Countermeasures of opioid-induced respiratory depression

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CHAPTER 8

Summary, conclusions and future perspectives

In general, opioids are safe drugs when administered or prescribed by specialists such as general practitioners, anesthesiologists or pain physicians and, equally important, the patient strictly adheres to the advice given by his or her physician on how to use these drugs in a safe manner. It is the prescription spree by a variety of physicians with limited knowledge on the proper use and/or dangers of opioids and the abuse of prescription or synthetic illicit opioids that are major concerns because of the likelihood of overdose that may cause often-fatal respiratory depression, and requires a countermeasure.[1,2] The red line through my thesis is therefore our ability or inability to reverse opioid-induced respiratory depression with such countermeasures. I discuss the opioid-receptor antagonist naloxone, among other respiratory stimulants, (**Chapter 1**), the partial opioid-receptor agonist buprenorphine (**Chapter 6**), and two agnostic respiratory stimulants (tianeptine, **Chapter 5,** and thyrotropin releasing hormone, TRH, **Chapters 3 and 4**) that do not interact with the endogenous opioid system and consequently leave the opioid effect on the brainstem respiratory network intact but stimulate breathing through specific stimulatory neuronal pathways. Apart from the respiratory stimulants that I discuss here, various respiratory stimulants and other countermeasures are being developed and/or studied. These include (See Table 1 for efficacy and limitations):[2] non- opioid scheduled substances such as cannabinoid type 2 receptors and ketamine, hormones such as oxytocin, nicotinic acetylcholine receptor agonists, ampakines, serotonin receptor agonists (note that some 5HT agonists produce respiratory depression)[3], antioxidants, drugs that mimic hypoxia at the carotid bodies, sequestration or scrubber techniques including container molecules and vaccination against opioids, and finally opioids with high receptor affinity but minimal respiratory action such as nalbuphine and butorphanol, next to buprenorphine.

As discussed in **Chapter 1**, the need for effective medication that can counteract OIRD is an unmet need given the potential lethality of opioids. Since the opioid crisis does not seem to vanish and in fact still increases in severity, non-opioid respiratory stimulants given as rescue medication or combined with opioids as a preventive measure (*e.g.* oxycodon tablets coated with a viable respiratory stimulant) appear to be attractive alternatives to naloxone, a drug that has serious limitations and therefore limited utility when potent synthetic opioids, such as fentanyl or carfentanil, are overdosed outside the healthcare setting, for hedonistic pleasures. Below, I give a summary of the results of each study.

In **Chapter 2,** we reviewed human studies on reversal of OIRD using models that describe and predict the time course of pharmacokinetics (PK) and pharmacodynamics (PD) of opioids and reversal agents and link PK to PD. The PK/PD models differ in their basic structure to capture the specific pharmacological mechanisms by which the reversal agents interact with the opioid's effect on breathing. The effect of naloxone, which competes with the opioid at the receptor, is described by combined effect-compartment receptor-binding model to quantify rate limitation at the level of drug distribution and receptor kinetics. The effects of reversal or stimulatory agents that act

Table 1. List of published respiratory stimulants and countermeasures of opioid-induced respiratory depression[3]

Class and drugs	Efficacy	Limitations in human use
Non-opioid scheduled substances		
- Dextro-amphetamine	+ (human data)*	Dependency issues, sympathico-excitation
- Cannabinoid 2 receptor agonists	+ (animal data)	Scheduled substance
- Cocaine	– (animal data)	
- Esketamine	+ (human data)*	Psychomimetic adverse effects, sympathico-excitation, continuous intravenous infusion
Hormones		
- Thyrotropin releasing hormone	+ (animal data)	
	– (human data)	Sympathico-excitation, arousal
- TRH analog taltirelin	+ (human data)	Muscle rigidity
- Oxytocin	+ (animal data)	Bell-shaped dose-response curve
Nicotinic acetylcholine receptor agonists		
- α4β2 nicotinic acetylcholine receptor agonists	+ (animal data)	
Ampakines		
- CX747	+ (animal data)	
	+ (human data)	Not registered, sedation
5HT-agonsists		
- Various 5HT agonists	+ (animal data)	
- Various 5HT agonists	– (human data)	Insufficient drug reaches the brainstem
Antioxidants		
- L-cysteine	+ (animal data)	
Drugs that mimic hypoxia at the carotid bodies		
- Doxapram	+ (animal data)	
	+/– (human data)	Neuroleptic side effects and sympathico-excitation, low potency
- ENA001, formerly GAL021	+ (animal data)	
	+ (human data)	Not registered, ceiling in efficacy, continuous intravenous infusion
Sequestration techniques		
- Scrubber molecules	+ (animal data)	May restrict medical use of specific opioids
- Immunotherapy	+ (animal data)	
High-affinity opioids		
- Buprenorphine	+ (human data)	Produces respiratory depression, dependency issues, scheduled medication, may reduce medical use of opioids, continuous administration (depot)

through non-opioidergic pathways, such as ketamine and the experimental drug ENA001/GAL021, are described by physiological models, in which stimulants act at CO_2 chemosensitivity and/or non-CO_2-dependent ventilation. The PK/PD analyses show that while all reversal strategies may be effective under some circumstances there are conditions at which reversal is less efficacious

and sometimes even impossible. Model-based drug development is needed to design an “ideal” reversal or stimulatory agent, *i.e.* one that is not influenced by opioid receptor kinetics, does not interfere with opioid analgesia, has a rapid onset of action with long-lasting effects and is devoid of adverse effects

In **Chapters 3 and 4**, potential strategies for reversal of OIRD with the hypothalamic hormone and neuromodulator thyrotropin-releasing hormone (TRH) were studied. We discuss the results of animal studies performed by our colleague and collaborator Joseph Cotten in Massachusetts General Hospital in Boston, and human studies performed in our research unit. In addition, we performed a search in electronic databases and collected 52 papers on the effect of TRH and TRH-analogs on respiration and their efficacy in the reversal of OIRD in awake and anesthetized mammals, including humans. Animal studies indicate that TRH and its analog taltirelin stimulate breathing via an effect at the preBötzinger-complex, a key respiratory rhythm generator within the brainstem respiratory network. An additional respiratory excitatory effect may be related to TRH’s analeptic effect. In awake and anesthetized rodents, TRH and taltirelin improved morphine- and sufentanil- induced respiratory depression, by causing rapid shallow breathing, although taltirelin did worsen opioid-induced muscle rigidity. This pattern of breathing increases the work of breathing, dead space ventilation, atelectasis, worsens V/Q mismatch and produces hypoxia. In awake humans, a continuous infusion of intravenous TRH with doses up to 8 mg, did not reverse remifentanil-induced respiratory depression. This is related to inadequate penetration of TRH into the brain compartment but also other explanations are considered. No human data on taltirelin are available. In conclusion, animal and human data demonstrate that TRH is not a viable reversal agent of OIRD. Further human studies on the efficacy and safety of TRH’s more potent and longer lasting analog taltirelin are needed since this agent appears to be a more promising reversal drug, although muscle rigidity may restrict its use in humans.

Chapter 5 (fig. 2**)** examines the efficacy of tianeptine, an antidepressant and AMPA receptor modulator, to counteract opioid-induced respiratory depression. The hypothesis was that oral or intravenous tianeptine can effectively counteract OIRD in humans. Healthy male and female volunteers participated in two studies that had a randomized, double blind, placebo-controlled, crossover design. First (Study 1), oral tianeptine (37.5 mg, 50 mg and 100-mg doses with 8 subjects per group) pretreatment followed by induction of alfentanil-induced respiratory depression (alfentanil target concentration, 100 ng/mL) was tested. Primary endpoint was ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg (VE55). Next, after determining the pharmacokinetics of intravenous tianeptine in 6 subjects (Study 2a), the ability of four subsequent and successive infusions of intravenous tianeptine (target tianeptine plasma concentrations 400, 1,000, 1,500, and 2,000 ng/mL, each administered over 15 min) to counteract remifentanil-induced respiratory depression was determined in 15 volunteers (Study 2b). Ventilation was measured at

isohypercpania (baseline ventilation 20 ± 2 L/min). The main endpoint was minute ventilation during the 60-min of tianeptine *versus* placebo infusion. Alfentanil reduced VE55 to 13.7 (95% CI 8.6-18.8) L/min after placebo pretreatment and to 17.9 (10.2-25.7) L/min after 50-mg tianeptine pretreatment (mean difference between treatments +4.2 (-11.5-3.0) L/min, p = 0.070). Intravenous tianeptine in the measured concentration range of 500 to 2,000 ng/ml did not stimulate ventilation but instead worsened remifentanil-induced respiratory depression: tianeptine, 9.6 ± 0.8 L/min *versus* placebo 15.0 ± 0.9 l/min; mean difference -5.3 l/min; 95% CI -2.5 to -8.2 L/min; p = 0.001, after 1 h of treatment. We conclude that neither oral nor intravenous tianeptine were respiratory stimulants. Intravenous tianeptine over the concentration range of 500 to 2,000 ng/mL exacerbated respiratory depression elicited by remifentanil

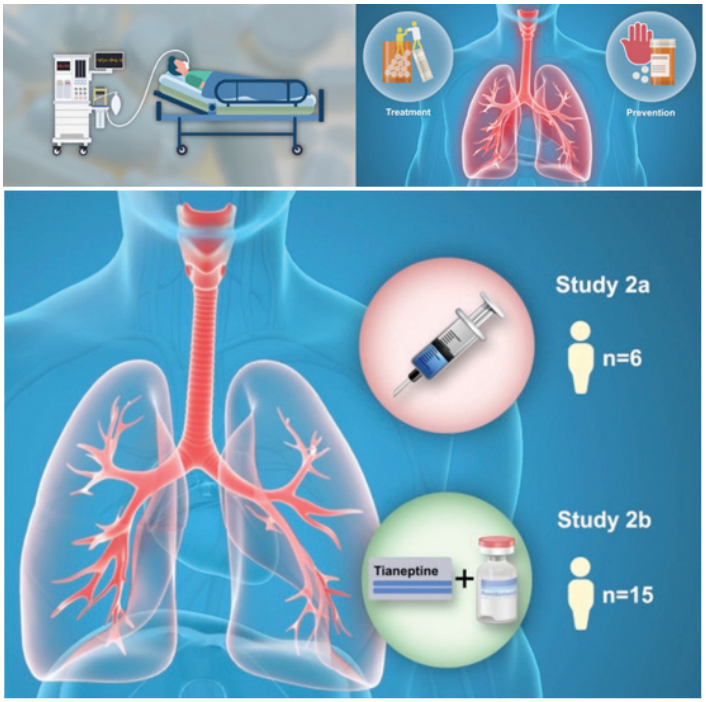

Fig 2. Three "stills" from the video that accompanied the study presented in **Chapter 5**, depicted on the website of the journal of the American Society of Anesthesiologists, *Anesthesiology*, (https://pubs.asahq.org/anesthesiology).

In **Chapter 6** the efficacy of the high-affinity mu- opioid receptor partial agonist buprenorphine to minimize respiratory depression from high-dose fentanyl was evaluated in opioid-naïve volunteers and patients with an opioid use disorder (OUD) who chronically use high-dose opioids. The effects of escalating i.v. fentanyl doses with range 0.075-0.35 mg/70 kg (opioid naïve) and 0.25-0.70 mg/70 kg (chronic opioid use) on iso-hypercapnic ventilation at 2 to 3 background doses of buprenorphine (target plasma concentrations range: 0.2-5 ng/mL) were quantified

using receptor association/dissociation models combined with biophase distribution models. In both populations, buprenorphine produced mild respiratory depression, but high doses of fentanyl caused pronounced respiratory depression and apnea. When combined with fentanyl, buprenorphine produced a receptor binding– dependent reduction of fentanyl-induced respiratory depression in both populations. In OUD patients, at buprenorphine plasma concentrations of 2 ng/mL or higher, had a protective effect against high-dose fentanyl. Overall, the results indicate that when buprenorphine mu-opioid receptor occupancy is sufficiently high, fentanyl is unable to activate the mu-opioid receptor and consequently will not cause further respiratory depression beyond the mild respiratory effects of buprenorphine.

Chapter 7 is the only study that did not test or discuss a respiratory stimulant, but instead uses PK/PD modeling to establish the effect of opioid dependency on the respiratory sensitivity of fentanyl. A decrease in opioid sensitivity is a sign of opioid tolerance or dose escalation to maintain the desired opioid effect. It is a planned secondary analysis of the study presented in Chapter 6. Fourteen opioid-naïve individuals and eight patients with OUD received escalating doses of intravenous fentanyl (opioid-naïve: 75–350 µg/70 kg; OUD: 250–700 µg/70 kg). Isohypercapnic ventilation was measured and the fentanyl plasma concentration-ventilation data were analyzed using nonlinear mixed-effects modeling. Opiod naïve subjects experienced apnea after a cumulative fentanyl dose (per 70 kg) of 225 ($n = 3$) and 475 µg ($n = 6$), Similarly, 7 OUD patients experienced apnea after a cumulative fentanyl dose of 600 ($n = 2$), 1,100 ($n = 2$), and 1,800 µg ($n = 3$). The time course of fentanyl's respiratory depressant effect was characterized using a biophase equilibration model in combination with an inhibitory maximum effect (Emax) model. Differences in tolerance between populations were successfully modeled. The effect-site concentration causing 50% ventilatory depression, was 0.42 ± 0.07 ng/mL in opioid- naïve subjects and 1.82 ± 0.39 ng/mL in OUD patients, indicative of a 4.3-fold sensitivity difference. Despite higher tolerance to fentanyl-induced respiratory depression, apnea still occurred in the opioid-tolerant population indicative of the potential danger of high-dose opioids in causing life-threatening respiratory depression in all individuals, opioid-naïve and opioid-tolerant.

To summarize:

(1) PK/PD studies on the reversal of OIRD demonstrate that naloxone reversal of OIRD is restricted by its short duration of action and its inability to reverse high- affinity opioids such as buprenorphine, carfentanil but also other more commonly used opioids such as sufentanil and high-dose morphine. Continuous infusions are then needed and is only possibly in an in-hospital setting with adequate monitoring of the respiratory state of the patient. Other stimulants discussed appear more promising such as esketamine that acts at the NMDA and AMPA receptors (AMPA activation *via* its metabolite hydroxynorketamine) and ENA001/GAL021,

a new drug that mimics cellular hypoxia at the carotid bodies. Still, both drugs have to be given *via* a continuous infusion. The PK/PD model that best described the effect of ENA001 is a multiplicative model with Ventilatory output = $V_{ENA001} \times V_{OPIOID}$. When the opioid produces severe respiratory depression (V_{OPIOID} is close to zero = apnea), the ventilatory output will also be low irrespective of effect of ENA001 at the carotid body. This then suggests that ceiling exists in ENA001's ability to produce effective reversal of OIRD. Whether such a limitation is offset by adding low-dose naloxone is uncertain and is the topic of future research by our research team.

(2) The hypothalamic hormone TRH has stimulatory effects on the ventilatory control system in awake and anesthetized animals. In contrast, in humans relatively low-dose TRH is devoid of stimulatory effects during exposure to remifentanil, possibly due to insufficient drug passage from blood to brain. Further studies are needed on TRH's analog taltirelin as this drug may be more potent and longer acting. Still, the animal data showing enhanced opioid-induced muscle rigidity may be a major constraint that needs to be explored to extent.

(3) The antidepressant and cognitive enhancer tianeptine showed promising results in an animal model of OIRD. However, in humans oral and intravenous tianeptine is devoid of any stimulatory effect on ventilation. In fact, intravenous tianeptine worsens OIRD. The outcome of this project is rather disappointing. We started more than a decade ago and initially studied oral tianeptine in a project sponsored by a Canadian company. When results were did not meet expectations, the company ended the collaboration but a new sponsor was found (Amo Pharma, in the UK). Together, we chose to develop intravenous tianeptine and evaluated the new formulation in a PK and later a PKPD study. The absence of the expected outcome is possibly related to a general observation that antidepressants have a negative effect on the ventilatory control system by acting at the serotonin system within the brainstem respiratory networks. For example, the selective serotonin-receptor reuptake inhibitor paroxetine enhances OIRD.[4] These are signs that antidepressants may behave as a class and worsen OIRD.

(4) Buprenorphine is an opioid that is capable of reducing fentanyl-induced respiratory depression, even in those individuals who abuse high doses of synthetic opioids. Because of its high affinity for the opioid receptor it is an attractive treatment for prevention of serious respiratory depression from potent synthetic opioids, particularly when opioid tolerance is low (or absent) as may be the case in OUD patients after a "drug holiday" such as occurs after an incarceration or after detoxification in a rehabilitation clinic. Subcutaneous buprenorphine depot formulations are available to treat opioid dependency While effective, there is also the tendency to remove the depot by self- mutilation allowing the return of the drug high from opioid abuse. This occurs, for instance, when people leave the rehabilitation clinic and falsely claim to be without opioid craving.

(5) Chronic opioid use reduces opioid respiratory potency (tolerance). We just studied tolerance to the respiratory effects of opioids and remain uninformed whether these observations are mirrored by tolerance to analgesia. There is some evidence that tolerance to OIRD develops slower than tolerance to analgesia and possibly drug high. This is potentially hazardous as it may provoke serious OIRD and cardiorespiratory collapse.

Future perspectives

The overall picture that emerges from this thesis is that none of the available drugs currently developed or under development as countermeasure of OIRD is sufficiently scrutinized with respect to efficacy and safety (see also Table 1) to allow further steps in their development, with the possible exception of ENA001/GAL021 or some yet unpublished hormones. Still, we also remain cautious with the agnostic respiratory stimulant ENA001 as it has yet to tested under the condition of severe OIRD and no formulations are yet available apart from the continuous intravenous solution.

The unfavorable conclusions of this thesis do not inspire great optimism. So where do we go from here? What measures should we take next?

One option is to search for more effective reversal agents that are simple to administer (*e.g.* intranasally), have a lengthy offset time and pose no safety concerns. Interestingly, recent studies in our research unit show promising results from 4 mg intranasal naloxone spray. Long-acting reversal of fentanyl- and sufentanil-induced respiratory depression were observed in opioid- naïve healthy volunteers. Currently, a rather expensive nasal spray is available for use outside of the hospital setting.

A novel possibility is to use neuropeptides that provoke wakefulness or arousal, or antagonists of peptides that induce sleep. It would be of particular interest to determine whether such molecules counteract OIRD. Another strategy is to accept the fact that no ideal reversal agent exist and that the solution is to combine drugs with different mechanisms of action to synergistically or additively enhance reversal efficacy. For instance, combining naloxone with ENA001 might be effective, even in case of severe OIRD. Further studies are needed to determine whether this assumption is correct. Finally, it might be appropriate to design analgesics, including opioid analgesics, that have a minimal impact on the ventilatory control system. For example, I tested tapentadol and oxycodone in a large cohort of volunteers (unpublished data). Tapentadol is a bi-functional opioid and acts at the mu-opioid receptor and simultaneously inhibits the reuptake of noradrenaline. Noradrenaline is an analgesic that acts at the alpha-2-adrenergic receptor in the spinal cord and brain. The two mechanisms of action synergistically promote analgesia. The two opioids had comparable effects on isohypercapnic ventilation when tested at equianalgesia but with a lower incidence of oxygen

desaturation ($SpO_2 \leq 92\%$) , apnea (absence of breathing for at least 20 s) or need for verbal or tactile stimulation to breathe (Fig. 1). Hence, I conclude that tapentadol is superior to oxycodone in terms of magnitude of OIRD. Other multifunctional opioids are being developed that either interact with multiple opioid receptor types such as the delta- and kappa-opioid receptors next to the mu-opioid receptor in order to counteract respiratory depression and reward (DPI-125)[5] or opioids in which the nociception opioid receptor is activated, again to offset respiratory depression (cebranopadol)[6]. These are certainly not the last developments and other drugs, opioids or alpha-2-adrenergic agents will certainly appear. Whether such drugs withstand the studies in our research unit remains to be seen.

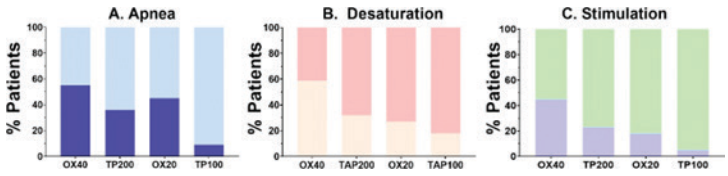

Figure 1. Effect of low and high doses of oral oxycodone (40 mg, OX40, and 20 mg, OX20) and tapentadol (100 mg, TP100, and 200 mg, TP200) on occurrences of apnea (cessation of breathing for at least 20 s), desaturation (oxygen saturation < 93%) and stimulation to resume breathing, in a population of healthy male and female volunteers. Unpublished observations.

References

1. Yeung D, Bough KJ, Harper JR, Platoff GE. National Institutes of Health (NIH) executive meeting summary: developing medical countermeasures to rescue opioid-induced respiratory sepression (a trans-agency scientific meeting)-August 6/7, 2019.
2. Bedene A, Dahan A, Rosendaal F, van Dorp E. Opioid epidemic: lessons learned and updated recommendations for misuse involving prescription versus non-prescription opioids. Exp Rev Clin Pharmacol 2022 [online ahead print].
3. van der Schrier R, Dahan JDC, Boon M, Sarton E, van Velzen M, Niesters M, Dahan A. Advances in reversal strategies of opioid-induced respiratory depression. Anesthesiology 2022; 136: 618-32.
4. Florian J, van der Schrier R, Gershuny V, Davis MC, Wang C, Han X, Burkhart K, Prentice K, Shah A, Racz R, Patel V, Matta M, Ismaiel O, Weaver J, Boughner R, Ford K, Rouse R, Stone M, Sanabria C, Dahan A, Strauss DG. Effect of paroxetine or quetiapine combined with oxycodone vs oxycodone alone on ventilation during hypercapnia: a randomized clinical trial. JAMA 2022
5. Yi S, Kong Q, Li Y, Pan C, Cui B, Wang Y, Wang G, Zhou P, Wang L, Gong Z, Su R, Shen Y, Yu G, Chang K. The opioid receptor triple agonist DPI-125 produces analgesia with less respiratory depression and reduced abuse liability. Acta Phramacol Sin 2017; 38: 977-989.
6. Dahan A, Boom M, Sarton E, Hay J, Groeneveld GJ, Neukirchen M, Bothmer J, Aarts L, Olofsen E. Respiratory effects of the nociceptin/orphanin FQ peptide and opioid receptor agonist, cebranopadol, in healthy human volunteers. Anesthesiology 2017;126: 697-707.