Pharmacotherapy and ventilatory control in health and disease

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Chapter 6

Summary, conclusions, and perspectives

This thesis represents the intricate journey between physiology and pharmacology. Our primary aim was to investigate the effects of different pharmacotherapies on antinociception and ventilatory control. Additionally, we delved into the inherent variabilities in patient phenotypes within the population to gain a deeper understanding of the individual effects of analgesics and the ventilatory effects of disease, particularly type 2 diabetes mellitus (T2DM).

Summary of the main findings

In **chapter 1**, we briefly introduce the reader to recent advancements in the use of ketamine in clinical practice (for pain management and depression), and the ventilatory depressant effect of opioids and alterations in ventilatory control in T2DM are discussed. Our goal was to highlight current challenges in pain management, emphasize the importance of considering risk factors and side effects, and propose strategies for investigating new or alternative therapies.

In **chapter 2**, we examined the pharmacokinetics of oral-thin-film (OTF) administration of 50 mg and 100 mg *S*-ketamine and its major metabolites. These films were rapidly absorbed, with bioavailabilities of 26% and 29%, respectively, and exhibited relatively small variability in their pharmacokinetics. Therapeutic plasma concentrations for antinociception were achieved. The majority of *S*-ketamine was metabolized into *S*-norketamine, with about half further metabolized into *S*-hydroxynorketamine. These findings were attributed to the swallowing of the active substance, gastrointestinal absorption of the majority of *S*-ketamine, and a significant first-pass effect.

In the complementary **chapter 3**, we investigated the pharmacodynamics of the aforementioned oral-thin-film. Both dosages exhibited antinociceptive effects with a rapid onset (approximately 30 minutes) and lasting effects of at least two hours. Psychotomimetic side effects, such as drug-high, followed a similar pattern. Our model did not detect contributions of *S*-norketamine and *S*-hydroxynorketamine to the antinociceptive or drug-high effects. We conclude that this administration form of *S*-ketamine may be suitable for the treatment of acute pain and breakthrough pain, a proposition that warrants further clinical studies.

Moving on to **chapter 4**, where we examined the respiratory effects of a biased ligand at the μ-opioid receptor, oliceridine. We observed a lower potency of the respiratory depressant effect induced by oliceridine compared to morphine, a lower C_{50} for respiratory depression for both opioids in the elderly population, a shortened onset/offset of respiratory depression with oliceridine, and differences in oliceridine's pharmacokinetic profiles due to *CYP2D6* polymorphisms

and phenotype variations. We could not relate the ventilatory effects to the antinociceptive effects, a critical aspect for evaluating the harm-benefit profile of this pharmacologic compound. We relate our inability to generate opioid-induced antinociception to the specific patient population that was examined by us (our population was insensitive to cold water stimuli). Elderly individuals have difficulty scoring nociception, particularly when exposed to opioids. This may be related to a series of age-related changes in physiology, such as reduced C-fiber density in the skin, alterations in central pain processing as well as cognitive changes. Additionally, obesity negatively affects the proper scoring of nociceptive stimuli.

Finally, in **chapter 5**, we compared hypoxic sensitivity between patients with T2DM with healthy controls and studied the effects of hyperinsulinemia on hypoxic sensitivity. During fasting, we observed no differences between these two groups, however, intriguingly, during euglycemic-hyperinsulinemia significant changes emerged. Heightened hypoxic sensitivity was observed in healthy controls, but not in insulin-resistant individuals. Moreover, during hyperinsulinemia, hyperoxic inhibition increased in patients with T2DM, indicating increased carotid body discharge in this group. This suggests that T2DM negatively affects the carotid bodies with an indication of insulin resistance of that particular organ, albeit the carotid system seems to be in a hyper-excitable state.

Clinical perspectives

All topics discussed above merit further studies. Regarding **chapter 2** and **chapter 3**, it is important to start clinical trials with the *S*-ketamine oral-thin-film in patients, either in patients in acute pain (including breakthrough pain) as well as with therapy-resistant depression. The high levels of *S*-hydroxynorketamine may hold promise for the management of the latter, as it has been identified as an active substance following (*R,S*)-ketamine administration.[1,2] Besides a possible benefit of this particular administration form, we need to explore the ideal ketamine compositions (pure enantiomer or racemic ratio), efficacy and safety of different dosing regimens, which are expected to differ depending on the indication.[3,4,5] Equally important is to determine the side effect profile for each indication. This may, for example, be done using utility function analysis, an approach that calculates the likelihood of benefit *versus* the likelihood of harm, as a function of effect-site concentration.[6] We expect that due to the production of high concentrations of the hydroxynorketamine the utility function may be particularly positive when the *S*-ketamine OTF is used in the treatment of depression, while a lesser positive function, or even a negative function, may be expected in the treatment of acute pain, an effect that relies mostly on the ketamine concentrations in the

brain and spinal cord.[7] Finally, we need to be aware of the fact that we recently showed that ketamine benefit and harm (*i.e.* its schizotypical adverse effects) are intricately connected, and when none of these adverse effects occur the likelihood of a benefit (pain relief or anti-depressive effects) is reduced.[8]

The results of **chapter 4**, the effect of the biased ligand oliceridine on ventilatory control in elderly volunteers, agrees with evidence in animal models that shows the reduced duration and magnitude of respiratory depressant effect of oliceridine, compared to morphine.[9] Also, clinical studies in postoperative patients point in that direction.[10] Whether these underlying features can be attributed to biased agonism or low intrinsic efficacy remains disputed among molecular researchers.[11] Considering the burden of perioperative respiratory effects, we need to realize that with proper monitoring the number of serious respiratory depression events following surgery is limited. For example, the PRODIGY trial, an observational study in more than 1,300 postoperative patients on opioids, showed that while 46% of patients had at least one respiratory event, there were just very rare incidences of the need for naloxone reversal, reintubation, or admittance to the intensive care unit because of opioid treatment.[12] Still, less than 20% of patients exclusively treated with oliceridine in the postoperative period have a respiratory event, and most of such events are not related to the opioid treatment per se, but relate to ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch and concomitant hypoxemia.[12] Further studies are needed to determine what the pharmacoeconomic advantage is of treatment with oliceridine in comparison to commonly used opioids and other analgesics such as morphine or hydromorphone. These generic opioids are cheap, effective, and albeit with a higher tendency to affect the ventilatory control system than oliceridine, are considered a safe drug when used appropriately in the perioperative setting. Furthermore, while outside the scope of this thesis, other actions are necessary beyond innovations in biomedical research, to reduce deaths and prevent further escalation of the opioid crisis around the globe. These include reforming regulatory systems, informed prescribing, and advancements in opioid stewardship. Additionally, efforts should be put towards preventing chronic pain and preventing substance use disorder by modification of risk factors at both individual and population levels.

Finally, in **chapter 5**, the effect of insulin on ventilatory control is examined. The two main observations, carotid body insulin resistance in T2DM coupled with a carotid body that seems to be in a basal hyper-excitable state are important findings that have important health-related effects.[13,14] The lack of increase in hypoxic response upon exposure to insulin in patients with T2DM, is relevant although an appreciable hypoxic response remained; the magnitude of the hypoxic response is quite variable among individuals. Still, the inability to enhance the response is a clear sign of insulin resistance. The carotid body

is considered the watchdog of the brain and a proper insulin response is needed to control the glucose exposure to the brain. Carotid body insulin resistance falls within the general concept of insulin resistance in T2DM. However, the hyperexcitability of the carotid body in T2DM is an important observation that may be linked to health outcome measures such as hypertension, cardiac arrhythmias, and heart failure.[15] Carotid body denervation or destruction has earlier been suggested as a treatment of a hyperexcitable carotid body related diseases, such as treatment-resistant hypertension, heart failure, myocardial infarction, and ventricular tachycardia.[16,17] Hence, our data suggest that patients with T2DM might be at an increased risk for such adverse health issues. While carotid sinus nerve denervation in T2DM may be a bridge too far due to adverse effects, electronic modulation has been shown to restore metabolic homeostasis in animal models.[18] Given the high prevalence of T2DM, further studies are warranted to determine the risks of a hyperexcitable carotid body in T2DM, determine how this is associated with alterations in ventilatory control, and evaluate preclinical therapeutic approaches.

In conclusion, the research conducted in this thesis has expanded our knowledge of pharmacology and pathophysiology on the control of breathing, both in health and disease. We anticipate that these findings will contribute to improved health outcomes and enhanced safety in pain management and foster further research.

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