CHAPTER 1
INTRODUCTION:

1.1 INTRODUCTION

Opioids are the first choice in the treatment of severe acute and chronic pain. Apart from their intended effect (analgesia), opioids come with a variety of side effects with respiratory depression as potentially life-threatening. Opioid-Induced Respiratory Depression (OIRD) is often moderate to mild from which the patient recovers spontaneously or is rescued by other means such as stimulation of the patient to take a deep breath or chin lift. In severe cases of OIRD, breathing becomes initially irregular, followed by cyclic breathing (breathing shows an on/off pattern alike Cheyne-Stokes breathing) and apnea. Rescue is by resuscitation, intubation and assisted ventilation and reversal of opioid effect by naloxone. The incidence of respiratory depression from opioid treatment, acute or chronic, is poorly documented. A recent systematic review of the literature on post-operative OIRD estimates an average incidence of 0.5% with a range of 0.2-2%.[1] This suggests that only 1 in 200 patients develops a respiratory event from opioids that requires an intervention. There are indications that this number is an underestimation with an incidence of OIRD many times higher than 1:200. For example, following patient controlled analgesia with morphine hypoventilation (defined by a respiratory rate < 8 breaths.min^{-1}) occurs in one in three patients.[2] No valid data are available on the occurrence of OIRD in chronic pain patients.[1] Accidental deaths from OIRD in this patient population are often attributed to the progression of underlying disease (for example cancer), old age or co-existing diseases. Although a recent systematic review of case reports on OIRD in chronic pain patients does not provide quantitative data on the occurrence of OIRD, it does provide important information on its development:[3] (i) Since the year 2000, methadone, fentanyl and oxycodone are predominantly involved in OIRD while before 2000 morphine was the most prevalent cause of OIRD, (ii) the incidence of OIRD increased sharply in non-cancer chronic pain patients over the last 10 years and (iii) co-medication affecting the opioid's pharmacokinetics and dynamics is an important cause for opioid toxicity. Observation #2 is probably related to an increased awareness to treat severe chronic pain and also due to the aggressive promotion of opioids by the pharmaceutical industry. Observation #3 is important in chronic pain patients but also important in perioperative and acute settings when opioids are combined with additional drugs that depress ventilation (such as midazolam, propofol, muscle relaxants).

1.2 MECHANISMS OF ACTION

The drive to breathe is generated in multiple respiratory centers in the brainstem.[1] Respiratory neurons receive inputs from various sites in the CNS (cortex, limbic system, hypothalamus, spinal cord), a set of receptors located in the brainstem (central chemoreceptors), and in the carotid bodies (peripheral chemoreceptors). These chemosensors send information, changes in pH, PCO_2 and PO_2 of the CSF and arterial blood, to the brainstem respiratory centers, which appropriately adjust breathing rate and pulmonary tidal volume. For example, acidosis, hypercapnia and hypoxia will cause

hyperventilation, while hypocapnia and alkalosis will reduce minute ventilation. Opioid effects on μ-opioid receptors (MOR), expressed on respiratory neurons, are the main cause for the reduction of the drive to breathe. When an opioid is administered to a patient and the injection rate is sufficiently slow (over minutes) or the passage of the opioid across the blood-brain barrier is slow, depression of the respiratory neurons in the brainstem coincides with the accumulation of arterial CO_2. The stimulatory effect of the increased CO_2 at the peripheral and central chemoreceptors will offset the decrease in tidal volume and reduced respiratory rate. OIRD is then observed as an increase in arterial (and end-tidal PCO2) with little effect on ventilation. When the opioid is infused rapidly and passage across the blood-brain barrier is fast, the depression of the respiratory neurons in the brainstem will dominate as there is insufficient time for CO_2 to accumulate in the body. This then will cause severe OIRD with hypoventilation and initially near normal PCO_2 values. See also Chapters 2 and 3 of this thesis.

Although the incidence of opioid-induced respiratory depression is low, fatalities do regularly occur. For example, Lötsch et al.[4] describe a young female (BMI 19 kg/m2) who had peripheral orthopaedic surgery under general anesthesia (sevoflurane 2-3% with 200 μg fentanyl). In the recovery room the patient received four doses of morphine over 2 hours, reaching a total of 35 mg or 0.7 $mg.kg^{-1}$. Forty minutes after the last dose she developed OIRD followed by a fatal cardiac arrest. At that time estimated brain concentrations were about 150 nM, which is above the toxic range for morphine. This case understates the need for a close understanding of the pharmacokinetics and dynamics of any opioid that is used in any patient. The physicians involved in this case did not take into account the very slow passage of morphine across the blood-brain barrier which caused a peak in central effect hours following peak plasma concentration. And while the onset of analgesic occurred relatively rapidly following the last dose, the fatal respiratory depression occurred 40 min later. This report demonstrates further the need to view OIRD in light of the opioid's wanted effect, analgesia. There are few studies that address the composite effects of opioids. One way to compare the different effects of one opioid is to construct a safety or utility function. These functions, originally used in economics and first applied in pharmacology by Sheiner and Melmon in 1978,[5] are constructed by estimating the difference in probability of analgesia and respiratory depression as derived from experimental pharmacokinetic/pharmacodynamic modelling studies. While application of these functions is currently difficult to envision in a clinical setting, they are useful in the development of novel opioids aimed at maximizing analgesia while simultaneously minimizing OIRD, for example when making a choice for a drug dose to test in a phase III trial from data obtained in phase II studies. For further elaboration see also Chapter 4 of this thesis.

1.3 DEVELOPMENT

Development of an opioid that is without any respiratory depression or other dangerous side effects (the holy grail of opioid pharmacology) seems not possible. At least no such drugs have been developed so far. Fortunately, the pharmaceutical industry still does attempt to develop opioids with restricted respiratory depressant properties. Various companies are focussing on single chemical molecules that activate multiple receptor system including the MOR and a secondary system that possibly counteracts the side effects of the activated MOR. Again the properties of such opioids should always be viewed in terms of their wanted effects. For example, the opioid buprenorphine is known to have a ceiling in its respiratory depressant effects. Such a phenomenon is only advantageous when respiratory ceiling does not coincide with ceiling in analgesia. Indeed ceiling in analgesia seems to occur at higher (supra clinical) doses than respiratory ceiling.[6] This is further adressed in Chapter 5 of this thesis.

Opioid effect is extremely variable with effects that may vary a factor 20-40 between patients. The cause of variety is multiple and has pharmacokinetic and pharmacodynamic origins. Known causes of variability include genetics (for example due to polymorphic enzymes involved in drug metabolism),[3] sex (women are more sensitive to opioids than men),[7] underlying disease (in children repetitive hypoxic events from obstructive sleep apnea are associated with increased opioid sensitivity; in Alzheimer's disease opioid sensitivity seems reduced due to the loss of descending inhibition), age (the elderly have an increased opioid sensitivity),[8,9] co-medication and smoking (smoke contains polycyclic aromatic hydrocarbons that interact with metabolizing enzymes in an often unpredictable fashion).[4] Other factors are less well known and poorly studied, such as for example the nutritional state of the patient and the circadian rhythm, factors that play an important role in the pharmacodynamics of other drugs such as inhalational anesthetics and opioids.[10] See also Chapter 6 of this thesis.

1.4 AIM OF THIS THESIS

The aim of this thesis is to investigate the influence of strong opioids on the control of breathing, taking into account their analgesic properties.

In **Chapter 2** the respiratory pharmacokinetics and dynamics of opioids are discussed. Furthermore, an overview is given of agents that are able to reverse OIRD. Apart from agents that antagonize the MOR, other agents are discussed that stimulate breathing via other receptor systems and theoretically restore breathing without compromising analgesia.

In **Chapter 3** the respiratory depressant effects of the potent opioid remifentanil are modelled using a mathematical model that incorporates the depressant effect of

remifentanil on respiratory neurons in the brainstem and the stimulatory effects of carbon dioxide on the chemoreceptors. This model enables us to predict the behaviour of the ventilatory control system under various remifentanil administration paradigms.

In **Chapter 4** a safety function or utility function is described for the strong opioid fentanyl. As discussed above, the function describes the opioid's behaviour in light of its benefit (analgesia) and harm (respiratory depression).

In **Chapter 5** the respiratory behaviour of an experimental opioid (MR30365/07) is studied and compared to placebo and fentanyl. By performing dose-response studies for respiratory depression and analgesia it is shown that this opioid behaves differently from fentanyl. Possible mechanisms are discussed.

In **Chapter 6** the influence of the circadian rhythm on pharmacodynamic effect of fentanyl is studied. In a first approach, fentanyl's analgesic effects are studied at 4 time points: 02 AM, 08 AM, 2PM and 8PM.

All experiments were performed in healthy young volunteers in the Anesthesia & Pain Research Unit of the Department of Anesthesiology of the Leiden University Medical Centre (LUMC).

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