Inspire or expire: a matter of life or death

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CHAPTER 1

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Introduction and thesis outline

Introduction

Opioids are a cornerstone of pain management for acute severe pain, but their therapeutic benefits come with potentially fatal consequences. The current opioid crisis has reached unprecedented proportions, with an estimated 800,000 people in the United States dying from drug overdoses over the past two decades, primarily due to potent opioids. The peak occurred in 2023, with more than 80,000 deaths in the United States alone.[1] Since then there has been a decrease, but it is still the number one cause of death for Americans aged 18-44 years.[2]

The primary mechanism underlying opioid-related fatalities is opioid-induced respiratory depression (OIRD), a life-threatening complication that occurs when opioids bind to mu-opioid receptors within the brainstem, suppressing respiratory centers and consequently depressing ventilation to potentially fatal levels.[3]

Respiratory suppression can progress from irregular breathing patterns and reduced respiratory rates to complete respiratory arrest (apnea), resulting in hypoxia, cardiac arrhythmias, and ultimately death if no intervention is initiated.[4]

The changing landscape of opioid overdoses

The nature of opioid overdoses has fundamentally changed over the past decades. While opioids derived from papaver somniferum (opium poppy), including morphine and subsequently heroin, were historically the predominant causes of opioid overdoses, illicit fentanyl and its analogs have now become the primary opioids of abuse. This shift is disturbing since synthetic opioids like fentanyl, sufentanil, and carfentanil possess significantly higher affinity for mu-opioid receptors compared to natural and semi-synthetic opioids. Fentanyl's receptor affinity is approximately 10-fold higher than heroin. These ultra-potent synthetic opioids cause more rapid and profound respiratory depression that may result in cardiac arrest, secondary to hypoxia or via blocking of the human ether a-go-go related gene (hERG) ion channel.[5, 6]

Naloxone: the current standard treatment and its limitations

Naloxone, first introduced in the early 1960s, is a competitive, non-selective opioid receptor antagonist, that remains standard of care for reversing opioid effects, most importantly for respiratory depression.[7, 8] It can be administered intravenously, intramuscularly, and intranasally, the latter is currently marketed as an over the counter/take home rescue drug for opioid overdose emergencies. The approval by the US Food and Drug Administration (FDA) of

over-the-counter intranasal naloxone in 2023 significantly increased access to this life-saving intervention. However, the effectiveness of naloxone is limited by drug pharmacokinetics and receptor binding properties of the opioid involved. Long-acting opioids and those with high affinity and slow receptor dissociation (*e.g.,* carfentanil or sufentanil) often require higher or repeated naloxone doses for reversal.[9-11] While 2 mg intranasal naloxone has shown success rates of 70 to 80% for reversal of heroin-induced respiratory depression, its efficacy in the context of overdoses with ultra-potent synthetic opioids remains uncertain, raising significant concerns as we expect it to be much less than 70-80%.[12-15] Furthermore, titration with intranasal naloxone could be difficult due to the relative slow uptake in the nasal mucosa.[16] Multiple intranasal administrations are required which can result in decreased uptake, negatively affecting the efficacy of the intranasal formulation.[11]

Challenges for in-hospital settings

Opioid-induced respiratory depression is not limited to the community setting. All hospitalized patients, in particular postoperative patients receiving opioids, are at risk. Studies indicate that up to 46% of general ward patients experience at least one episode of respiratory depression, while in 21% of postoperative patients oxygen desaturations were observed, often attributable to opioid administration.[17] In the perioperative setting, opioids are frequently combined with anesthetics and neuromuscular blockers, complicating the assessment of their specific impacts on effective ventilation. Traditional monitoring, such as intermittent pulse oximetry and respiratory rate measurement, might prove inadequate. Over 90% of hypoxic episodes are currently missed with intermittent monitoring, and excessive false alarms contribute to alarm fatigue among healthcare providers.[18] Current clinical guidelines define bradypnea as a respiratory rate below 8 breaths per minute, a common threshold for bedside interventions. However, opioid-induced respiratory depression often develops gradually, meaning patients may already be in critical decline before the clinical threshold is met and detected. This highlights an urgent need for advanced, continuous monitoring technologies, for example using artificial intelligence, trained to detect early signs of ventilatory compromise.

Beyond naloxone: the need for the agnostic respiratory stimulant

While naloxone remains the cornerstone in treating OIRD, it has limitations, particularly in cases involving polysubstance overdoses. The frequently observed combination of opioids with tranquilizers such as xylazine (a veterinary anesthetic and alpha$_2$ adrenergic agonist) or the abuse of extremely high-affinity opioids can blunt naloxone's efficacy.[19] Naloxone administration can induce precipitated withdrawal, which can be both distressing to the patient

and bystanders, and potentially dangerous (e.g. lung edema and agitated delirium).[20] This underscores the need for true respiratory stimulants, drugs that restore breathing regardless of the cause of depression through stimulation of the respiratory networks in the brainstem. Respiratory stimulants could not only provide a safer alternative in mixed-drug overdose scenarios but also reduce withdrawal by bypassing opioid receptor antagonism entirely or by needing lower doses of naloxone. There are currently stimulants under development including substances acting at the carotid bodies, *i.e.,* drugs that mimic hypoxia by blocking the oxygen sensor in type 1 carotid body cells (*e.g.*, doxapram, almitrine and ENA-001), and drugs that interact with excitatory receptors in the respiratory networks of the brainstem.[21-23] Examples of such drugs include ampakines, 5HT agonists, and orexin agonists.[24, 25] Interestingly, drugs that interact with the 5HT receptor system may either be excitatory or inhibitory depending on the 5HT subunits that are targeted, underlining the complexity of the matter.

Thesis structure and scope

The thesis is divided in three parts. The first part focuses on the mechanism of opioid-induced respiratory depression and how to detect it, the second part concentrates on naloxone, the final part describes reversal agents.

Part I Understanding and detecting opioid-induced respiratory depression

Chapter 2 presents a novel principal component-based breath clustering method for early recognition of severe opioid-induced respiratory depression, demonstrating the ability to detect impending apnea.

Chapter 3 describes a population pharmacokinetic-pharmacodynamic framework for evaluating fentanyl's isolated effects on ventilatory control, revealing that physiological models incorporating CO_2 kinetics provide a more accurate representation of potency estimates than empirical approaches.

Part II Naloxone

Chapter 4 provides an extensive review of the limitations of naloxone in the treatment of opioid-induced respiratory depression and the prevention of cardiac arrest. The addenda provided with this chapter are correspondence with clinicians and reflect the importance and the ongoing discussion related to this topic.

Chapter 5 discusses a direct comparison between intramuscular (ZIMHI™ naloxone 5 mg) and intranasal naloxone (Narcan® or naloxone 4 mg) formulations in reversing fentanyl-induced apnea, showing the superiority of intramuscular administration in requiring fewer doses and faster complete reversal.

Chapter 6 reports on the effectiveness of naloxone 4 mg IN in reversing moderate respiratory depression induced by fentanyl and sufentanil in both opioid-naïve and daily opioid users, demonstrating rapid respiratory recovery but delayed and sometimes incomplete end-tidal CO_2 normalization. The study was made possible by an award from the US FDA and was conducted in close collaboration with the Division of Applied Regulatory Science, part of the Center for Drug Evaluation and Research, of the FDA.

Part III Respiratory stimulants

Chapter 7 provides a comprehensive overview of mechanism-agnostic respiratory stimulants that could serve as alternatives or adjuncts to naloxone in cases of polysubstance overdose or naloxone-resistant respiratory depression.

Chapter 8 reports on the clinical evaluation of TAK-925 (danavorexton), an orexin receptor 2 agonist, demonstrating its ability to reduce opioid-induced respiratory depression and sedation without compromising analgesia.

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