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

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Chapter 1

Introduction

Ketamine - *the tiger still roars*¹

Ketamine, 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, was first developed in 1962 as an alternative to phencyclidine, and first used as an anesthetic in humans in 1964. Phencyclidine produced an anesthetic state coupled to a prolonged emergence delirium (a “centrally-mediated sensory deprivation syndrome” which resembles some of the symptoms of schizophrenia).¹ Ketamine produces a so-called dissociative anesthetic state in which the patient is dissociated from their surroundings, and although it also causes an emergence reaction, the symptoms are less severe than those produced by phencyclidine. Both drugs have effects at multiple receptor systems, but their main effect is blockade of the *N*-methyl-D-aspartate receptor (NMDAR), an excitatory ionotropic glutamate receptor present in the spinal cord and brain. Ketamine is considered a ‘safe’ anesthetic, as it is not associated with profound respiratory depression or hypotension; however, when anesthetics that caused fewer or no emergence reactions became available, the use of ketamine as an anesthetic declined and became restricted to specific indications, e.g. patients with severe hypotension or trauma.

Numerous studies in volunteers and patients have shown that apart from its anesthetic action, ketamine produces potent analgesia at subanesthetic plasma concentrations (Chapter 2 of this thesis). Anesthesiologists and pain physicians make use of this by combining opioids and ketamine to reduce opioid consumption and improve the quality of pain relief in patients after surgery. These observations led to a significant expansion of ketamine’s use as an analgesic in chronic (neuropathic) pain patients and ketamine began a second life as an analgesic. Because the evidence that ketamine is efficacious in these patients is limited (Chapter 2 of this thesis), studies are still conducted to establish efficacy and improve administration strategies in a variety of chronic pain conditions (Chapters 3 and 4 of this thesis). For ketamine it is obvious that it produces pain relief during intravenous infusion, but its effect following infusion is dependent on the duration of infusion and long-term infusions are probably required to cause long-term analgesic effects (Chapter 2 of this thesis). The use of drugs outside of their initial indication (so-called off-label use), in this case the use of ketamine for analgesia, raises important questions, not only regarding efficacy, but also regarding short-term and long-term safety. This is especially relevant when the mode of administration changes from single or short-term infusions for induction of anesthesia to long-term and/or repeated administration for treatment of chronic pain.

Ketamine - *side-effects and safety*

Ketamine-induced side-effects may be subdivided in:

- (i) transient cardiovascular effects;
- (ii) psychotomimetic or schizophrenia-like effects;
- (iii) cognitive impairment;
- (iv) long-term neurotoxic effects; and
- (v) other somatic effects (including liver injury, renal injury and bladder dysfunction).

(i) Ketamine has a biphasic action on the cardiovascular system²: a direct cardiac depressive effect (i.e., a direct negative inotropic effect) and an indirect stimulatory effect (due to activation of the sympathetic system). Cardiac depression precedes stimulation after high-dose ketamine administration or after repeated infusions when presynaptic catecholamine stores become depleted. Cardiovascular stimulation occurs with low dose-ketamine infusion and is characterized by tachycardia, systemic and pulmonary hypertension, and an increase in cardiac output and myocardial oxygen consumption. These properties restrict the use of ketamine in the cardiac compromised patient, even when used at low-dose. Sympathetic stimulation may also cause other symptoms including nausea and vomiting.

(ii) Psychotomimetic effects mimic symptoms observed in schizophrenia.³ Symptoms include feelings of euphoria or dysphoria, depersonalization, out of body experiences, hallucinations, anxiety, fear and panic attacks. The incidence of these side effects is dose related and there is a wide variety in occurrence and severity between patients. During prolonged continuous administration side effects will often decline even though the infusion rate is not changed. Side effects usually disappear rapidly upon termination of the low dose ketamine administration. In some patients side effects will persist for some time, and may even recur after initially disappearing. Simultaneous treatment with a benzodiazepine or clonidine reduces the severity of side effects.

(iii) Cognitive impairment, including memory and learning deficits can occur during and following ketamine treatment (frequent abuse of ketamine has been shown to cause long-lasting memory impairment and so-called flash-backs).⁴ See also Chapter 6.

(iv) Animal studies associate ketamine with neurotoxicity (Chapter 2 of this thesis). Neuronal injury (vacuolization in neurons and apoptotic neurodegeneration) is caused by loss of inhibitory pathways leading to an increase of excitatory neuronal activity. Studies on this topic have not been performed in

humans. Data from one case report on the epidural use of ketamine indicated that neurotoxicity occurred. This was based on histological findings, clinical signs were absent. This patient received long-term high-dose preservative free S-ketamine, suggesting a role for the NMDA receptor in causing neurotoxicity.

(v) The effects of ketamine on non-neuronal or non-cardiovascular tissues have not been widely studied. 'Older' studies (1979-1980)⁵ indicate increases in liver enzymes from anesthetic doses of the racemic mixture (at higher incidences than observed during halothane anesthesia) (Chapter 3 of this thesis). This topic has been relatively untouched until recently other publications became available. Recreational ketamine abusers and ketamine addicts often present themselves at the emergency department with kidney injury, elevated liver enzymes and hemorrhagic cystitis.⁶

There is a thin line between short-term transient ketamine side effects and long-lasting ketamine-induced tissue injury. Despite the above-mentioned adverse effects, ketamine has been used with success as an anesthetic agent for the last 50 years.¹ This indicates its safety when used by anesthesia specialists for short-term administration. Knowledge on the safety of ketamine in chronic clinical use is limited and deserves further study (see also Chapter 3).

Ketamine - is it the parent or the metabolite?

Norketamine is the main metabolite of ketamine. It is an active NMDAR antagonist, albeit with lesser affinity for the receptor. Few animal studies have addressed the issue of norketamine potency with respect to the spectrum of effects elicited by ketamine. They show that norketamine produces analgesia in acute and chronic pain models, but that its potency is only about one-third of that of the parent compound.⁷ Similarly, side effects were present after norketamine administration that were indistinguishable from those observed after equi-analgesic doses of ketamine, although there are some indications that the potency of norketamine for causing side effects is less than that for analgesia. No human data exist on the potency of norketamine, as norketamine is not available for use in humans. Previous modeling studies, assuming an additive affinity of ketamine and norketamine for the same receptor, suggest that norketamine does not contribute significantly to the effects of ketamine because its potency in humans is probably lower than that suggested from animal studies.⁸

Outline of this thesis

This thesis has three major topics:

1. S-ketamine efficacy (Chapters 2, 3 and 4);
2. S-ketamine safety focusing on liver enzymes (Chapter 3), cognition (Chapter 6), and other side effects (Chapter 4); and
3. S-ketamine metabolism and contribution of norketamine to effect (Chapters 5 and 6).

Experiments were performed in chronic pain patients with complex regional pain syndrome type 1 (Chapter 3) and fibromyalgia (Chapter 4) and in healthy volunteers (Chapters 5 and 6).

In **Chapter 2** an overview is given of the efficacy and safety of ketamine in the treatment of chronic non-cancer pain. The available randomized controlled trials (RCTs) on ketamine in chronic non-cancer pain patients were evaluated and a semi-quantitative analysis of the data was performed.

The efficacy and safety of a repeated S-ketamine infusion on pain relief in chronic pain patients was studied in **Chapter 3**. A 100-h infusion of S-ketamine was repeated three weeks after the start of an initial infusion period of 100 h in chronic pain patients with complex regional pain syndrome type 1 (CRPS-1). The emphasis of this report will be on the effects of ketamine on the liver function of these patients.

Chapter 4 consists of a study on the efficacy and side-effect profile of a short-term infusion of relatively high-dose S-ketamine (0.5 mg/kg) in patients with fibromyalgia. The emphasis of this study was on the long-term effects of ketamine (i.e., did pain relief sustain following the infusion period?).

In **Chapter 5** the metabolism of S-ketamine and S-norketamine was manipulated by induction of the cytochrome P450 system. This provides information on the specifics of the metabolism of S-ketamine and its active metabolite S-norketamine. A simulation study was performed to predict the contribution of norketamine to ketamine's analgesic effects in the context of acute and chronic pain relief.

In healthy volunteers the contribution of S-norketamine to S-ketamine-induced pain relief, psychotomimetic side-effects and cognitive effects was measured in **Chapter 6**. To that end the plasma concentrations of S-ketamine and its metabolite were manipulated by cytochrome P450 induction.

Chapter 7 consists of a summary of the topics discussed in this thesis, followed by the conclusions and future perspectives.

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