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Ketamine's second life : Treatment of acute and chronic pain

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SECTION V

Conclusions

CHAPTER 8

Summary and conclusion

Summary

Chronic pain is a widespread condition in the general population. In recent years both in clinical practice and in scientific research chronic pain management received increased attention. For patients suffering from several benign pain conditions there is still a lack of adequate pain management resulting in low quality of life scores. This thesis described experiments which studied the efficacy and safety of S(+)-ketamine in subanesthetic doses. For the studies both healthy volunteers and chronic pain patients were recruited. Complex Regional Pain Syndrome type 1 (CRPS-1) was chosen for the chronic pain condition. This condition is characterized by chronic pain, which currently can be hardly treated with pharmacotherapeutic interventions.

In **chapter 2** we evaluated the effects of (individual) N-methyl-D-aspartate (NMDA) antagonists on neuropathic pain and the response (sensitivity) of individual neuropathic pain disorders to NMDA receptor antagonist therapy. We performed a meta-analysis with data from randomized placebo controlled trials (RCTs) obtained from the literature up to October 26th 2009 using PubMed, EMBASE and CENTRAL. Two independent investigators evaluated the papers for quality methodologically according to the Delphi list. Fixed or random effects model were used to calculate the summary effect size using Hedges' g . Twenty-seven studies were included meeting the inclusion criteria; individual effect sizes could be calculated for 16 good quality studies, while the summarize effect size could only be calculated for 2 studies evaluating ketamine IV in Complex Regional Pain Syndrome (CRPS) and for 2 studies investigating oral memantine in postherpetic neuralgia patient. No significant effect on pain reduction could be established for both the ketamine IV in CRPS (pooled summary effect size -3.05 (95% CI $-7.98 - 1.88$), $p = 0.22$) and the oral memantine in postherpetic neuralgia treatment (pooled summary effect size 0.08 (95% CI $-0.46 - 0.61$), $p = 0.78$) Based on the results found in this systematic review, no conclusions can yet be made about the efficacy of NMDA antagonists on neuropathic pain. However, evidence in favour of the effectiveness of NMDA antagonists for the treatment of neuropathic pain, is accumulating. Additional randomized placebo controlled studies in homogenous groups of pain patients are needed to explore the therapeutic potential of NMDA antagonists in neuropathic pain.

Recent data suggest that low-dose ketamine behaves as an analgesic in the treatment of acute and chronic pain. To further understand ketamine's therapeutic profile, in **chapter 3** we performed a population pharmacokinetic-pharmacodynamic analysis of the S(+)-ketamine analgesic and nonanalgesic effects in healthy volunteers. Ten men and ten women received a 2-h S(+)-ketamine infusion. The infusion was increased at 40 ng/ml per 15 min to reach a maximum of 320 ng/ml. The following measurements were made: arterial plasma S(+)-ketamine and S(+)-norketamine concentrations, heat pain intensity, electrical pain tolerance, drug high, and cardiac output. The data were modeled by using sigmoid E_{max} models of S(+)-ketamine concentration versus effect and S(+)-ketamine + S(+)-norketamine concentrations versus effect. Sex differences

observed were restricted to pharmacokinetic model parameters, with a 20% greater elimination clearance of S(+)-ketamine and S(+)-norketamine in women resulting in higher drug plasma concentrations in men. S(+)-ketamine produced profound drug high and analgesia with six times greater potency in the heat pain than the electrical pain test. After ketamine-infusion, analgesia rapidly dissipated; in the heat pain test but not the electrical pain test, analgesia was followed by a period of hyperalgesia. Over the dose range tested, ketamine produced a 40 – 50% increase in cardiac output. A significant consistent contribution of S(+)-norketamine to overall effect was detected for none of the outcome parameters. S(+)-ketamine displays clinically relevant sex differences only in its pharmacokinetics. It is a potent analgesic at already low plasma concentrations, but it is associated with intense side effects.

Ketamine is used as analgesic for treatment of acute and chronic pain. However, its use is limited by its side effects profile. In **chapter 4** we examined the effect of S(+)-ketamine on cardiac output in CRPS-1 patients and healthy volunteers. For this study we recruited 10 CRPS-1 patients (mean age 43.2 ± 13 years, disease duration 8.4 years, range 1.1 – 21.7 years) and 10 healthy volunteers (21.3 ± 1.6 years) which were treated with seven increasing iv doses of S(+)-ketamine over 5 min at 20 min intervals starting with 1.5 mg with 1.5 mg increments. Cardiac output (CO) was calculated from the arterial pressure curve obtained from an arterial catheter in the radial artery. A pharmacokinetic-pharmacodynamic model was constructed to quantify the direct stimulatory effect of ketamine on CO and the following adaptation/inhibition. We observed that S(+)-ketamine caused dose-dependent increases in CO in patients and volunteers. Significant differences in pharmacokinetic estimates but not in pharmacodynamic model parameters were observed in CRPS-1 patients versus volunteers. S(+)-ketamine caused dose-dependent increases in CO. The concentration S(+)-ketamine causing a 1 L/min increase in CO was 243 ± 54 ng/ml with an onset/offset half-life of 1.3 ± 0.21 min. Inhibition was slow (time constant 67.2 ± 17.0 min). The data from our study showed that the CO effect of ketamine did not differ in healthy volunteers compared to CRPS-1 patients despite differences in age and evidently their medical condition. Since ketamine causes cardiovascular stimulation through activation of the sympathetic system, we conclude that this system function properly and is not affected in CRPS-1 patients.

The aim of the study described in **chapter 5** was to explore the analgesic effect of the NMDA receptor antagonist ketamine in acute experimental versus chronic spontaneous pain in Complex Regional Pain Syndrome type 1 (CRPS-1) patients. Ten patients suffering from chronic CRPS-1 and with a Visual Analogue pain Score (VAS) of > 5 were recruited. Seven intravenous 5-min low-dose S(+)-ketamine infusions with increasing doses at 20-min intervals were applied. Spontaneous pain ratings and VAS responses to experimental heat stimuli were obtained during infusion and for 3-h following infusion. Ketamine produced potent analgesia with a significant VAS reduction from 6.2 ± 0.2 to 0.4 ± 0.3 cm at the end of infusion for the spontaneous CRPS pain. Analgesia persisted beyond the infusion period (VAS = 2.8 ± 1.0 cm at 5-h), when measured plasma

ketamine concentrations were low (< 100 ng/ml). Ketamine had a dose-dependent antinociceptive effect on experimental pain that ended immediately upon the termination of infusion. The data indicate that while ketamine's effect on acute experimental pain is driven by pharmacokinetics, its effect on CRPS pain persisted beyond the infusion period when drug concentrations were below the analgesia threshold for acute pain. This indicates a disease modulatory role for ketamine in CRPS-1 pain, possibly via desensitization of NMDA receptor in the spinal cord or restoration of inhibitory sensory control in the brain.

CRPS-1 responds poorly to standard pain treatment. In **chapter 6** we evaluated if the NMDA receptor antagonist S(+)-ketamine improves pain in CRPS-1 patients. Sixty CRPS-1 patients (48 females) with severe pain participated in a double-blind randomized placebo-controlled parallel-group trial. Patients were given a 4.2-day intravenous infusion of low-dose ketamine ($n = 30$) or placebo ($n = 30$) using an individualized stepwise tailoring of dosage based on effect (pain relief) and side effects (nausea/vomiting/psychomimetic effects). The primary outcome of the study was the pain score (numerical rating score: 0 – 10) during the 12-week study period. The median (range) disease duration of the patients was 7.4 (0.1 – 31.9) years. At the end of infusion, the ketamine dose was 22.2 ± 2.0 mg/h/70 kg. Pain scores over the 12-week study period in patients receiving ketamine were significantly lower than those in patients receiving placebo ($P < 0.001$). The lowest pain score was at the end of week 1: ketamine 2.68 ± 0.51 , placebo 5.45 ± 0.48 . In week 12, significance in pain relief between groups was lost ($P = 0.07$). Treatment did not cause functional improvement. Patients receiving ketamine more often experienced mild to moderate psychomimetic side effects during drug infusion (76% *versus* 18%, $P < 0.001$). In conclusion, in a population of mostly chronic CRPS-1 patients with severe pain at baseline, a multiple day ketamine infusion resulted in significant pain relief without functional improvement. Treatment with ketamine was safe with psychomimetic side effects that were acceptable to most patients.

In order to enhance our insight in the complex interaction between analgesic drug and chronic pain relief, we performed in **chapter 7** a pharmacokinetic-pharmacodynamic (PK-PD) modeling study on the effect of S(+)-ketamine on pain scores in Complex Regional Pain Syndrome type 1 (CRPS-1) patients. Sixty CRPS-1 patients were randomly allocated to received a 100-h infusion of S(+)-ketamine or placebo. The drug infusion rate was slowly increased from 5 mg/h (per 70 kg) to 20 mg/h based upon the effect/side effect profile. Pain scores and drug blood samples were obtained during the treatment phase and pain scores were further obtained weekly for another 11 weeks. A population PK-PD model was developed to analyze the S(+)-ketamine-pain data. The plasma concentrations of S(+)-ketamine and its metabolite decreased rapidly upon the termination of S(+)-ketamine infusion. The chance for an analgesic effect from ketamine and placebo treatment was 70% and 20%, respectively. The pain data were well described by the PK-PD model with parameters $C_{50} = 10.5 \pm 4.8$ (population value SE) ng/ml (95% CI 4.37 – 21.2 ng/ml) and $t_{1/2}$ for onset/offset = 10.9 ± 4.0 days (5.3

– 20.5 days). Long-term S(+)-ketamine treatment is effective in causing pain relief in CRPS-1 patients with analgesia outlasting the treatment period by 50 days. These data suggest that ketamine initiated a cascade of events, including desensitization of excitatory receptor systems in the central nervous system, which persisted but slowly abated when ketamine molecules were no longer present.

Conclusion

The data collected in this thesis show:

1. Ketamine in subanesthetic doses result in analgesia in acute pain.
2. Ketamine in subanesthetic doses result in analgesia in spontaneous pain in complex regional pain syndrome pain type 1 patients.
3. Low dose treatment with ketamine (plasma concentration about 320ng/ml) result in a 49% increase of the cardiac output in healthy volunteers.
4. Treatment with ketamine is associated with the occurrence of psychomimetic side effects.
5. For the measured norketamine plasma concentrations (< 250 ng/ml) no significant contributions to the analgetic effect of ketamine was observed.
6. There were no sex differences observed for the efficacy of ketamine; sex differences were directly related to higher ketamine elimination ratios for women compared to men.

Future perspectives

Since ketamine mainly acts on the NMDA receptor, we conclude that this receptor is involved in the development and maintenance of complex regional pain syndrome type 1. The data presented in this thesis is not conclusive whether the NMDA receptor is involved in other chronic pain states such as fibromyalgia. Specific other chronic pain condition must be subject of future research. Although cardiovascular side effects of ketamine, *e.g.* increased cardiac output, is present at subanesthetic doses, the psychomimetic side effects might limit its clinical use. In postoperative pain setting there is some evidence that the incidence of hallucinations can be decreased with benzodiazepines as premedication. Studies with benzodiazepines as an adjuvant to ketamine treatment to reduce these hallucinogenic side effects in chronic pain conditions are needed. However some patients studies in this thesis, evaluated the side effects only being mild and were willing to be treated in several consecutive sessions. More studies have to be performed to obtain data for the beneficial effect for this approach in the clinical setting.