Naloxone : actions of an antagonist

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Chapter 7

Summary and conclusions

Opioids still form the gold standard in severe pain therapy, despite their many side-effects. One of the most important side-effects of opioid therapy is respiratory depression, a condition which is easily treatable using opioid antagonists. One such antagonist is naloxone, a short acting opioid antagonist which has high affinity for the the μ-opioid receptor, but with lower affinity for the κ- and δ- opioid receptors. In Chapters 2, 3 and 4, we investigated the use of naloxone in respiratory depression that was caused by morphine, morphine-6-glucuronide (M6G) and buprenorphine.

In Chapter 2, we investigated the possible existence of a separate opioid receptor for M6G by using a derivative of naloxone, 3-methoxy-naltrexone (3mNTX). We compared morphine and M6G's respiratory effects in the anesthetized cat, using the dynamic end-tidal forcing (DEF) technique. Using the DEF technique, we can distinguish between carbon dioxide (CO_2) sensitivity of the peripheral and the central chemoreflex loops (G_p and G_c, respectively) which are parameters in a two compartmental model for the relationship between CO_2 and ventilation. We conducted three separate studies. In study 1, we assessed the effect of morphine, 3mNTX and M6G successively, on the ventilatory response to CO_2. In study 2 we assessed the effect of M6G, 3mNTX and morphine successively. Study 3 assessed the effect of 3mNTX alone on the ventilatory response to CO_2. With these studies, we showed that both M6G and morphine shifted the ventilatory CO_2 responses to higher end-tidal CO_2 levels. Morphine had a preferential depressant effect within the central chemoreflex loop. In contrast, M6G had a preferential depressant effect within the peripheral chemoreflex loop. Irrespective of the opioid, 3mNTX caused full reversal of, and prevented respiratory depression. The conclusions that could be drawn from these are twofold. We found that in anesthetized cats, the μ-opioids morphine and M6G induce respiratory depression at different sites within the ventilatory control system. Another conclusion drawn from this study is that it is unlikely that a 3mNTX sensitive receptor is the cause of the differential respiratory behaviour of morphine and M6G, as 3mNTX caused full reversal of the respiratory depressant effects of both opioids.

For Chapter 3, we obtained data from an extensive group of healthy volunteers (n=67) on buprenorphine's respiratory effects and the reversal of those effects using naloxone. The rationale behind these studies was the worldwide belief that buprenorphine's respiratory effects are supposedly hard to reverse. We combined data from three separate studies in this Chapter. In all studies, respiration was measured against a constant, increased end-tidal CO_2-level. In the first study, we investigated the effect of an intravenous bolus dose of 0.8 mg naloxone on 0.2 mg buprenorphine-induced respiratory depression versus the effects of placebo. As this turned out to be insufficient to cause reversal of the respiratory effects, we decided to test a dose range of naloxone (0.5 – 7 mg), given in a 30 minute infusion. Using the information from this study, the third step was to test the effect of a combination of a bolus dose of naloxone and a longer continuous naloxone infusion (lasting two hours) on 0.2 and 0.4 mg buprenorphine induced respiratory depression.

A bolus dose of naloxone turned out to be ineffective for the reversal of respiratory depression from buprenorphine, as was observed in study 1. From study 2, we found out that in the dose range between 2 – 4 mg, naloxone was able to cause full reversal of respiratory depression. A higher dose (above 5 mg) caused a decline in reversal activity. In the third study, we saw that it is possible to reverse both 0.2 and 0.4 mg buprenorphine's respiratory effects by using a combination of a bolus dose (2 – 3 mg) and a subsequent continuous infusion of naloxone of 4 mg/h. The main conclusions from this study were that reversal of buprenorphine's respiratory effect is possible, but that it depends on doses of both naloxone and buprenorphine. There seems to be an inverse U-shaped curve for naloxone reversal of buprenorphine's effects (see figure 3.3), meaning that a higher naloxone dose does not neccesarily cause more reversal of respiratory depression. Next to that, the respiratory effects may outlast short lasting infusions of naloxone, so it is important to use a continuous infusion of naloxone for the reversal of buprenorphine induced respiratory depression.

In Chapter 4, we modelled the effects of naloxone on M6G- and morphine-induced respiratory depression. We conducted a study in 56 healthy volunteers. First we compared the effects of 400 μg naloxone and placebo on the respiratory effects of morphine and M6G. Next, we investigated the effects of different naloxone doses (200 μg in the morphine group, 25 and 100 μg in the M6G group) in both opioids. All studies were performed under constant end-tidal CO_2 pressures. We found that morphine's effects were quickly reversed and that this reversal was shortlasted, whilst in the M6G group, the time to maximum effect was longer (45 minutes versus 13 minutes in the morphine group), and the reversal lasted longer (up to 90 minutes). We fitted the data to a PK/PD model, from which we were able to conclude two things. The first was that a Hill factor (γ) needed to be introduced to our model for an appropriate fit and the second was that there were differences in naloxone C_{50} in the morphine and M6G studies. This means that naloxone has a different potency in M6G and morphine (less naloxone is needed to reverse M6G induced respiratory depression than in morphine induced respiratory depression). The conclusion from these studies is that morphine's and M6G's effects are differently reversed by naloxone. We can still only speculate as to how these differences are caused, but most likely is that naloxone does not only act at the μ-opioid receptor itself, but also at a different site of action in the signalling cascade.

Reversal of respiratory depression is not the only application of naloxone, however. Chapters 5 and 6 elaborate on different uses of naloxone, i.e., in hyperalgesia (Chapter 5) and in opioid addiction (Chapter 6).

Opioid induced hyperalgesia has recently gained the interest of researchers. It is probably caused by activation of the NMDA-receptor, which in turn could be caused by μ-opioid receptor-activation. In Chapter 5 we tested this hypothesis specifically for M6G in mice (outbred CD-1 and opioid receptor triple knockout mice) and men (healthy vol-

unteers). In mice, we studied the effect of chronic and acute infusions of M6G against a background of naltrexone or normal saline. In human volunteers, we tested the effect of a bolus dose of M6G to a heat pain stimulus, in the presence of a continuous high dose naloxone infusion or saline infusion. The results from the mice studies show that acute and chronic injections of M6G cause hyperalgesia, both in naltrexone and saline treated mice. Injection of NMDA-receptor antagonist MK-801 blocked and reversed hyperalgesia in the chronic and the acute M6G treatment. The data from the human volunteers indicate that M6G causes hyperalgesia after an acute injection, lasting more than six hours. We can conclude that M6G induced hyperalgesia is independent of opioid receptor activation and that a causal role for the NMDA receptor is indicated in mice.

In Chapter 6, we undertook a literature search for all uses of naloxone in opioid addiction. Naloxone is a non-selective, short-acting opioid receptor antagonist that has a long clinical history of successful use and is presently considered a safe drug, even at high doses (up to 10 mg). In opioid-dependent patients, naloxone is used in the treatment of opioid-overdose induced respiratory depression, in (ultra)rapid detoxification and in combination with buprenorphine for maintenance therapy (to prevent intravenous abuse). There are several risks related to naloxone use in opioid-dependent patients. The induction of an acute withdrawal syndrome is is a potentially life threatening one, due to possible occurrence of vomiting and aspiration. When used in the treatment of opioid-induced respiratory depression, the effect of naloxone may wear off prematurely and cause renarcotization and subsequent coma. The final risk is that in patients treated for severe pain with an opioid, high-dose naloxone and/or rapidly infused naloxone may cause catecholamine release and consequently pulmonary edema and cardiac arrhythmias. These risks warrant the cautious use of naloxone, together with adequate monitoring of the cardiorespiratory status of the patient during naloxone administration.

Conclusions

The data collected in this thesis show

- There is probably no separate M6G receptor in the respiratory system of the cat.
- M6G has its respiratory effects mainly on the central chemoreceptor and not on the peripheral chemoreceptor in the respiratory system of the cat.
- Buprenorphine induced respiratory depression can be reversed using a continuous, high dose infusion of naloxone.
- The reversal of buprenorphine's respiratory effects by naloxone has an inverse U-shaped dose-response curve.
- M6G and morphine's respiratory effects are differently reversed by naloxone, in both time of maximum reversal and duration of reversal.
- M6G induced hyperalgesia is independent of opioid receptor activation.
- In opioid dependence, naloxone has its use mostly in reversing opioid overdose.