine



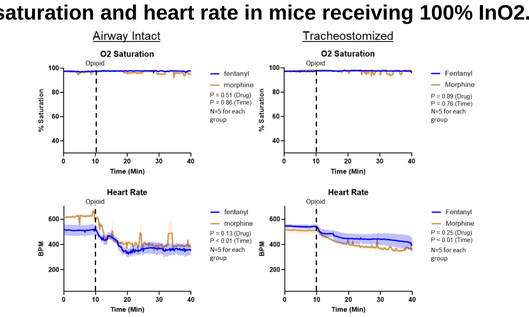
To examine the reversal of fentanyl-induced airway obstructions, the fast-acting bronchodilators salbutamol (15µg/kg, I.P) or epinephrine (7µg/kg, I.P) were administered 15 minutes post 500µg/kg fentanyl (I.P) in airway intact mice under room air conditions (21% InO2). After fentanyl administration, mice exhibited a typical increase in the delay between diaphragmatic EMG activation and inspiratory airflow (A, B, C), suggesting the occurrence of airway obstruction. This effect was fully reversed within seconds post administration of either salbutamol (N= 6) (B) or epinephrine (N= 6) (C). * Indicates P<0.05.

Figure 5. Reduction in physiological sigh incidence by fentanyl and morphine



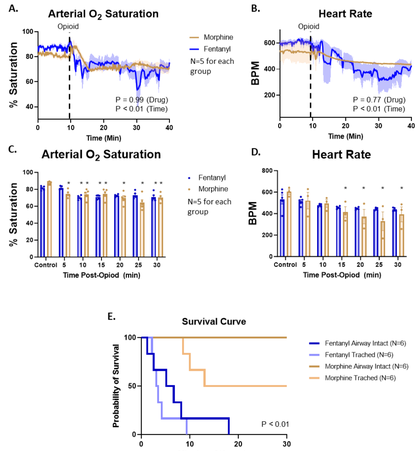
Physiological sighs, vital in preventing alveolar collapse (atelectasis), exhibit characteristic augmented biphasic activity visible in diaphragm, laryngeal complex, and airflow signals (A). These sigh activities, visible under control conditions before opioid administration in both airway intact and tracheostomized mice (B, C, D, E), are markedly reduced post opioid administration. Specifically, 500µg/kg fentanyl (I.P.) administration resulted in a complete blockade of sigh incidences throughout the 30 minutes recorded post injection (B, C). Administration of 150mg/kg morphine (I.P) also notably reduced sigh incidence during the same time frame, although it did not entirely block their occurrence (D, E). * Indicates P<0.05.

Figure 6. Impact of morphine and fentanyl on O2 saturation and heart rate in mice receiving 100% InO2.



Following either morphine (N= 5) or fentanyl injection (N= 5) (I.P.), no significant change was observed in arterial O2 saturation in mice receiving 100% InO2 (A, B). In contrast, heart rate was significantly reduced by nearly 200bpm in airway intact and tracheostomized mice following either morphine or fentanyl (C, D).

Figure 6. Morphine and fentanyl's impact on O2 saturation, heart rate, and risk of death in hypoxic conditions



Following 500µg/kg fentanyl (N= 5) (I.P.) or 150mg/kg morphine (N= 5) (I.P) to airway intact mice breathing room air (21% InO2), we observed a nearly 20% reduction in arterial O2 saturation (A, C), and a gradual decline in heart rate over 30 minutes (B, D). Upon exposure to 10% InO2 post-injection, fentanyl-treated mice showed a significantly higher death incidence compared to morphine-treated mice (E). * Indicates P<0.05 compared to control period. Black bar indicates P<0.05 between fentanyl and morphine.

Conclusions

- Morphine and fentanyl exhibit comparable suppression of breathing frequency with scaled dosages.
- Despite the similarity in breathing frequency suppression, fentanyl uniquely induces transient obstructions to airflow during the inspiratory phase, a phenomenon not observed with morphine at the administered dose.
- Tracheostomy can mitigate fentanyl-induced airflow obstructions, indicating a role of the upper airway in these obstructions. Yet, the equal suppression of laryngeal activity by both opioids points to the lower airways as the obstruction site.
- The administration of sympathetic mimetics, salbutamol and epinephrine, which target the smooth muscle in the lower airways, effectively reverses fentanyl-induced airflow obstructions. This highlights the smooth muscle-containing airways as the primary site of airflow obstructions post-fentanyl administration.
- Fentanyl more potently inhibits the occurrence of sighs compared to morphine, suggesting a heightened suppression of airway defense mechanisms following fentanyl administration.
- Fentanyl exacerbates survivability risks during hypoxic conditions compared to morphine, highlighting the importance of preventing airflow obstructions during a fentanyl overdose to avoid further hypoxemia.
- Employing adjunctive therapies that combine bronchodilators with traditional opioid antagonists like naloxone, may reduce the necessary dose of opioid antagonist and mitigate side effects such as acute withdrawal and severe agitation.

Funding

P01 HL090554 (J.M.R.), R01 HL126523 (JMR), R01 HL144801 (J.M.R.), R01 HL151389 (J.M.R.), F32 HL154558 (NJB) and R00HL145004 (NAB), R01HL166317 (NAB)