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Safety-efficacy balance of S-ketamine and S-norketamine in acute and chronic pain

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Chapter 7

Summary, conclusions and future perspectives

Summary

The balance between safety and efficacy is important in pharmacotherapy, and registration authorities emphasize the need for pre- and post-registration safety studies. Sometimes, the indication of a registered drug shifts to another disease or a different patient population. Apart from the need for studies on efficacy in this 'new' indication and 'new' population, also safety needs to be addressed. Unfortunately safety is often not studied as clinicians (and the pharmaceutical industry) are convinced that safety can be extrapolated from one population, one disease or one specific mode of administration to the other. An example that such thinking is not justified comes from an important observation in this thesis (Chapter 3). A trial on the safety and efficacy of repeated long-term infusions of S-ketamine in CRPS-1 patients was terminated early because of a high and unexpected incidence of liver damage in patients receiving S-ketamine at 3-week intervals.

Ketamine is a relatively 'old' drug and used for almost 50 years as an anesthetic, but recently there has been a renewed interest for the treatment of therapy-resistant chronic pain. S-ketamine at subanesthetic concentrations produces potent analgesia. Consequently, low-dose ketamine is used perioperatively to improve opioid analgesia, and in chronic pain patients where other more conventional therapies are without significant effect. In this thesis the effects of the *N*-methyl-D-aspartate receptor (NMDAR) antagonist S-ketamine in patients with chronic pain (CRPS-1 and fibromyalgia patients) and healthy volunteers are described. Low-dose ketamine has, apart from its intended effect (analgesia), a variety of side effects, including effects on the cardiovascular system (e.g., hypertension), psychotomimetic effects, cognitive dysfunction and liver damage (see above).

This thesis has three main topics: efficacy, safety and metabolism of low-dose S-ketamine. These three topics were addressed in the different studies as efficacy and safety are inherently linked, and as such naturally part of the complex pharmacokinetics and pharmacodynamics of S-ketamine.

Chapter 2 is a review of the efficacy of ketamine treatment in chronic non-cancer pain. Worldwide the number of patients affected by chronic pain is increasing and conventional treatment is often insufficient. Recently the importance of NMDAR in the mechanisms and maintenance of chronic pain was established. Ketamine is the most studied NMDAR antagonist in the treatment of various chronic pain syndromes. This review focuses on the efficacy, safety, pharmacology and toxicology of ketamine. Electronic databases were scanned for prospective, randomized controlled trials that assessed ketamine's analgesic effect in patients with chronic pain, with a particular focus on trials published after 2008

that applied long-term intravenous infusions. While most studies on intravenous ketamine show acute analgesic effects, three recent trials on long-term ketamine treatment (days to weeks) demonstrated the effectiveness of ketamine in producing long-term (months) relief of chronic pain. Despite these positive results, further studies are needed on safety/toxicity issues. Other administration modes, i.e., short-term intravenous administration, are less effective in causing long-term pain relief. Therefore, there is now evidence from a limited number of studies that pain relief lasting for months can occur after long-term intravenous ketamine infusion, suggesting a modulatory effect of ketamine in the process of chronic pain, possibly via blockade of upregulated NMDAR.

Chapter 3 As reviewed in Chapter 2, studies on the efficacy of ketamine in the treatment of chronic pain indicate that prolonged or repetitive infusions are required to ensure prolonged pain relief. Few studies address ketamine-induced toxicity. In this chapter data are presented on the occurrence of ketamine-induced liver injury during repeated administrations of S-ketamine for treatment of chronic pain in patients with complex regional pain syndrome type 1. This study was designed to explore possible time frames for ketamine re-administration. Six patients were planned to receive two continuous intravenous 100-h S-ketamine infusions (infusion rate 10-20 mg/h) separated by 16 days. Three of these patients developed hepatotoxicity. Patient A, a 65-year-old female, developed an itching rash and fever during her second exposure. Blood tests revealed elevated liver enzymes (ALT, APT, AST and γ GT, all ≥ 3 times the upper limit of normal) and moderately increased eosinophilic leucocyte counts. Patient E, a 48-year-old female, developed elevated liver enzymes of similar pattern as Patient A during her second ketamine administration and a weakly positive response to anti-nuclear antibodies. In a third patient, Patient F, a 46-year-old male, elevated liver enzymes (ALT and γ GT) were detected on the first day of his second exposure. In all patients the ketamine infusion was promptly terminated and the liver enzymes slowly returned to normal values within two months. These data suggest an increased risk for development of ketamine-induced liver injury when the infusion is prolonged and/or repeated within a short time frame. Regular measurements of liver function are therefore required during such treatments.

Chapter 4 Prolonged and/or repeated ketamine infusions can cause serious side effects. In contrary to the evidence from Chapter 2, short S-ketamine infusions seem to produce good effect on pain in fibromyalgia according to non-experimental data. To explore the efficacy of a short-term infusion with S-ketamine on fibromyalgia pain, a randomized double blind, active-placebo controlled trial was performed. Twenty-four fibromyalgia patients were randomized to receive a 30-min intravenous infusion with S-ketamine (total dose 0.5 mg/kg, n = 12) or the active placebo, midazolam (5 mg, n = 12). Visual Analogue Pain Scores (VAS) and ketamine plasma samples were obtained for

2.5 h following termination of treatment; pain scores derived from the Fibromyalgia Impact Questionnaire (FIQ) were collected weekly during an 8-week follow-up. Fifteen minutes after termination of the infusion the number of patients with a reduction in pain scores of > 50% was 8 versus 3 in the placebo group ($P < 0.05$), at $t = 75$ min 6 versus 2 (ns), at the end of week-1 2 versus 0 (ns), and at end of week-8 2 patients in each of the ketamine and midazolam groups. The effect of S-ketamine on VAS closely followed the changes in ketamine plasma concentrations. For VAS and FIQ scores no significant differences in treatment effects were observed in the 2.5-h following infusion or during the 8-week follow-up. Side effects, as measured by the Bowdle questionnaire (which scores for 13 separate psychedelic symptoms), were mild to moderate in both groups and declined rapidly, indicating adequate blinding of treatments. Efficacy of S-ketamine was limited and restricted in duration to its pharmacokinetics. In common with earlier findings (see Chapter 2) a short infusion of S-ketamine has no long-term effects on fibromyalgia pain. Alternatively, there may be a subset of patients in which sensitized NMDAR play only a minor role in the development of chronic fibromyalgia pain.

Chapter 5 Ketamine is metabolized in the liver to norketamine via cytochrome P450 enzymes (CYP enzymes). There are few human data on the involvement of CYP enzymes on the elimination of norketamine and norketamine's possible contribution to the analgesic effect. The aim of this study was to investigate the effect of cytochrome P450 enzyme induction by rifampicin on the pharmacokinetics of S-ketamine and its major metabolite, S-norketamine, in healthy volunteers. Twenty healthy male subjects received 20 mg/70kg/h ($n = 10$) or 40 mg/70kg/h ($n = 10$) intravenous S-ketamine twice for 2 h, following either 5 days of oral rifampicin (once daily 600 mg) or placebo treatment. During and 3 h following drug infusion arterial plasma concentrations of S-ketamine and S-norketamine were obtained at regular intervals. The data were analyzed with a compartmental pharmacokinetic model consisting of three compartments for S-ketamine, three sequential metabolism compartments and two S-norketamine compartments using NONMEM. Rifampicin caused a 10% and 50% reduction in the area-under-the-curve of the plasma concentrations of S-ketamine and S-norketamine, respectively. The compartmental analysis indicated a 13% and 200% increase in S-ketamine and S-norketamine elimination from their respective central compartments by rifampicin. A novel observation is the large effect of rifampicin on S-norketamine concentrations, and indicates that rifampicin induces the elimination of S-ketamine's metabolite, probably via induction of the CYP3A4 and/or CYP2B6 enzymes.

Chapter 6 As described in the previous chapters, S-ketamine has analgesic, cognitive and psychotomimetic effects. The contribution of S-norketamine to these effects is unknown and is explored in this chapter. Twelve healthy young

male volunteers participated in this randomized, single blind, cross-over study. Volunteers were studied on 3 occasions and received 20 mg/70kg/h intravenous S-ketamine or placebo for 2 h, following either 5 days of oral rifampicin (once daily 600 mg) or placebo treatment. Before, during, and after the infusion the subjects performed computerized neurocognitive tests (e.g. memory and reaction time), and pain responses to a painful stimulus and side effects (drug high) were recorded. S-ketamine infusion caused pain relief, drug high and impaired cognition during infusion. All of the effects decreased within the three hours following infusion, with parameters not different between treatments at $t = 3$ h following the termination of the ketamine infusion. Using the pharmacokinetic data obtained in Chapter 5, the contribution of norketamine to ketamine effect was modeled using a linear, additive population pharmacokinetic-pharmacodynamic model. Modeling showed that S-norketamine diminished S-ketamine analgesia, but had no effect on cognitive impairment. These findings are intriguing, but should be considered with care as this is the first study, using “complex” modeling and simulated PK data, showing an excitatory effect of norketamine on pain, but an antagonistic effect on psychotomimetic side effects. A more sensible conclusion would be that norketamine does not contribute to ketamine’s effects, although a small negative or antagonistic effect relative to ketamine’s effects cannot be excluded. No conclusions can be extrapolated to clinical use, because of the difference in population and administration duration.

Conclusions

The conclusions that may be drawn from this thesis are:

1. There is evidence from a limited number of studies ($n = 3$) that chronic non-cancer pain relief can last for months after long-term intravenous ketamine infusions (duration at least 35 h). *This is insufficient to warrant the clinical (i.e., non-experimental) use of S-ketamine in chronic neuropathic pain patients;*
2. S-ketamine may cause liver enzyme elevations when a repeated dosing regimen is used with just 2 weeks between treatments and the dosing duration is long-term (100 h). *This observation warrants the measurement of liver enzymes in all patients receiving long-term ketamine treatment;*
3. A 30-min infusion with S-ketamine has no long-term efficacy in the treatment of fibromyalgia patients. *Treatment of fibromyalgia pain with a short-term exposure to ketamine is currently not advisable;*

4. Rifampicin has a large impact on the pharmacokinetics of S-norketamine and a lesser impact on the pharmacokinetics of S-ketamine, causing a 50 and 10% reduction of their respective area-under-plasma concentration-time-curves;
5. A 2-h infusion with low-dose S-ketamine causes neurocognitive impairment that rapidly dissipates upon the termination of the infusion;
6. S-norketamine does not contribute to ketamine's effects, although a small negative or antagonistic effect relative to ketamine's effect, cannot be excluded. *These data suggest that pursuing of this agent as an alternative to ketamine is not warranted.*

Future perspectives

Since ketamine is currently the most potent NMDAR antagonist available, it will remain popular in the (experimental) treatment of diseases in which the sensitized NMDAR plays a crucial role. Such a disease is chronic neuropathic pain. In fact, this is a rather new indication for a drug that was originally developed as an anesthetic, and leaves considerable room for further exploration. Future studies should be directed in two directions:

1. Further explore the S-ketamine safety-efficacy balance in chronic pain patients, possibly in outpatient or ambulatory settings, and with new administration modes (such as intranasal ketamine or iontophoretic cutaneous applications);
2. Since the prolonged S-ketamine treatment is a serious disadvantage with respect to patient discomfort (the side effects are often such that patient compliance is limited, even during low-dose administration), and cost to health care (in-patient treatment is expensive and currently not reimbursed by healthy insurance), it is advisable to seek affordable alternatives. Alternatives may be aimed at the NMDAR, an example is traxoprodil (Pfizer BV), a NR1/NR2B selective NMDAR antagonist, possible with lesser psychotomimetic and cognitive side effects, or at other processes that enhance pain, such as the spinal inflammatory response at the spinal and supraspinal level involving astrocytes and microglia cells. An example of agents that may be used to target spinal inflammation include anti-TNF α -drugs or erythropoietin-derivatives (erythropoietin is the natural anti-TNF α produced during inflammation in the affected tissues to control excessive tissue damage from TNF). There is now evidence from our laboratory that ARA290 (a peptide that mimics the three dimensional structure erythropoietin), when given after nerve injury in a rat, is able to prevent allodynia for weeks to months depending on the treatment regimen.

Possibly combinations of pharmacological agents aimed at different parts of the chronic pain process are optimal (e.g., S-ketamine together with ARA290), but should be looked upon in further studies.

