Balancing between pain relief and respiratory depression

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CHAPTER

7

SUMMARY AND CONCLUSIONS

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In an era where constant progress and innovation shape our everyday lives, it is easy to overlook the successes that modern medicine -especially the field of anesthesiology- has achieved. Anesthesia has undergone a remarkable (r)evolution, from its early days when narcosis during surgery was delegated to general practitioners, into a highly specialized field that is now one of the cornerstones of contemporary medical practice. For centuries, surgery was performed without anesthesia, and the pain associated with such endeavors was considered the most dreadful aspect of any operation (Benjamin Bell, 1789).[1] The first successful use of ether anesthesia in 1846 marked a turning point, significantly improving patient well-being and effectively reshaping the future. [1]

Today, anesthesiology is a sophisticated discipline that is essential not only for surgery but also for a wide range of other medical applications, from diagnostic procedures to intensive care and palliative treatments. Yet, despite this success, challenges remain - challenges that, if overlooked, could jeopardize the main goal of anesthesia: safe-guarding the patient.

Striking the right balance between achieving the desired effect and ensuring patient safety is one of the most critical -and delicate- tasks in anesthesiology. This balance becomes especially challenging when it comes to respiratory depression, a common side effect of many anesthetic agents, that if not managed carefully, can quickly be-come life-threatening.

And now, with the increasing complexity of surgeries, advancements in technology, and the rise in comorbidities and underlying diseases in patients deemed fit for surgery these challenges have become even more pronounced.

This thesis casts a critical eye on these more persistent aspects of anesthesia care. It draws attention to the risks associated with opioid use (**Chapter 1**), exploring alter-native strategies to reduce respiratory depression without sacrificing analgesia. The exploration of cebranopadol, a novel dual agonist targeting both the μ-opioid and nociceptin opioid peptide receptors, promises a safer path forward, offering pain relief while reducing the risk of respiratory compromise (**Chapter 2**). Similarly, the use of agnostic respiratory stimulants such as ENA-001 (**Chapter 3**) and esketamine (**Chap-ter 4**) represents an alternative approach, that seeks to treat respiratory depression without compromising the wanted effect of the drugs of choice.

However, even the most advanced pharmacological interventions can be rendered ineffective if we fail to adequately monitor and assess their effects. Pulse oximetry, long considered a vital tool in respiratory monitoring, has its limitations, especially when it comes to accurately detecting respiratory compromise in diverse populations. The variability in its effectiveness, particularly in patients with darkskin tones, raises pressing concerns about the influence of (historically rooted) bias that may continue to influence patient healthcare today (**Chapter 5**).

The following inferences can be drawn from these chapters:

Chapter 1 explains that to this day, opioids remain crucial in the management of pain, but their most potent side effect, respiratory depression, continues to pose a significant challenge. Predicting the impact of opioids on ventilatory control is complex, with multiple factors such as age, sex, opioid tolerance, and co-existing conditions contributing to the risk and severity of opioid-induced respiratory depression (OIRD). In clinical settings, monitoring patients is essential to prevent severe OIRD from escalating into life-threatening situations. While low doses of naloxone can often reverse the effects of OIRD, managing overdose situations, particularly with potent opioids like fentanyl, remains difficult due to factors like opioid potency, dose, tolerance, and potential interactions with other substances. Effective rescue in such cases depends on timely detection allowing timely intervention, proper administration of naloxone, and various individual factors, highlighting the complexities of reversing opioid overdoses. However, while developments of opioid receptor agonists with fewer side effects and agnostic respiratory stimulants are emerging, it is important to realize that they do not address the full range of opioid-related issues, particularly the continuously evolving opioid crisis. Overcoming this crisis requires more than medical solutions; it calls for a multifaceted approach that incorporates comprehensive socioeconomic factors to ensure long term sustainable change.

In **Chapter 2**, we report on a randomized, partial crossover trial in 30 healthy volunteers that determined the respiratory and antinociceptive effects of new opioid receptor agonist, cebranopadol, compared to oxycodone. Cebranopadol is a dual nociceptin/orphanin FQ (NOP) receptor and mu receptor (MOP) agonist. Preclinical and clinical data indicate that NOP receptor agonism modulates MOP receptor side effects, such as respiratory depression and addictive behavior. We hypothesized that cebranopadol compared to oxycodone produces less respiratory depression at equianalgesia. In addition, we sought to explore if, as suggested by a previous clinical trial

performed by our team, cebranopadol produces a plateau for respiratory depression.

Our results show that cebranopadol has a more favorable safety profile, causing 25% less respiratory depression compared to oxycodone at equianalgesic doses. Additionally, cebranopadol exhibited slower onset and offset times for both respiratory depression and analgesia, providing a metabolic advantage. The slower onset allows for CO_2 accumulation, which helps mitigate the full extent of respiratory depression. However, we were unable to confirm the presence of a plateau effect in respiratory depression, as suggested by previous trials. This limitation could be due to factors such as the unbalanced study design, high variability in drug plasma concentrations as a result of the re-encapsulated formulation, and the possibility that higher doses are needed to observe such effects. Further research is needed to better understand the plateau effect and to address these study limitations.

In **Chapter 3**, we report on a randomized, double-blind crossover trial, that investigated whether ENA-001, a respiratory stimulant that blocks BK_{Ca}-channels in the carotid body, can reverse the hypoxic ventilatory response (HVR) depressed by propofol, a commonly used anesthetic. It builds on previous studies performed in our laboratory demonstrating that under isohypercapnic and poikilocapnic conditions ENA-001 (previously known as GAL021) is able to stimulate ventilation in the presence of the opioid alfentanil.

We hypothesized that ENA-001 can restore HVR during propofol infusion. A total of 14 healthy volunteers received placebo or low- and high-dose ENA-001 during propofol infusion during which HVR was measured under conditions of hypoxia and hypercapnia. ENA-001 effectively restored the HVR depressed by propofol. The required ENA-001 concentration for full reversal was 1 µg/ml, matching the propofol dose that reduced the HVR by 50%. This suggests that ENA-001 could serve as a potential respiratory stimulant in clinical settings where central respiratory depression occurs (i.e. due to anesthetics such as propofol). Further research is needed to explore ENA-001's efficacy in patients with comorbidities or under different anesthetic conditions.

In **Chapter 4**, we report on an open-label study aimed to evaluate the effects of esketamine on the ventilatory response to isocapnic hypoxia, continuing a series of studies on esketamine' s respiratory effects. Esketamine, the S-enantiomer of ketamine, has been shown to stimulate isohypercapnic ventilation in the presence of remifentanil-in-

duced respiratory depression. In this study, 18 healthy subjects received an escalating intravenous infusion of esketamine, totaling 1.0 mg/kg over 3 hours. Ventilation was measured during the first 5 minutes (acute hypoxic ventilatory response) and over 20 minutes (sustained hypoxic ventilatory response) of isocapnic hypoxia. Hemodynamics and brain function were also assessed.

The results showed that esketamine caused a small, independent increase in ventilation (3.1 L/min), regardless of hypoxia. However, it did not affect the ventilatory response to acute or sustained hypoxia. Esketamine increased mean arterial pressure by 10 mmHg and heart rate by 10 beats/min, both during normoxia and hypoxia. Additionally, esketamine increased anxiety, alertness, and affected external perception, with these arousal effects potentially contributing to the sustained ventilatory response during the infusion.

In **Chapter 5**, we report on an open-label study with 36 healthy individuals, in which we evaluated pulse oximeter accuracy in real-world clinical settings, focusing on the impact of skin tone using Individual Topology Angle (ITA) to quantify pigmentation. We found a significant performance discrepancy, with darker skin tones (ITA < -30) showing higher accuracy root mean square (ARMS) values, suggesting measurement overestimation. This is likely due to the underrepresentation of dark-skinned individuals in calibration studies. Current standards only require 15% of participants to have dark skin, which skews calibration toward lighter skin tones.

Using the Masimo Radical-7, we observed an ARMS of 3.14 in dark-skinned individuals, much higher than the manufacturer-reported value of 1.6. This discrepancy indicates that occult hypoxemia rates in dark-skinned individuals could be as high as 45%. Current validation protocols, which focus on stable SpO_2 readings, do not account for dynamic fluctuations in oxygen levels seen in clinical settings. We recommend updating validation methods to include fluctuating oxygen levels and using the Maximum Absolute Error metric for more reliable performance assessment. Additionally, we found that sensor placement, particularly on the dorsal upper arm, reduces the impact of skin pigmentation on accuracy compared to the finger. This suggests that selecting less pigmented areas could improve pulse oximeter performance. Our study underscores the need for more inclusive validation protocols that consider diverse skin tones and dynamic clinical conditions, ensuring pulse oximeters provide accurate readings for all patients, especially those with darker skin.

In conclusion, the data collected and reported in this thesis shows that while anesthesiology has undoubtedly reshaped modern medicine, the road ahead is far from smooth. The ongoing quest to find safer analgesics, more effective respiratory stimulants, and better monitoring techniques is not just an academic exercise but a vital necessity. The research presented here serves as a reminder that even in fields that have made remarkable advancements, there is always room for improvement. By developing more advanced, generalized, and patient-centered approaches to both pharmacology and monitoring, we can ensure that the future of anesthesiology will not only be safer and more effective but truly in tune with the unique needs of every patient.

Future perspectives

In light of these findings, future research should focus on several key areas. The development of 'safer' opioid-like peptides and modulators has highlighted several promising new compounds. As agonism of the μ-opioid receptor is still the primary mechanism of analgesia, alternative compounds incorporating this strategy are currently being explored.

One such compound is BMS-986122, a selective positive allosteric modulator of the μ-opioid receptor. Unlike traditional opioids, this allosteric modulation enhances the efficacy of endogenous opioid compounds without directly activating the receptor.[2] Preclinical data indicate that BMS-986122 enhances antinociceptive action of both exogenous and endogenous opioids in mouse models of acute and persistent pain, with reduced μ-opioid receptor-related side effects, such as reward and respiratory depression, when compared to morphine.[3] This suggests that BMS-986122 could provide an alternative strategy for μ-opioid receptor-mediated antinociception while mitigating the full scale of side effects typically associated with conventional opioids.

Beyond preclinical studies, another promising strategy involves structural modifications of endomorphins. This approach has already shown potential in clinical trials.[4] The endogenous opioid system effectively alleviates pain without significant side effects.[5] Notably, cyclic endomorphin CYT-1010, produced by cyclizing endomorphins, is currently undergoing phase 2 clinical trials for pain management. Phase 1 trials have shown that CYT-1010 provides antinociceptive effects without compromising respiratory function at the dose levels tested.[6] Further studies are needed to fully evaluate its

therapeutic potential.

Agnostic stimulants are also being further developed. Recently, our team evaluated the effects of the orexin receptor 2 agonist TAK-925 on remifentanil-induced respiratory depression in healthy male volunteers.[7] We showed that, compared to placebo, both low and high doses of TAK-925 significantly stimulated respiration without affecting pain tolerance, as measured by the electrical pain stimulation model. This suggests that TAK-925, like ENA-001, could complement traditional opioid-based analgesic strategies by counteracting opioid-induced respiratory depression without compromising analgesic efficacy. Since orexin is known to be involved in the wakefulness pathway, this opens up the possibility for (re) exploring other wakefulness stimulatory agents, such as caffeine and possibly amphetamines.

Surprisingly, with respect to monitoring, not all developments lie in the future. At the beginning of 2025, the FDA issued a draft guidance with non-binding recommendations for the performance testing and labeling of pulse oximeters.[8] Most importantly, they emphasized the need for clear demographics of all study participants, including standardized Monk Skin Tone and ITA colorimetry evaluation, as well as a new consensus on the ARMS value of ≤3%. However, no further propositions have been made regarding the ARMS metric itself or the protocol for the static desaturation, leaving room for future developments and perspectives.

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