Ketamine pharmacology revisited

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Chapter 7

Summary, future perspectives and conclusions

Ketamine is registered and used since 1965 as anesthetic drug. It produces a dissociate anesthetic state due to the dissociation of connectivity between the thalamus and the limbic system and is used in both human and veterinarian clinical practice. The success of ketamine anesthesia is related to its ability to maintain cardiorespiratory stability during induction and maintenance of anesthesia and rapid recovery.[1] Only in the 1990s low-dose or subanesthetic ketamine was used in the treatment of complex and therapy-resistant chronic pain.[2,3] And again another 10 years passed before ketamine was first introduced as antidepressant agent for treatment of therapy-resistant depression.[4-6] Additionally, ketamine is used to induce sedation for small diagnostic and therapeutic procedures (especially in children) and there is some evidence that ketamine is beneficial in the treatment of post-traumatic stress disorder.[1] In the US especially, but also in the Netherlands, clinics are emerging that use ketamine for a myriad of indications, often without any scientific proof. For example, in the US soldiers returning from active duty in Afghanistan or Iraq with stress-related disorders are being treated in such clinics; in the Netherlands, ketamine clinics offer their services for treatment of chronic pain of any origin. It is important to realize that in all of these indications low-dose ketamine does not produce unconsciousness but equally important cognition and external and internal perception are often impaired.

In the thesis I present a series of studies that focus on the use and optimization of use of low-dose ketamine in clinical practice by:
(1) reviewing the proof for its use in alleviation and prevention of acute and chronic (cancer and non-cancer) pain;
(2) testing a possible novel administration route of ketamine, *i.e.* inhalation;
(3) applying ketamine in a novel indication: the use of the S-enantiomer as respiratory stimulant during opioid-induced respiratory depression;
(4) studying the effect of a nitric oxide donor on ketamine (the racemic and S-ketamine variant) typical side effects that hamper it's use in chronic pain therapy.

A review of the latest evidence for ketamine in pain relief is given in **Chapter 2**. We performed a literature search for systematic reviews and meta-analysis for the efficacy of ketamine in acute and chronic pain treatment. We searched in de PubMed, Web of Science, Embase and Cochrane Library of for systematic reviews and meta-analysis published between January 2009 and December 2016. In total 189 articles were obtained of which 29 articles seemed suitable. A distinction was made by different pain phenotypes: acute non-postoperative pain, acute postoperative pain, prevention of chronic pain following surgery, chronic non-cancer pain, pain related to cancer.

In acute pain, ketamine seems not to be more effective than placebo and was related to more neurological and psychological events. Ketamine was most effective in the treatment of postoperative pain, reducing opioid consumption and postoperative nausea and vomiting. In other circumstances (prevention of postoperative pain and chronic pain) ketamine does not seem to be effective solely or as adjuvant to opioids as analgesic and psychomimetic side effects are more pronounced. Until now, the effectiveness for ketamine as analgesic in randomized clinical trials is lacking. Although there are numerous open-label and case-reports describe the efficacy of ketamine as adjuvant to opioids in the treatment of different kinds of pain. In other words, *the lack of proof is not the same as lack of benefit*. It may well be that ketamine is not a suitable drug for testing in rigid clinical trials that do not allow dose variations or use of interventions to reduce (psychomimetic) side effects. For example, it may well be that: (1) patients selected for enrolment in randomized clinical trials have less disease progression than patients treated outside rigid trials; (2) ketamine effects may not be captured by efficacy measurements used in clinical trials such as the pain intensity rating scale; (3) ketamine's effect on cognition may reduce the ability of the patient to properly score pain; (4) patient-reported health-related outcomes other than pain relief may dominate the improvement of the patient's well-being such as improvement of mood and the quality of life. Overall new readouts are needed in the assessment of ketamine's efficacy in the treatment of pain. It is evident that simple rating scale of pain intensity are insufficient.

Ketamine is administered in various ways, most common routes of administration are intravenous, subcutaneous or intra-muscular. In **Chapter 3** we investigated the safety and feasibility of the inhalation of nebulized preservative-free esketamine in healthy volunteers. In this first study, the primary end-point was the safety. The efficacy measured by esketamine and norketamine plasma concentration was the secondary end-point. Three increasing doses of inhaled esketamine (0.35, 0.5 and 0.7 mg kg^{-1}) followed by an intravenous administration (0.3 mg kg^{-1} infused over 20 minutes) was given to nine healthy volunteers of either gender. Concerning the safety profile, no respiratory adverse events or cardiac dysrhythmias were observed. Only mild, dose-related hypertension, nausea and vomiting and drug high were observed. Psychedelic side effects measured by the Bowdle questionnaire were less pronounced in inhaled ketamine than with intravenous administration, probably related to lower plasma concentrations. Drug high was the most noticeable effect. None of the subjects were sedated to a level they would not be able to use the nebulizer. In our study plasma concentration varied between 128 and 227 ng/mL for the lowest and highest inhalation dose. Concentration above 100 ng/mL are considered therapeutic. The coefficient in variation was in the same range for inhalation and intravenous administration, 16% vs 25%. The bioavailability was estimated around 50%. In this exploratory study we demonstrated that the inhalation of preservative-free

esketamine is safe and feasible and seems a valid alternative as non-invasive administration route.

In continuation of the exploratory study of Chapter 3, we developed a model to analysis the pharmacokinetics of inhaled esketamine in **Chapter 4**. In contrast to the data obtained in Chapter 3, where the concentration of the inhalant was kept constant to 5 mg/mL, we kept the amount of the inhalant constant at 5 mL, but the concentration increased from 5, 10 to 20 mg/mL. Nineteen volunteers participated in the study. During and following inhalation blood samples were obtained for measurement of esketamine and esnorketamine concentrations. A pharmacokinetic model was successfully developed that consisted of three esketamine, two noresketamine and three metabolism compartments. Nebulized esketamine is inhaled with a limited or reduced bioavailability due to retention of large drug particles in the oropharynx and exhalation (and not absorption) of small particles. Additionally, the reduction in *dose-dependent* bioavailability is probably due to sedation-related loss of drug into the air. Whether the use of inhaled ketamine is feasible in settings outside of the laboratory needs further study. Despite the reduced bioavailability (that seems still sufficient for induction of specific wanted effects), I see various indications for the use of inhaled ketamine. The first one is its use in patients with moderate to severe pain in the palliative setting. Inhaled ketamine may be used at home or in a hospice when pain becomes a devastating symptom and opioids adverse effects limit their use. Ketamine may than not only alleviate pain but also improve the quality of life. A second important indication is the use of inhaled ketamine in the battle field. It seems that currently major conflicts with all of their destructive consequences are part of daily life. The ability to use a rapid acting analgesic that is easy to administer is then a major asset in the treatment of wounded soldiers as well as wounded civilians.

We are currently living in a global opioid epidemic. This has major implications that are difficult to comprehend. For example, in the United States of America alone yearly tens-of-thousands individuals perish because of an opioid overdose.[7,8] Also in the Netherlands, opioid prescriptions reach soaring numbers within 2018 1.3 million opioid users, mostly tramadol (500,000 users) and oxycodone (500,000 users).[9] One way of reducing opioid load is to add non-opioid analgesics (multimodal pain therapy). In perioperative practice ketamine may be used as adjuvant to reduce opioid dose but additionally to improve respiratory stability and possibly even stimulate breathing. In **Chapter 5** we investigated whether esketamine stimulates breathing and if it could offset OIRD in healthy volunteers. Two studies were performed. First, in a double-blind, randomized, placebo-controlled crossover trial the ability of esketamine to reduce remifentanil-induced respiratory depression was tested. Second, in an observational study, we examined if esketamine stimulates when no opioid is present. A population pharmacokinetic-pharmacodynamic

model was used to analyze the data. Placebo showed no effect on remifentanil-induced respiratory depression, ventilation changed from 12.3 (1.3) to 12.3 (2.2) L/min. Esketamine increased ventilation by 35% from 12.2 (2.3) to 16.6 (4.1) L/min ($p < 0.01$ vs placebo). Without opioid (*i.e.* without opioid-induced respiratory depression) esketamine was without effect on breathing. In conclusion, esketamine seems to stimulate breathing when breathing is depressed by an opioid. These data are important as they indicate that ketamine is a useful tool to optimize perioperative care. Since there is ample evidence that ketamine improves pain control in postoperative patients with consequently less opioid consumption, the control of breathing is optimized in two ways, that is by the stimulatory effects of ketamine on breathing and the lesser opioid load. I would recommend the use of (es)ketamine in perioperative care following major (abdominal/thoracic) surgeries that require opioids for postoperative pain relief, especially in patients with a high risk of respiratory compromise.

The use of ketamine in clinical practice is limited due to its psychedelic side effects. Animal studies suggest that a decline in intracellular nitric oxide (NO) caused by NMDAR hypofunction can be responsible for these side effect. In **Chapter 6** we evaluated the effect of sodium nitroprusside, a NO donor, on racemic ketamine and esketamine induced psychomimetic side effects. Twenty healthy male volunteers visited the laboratory on four separate occasions. On each visit they received nitroprusside (dosage 0.5 µg kg^{-1} min^{-1}) or placebo one hour before and during a 3 h-dose escalating ketamine (racemic or esketamine) infusion. The Bowdle questionnaire was used to measure the psychedelic effect on three different points: drug high, internal perception and external perception. The area under the curve was calculated for analysis. Nitroprusside significantly reduced drug high AUC, internal perception AUC during racemic ketamine infusion, but showed no effect on any of these points during esketamine infusion. Internal validation by performing bootstrap simulation confirmed these results. The effect of nitroprusside on only the R-isomer was unexpected. Future studies must give inside if this is related to different affinity of the isomers to the NMDAR, by dosage of the nitroprusside or that both ketamine-isomers act by different pathways. While these results are promising, we need to further assess what the effect of NO is on the desired effects of ketamine. If reduction of pain relief (or mood improvement) is the consequence of the use of nitric oxide donors than such adjuvant therapy is counterproductive. Additionally, dose-response studies are needed in this respect to optimize treatment with reduced adverse effects. The construction of so-called utility functions may be useful to quantify the interaction between NO donors and wanted and unwanted ketamine effects.

Conclusions

Based on the data presented in this thesis, the following conclusions can be made:

1. Currently, the proof for use of ketamine in the treatment of chronic pain from randomized controlled trials is insufficient, albeit that open label trials do give proof of benefit;
2. There is ample proof for the use of ketamine in the treatment of postoperative pain;
3. Nebulization of ketamine is a safe and effective non-invasive administration route;
4. The bioavailability of nebulized ketamine is based on a dose-dependent and dose-independent pathway;
5. In case of opioid-induced respiratory depression, esketamine stimulates and stabilizes breathing.
6. Esketamine is without effect on breathing when breathing is not depressed by an opioid;
7. The administration of nitroprusside reduce psychomimetic side effects in combination with racemic ketamine, but has no influence on esketamine.

Future perspectives

Ketamine is possibly one of the most versatile drugs currently available in clinical practice in use by anesthesiologists and more and more psychiatrists. Still ketamine is a complicated drug that has many complexities that remain poorly understood. For example, ketamine's metabolites norketamine and hydroxynorketamine are both active but their mechanisms of action, their pharmacokinetics and dynamics and their interactions are yet to be unearthed for all of the indications mentioned above. The same holds true for the ketamine isomers and the S- and R-metabolites. Hence more experimental studies in animals and humans are needed to complement the currently restricted picture that we have of ketamine's molecular and biological behavior. Next, we need a better understanding of the clinical effects of ketamine in the treatment of non-anesthesia indications such as pain, depression and opioid-induced respiratory depression. As explained above, rigid randomized trials may be unsuited for "subjective" end-point such as patient-reported outcome measures in trials on ketamine-induced pain relief. Prospective case-controlled trials may be a better option. Finally, ketamine's schizotypical adverse effects are a major complication that restrict its use especially when higher doses are required. Further research is needed to develop ketamine analogues that possess less such effects or to develop adjuvants that reduce adverse effects without compromising pain relief. One such drug could be the α_2 agonist clonidine that possibly restricts schizotypical effects and further improves pain relief.[10]

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