Countermeasures of opioid-induced respiratory depression

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CHAPTER 1

Introduction

Opioids are the most efficacious painkillers known to mankind. Ironically, this high efficacy comes with multiple side effects that range from mild and acceptable to severe and life-threatening. It is the life-threatening opioid-induced respiratory depression (OIRD) and our (in)ability to reverse OIRD that is the theme of this thesis.

Natural opioids (also called opiates) are derived from the poppy *Papaver somniferum*. Its sap (opium) has been used for millennia for various ailments including the relieve of pain but also for hedonistic purposes.[1] In the early 1800s, just two centuries ago, the German pharmacists and chemist Friedrich Sertürner extracted morphine from opium sap, paving the path for the production of various opiates such as heroin, which were all believed to produce less side effects than morphine.[1] In the end of the nineteenth century and throughout the twentieth century strong synthetic opioids were manufactured for use in veterinary medicine, to suppress stress reactions during surgery, to treat acute pain and as potent pain relievers in palliative care. Worldwide opium addiction became prevalent in the 19th century with opium smoking in opium dens.[2] The single components derived from the opium sap (*e.g.* morphine and heroin) and all synthetic opioids (*e.g.* fentanyl, sufentanil and carfentanil) are similarly addictive and have many more adverse effects, such as development of hyperalgesia, tolerance, nausea, vomiting, constipation, sedation, euphoria, dysphoria, dizziness, lightheadedness, confusion, delirium, insomnia, pruritis, vasodilation and orthostatic hypotension, muscle rigidity, reward and moderate to potentially fatal respiratory depression. Opioid dependency and OIRD are a particular lethal combination shared by all opioids, despite the fact that the incidence of the other side effects may differ among opioids. The addiction/OIRD combination is the root cause of the present opioid crisis in the United States, Canada and certain European nations (*e.g.* Scotland).[3] The addiction/OIRD combination is the cause of thousands of monthly opioid deaths from oxycodone, heroin or fentanyl overdoses, or lethal drug combinations, such as oxycodone laced with fentanyl or carfentanil or heroin mixed with xylazine.[3]

The opioid crisis is not the topic of this thesis. I will concentrate on the possibility to reverse OIRD with naloxone and respiratory stimulants that do not interact with the opioid system. The need for other agents than naloxone stems from the fact that naloxone may not always be the first-line treatment to reverse OIRD (**Chapter 2**). Naloxone is most beneficial in the perioperative and emergency setting when OIRD is mild to moderate and all that is needed is that (sometimes high-dose) naloxone will restore rhythmic respiratory activity. Nevertheless, various situations preclude the use of naloxone such as overdosing on high-dose potent, long-acting or high-affinity opioids (this includes all of the phenylpiperidines), an opioid overdose in combination with a potent sedative (*e.g.* etizolam or xylazine), conditions that will precipitate naloxone-induced aggression, agitation, severe stress or excited delirium, mass accidental or intentional poisoning (*e.g.* terror attack) from (inhaled) opioids in which hundreds of individuals lose consciousness and become apneic and insufficient naloxone is available or naloxone is just ineffective, and finally in case of an opioid

use disorder in which naloxone will precipitate a withdrawal response.[4] The mass poisoning using high affinity opioids of a crowd is certainly not a hypothetical scenario. In 2002, Chechen suicide terrorists took almost 1,000 hostages in a Moscow theatre. In an effort to rescue the innocent theatregoers, security forces exposed all theatregoers to potent opioids (probably carfentanil without or with buprenorphine) through the release of opioid aerosols *via* the theatre air venting system.[5,6] This had catastrophic consequences, and despite the presence of medical personnel and (some) naloxone, hundreds of individuals had to be taken to a medical facility for airway control and manual ventilation and at least 170 people died as a result of cardiorespiratory collapse. Given this example, some Western governments consider the mass casualty from aerosolized opioids alongside biological and nuclear threads a grave concern to public safety.[7] Whether this scenario develops at the hand of terrorist or arises from actions of hostile nations is in this regard irrelevant; both require innovative, effective and long-lasting medical countermeasures. A first step in this respect is to improve our understanding of ventilatory control, the mechanisms through which opioids affect ventilatory control, and understanding naloxone pharmacokinetics (PK) and pharmacodynamics (PD). Particularly naloxone PK and receptor kinetics appear to be a limiting factor in its role as an effective countermeasure of opioid toxicity (see **Chapter 2**). Naloxone has a short elimination half-life, much shorter than that of most opioids. Consequently, continuous naloxone infusions are then required.

For these reasons new drugs are being developed that might be able to restore rhythmic respiratory activity during OIRD, without requiring uncoupling of the opioid ligand from its receptor, the mu-opioid receptor, expressed on respiratory neurons in the brainstem. Given the large number of distinct receptor systems in the respiratory networks in the brainstem involved in rhythmogenesis, such as serotonin receptors, cannabinoid receptors, N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid (AMPA) receptors, thyrotropin releasing hormone (TRH) receptors, nicotinic acetylcholine receptors, oxytocin receptors, etc., the number of proposed stimulants is large as well; see for a review Ref. 4. In this thesis I will focus on a few of these respiratory stimulants, including the partial opioid receptor agonist buprenorphine, and demonstrate that while some are successful, several of such receptors are incapable of producing effective reversal of OIRD.

First (**Chapter 2**), I will provide an overview of previously conducted PK/PD studies that investigated the ability of naloxone to reverse OIRD from buprenorphine, morphine and morphine-6-glucuronide, ketamine to reverse OIRD from remifentanil, and two potassium- channel blockers, ENA001 (formerly known asGAL021) and doxapram. The last two drugs stimulate breathing *via* activation of the type 1 glomus cell of the carotid bodies (the peripheral chemoreceptors).

Next, I will discuss to extent animal and human studies on the hormone TRH and its analog taltirelin (**Chapters 3 and 4**). While animal studies claim TRH-induced reversal of OIRD, I report on animal data that indicate that TRH enhances OIRD by worsening opioid-induced muscle rigidity and human data that show that TRH is ineffective in reversal of OIRD.

In **Chapter 5**, I discuss the atypical tricyclic antidepressant and cognitive enhancer tianeptine and its ability to reverse OIRD in human volunteers. Tianeptine is a used as antidepressant in France, Germany and the United States. Recent studies from our group in collaboration with the US Food and Drug Administration indicate that selective serotonin- receptor reuptake inhibitors (SSRIs) enhance OIRD, whereas earlier animal data point towards a respiratory stimulatory effect and effective reversal of OIRD from tianeptine through its activity at the AMPA receptor. Nonetheless, in a project that spanned more than a decade and involved multiple steps (studies on oral tianeptine, development of intravenous tianeptine and studies on the PK and PD of intravenous tianeptine) and interaction with various pharma companies, we reached a negative conclusion and were forced to conclude that tianeptine, like other antidepressants, enhances OIRD.

In **Chapter 6**, I examined the efficacy of the high- affinity mu-opioid receptor partial agonist buprenorphine in taming down the respiratory effects of buprenorphine in opioid-naïve volunteers and individuals with an opioid-use disorder (OUD). In this mechanism-based PK/PD study, it was found that buprenorphine produces receptor-binding dependent reduction of fentanyl-induced respiratory depression in both study populations. Still, even in individuals with an OUD, a fentanyl overdose may cause apnea despite buprenorphine on board.

Finally, in **Chapter 7**, I studied the relationship between opioid dependency and opioid respiratory sensitivity.

In summary, in this thesis the ability of naloxone and alternate treatments (TRH, tianeptine and buprenorphine) for opioid-induced respiratory depression are explored. Studies are performed in human volunteers that were opioid-naïve or that were suffering from an opioid-use disorder. Conclusions drawn (**Chapter 8**) are predominantly but not exclusively negative and leave room for improvement and development of novel strategies to make treatment of pain with strong opioids safer and reduce the likelihood of an accidental lethal opioid overdose, regardless of whether the opioid is used for medical or hedonistic purposes.

References

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