Pharmacotherapy and ventilatory control in health and disease

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Chapter 1

Introduction

Background

Inherently dangerous, anesthesia has matured into an essentially safe practice due to major advancements in the field. Over the decades, even since the 1950s, the field of anesthetic and perioperative care has witnessed a continuous decline in mortality rates.[1] These advancements can be attributed to the utilization of safer anesthetic agents, the development of advanced technical instruments and techniques, and comprehensive training programs, among other pivotal factors. Despite these remarkable progressions, challenges and gaps in our understanding persist.

The evolution of drug use in anesthesiology is particularly noteworthy. Initially focused on facilitating surgical procedures and enhancing patient health outcomes, in the current landscape of 2023, anesthetics have expanded their applications well beyond the confines of the operating room. They are now integral in diverse medical contexts, including trauma care, resuscitation, sedation, intensive care, and the management of acute and chronic pain.[2] Furthermore, the exploration of unconventional agents, such as psychedelics for pain, and the use of anesthetic agents in other disciplines, underscores the dynamic nature of modern medical practice and interdisciplinary research.[3]

For instance, consider ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) blocker, introduced as an intravenous anesthetic in 1965. Since the 1990s its applications have extended to include the management of acute and chronic pain. More recently, since the early 2000s, nasal *S*-ketamine marketed as Spravato, has also found utility in psychiatry, offering an alternative treatment for therapy-resistant depression and post-traumatic stress disorder. This presents a potential replacement for traditional treatments like electroconvulsive therapy or antipsychotic therapy in specific cases.[4,5] Studies on this fascinating drug can be advantageous for both the fields of psychiatry and anesthesiology.

One persistent challenge of drugs in anesthesiology revolves around the efficacy and side-effect profile of contemporary analgesics. Both non-opioid and opioid analgesics, while indispensable in pain management, exhibit limitations in certain patient groups, particularly those suffering from chronic pain. Conversely, these drugs have adverse effects, including the potential for abuse, as observed with ketamine and opioids, as well as the life-threatening risk of opioid-induced respiratory depression. The combination of addiction and respiratory depression stands at the core of the current opioid epidemic in the United States, characterized by more than 100,000 deaths from opioid overdose in 2022.[6]

Both the efficacy and side-effect profile of these analgesics are intertwined with the critical role played by the patient's phenotype. *"One Size Fits All"* is a thing of the past and research and guidelines are increasingly tailored to

individual factors due to the heterogeneity of clinical effects. Notably, a recent observational study involving over 1,300 patients highlighted that factors such as male sex, older age, opioid naivety, sleep-disordered breathing, and heart failure are associated with an increased risk of opioid-induced respiratory depression.[7] Additional risk factors encompass the presence of comorbidities, concomitant use of systemic opioids and sedatives, and higher BMI.[8,9] While clinical trials, typically conducted on young and healthy subjects, illuminate drug effects, questions are raised about the applicability of their findings. Therefore, we focus on studying a new opioid in a representative study sample comprising male and female volunteers of older age, including overweight participants.

Of particular interest is the role of obesity as a risk factor for opioid-induced respiratory depression. Obesity's global prevalence is staggering, and it directly heightens the risk of opioid-induced respiratory depression due to obesity-related changes in the respiratory system, alterations in respiratory drive, and breathing abnormalities during sleep.[9,10] Furthermore, obesity increases the likelihood of developing insulin resistance and type 2 diabetes. Intriguingly, studies indicates that insulin resistance can modulate ventilatory drive, and type 2 diabetes can lead to the development of sleep-disordered breathing, independent of obesity.[11,12,13] While speculative, these factors may contribute to an elevated risk of premature mortality among individuals with type 2 diabetes who use opioids over an extended period.[14]

In this thesis, I will present a series of studies conducted in our laboratory, focusing on the pharmacology of ketamine oral and buccal thin film, intravenous oliceridine and morphine, and type 2 diabetes. The studies encompass pharmacological aspects (ketamine, oliceridine, and morphine) and their effects on ventilatory control (morphine, oliceridine, and type 2 diabetes), spanning the important effects of these drugs in clinical practice.

Thesis overview

While ketamine has been used for nearly six decades, ongoing developments have led to new indications and new formulations are still being developed. As an analgesic, ketamine is employed in the prehospital setting, emergency ward, perioperatively, and for chronic pain syndromes.[15,16,17,18] Substantial gaps persist in our understanding of its efficacy and safety when considering different routes of administration, varied durations, dosages, and distinct enantiomers in diverse clinical contexts.

This thesis delves into the pharmacology of a novel *S*-ketamine oral and buccal thin film in **Chapters 2 and 3**, exploring its pharmacokinetics and pharmacodynamics, respectively. To achieve this, we employ a population pharmacokinetic/pharmacodynamic model, which integrates the changes in

concentration over time with the relationship between the concentration at the effect site and the intensity of the observed response, while considering multiple covariables.[19] While the precise clinical indications for *S*-ketamine films remain undefined, our research primarily centers on evaluating its analgesic efficacy and its profile of side effects. It is conceivable that this thin film formulation may eventually find application as a potential treatment for therapy-resistant depression, akin to its intranasal counterpart.

In **Chapter 4**, we compare the respiratory effects of oliceridine, a *mu*-opioid receptor agonist with biased characteristics, to morphine, a prototypical *mu*-opioid receptor agonist. The concept of biased agonism, or functional selectivity, underscores the origins of these distinctive characteristics.[20] The respiratory effects of opioids are exerted via *mu*-opioid receptors in important brainstem respiratory centers. Upon binding to the *mu*-opioid receptor, opioids trigger the activation of distinct intracellular pathways. Earlier studies pointed towards the role of *beta*-arrestin recruitment in adverse effects of opioids, including respiratory depression.[21] This understanding paved the way for the development of oliceridine, a *mu*-opioid receptor agonist exhibiting a pronounced bias in favor of G-protein signaling.[22] The resultant net effect is an opioid that mitigates the extent of respiratory depression, offering a potential therapeutic advantage.

Finally, in **Chapter 5**, we explore the effect of type 2 diabetes and hyperinsulinemia on ventilatory control. Only recently, a link between metabolic disorders and changes in ventilatory control has been established in animal and preclinical studies.[23,24,25] These changes comprise changes in chemoreflex sensitivity, modifications in breathing patterns, and adjustments in carotid-body mediated sympathetic outflow.[26,27,28] Given the increased incidence, morbidity, and mortality associated with SARS-COV-2 among individuals with type 2 diabetes, our particular interest was the ventilatory effect of hypoxia in this group of patients. The hypoxic ventilatory response is crucial in determining an individual's predisposition to hypoxia-related pathologies. Therefore, this response was obtained in individuals with type 2 diabetes and compared to healthy controls, both during fasting conditions and under the influence of a hyperinsulinemic-euglycemic clamp. This study provides insight into the effects of metabolic dysregulation on ventilatory control. Given the large increase in patients with type 2 diabetes worldwide, this is an important study that may guide our approach to type 2 diabetics, particularly under conditions of changes in ventilatory control, such as those encountered perioperatively or following opioid administration.

Ventilatory control

Two chapters in this thesis are dedicated to ventilatory control and the effect of drugs (morphine and oliceridine in **Chapter 4**) and type 2 diabetes (**Chapter 5**) on the ventilatory control system. In the field of anesthesiology, the study of ventilatory control has been of particular interest due to its implications for patient safety. Comprehending its underlying mechanisms is crucial, since disturbances in the normal respiratory rhythm generation may have severe cardiorespiratory consequences.

The generation of respiratory rhythms occurs in specialized respiratory networks located in the pons and medulla. These networks receive afferent input from various sources, including the central and peripheral chemoreceptors, mechanoreceptors, and behavioral control from higher centers.[29] The central chemoreceptors, dispersed in the hindbrain, sense minor changes in CO_2/H^+within the cerebrospinal fluid.[30] The carotid bodies, the main peripheral chemoreceptors located in the fork of the carotid arteries, monitor hypoxia, hypercapnia as well as a variety of metabolic stimuli including arterial blood glucose concentrations.[31] These chemoreceptors work together in an additive fashion. Upon metabolic acidosis, the input from the chemoreceptors activates the respiratory networks causing a hyperventilatory response, aimed a compensating the metabolic acidosis. A similar response is triggered by the exogenous administration of carbon dioxide, the hypercapnic ventilatory response or HCVR, and is used to determine the sensitivity of the ventilatory control system to CO_2. The HCVR is particularly sensitive to the effects of opioids.

In case of hypoxia, the carotid bodies are activated and a hyperventilatory response occurs that is biphasic.[32] An initial acute response is followed by a slow decline, the hypoxic ventilatory decline. The secondary adaptation has a central origin, although its exact mechanism has yet to be elucidated. Apart from inducing a brisk hypoxia-induced hyperventilatory response, the carotid bodies induce an arousal response, as is observed in patients with obstructive sleep apnea. The obstruction and ensuring hypoxia stimulate the carotid bodies, causing an arousal response that clears the upper airways, followed by a short hyperventilatory response.

In **Chapter 4**, we obtain hypercapnic ventilatory responses induced by CO_2 rebreathing according to the method developed by the Australian investigator D.J.C Read in the mid-1960s. Inhalation of 7% CO_2 (in 93% O_2) from a 4-6 liter rebreathing bag results in a linear increase in ventilation. We used the ventilation at an extrapolated end-tidal PCO_2 of 55 mmHg as the main endpoint in our study. Recent studies from our laboratory indicate that this is the most sensitive parameter when determining the effect of drugs on ventilatory control.[33]

In **Chapter 5**, we use the more sophisticated dynamic end-tidal forcing

technique to obtain the ventilatory response to acute (5 min) hypoxia. This technique uses computer-controlled feedforward input to a series of mass flow controllers that allow manipulation of the inspired gas concentrations to induce a change in end-tidal gas concentration (and thus also arterial gas concentration) independent of the content of the venous return.

Study objectives

The objectives of this thesis are:

1. To quantify the pharmacokinetics and pharmacodynamics (pain relief and psychomimetic adverse effects) of a novel *S*-ketamine oral thin film;
2. To quantify the pharmacokinetics and respiratory pharmacodynamics of the biased ligand oliceridine, in comparison to morphine;
3. Explore the effects of insulin on the hypoxic ventilatory response in type 2 diabetics compared to healthy controls.

References

1. Bainbridge D, Martin J, Arango M, Cheng D. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. *The Lancet*. 2012; **380**: 1075–1081
DOI: 10.1016/s0140-6736(12)60990-8.

2. Nagrebetsky A, Gabriel RA, Dutton RP, Urman RD. Growth of Nonoperating Room Anesthesia Care in the United States: A Contemporary Trends Analysis. *Anesthesia & Analgesia*. 2017; **124**: 1261–1267
DOI: 10.1213/ane.0000000000001734.

3. Goel A, Rai Y, Sivadas S, Diep C, Clarke H, Shanthanna H, Ladha KS. Use of Psychedelics for Pain: A Scoping Review. *Anesthesiology*. 2023; **139**: 523–536
DOI: 10.1097/aln.0000000000004673.

4. Anand A et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. *New England Journal of Medicine*. 2023; **388**: 2315–2325
DOI: 10.1056/nejmoa2302399.

5. Reif A, Bitter I, Buyze J, Cebulla K, Frey R, Fu DJ, Ito T, Kambarov Y, Llorca PM, Oliveira-Maia AJ, Messer T, Mulhern-Haughey S, Rive B, Holt C von, Young AH, Godinov Y. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. *New England Journal of Medicine*. 2023; **389**: 1298–1309
DOI: 10.1056/nejmoa2304145.

6. Humphreys K, Shover CL, Andrews CM, Bohnert ASB, Brandeau ML, Caulkins JP, Chen JH, Cuellar MF, Hurd YL, Juurlink DN, Koh HK, Krebs EE, Lembke A, Mackey SC, Larrimore Ouellette L, Suffoletto B, Timko C. Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-Lancet Commission. *The Lancet*. 2022; **399**: 555–604
DOI: 10.1016/S0140-6736(21)02252-2.

7. Khanna AK et al. Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards Using Continuous Capnography and Oximetry: An International Prospective, Observational Trial. *Anesthesia & Analgesia*. 2020; **131**: 1012–1024
DOI: 10.1213/ane.0000000000004788.

8. Overdyk FJ, Dowling O, Marino J, Qiu J, Chien HL, Erslon M, Morrison N, Harrison B, Dahan A, Gan TJ. Association of Opioids and Sedatives with Increased Risk of In-Hospital Cardiopulmonary Arrest from an Administrative Database. *PLOS ONE*. 2016; **11**: e0150214
DOI: 10.1371/journal.pone.0150214.

9. Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*. 2010; **112**: 226–238
DOI: 10.1097/ALN.0b013e3181c38c25.

10. Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. *Journal of Applied Physiology*. 2010; **108**: 199–205
DOI: 10.1152/japplphysiol.00713.2009.

11. Ramadan W, Dewasmes G, Petitjean M, Wiernsperger N, Delanaud S, Geloen A, Libert JP. Sleep Apnea Is Induced by a High-fat Diet and Reversed and Prevented by Metformin in Non-obese Rats∗. *Obesity*. 2007; **15**: 1409–1418
DOI: 10.1038/oby.2007.169.

12. Lecube A, Simó R, Pallayova M, Punjabi NM, López-Cano C, Turino C, Hernández C, Barbé F. Pulmonary Function and Sleep Breathing: Two New Targets for Type 2 Diabetes Care. *Endocrine Reviews*. 2017; **38**: 550–573
DOI: 10.1210/er.2017-00173.

13. Sánchez E, Sapiña-Beltrán E, Gavaldà R, Barbé F, Torres G, Sauret A, Dalmases M, López-Cano C, Gutiérrez-Carrasquilla L, Bermúdez-López M, Fernández E, Purroy F, Castro-Boqué E, Farràs-Sallés C, Pamplona R, Mauricio D, Hernández C, Simó R, and AL. Prediabetes Is Associated with Increased Prevalence of Sleep-Disordered Breathing. *Journal of Clinical Medicine*. 2022; **11**: 1413
DOI: 10.3390/jcm11051413.

14. Nalini M, Khoshnia M, Kamangar F, Sharafkhah M, Poustchi H, Pourshams A, Roshandel G, Gharavi S, Zahedi M, Norouzi A, Sotoudeh M, Nikmanesh A, Brennan P, Boffetta P, Dawsey SM, Abnet CC, Malekzadeh R, Etemadi A. Joint effect of diabetes and opiate use on all-cause and cause-specific mortality: the Golestan cohort study. *International Journal of Epidemiology*. 2020; **50**: 314–324
DOI: 10.1093/ije/dyaa126.

15. Niesters M, Dahan A, Swartjes M, Noppers I, Fillingim RB, Aarts L, al. et. Effect of ketamine on endogenous pain modulation in healthy volunteers. *Pain*. 2011; **152**: 656–663
DOI: 10.1016/j.pain.2010.12.015.

16. Jonkman K, Dahan A, Donk T van de, Aarts L, Niesters M, Velzen M van. Ketamine for pain. *F1000Research*. 2017;
DOI: 10.12688/f1000research.11372.1.

17. Brinck E, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews*. 2018;
DOI: 10.1002/14651858.cd012033.pub4.

18. Bansal A, Miller M, Ferguson I, Burns B. Ketamine as a Prehospital Analgesic: A Systematic Review. *Prehospital and Disaster Medicine*. 2020; **35**: 314–321
DOI: 10.1017/s1049023x20000448.

19. Olofsen E, Dahan A. Population pharmacokinetics/pharmacodynamics of anesthetics. *The APPS Journal*. 2005; **7**: E383–9
DOI: 10.1208/aapsj070239.

20. Smith JS, Lefkowitz RJ, Rajagopal S. Biased signalling: from simple switches to allosteric microprocessors. *Nature Reviews Drug Discovery*. 2018; **17**: 243–260
DOI: 10.1038/nrd.2017.229.

21. Raehal KM, Walker JKL, Bohn LM. Morphine side effects in -arrestin 2 knockout mice. *J Pharmacol Ther*. 2005; **314**: 1195–2001
DOI: 10.1124/jpet.105.087254.

22. Stahl EL, Bohn LM. Low intrinsic efficacy alone cannot explain the improved side effect profiles of new opioid agonists. *Biochem*. 2021;
DOI: 10.1021/acs.biochem.1c00466.

23. Ribeiro MJ, Sacramento JF, Gonzalez C, Guarino MP, Monteiro EC, Conde SV. Carotid body denervation prevents the development of insulin resistance and hypertension induced by hypercaloric diets. *Diabetes*. 2013; **62**: 2905–16
DOI: 10.2337/db12-1463.

24. Cunha-Guimaraes JP, Guarino MP, Timoteo AT, Caires I, Sacramento JF, Ribeiro MJ, Selas M, Santiago JCP, Mota-Carmo M, Conde SV. Carotid body chemosensitivity: early biomarker of dysmetabolism in humans. *European Journal of Endocrinology*. 2020; **182**: 549–557
DOI: 10.1530/EJE-19-0976.

25. Sacramento JF, Chew DJ, Melo BF, Donega M, Dopson W, Guarino MP, Robinson A, Prieto-Lloret J, Patel S, Holinski BJ, Ramnarain N, Pikov V, Famm K, Conde SV. Bioelectronic modulation of carotid sinus nerve activity in the rat: a potential therapeutic approach for type 2 diabetes. *Diabetologia*. 2018; **61**: 700–710
DOI: 10.1007/s00125-017-4533-7.

26. Lecube A, Sampol G, Hernández C, Romero O, Ciudin A, Simó R. Characterization of Sleep Breathing Pattern in Patients with Type 2 Diabetes: Sweet Sleep Study. *PLOS ONE*. 2015; **10**: e0119073
DOI: 10.1371/journal.pone.0119073.

27. Gutiérrez-Carrasquilla L, López-Cano C, Sánchez E, Barbé F, Dalmases M, Hernández M, Campos A, Gaeta AM, Carmona P, Hernández C, Simó R, Lecube A. Effect of Glucose Improvement on Nocturnal Sleep Breathing Parameters in Patients with Type 2 Diabetes: The Candy Dreams Study. *Journal of Clinical Medicine*. 2020; **9**: 1022
DOI: 10.3390/jcm9041022.

28. Sacramento JF, Andrzejewski K, Melo BF, Ribeiro MJ, Obeso A, Conde SV. Exploring the Mediators that Promote Carotid Body Dysfunction in Type 2 Diabetes and Obesity Related Syndromes. *International Journal of Molecular Sciences*. 2020; **21**:
DOI: 10.3390/ijms21155545.

29. Feldman JL, Mitchell GS, Nattie EE. Breathing: rhythmicity, plasticity, chemosensitivity. *Annual Review of Neuroscience*. 2003; **26**: 239–66
DOI: 10.1146/annurev.neuro.26.041002.131103.

30. Nattie E, Li A. Central chemoreceptors: locations and functions. *Comprehensive Physiology*. 2012; **2**: 221–54
DOI: 10.1002/cphy.c100083.

31. Lopez-Barneo J. Neurobiology of the carotid body. *Handbook of Clinical Neurology*. 2022; **188**: 73–102
DOI: 10.1016/B978-0-323-91534-2.00010-2.

32. Pamenter ME, Powell FL. Time Domains of the Hypoxic Ventilatory Response and Their Molecular Basis. *Comprehensive Physiology*. 2016; **6**: 1345–1385
DOI: 10.1002/cphy.c150026.

33. Hellinga M, Algera MH, Schrier R van der, Sarton E, Velzen M van, Dahan A, Olofsen E, Niesters M. A Biomarker of Opioid-induced Respiratory Toxicity in Experimental Studies. *iScience*. 2023; **24**: 106520
DOI: 10.1016/j.isci.2023.106520.