CHAPTER 7

SUMMARY & CONCLUSIONS

7.1 SUMMARY

Despite many side effects opioids remain the first choice in the treatment of severe acute and chronic pain in contemporary medicine. In this thesis, the influence of strong opioids, used in the treatment of severe acute and chronic pain, on the control of breathing are studied and discussed relative to their wanted effect, analgesia. The issue of opioid-induced respiratory depression is highly relevant as accidental casualties due to OIRD do regularly occur. In some areas, such as the US and Canada, the number of accidental deaths from legally prescribed drugs (predominantly opioids prescribed for chronic non-cancer pain and sedatives voor anxiety and sleeping disorders) is high with a frightening 70 deaths per day.[1,2]

In **Chapter 2** the detrimental respiratory effects of opioids and their relevant pharmacokinetics and dynamics are discussed in the first part of the chapter. Opioids induce respiratory depression via activation of μ-opioid receptors (MORs) at specific sites in the central nervous system including the pre-Bötzinger complex, a respiratory rhythm generating area in the pons. A distinction is made between full and partial MOR agonists. Full opioid agonists like morphine and fentanyl affect breathing with onset and offset profiles that are primarily determined by opioid transfer to the receptor site, while the effects of partial MOR agonists such as buprenorphine are governed by transfer to the receptor site together with receptor kinetics, in particular dissociation kinetics. In the second part of the chapter respiratory depression reversal options are discussed. Opioid-induced respiratory depression (OIRD) may be reversed by the opioid receptor antagonist naloxone, an agent with a short elimination half-life (30 min). The rate-limiting factor in naloxone-reversal of opioid effect is the receptor kinetics of the opioid agonists that requires reversal. Agents with slow dissociation kinetics (buprenorphine) require a continuous naloxone infusion while agents with rapid kinetics (fentanyl) will show complete reversal upon a single naloxone dose. Since naloxone is non-selective and reverses analgesia as well, efforts are made by several pharmaceutical companies on the development of compounds that reverse OIRD without affecting analgesic efficacy. Such agents include ampakines and 5HT-receptor agonists which are aimed at selectively enhancing central respiratory drive. A novel approach is aimed at the reduction of respiratory depression from opioid-activation of (micro-)glia cells in the pons and brainstem using microglia cell stabilizers. Since this approach simultaneously enhances opioid analgesic efficacy it seems an attractive alternative to the classical reversal strategies with naloxone.

In **Chapter 3** the dynamic effects of the potent opioid remifentanil on respiration are described and a mathematical model of respiratory depression is developed. Studies as described here are rarely performed possibly due to the complexity of the respiratory control system. We show here that a model with intact feedback control of carbon dioxide on ventilation (non-steady-state models) that correctly incorporates the complex interaction between drug concentration, PCO_2 and ventilation yields reliable descriptions and predictions of the opioid's behavior. We measured the respiratory effect of remifentanil

with and without a background infusion of propofol.
Ten male healthy volunteers received remifentanil infusions with different infusion speeds (target concentrations of 4 to 9 ng.ml^{-1} at infusion rates of 0.17 to 9 ng.ml^{-1}.min^{-1}) while awake and at the background of low-dose propofol. The data were analyzed with a non-linear model consisting of two additive linear parts, one describing the depressant effect of remifentanil and one the stimulatory effect of carbon dioxide on ventilation.
The model adequately described the data including the occurrence of apnea. Most important model parameters were: C_{50} for respiratory depression with an estimated value of 1.6 ± 0.03 ng.ml^{-1} (median ± SE), the gain of the respiratory controller (G) with an estimated value of 0.42 ± 0.1 L.min^{-1}.Torr^{-1} and the remifentanil blood effect-site equilibration half-life ($t_{½}k_{e0}$) with a value 0.5 3± 0.2 min. Propofol caused a 20-50% reduction of C_{50} and G but had no effect on $t_{½}k_{e0}$. Apnea occurred during propofol infusion only. A simulation study revealed an increase in apnea duration at infusion rates of 2.5 to 0.5 ng.ml^{-1}.min^{-1} followed by a reduction in duration. At speeds ≤ 0.31 ng.ml^{-1}.min^{-1} no apnea was present. This is related to the slow accumulation of CO_2. This study shows that the mathematical description of the respiratory depressant effects of remifentanil together with the respiratory stimulating effects of carbon dioxide is possible. Furthermore it allows for the prediction of the opioid's respiratory behavior and as such may be used in the development of infusion regimens aimed at the sustainment of spontaneous breathing activity even at high remifentanil infusion dosages. With the presented model we were able to remove some of the limitations of models derived from earlier studies. Further studies are required to incorporate a fourth and fifth factor, next to drug concentration, PCO_2 and ventilation, in the model, namely pain and upper airway obstruction. These factors have excitatory (pain) and disturbing (upper airway obstruction) influences on the control of breathing. Both factors are present in our (often obese) patient population treated with potent opioids for a variety of reasons (such as postoperative pain relief, chronic pain relief, sedation for diagnostic procedures, dyspnea, palliation), although their presence is often episodic rather than continuous, a fact that makes incorporation in a predictive model difficult but hopefully not impossible.
Integrating opioid risk and benefit is important as it allows for the comparison of net efficacy among opioids. In **Chapter 4** an explorative study on the effects of fentanyl on analgesia and respiratory depression was performed to construct fentanyl risk-benefit or utility functions, a new concept in opioid pharmacology. Twelve volunteers received a 3.5 μg.kg^{-1} fentanyl intravenous injection on two separate study days. On one occasion ventilation at a clamped elevated carbon dioxide was measured, on another the pain tolerance to electrical stimulation. In both sessions arterial plasma samples were obtained. The data were analyzed with a population pharmacokinetic-pharmacodynamic (PKPD) model. Two-times 9,999 simulations were performed, using the PK-PD parameter estimates and their variabilities, in which simulated subjects received 3.5 μg.kg^{-1} fentanyl. The resultant distributions were used to calculate the utility functions, defined as the

probability of at least 50% analgesia (an increase in pain tolerance by at least 50%) minus the probability of at least 50% respiratory depression. Utility functions were constructed in concentration (UFc) and time domains (UFt). The PKPD analysis showed that fentanyl had an approximate two-fold faster onset/offset and two-fold greater potency with respect to respiratory depression compared to analgesia. The constructed utility functions were successful with negative UFc values at effect-site concentrations > 0.5 $ng.mL^{-1}$ and negative UFt values in the first 90 min following the 3.5 $\mu g.kg^{-1}$ bolus infusion. From these results it may be concluded that successful construction of clinically relevant utility functions is possible. UF of other opiods may be constructed from previous studies performed in our laboratory. One such opioid, morphine, displays UFc and UFt values more positive than fentanyl. While this suggest that morphine has a lower probability than fentanyl in producing respiratory depression for a given amount of analgesia it is important to be vigilant as severe respiratory depression in an individual patient remains possible, even at low dose morphine. Further studies should address the issue of applicability of the UF under clinical circumstances and assess the influence of pain of the function. For now it can be concluded that the UF is useful in drug selection in drug development programs and dose selection for experimental Phase III studies.

In **Chapter 5** a phase 1 study is presented, in which the effect of an experimental opioid from Mundipharma Research Ltd (Cambridge, UK), MR30365/07, with high affinity for the three classical opioid receptors (MOR, delta-opioid receptor, (DOR), kappa-opioid receptor, (KOR)) and low affinity for the recently discovered opioid-receptor-like (ORL1) receptor, on respiration and analgesia was compared to fentanyl, a selective, high affinity MOR agonist that, at high doses, produces dose dependent respiratory depression and apnea. In this double-blind, randomized controlled study 46 healthy male volunteers participated in respiratory studies, 46 others in analgesia studies. In each group, six subjects received placebo, twenty received MR30365/07 (four received 0.0125, six 0.075, six 0.125 and four 0.15 $\mu g.kg^{-1}$) and twenty received fentanyl (four received 0.5, six 1.0, six 2.0 and four 3.0 $\mu g.kg^{-1}$). Active and placebo treatment was given intravenously over 10 min. Breathing was measured on a breath-to-breath basis at a fixed elevated end-tidal PCO2. Analgesic responses to pain detection (pain threshold) were measured using transcutaneous electrical stimulation.

Fentanyl displayed typical dose-dependent effects in respiratory depression and analgesia. MR30365/07 showed dose-dependent respiratory depression with ceiling starting at a dose of 0.075 $\mu g.kg^{-1}$, with a minimum ventilation of 32.8% of baseline. No ceiling was observed in the analgesic effects of MR30365/07 over the dose range tested. MR30365/07 was about 18 times more potent than fentanyl in producing analgesia.

These data are promising in that this is an opioid with limited respiratory effect (at least as observed over the dose range tested) retaining full analgesia efficacy. In contrast to buprenorphine which shows similar behavior, this drug is a full agonist for the MOR. Possibly the favorable behavior of MR30365/07 is due to its agonist effect at the KOR

although other mechanisms are not excluded (including a differential effect at recruitment of second messengers and intracellular peptides). Further studies are required to assess the behavior of this opioid at higher doses, in clinical settings and in the combination with other drugs (such as sedatives) to assess whether the ceiling in respiratory depression is sustained.

Chronopharmacology studies the effect of the timing of drug administration on drug effect and may have important effects in clinical practice and is possibly an important cause of opioid variability. In **Chapter 6**, the influence of four timing moments on fentanyl-induced analgesia was evaluated. Eight healthy volunteers received 2.1 $\mu g.kg^{-1}$ intravenous fentanyl at 2 PM and 2 AM, with at least 2 weeks between occasions, eight others at 8 AM and 8 PM. Heat pain measurements using a thermode placed on the skin were taken at regular intervals for 3 h and Verbal Analogue Scores (VAS) were then obtained. The data were modeled with a sinusoid function using the statistical package NONMEM. A significant circadian sinusoidal rhythm in the antinociceptive effect of fentanyl was observed. Variations were observed for peak analgesic effect, duration of effect and the occurrence of hyperalgesia. A peak in pain relief occurred late in the afternoon (5:30 PM) and a trough in the early morning hours (5:30 AM). The difference between the peak and trough in pain relief corresponds to a difference in VAS of 1.3 to 2 cm. Only when given at 2 AM did fentanyl cause a small but significant period of hyperalgesia following analgesia. No significant changes were observed for baseline pain, sedation or the increase in end-tidal CO_2. The observed possible influence of the circadian rhythm may be a direct effect through shared pathways of the circadian and opioid systems or an indirect effect via diurnal variations in hormones or endogenous opioid peptides that rhythmically change the pain response and/or the analgesic response to fentanyl.

These data show significant but small effects of the circadian clock on fentanyl-induced analgesia. It remains questionable whether such effects may be unearthed from the noise (related to a multitude of other factors, including sex, age, underlying disease, comedication, anxiety, and genetics) in a clinical setting.

7.2 CONCLUSIONS

The following conclusions may be drawn from the data presented in this thesis:

1. The results from this thesis indicate that currently-used opioids may produce life-threating respiratory depression. Despite our efforts to understand OIRD, individual prediction of development of OIRD is limited and therefore titration to effect is the best option when treating patients with potent opioid analgesics. This is true for all patients receiving opioids, irrespective of the indication.
2. The ideal drug for antagonism of respiratory depression has not yet been found. At present naloxone seems the most appropriate drug although reversal of OIRD coincides with loss of analgesia. New reversal agents acting via non-opioidergic pathways are under investigation and are aimed at reversal of OIRD without compromising analgesia.

3. Mathematical modeling of the non-steady state effects of respiratory depression by opioids is not only possible, but also yields comprehensible results. Still despite adequate prediction of a drug's respiratory behavior on a population level, the model does not allow individual prediction.
4. Utility functions may serve as a composite function to describe the effect-side effect profile of a drug. For example, the utility function of fentanyl is predominantly negative except at low dose, indicating that for the dose tested the probability of respiratory depression exceeds the probability for analgesia. While this function seems applicable in experimental and phase I/II/III settings, its clinical use requires further validation.
5. The Anesthesia & Pain research Unit is especially appropriate for studying the effect of experimental drugs on respiration and analgesia. An example of such a drug is MR30365/07, an opioid acting at all three classical opioid receptors. In contrast to fentanyl this agents produces ceiling in respiratory depression but not analgesia over the dose range tested.
6. Fentanyl-induced pain relief is influenced by the circadian clock with increased efficacy during the later hours of the afternoon. Whether such effects are sustained in a clinical setting remains unknown.

REFERENCES

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