Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain therapy

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Abstract

Ketamine is a phencyclidine derivative, which functions primarily as an antagonist of the N-methyl-D-aspartate receptor. It has no affinity for GABA receptors in the central nervous system. Ketamine shows a chiral structure consisting of two optical isomers. It undergoes oxidative metabolism, mainly to norketamine by cytochrome P450 3A and 2B6 enzymes. The use of S-ketamine is increasing worldwide, since the S(+)-enantiomer has been postulated to be a four times more potent anesthetic and analgesic than R(-)-enantiomer, and approximately two times more effective than the racemic mixture of ketamine. Because of extensive first-pass metabolism, oral bioavailability is poor and ketamine is vulnerable to pharmacokinetic drug interactions. Sublingual and nasal formulations of ketamine are being developed, and especially nasal administration produces rapid peak ketamine plasma concentrations with relatively high bioavailability. Ketamine produces hemodynamically stable anesthesia *via* central sympathetic stimulation without affecting respiratory function. Animal studies have shown that ketamine has neuroprotective properties and there is no evidence of elevated intracranial pressure after ketamine dosing in humans. Low-dose perioperative ketamine may reduce opioid consumption and chronic postsurgical pain after specific surgical procedures. However, long-term analgesic effects of ketamine in chronic pain patients have not been demonstrated. Besides analgesic properties, ketamine has rapid-acting antidepressant effects, which may be useful in treating therapy resistant depressive patients. Well known psychotomimetic and cognitive adverse effects restrict the clinical usefulness of ketamine, even though fewer psychomimetic adverse effects have been reported with S-ketamine compared to racemate. Safety issues in the long-term use are yet to be resolved.

Key points

Ketamine has a low oral bioavailability, which reflects its extensive first-pass metabolism by cytochrome P450 3A and 2B6 enzymes. Novel sublingual and nasal formulations may offer practical alternatives for intravenous ketamine when treating acute pain. The safety profile for long-term use of ketamine is not known.

In the central nervous system, ketamine has affinity to various receptors. Unlike many other anesthetics, it does not affect GABA receptors at clinically relevant concentrations. The analgesic effects are mediated mainly via blockade of N-methyl-D-aspartate receptors and possibly by enhancement of descending inhibition in the spinal cord in chronic pain conditions.

Since ketamine preserves cardiac output, it is an excellent anesthetic for hemodynamically unstable patients. Low-dose intravenous ketamine reduces perioperative opioid consumption and may have a role in reducing chronic postsurgical pain. Antidepressant and anticonvulsive effects of ketamine have been utilized in the treatment of depression and drug-resistant status epilepticus.

1 Introduction

Phencyclidine derivative ketamine was first synthesized in 1962 in need for a less hallucinogenic compound than phencyclidine [1]. The first clinical study in humans was conducted in 1964 [2], and the drug was introduced into clinical use in 1970. Ketamine was initially used as a battlefield anesthetic, sedative agent for unco-operative children and in veterinary medicine [3,4]. It produced “dissociative anesthesia”, as patients fell into a trance-like state and were “disconnected” from their environment. The role of ketamine as a safe anesthetic agent was established [1], and despite a mild decrease in its use in the 1980s due to psychotomimetic reactions, it appears now to be going through a new renaissance because of its potential therapeutic uses in pain therapy, neurology and psychiatry [1].

Chemically, ketamine molecule has a chiral structure consisting of two optical enantiomers, S(+)-ketamine and R(-)-ketamine. The different potencies of the two enantiomers were known already in 1970. However, it was not until in the early 1990´s when optical isomers of ketamine were thoroughly studied in order to develop an anesthetic agent more sophisticated than racemic ketamine. Ketamine free base is a lipid-soluble molecule, which rapidly crosses the blood-brain barrier. The uses of intravenous, oral, intranasal and sublingual formulations of ketamine are increasingly being studied and used [5–9]. Oral bioavailability of ketamine is poor, only 8-24% [7,10–14]. Due to its oxidative metabolism, ketamine is vulnerable to pharmacokinetic drug interactions, especially when used orally [13,15].

In high doses, ketamine produces anesthesia and analgesia and in low doses it acts as an analgesic drug. These effects are mainly mediated by noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptors in the central nervous system. In animal studies, the main metabolite norketamine has antinociceptive properties with a potency of one-fifth to one-third of ketamine [16–19], but its analgesic effects in humans are mainly unknown [14]. After oral intake of ketamine, norketamine plasma concentrations are much higher than that of the parent drug [14].

The use of ketamine is increasing in various clinical settings [1,20] and the emergence of S-ketamine might offer some advantages compared to the racemate [14,21,22]. However, most of the published pharmacokinetic and pharmacodynamic studies of ketamine have been conducted with racemic ketamine (search from PubMed.gov returns 10762 publications for "(ketamine) AND (pharmacokinetics OR pharmacodynamics)", whereas the same with "S-ketamine" returns only 302 publications). S(+)-isomer of ketamine has a higher affinity for the NMDA receptor than the racemic compound, and thus lower doses are required to produce anesthesia and analgesia [4]. S-ketamine is two and four times more potent anesthetic and analgesic than the racemate and R(-)-isomer, respectively [22–25]. Numerous clinical studies have been published which suggest that ketamine has short-term analgesic properties in various chronic pain syndromes. Ketamine is also useful as an adjuvant in the multimodal management of acute perioperative pain to improve pain therapy and it reduces postoperative requirements and side effects of opioids [26,27]. Antidepressant effects of ketamine have been utilized in depressive patients not responding to traditional antidepressants [28]. Ketamine appears to be effective also in the treatment of drug-resistant refractory status epilepticus [29].

The availability of S(+)-enantiomer, new subanesthetic dosing schemes and administration modalities have increased the use of ketamine during recent years. The aim of this review is to critically review the published data on the clinical pharmacokinetics and pharmacodynamics of ketamine in healthy subjects, patients and special patient populations. Our scope was also to discuss clinical implications and new areas where further research is required.

2 Methods

Relevant articles in the PubMed Medline database (last search: 2 February 2016) were identified using the following keywords: 'ketamine', 'pharmacokinetics', 'pharmacodynamics', 'anesthesia' 'chronic pain', 'cancer pain', 'modeling', 'pain', 'OIH'. Our search was limited to English-language studies published in peer reviewed journals. Additional publications were identified from review articles. All article titles thus retrieved were then searched; any relevant to the aim of this review

were compiled into a Mendeley Library, and electronic copies of the full papers were obtained. Bibliographies of relevant papers were reviewed manually to identify additional potentially relevant studies. After critical examination, data were extracted from these papers and compiled into tables and figures.

Most of the published studies of ketamine have been conducted using racemic ketamine, and in the following review we use “ketamine” when referring to the racemate and indicate the enantiomers, where applicable.

3 Chemical properties and physiochemical characteristics

Chemically, ketamine is a 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone (molecular weight 274.4) [4]. It is a lipid-soluble molecule with a dissociation constant near to physiologic pH [4]. The melting point of ketamine is around 260°C [4]. Ketamine has a chiral structure consisting of two optical isomers (Fig. 1), S-ketamine and R-ketamine, because of an asymmetric carbon atom in the C2 position [4]. For human use, the racemate and S-ketamine are available commercially as a HCl salts, both of which are water-soluble [1].

4 Pharmacokinetics of ketamine

After systemic absorption, ketamine is rapidly distributed into the brain and other well-perfused tissues. It has a short α half-life (2-4 minutes) and longer β half-life (2-4 h) in humans [1,4]. A short α half-life and a short context-sensitive half-time are consistent with fast recovery after intravenous ketamine anesthesia [22]. Plasma protein binding of ketamine is low (10-30%) [30,31]. As a lipophilic molecule, ketamine has a large steady state volume of distribution (160-550 l/70kg). Systemic clearance is 60-147 l/h/70 kg, which equals the liver blood flow explaining the low bioavailability of oral ketamine [13,14,32–38]. S-ketamine has a significantly higher systemic clearance when dosed alone than in the racemate, suggesting an inhibition of S-ketamine clearance by the R-ketamine [39]. A decrease in the hepatic blood flow in elderly or patients with hepatic cirrhosis decreases the clearance of ketamine causing an increase in its oral bioavailability

[14]. Elimination half-life of S-ketamine seems to be slightly longer (4-7 h) than that of the racemate [13,15,40–42].

4.1 Biotransformation and pharmacokinetic drug-drug interactions

Ketamine undergoes extensive oxidative metabolism. It is N-demethylated into norketamine, 4-hydroxy-ketamine and 6-hydroxy-ketamine (Fig. 2). Norketamine is considered to be the major metabolite in humans. It is also pharmacologically active and is further metabolized to 6-hydroxy-norketamine [12,43,44]. However, recent studies have indicated that norketamine is rapidly further metabolized and is not the major metabolite in the circulation [45]. Metabolites are excreted in bile and urine after glucuronidation [22], but only traces of the parent drug are found in urine [32]. Human liver microsomes demethylate the two optical isomers of ketamine similarly [36]. R-ketamine is not formed after an intravenous administration of S-ketamine in humans, demonstrating the lack of interconversion [32,39].

Inhibition of CYP3A, CYP2B6 and CYP2C9 enzymes decrease the N-demethylation of ketamine *in vitro* [44–46]. *In vivo* studies with healthy volunteers and patients have confirmed these findings (Table 1) showing that the metabolism of ketamine depends both on the CYP3A and CYP2B6 activity during absorption and elimination (Fig. 3 and 4) [13,15,40–42,47]. Inhibition of CYP3A-mediated metabolism by clarithromycin and grapefruit juice significantly increased the exposure to oral S-ketamine [15,41]. However, a well-documented CYP3A4 and P-glycoprotein (P-gp) inhibitor, itraconazole, had no significant interactions with oral S-ketamine suggesting that there may be concomitant action of other transporter proteins than P-gp counteracting the effect of CYP3A4 inhibition [42]. A potent CYP3A inducer rifampicin and St. John´s wort reduced the plasma concentrations of oral S-ketamine substantially, but after intravenous administration the effect was smaller [13,40,47]. Considering CYP2B6, *in vitro* studies in human liver microsomes indicated that CYP2B6 metabolizes ketamine [44,46]. This finding was later confirmed in *vivo* in healthy volunteers, as CYP2B6 inhibitor ticlopidine impaired the metabolism of oral S-ketamine [42]. About 80% of ketamine is N-demethylated to norketamine, which can be measured in plasma 2-3 min

after ketamine i.v. bolus and the maximum plasma concentration is reached after 30-60 min [13,22].

4.2. Clinical pharmacometric studies of ketamine in anesthesia and pain therapy

Application of pharmacometrics (so-called 'population approach') opens new perspectives for clinical drug trials in various populations. Pharmacometric analysis involves the application of concepts of non-linear mixed effects modeling to subject data in order to describe dose-effect relationship and unexplained inter- and intraindividual variability [49–51]. Pharmacometric research can identify subject-specific factors (i.e. covariates) that may be valuable when optimizing drug-dosing strategies. Infrequently obtained samples and observations from actual patients compatible with clinical care can be used instead of designing a specific experimental setting. Because of this, the burden for each individual studied can be minimized. Importantly, the obtained information can be directly applied into clinical practice.

The first population pharmacokinetic study describing the stereoselective pharmacokinetics of ketamine was published more than ten years ago [39]. Both racemate and S-ketamine were administered to ten healthy male volunteers by a computer-controlled device in a randomized double-blind crossover setting. S-ketamine clearance was significantly higher (26.3 ml/kg/min) compared to racemic ketamine (14.8 ml/kg/min). Interestingly, the clearance of S-ketamine was smaller (18.5 ml/kg/min) in the racemate than when given as a pure isomer, demonstrating that R-ketamine inhibits the clearance of S-ketamine [39].

Population pharmacokinetics and –dynamics of ketamine and norketamine were evaluated from intravenous blood samples in 54 children (mean age 8.15 ± 3.5 years) given 1-1.5 mg/kg of racemic ketamine in an emergency department [48–50]. A two-compartmental linear model was developed and according to goodness-of-fit plots, it described the data satisfactorily. Population parameter estimates standardized to a 70-kg person were central volume of 38.7 l/70 kg, elimination clearance 90 l/h/70 kg, peripheral volume of distribution 102 l/70 kg and

intercompartmental clearance 215 l/h/70 kg [48]. Furthermore, a two compartmental linear model with an additional metabolite compartment linked to the ketamine central compartment could be used to estimate norketamine pharmacokinetics [54]. The model showed that norketamine has a shorter elimination half-life than ketamine (1.1 h vs 2.1 h, respectively) and a simulation study suggested that norketamine affects analgesia 4 hours after 2 mg/kg of intravenous ketamine administration [50].

A third study by the same group evaluated the pharmacodynamics of the same population described above and showed that concentrations associated with arousal in children are analogous to adults [49]. A simulation study later evaluated these models to describe ketamine dosing regimens for children at different ages during brief procedural sedation [51].

Brunette et al (2011) evaluated the pharmacokinetics of oral racemic ketamine in children suffering from burn injury [52]. Additional intravenous ketamine was administered as a bolus or infusion if needed. A pooled analysis from 91 subjects was performed and a two-compartmental linear model described the data best. The results showed that the pharmacokinetic profile of ketamine is not changed in children with minor burns ([52]. A 10mg/kg oral dose with subsequent 1 mg/kg iv ketamine is suggested for a short-duration surgical procedure. Recent study described a two-compartment linear model to evaluate the effect of pre-existing congenital heart disease in ketamine disposition [53]. Parameters were allometrically scaled and clearance was shown to be comparable to values reported in healthy children. Computer simulations indicated that an initial intravenous 2 mg/kg loading dose followed by a constant rate infusion of 6.3 mg/kg/h and 3.9 mg/kg/h from 1 to 29 and 30 to 80 are needed, respectively to achieve and maintain anesthesia in children over 1 years of age.

Dahan et al (2011) modeled ketamine-induced pain relief in 60 chronic pain patients randomized to receive either 100-h infusion of S-ketamine or placebo [33]. A two-compartment model describing parent drug with one compartment norketamine model was used to fit concentration data. A separate time series analysis was performed for pharmacodynamic data and a stochastic

differential equation was implemented for pharmacokinetic-pharmacodynamic analysis that was performed using an inhibitory sigmoid-E_{max} model. The results demonstrated that the models captured data well and that long term S-ketamine treatment was effective in causing pain relief in CRPS-1 patients [34].

Modelling studies in healthy volunteers indicated that contrary to earlier findings, norketamine has a minimal contribution to either acute or chronic ketamine antinociception [47] and suggested that norketamine might facilitate pain after ketamine dosing [54]. Another study including nine patients receiving a 40-min infusion of 0.5 mg/kg of racemic ketamine suggested further that norketamine might not be the main metabolite, although it is initially occurring after ketamine dosing [55]. Stereoselective bioanalytical methods were applied to analyse dehydronorketamine and hydroxyketamine enantiomers in addition to ketamine, norketamine and hydroxyketamine concentrations and simultaneous population pharmacokinetic modeling of ketamine and its three major metabolites were performed [55].

A recent study showed in healthy volunteers, that the steady state of oral S-ketamine is achieved after the third dose with no accumulation of ketamine or metabolites when S-ketamine is ingested twice daily [14]. Although the oral bioavailability of S-ketamine is poor, the amount of S-norketamine is approximately an order of magnitude higher compared to S-ketamine. The authors calculated based on their results that a 2.4 times larger dose of oral S-ketamine is required to produce the same area under the concentration-time curve as intravenous S-ketamine as S-norketamine's analgesic potency is less than that of S-ketamine [14].

Three different individually fitted compartmental models were compared in four independent trials pooling up 58 healthy volunteers, who receiving racemic ketamine with target controlled infusion using a target from 50 to 200 ng/ml [56]. Another study evaluated a three-compartment model with 20 elective day case surgical patients using target-controlled infusion with a target of 250 ng/ml [37]. The results indicate that the bias was -4.6 to -0.3%/h and the precision from 26.5 to 64.2% [37,56]. It should be emphasized that only the recent pharmacometric models described here

[14,33,47,54,55] employ some of the validation methods described earlier [57,58] to internally validate the models. Only one of recent pharmacometric models have been externally validated in a healthy volunteer study using simulations [59]. Therefore most of the results of these studies should be considered as preliminary and interpreted cautiously.

5. Mechanisms of ketamine action in central nervous system

5.1 Effects on the NMDA-receptor

Ketamine has a complex neuropharmacology, and its anesthetic and analgesic effects are mediated via ionotropic glutamate receptors [1,22]. Mion and Villevielle (2013) have recently described the neuropharmacology of the NMDA receptor and neurophysiological effects of ketamine thoroughly in their excellent review [22]. Briefly, glutamate receptors are usually classified as NMDA and non-NMDA receptors, such as alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid and kainate- receptors. Most of the NMDA receptors are constituted by two NR1 and by two NR2 subunits, which form an ionic channel selective for the cations to the cytoplasmic membrane [22].

The primary mechanism of action of ketamine is noncompetitive antagonism of transmembrane NMDA receptors in the brain and spinal cord [22]. The antagonism of NMDA causes amnesic, psychosensory and analgesic effects and makes ketamine a very unique drug in the field on anesthesia and analgesia [1,60,61].

NMDA receptors are triggered by excitatory amino acids such as glutamate. The activation of the NMDA-receptor is a very complex phenomenon, modulated by e.g. zinc (Zn^{2+}) and hydrogen (H^{+}) ions [62]. NMDA activation requires phosphorylation and binding of glycine and glutamate on the receptor [22]. At resting state, magnesium (Mg^{2+}) ions located in the ~~in the~~ NMDA-receptor channel block the calcium (Ca^{2+}) ion influx even if glutamate and glycine are bound on their sites. Neuronal cell depolarization releases Mg^{2+} and allows Ca^{2+} influx.

The activation of the NMDA receptor leads to influx of Ca^{2+}, which activates intracellular formation of secondary messengers, prostaglandins and nitric oxide (NO). Nitric oxide enhances the release of presynaptic glutamate and plays a crucial role in the nociception and neurotoxicity [63]. Blockade of the NMDA receptor by ketamine is non-competitive. It reduces the frequency and mean opening time of the Ca^{2+} channel and also prevents Ca^{2+} influx [64].

NMDA-receptors are involved in pain transmission and modulation. They contribute to phenomena like central sensitization and wind-up, which are some of the mechanisms behind chronic pain [65]. In the presence of repetitive spinal C-fiber stimulation, NMDA receptors increase the spontaneous activity of the fibers and receptive fields [25,66]. This can theoretically be blocked by ketamine and prevent pain from becoming chronic [67,68].

5.2 Effects on other receptors in central nervous system

Part of the analgesic effect of ketamine in animals is derived from the agonism of μ-, δ- and κ-opioid receptors, but the inhibition constant (K_i) values are high for these receptors [69–71]. S-ketamine has two to three times higher affinity for opioid receptors than R-ketamine [71]. However, naloxone has no effect on the action of ketamine in humans, indicating a minor role of opioid receptors in the treatment of clinical pain with ketamine [72].

In an experimental model, ketamine inhibits monoamine transporters expressed in human embryonic kidney cells in a dose-dependent manner [73]. This could explain the psychotomimetic and sympathomimetic effects of ketamine, but according to an *in vitro* study, high ketamine concentrations are needed [73]. Ketamine and especially S-ketamine inhibit neuronal and extra-neuronal uptake of catecholamines, causing a hyperadrenergic state that increases norepinephrine concentrations in the circulation [74]. Interestingly, alpha-2 adrenoceptor agonist dexmedetomidine attenuates the cardiostimulatory effects of ketamine and postanesthetic delirium even more effectively than the traditionally used benzodiazepine, midazolam [75].

GABA-receptors appear not to be involved in ketamine anesthesia or analgesia. In contrast to many other anesthetics, ketamine has no affinity for $GABA_A$ receptors in the human brain at subanesthetic doses as demonstrated by positron emission tomography study in healthy volunteers [76]. In this study target controlled infusion was used with serum ketamine target set to 300 ng/mL using STANPUMP software [77]. At analgesic doses of ketamine, spinal GABA receptors are nor involved in pain inhibition, as very high ketamine concentrations are needed to stimulate spinal GABA-receptors [27,78].

In rats central nervous system, ketamine interacts with several receptors but shows low K_i values for NMDA, dopamine D_2 and serotonin 5-HT receptors [79,80]. Ketamine also mediates its effects via cholinergic, nicotinic and muscarinic receptors [22]. Inhibitory effect on muscarinic receptors can explain the increase of bronchial secretion and mucus formation after ketamine [4]. Physostigmine has been proposed to reverse the central anticholinergic effects of ketamine and improve recovery from ketamine anesthesia in humans [81,82]. However, it did not shorten the recovery time after ketamine anesthesia and did not reduce hallucinations [83].

Ketamine has local anesthetic-like actions via blockade of voltage-operated sodium channels. These effects, however, are less potent when compared to lidocaine [84]. High intramuscular bioavailability with possible systemic effects, limit the clinical use of ketamine as a local anesthetic.

6 Pharmacodynamics and clinical use of ketamine

Racemic ketamine and S-ketamine show a mean effective plasma concentration (EC50, mean ± SD) of 241 ± 90 and 111 ± 30 ng/ml for loss of consciousness and 148 ± 46 and 75 ± 21 ng/ml for return of consciousness, respectively [85]. Psychedelic side effects may appear at far lower concentrations (50 ng/ml), but their intensity increases linearly with a racemate concentration range of 50 to 200 ng/ml [86]. In experimental pain models, intravenous use of the racemate produces analgesic effects above 100-160 ng/ml [11,87]. After oral dosing, much lower ketamine concentrations (40 ng/ml) are needed [88].

In perioperative use, ketamine is a rapidly acting general anesthetic and analgesic, which produces so-called dissociative anesthesia. Emergence from S-ketamine is faster than that from R-ketamine or racemic mixture [89]. Psychotomimetic adverse effects are dose-dependent and can be attenuated by co-application of sedatives or hypnotics such as propofol, benzodiazepines and alpha-2 adrenergic agonists [1,4,75]. The S(+)-and R(-)-enantiomers of ketamine have similar pharmacokinetic profiles, but show different effects. Some studies indicate that S(+)-enantiomer may be about four times more potent analgesic than R(-)-isomer in humans, but produces more auditory and visual disturbances. [23,24,90]. Furthermore, R-ketamine produces more agitation in surgical patients than S-ketamine [23]. The difference in the analgesic efficiency between these two enantiomers can be explained by S-ketamine's four times higher affinity to NMDA-receptors compared to R(-)-enantiomer [24].

6.1 Ketamine in perioperative anesthesia and analgosedation

For hemodynamically unstable patients, ketamine is an excellent choice as an anesthetic, because it preserves cardiac output [4,74]. Another major advantage compared to other anesthetics and opioids is that ketamine preserves protective pharyngeal and laryngeal reflexes without depressing respiration, which makes it an attractive field anesthetic [91]. In contrast to opioids, ketamine has no negative impact on gut motility but has favorable effects on cardiovascular and pulmonary parameters, making it a tempting option for add-on analgosedation in intensive care units [92]. Low-dose ketamine have been used as adjunct to iv opioids to improve pain relief in the pre-hospital setting and in the emergency department [93–95]. The rate of side effects may be reduced by a low-dose infusion (10 minutes) of ketamine instead of a bolus [94]. Multimodal analgesic strategy, including regional anesthesia and ketamine, may reduce persistent postsurgical pain [96].

6.2 Low-dose perioperative ketamine

Low-dose ketamine is defined as a bolus dose of ketamine less than 2 mg/kg of i.m. or 1 mg/kg of i.v. [97]. For continuous low-dose i.v. administration, a dose under 1.2 mg/kg/h has been

suggested [97,98]. Perioperative low-dose ketamine reduces postoperative pain, and diminishes postoperative opioid requirements and postoperative nausea and vomiting [102]. Recently, low-dose ketamine has been shown to reduce perioperative opioid consumption by 40% with no major side effects [98]. Also, low-dose ketamine used as a part of general anesthesia with or without benzodiazepines reduces the risk of hallucinations [99].

A typical perioperative ketamine bolus dose is 0.15 mg/kg and infusion rate varies between 0.15-1.2 mg/kg/h. Duration of treatment varies from 2 to 48 hours [98,100]. When the cumulative dose of ketamine is kept minimal, psychotomimetic side effects are rare. Some contradicting studies about the benefit of low-dose ketamine in perioperative use have been published [101,102], but they may reflect too mild an overall pain stimulus after surgery. The optimal dose, route and duration of ketamine administration ~~of ketamine~~ are currently to be elucidated.

Entropy and bispectral index (BIS) devices have been developed to process human electroencephalography (EEG) under anesthesia. Monitors present the content of a complex signal as a simple numerical index to estimate the depth of hypnosis during propofol, thiopental, sevoflurane, desflurane and isoflurane anesthesia. However, these devices fail to give a reliable estimate of hypnosis under ketamine anesthesia [99,100,103]. Several studies have showed an increase in BIS values when ketamine 0.5 mg kg-1 is administered as a rapid bolus under general anesthesia [101,104]. There is no effect on BIS when the dose of ketamine is kept low (0.2 mg kg-1) under propofol anesthesia [101].

6.3 Pharmacodynamics of ketamine in special surgical patient groups

6.3.1 Effect on heart and immune system

Unlike many other intravenous anesthetics, ketamine is an excellent option for hemodynamically unstable patients because it preserves cardiac output via central sympathetic stimulation and inhibition of neuronal catecholamine uptake [4,74]. Ketamine stimulates noradrenergic neurons, releasing norepinephrine, dopamine and serotonin to the blood flow [24]. S-ketamine does not

increase postoperative troponin T-levels after hemodynamically stable elective coronary artery bypass grafting (CAGB) patients [105]. However, in failing human heart muscles *in vitro*, ketamine decreases contractility and reduces the effect of β-adrenergic stimulation in a dose-dependent manner [106]. At end-stage heart disease, ketamine may decrease the myocardial contractility in a similar manner as other anesthetics. In CABG-patients opioid consumption is reduced and patient satisfaction is better after S-ketamine treatment when compared to opioid use alone [107]. American Heart Association (AHA) recommendation for the use of ketamine in cardiac surgery is "class intermediate" [108].

In vitro, ketamine reduces lipopolysaccharide-induced TNF-α, interleukin-6 (IL-6) and IL-8 production in human whole blood, and neutrophil adhesion to the endothelium in isolated guinea pig heart specimens [109,110]. Ketamine attenuates neutrophil activation in patients after coronary surgery with cardiopulmonary bypass [111], and decrease IL-6 levels compared to placebo, which may correlate with patient´s better clinical condition [112].

6.3.2 Effect of ketamine on neurotoxicity, neuroprotection and intracranial pressure

When determining ketamine's safety profile for neurosurgical patients, two different mechanisms have to be evaluated; neurotoxicity and potency to raise intracranial pressure by increasing cerebral blood flow.

Animal studies have shown dose dependent pathomorphological neuronal changes in developing cerebral cortex and in adult brain [113–115]. GABA- and anticholinergic drugs have been shown to eliminate neuronal cell damage caused by ketamine in an experimental animal model [113]. Interestingly, the drugs that elicit neuroprotective effects against ketamine in animals, also suppress the psychotomimetic side effects of ketamine in humans. Considering anesthetic practice with normal clinical iv doses, there are no *in vivo* studies indicating that ketamine is neurotoxic in adults [116]. Animal studies with intrathecal ketamine support its safety if used without a

preservative benzethonium chloride [117]. The neurotoxicity of spinal ketamine has not been evaluated in humans and intrathecal ketamine cannot be recommended in clinical practice [117].

In pediatric anesthesia, ketamine is widely used for repetitive painful procedures. However the effects of ketamine on developing brains have raised some concern. Studies with human neural stem cell cultures showed a significant neuronal apoptosis after a 24-hour exposure to ketamine [118]. Repeated ketamine doses may be neurotoxic to immature central nervous system in the absence of noxious stimuli, but neuroprotective in the same brains in the presence of strong painful stimuli [119]. This may be due to suppression of the neuroexcitatory glutamate effect and excess calcium influx to neurons in the CNS by ketamine. However, the majority of the studies on the effects of anesthesia-induced neurodevelopment are retrospective, and the effects of ketamine on the developing brain are not thoroughly evaluated.

The neuroprotective properties of ketamine (especially S-ketamine) have been reported in hypoxic-ischemic and traumatic brain injury in experimental animals [120–123]. The underlying mechanism may be the ketamine-induced inhibition of glutamate receptors and reduced production on intracellular nitric oxide (NO) and NO-dependent cyclic guanosine monophosphate production [123]. Ketamine's neuroprotective effects may also be derived from suppression of the inflammatory cascade [109,110].

An anesthetic dose of S-ketamine increases whole brain cerebral blood flow by 36% whereas a subanesthetic dose by only 13% as shown in a positron emission tomography study with healthy volunteers [124]. The metabolic rate of oxygen and glucose remained virtually unaffected so S-ketamine produced luxury perfusion especially to the insula and anterior cingulate [124]. A similar study with low-dose racemic ketamine showed a tendency to increased glucose metabolic rate and cerebral blood flow in a dose dependent manner [125,126].

Recent study postulated that ketamine might be an effective and safe drug in the treatment of multidrug-resistant status epilepticus [29]. During prolonged seizures, the commonly used first- and

second-line antiepileptic drugs may gradually fail, because the number and activity of GABA receptors decrease. At the same time, the activity and number of NMDA receptors increase making ketamine a tempting choice to treat status epilepticus. Additionally, ketamine may have neuroprotective effects in ischemic neurons in central nervous system. Many clinical studies and case reports have been published, but prospective controlled studies are lacking.

Historically, the use of ketamine has been restricted in patients with neurological illness because of concerns on raised intracranial pressure (ICP) [127,128]. Recently, it was suggested that ketamine does not raise ICP in traumatic brain injury patients who are sedated and mechanically ventilated [128]. The level of evidence was judged to be grade C, so there were severe methodological limitations in the reviewed studies. Similar findings were reported after ketamine was administered to patients with nontraumatic neurological illness [128]. However, these preliminary results should be interpreted carefully, since ketamine may increase the brain total blood volume, brain glucose metabolism and raise ICP when compensatory mechanisms have run out.

6.4 Ketamine in chronic pain patients

6.4.1 Ketamine in the prevention of chronic pain

Approximately 10-50% of patients suffer from persistent pain after surgical procedures [129]. Prolonged pain after amputations, thoracotomies and mastectomies is usually caused by iatrogenic nerve injury. Due to its ability to block NMDA-receptors and subsequently diminish central sensitization, use of perioperative ketamine has gained interest in preventing chronic postsurgical pain.

In two recent systematic reviews, the perioperative use of low-dose intravenous or epidural ketamine did not reduce risk of developing chronic postsurgical pain [130,131]. However, when only studies with intravenous administration of ketamine were analyzed, relative risk of developing chronic pain was reduced by 25% (with an NNT of 12) at 3 months and 30 % at 6 months after surgery [130]. In two more recent RCTs, perioperatively used intravenous or epidural ketamine did

not reduce chronic postthoracotomy pain [132,133]. In these studies, low-dose perioperative ketamine was well tolerated. Thus, it is possible that low-dose intravenous perioperative ketamine may have a role in reducing chronic postsurgical pain, at least after specific surgical procedures.

6.4.2 Ketamine and chronic pain

Ketamine reduces chronic pain associated with various neuropathic pain conditions, migraine, fibromyalgia, ischemic pain, pain after whiplash injury, and temporomandibular pain in the short term [134,135]. However, long-term analgesic effects in chronic pain conditions are less well described. Analgesic effects are mediated mainly via blockade of NMDA receptors and possibly by enhancement of descending inhibition, which are mechanisms involved in chronic pain conditions [22,136,137]. Ketamine has affinity to other receptors as well, including opioid receptors, but their role in the analgesic effects of ketamine in humans is less clear.

Long-term analgesic effects of ketamine have mainly been studied in patients with complex regional pain syndrome (CRPS). Schwartzman et al. (2009) reported that a daily 4-h intravenous infusion of ketamine decreased pain scores in patients with CRPS up to 3 months [138]. However, the study was prematurely stopped ~~at~~ halfway. Another RCT in 60 patients with CRPS type 1 showed that a 4.2-day low-dose ketamine infusion reduced pain scores significantly during 3 months, but the functional status of patients was not improved and most patients experienced side effects [6]. There were methodological shortcomings in both studies, and more studies are needed to confirm these results.

Topical ketamine has also been studied in RCTs in patients with chronic pain. Finch et al. (2009) showed that topical ketamine applied on a CRPS limb did not relieve pain but reduced allodynia, which is one of the most unpleasant symptoms of CRPS [142]. Topical 2% ketamine and 4% amitriptyline cream did not reduce chemotherapy-induced pain, numbness or tingling in 462 cancer survivors [139].

When considering ketamine in the treatment of chronic pain, safety issues such as increasing recreational use of ketamine should be considered. In addition to its well-known psychotomimetic and cognitive adverse effects, urological and hepatic toxicity have been reported as adverse events when ketamine has been used in the treatment of pain [140].

6.4.3 Ketamine and cancer pain

Although ketamine has been used as an adjuvant to opioid therapy in the treatment of intractable cancer pain, current evidence is insufficient to recommend ketamine as add-on therapy in the treatment of cancer pain [26]. When ketamine was administered subcutaneously as an adjunct to opioids and other analgesics to 185 patients with cancer pain, pain scores did not decrease when compared to placebo [141].

6.4.4 Opioid-induced hyperalgesia

Opioid-induced hyperalgesia (OIH) is an enhancement of pain during opioid use. The mechanism of OIH is probably multifactorial, but activation of NMDA receptors is thought to play a central role. Thus, NMDA receptor antagonists such as ketamine may theoretically be beneficial in the prevention or treatment of OIH. A recent systematic review of 35 articles on remifentanil-associated OIH included 10 RCTs, which studied the preventive effect of ketamine on OIH [142]. Half of the outcomes supported ketamine in the prevention of OIH and half of the studies failed to show a preventive effect of ketamine on OIH. Thus the role of ketamine in the prevention of OIH is yet to be established.

6.5 Ketamine and depression

Existing antidepressant drugs have limited efficacy and relatively slow onset [143]. Ketamine's rapid-acting antidepressant properties emphasize the peculiar nature of this anesthetic drug. A proposed antidepressant mechanism involves rapamycin pathway activation, synaptogenesis in the prefrontal cortex and glycogen synthase kinase-3 beta inactivation [143]. The role of NMDA

receptor inhibition is not clear [144]. Interestingly, GSK-3-receptor inhibitor lithium, when combined with ketamine potentiates and prolongs the antidepressant effects of ketamine [145].

In the first clinical placebo controlled study testing ketamine's antidepressant effect, racemic ketamine was administered as a 0.5 mg/kg single intravenous infusion over 40 minutes [146], but the effect was not long lasting. Subsequently, repeated ketamine therapy of six infusions over 12 days was used [147]. In animals, R-ketamine shows greater potency and longer lasting antidepressant-like effects than S-isomer [148]. A case series with therapy resistant depression patients, who were treated with 0.25 mg/kg infusion of S-ketamine showed promising results [144]. However, at the moment, racemic ketamine is a better-documented antidepressant than S-ketamine.

Ketamine is an effective and safe choice as an anesthetic agent during electroconvulsive therapy (ECT) and has synergistic antidepressant effects with ECT in the treatment of therapy-resistant depression [149].

7. Clinically used ketamine formulations

7.1 Intravenous ketamine

Currently both racemic ketamine and S-ketamine are in clinical use, but it has been suggested that S-ketamine offers better titratability than racemate because of higher clearance and a steeper concentration-effect curve [14,21,22]. Furthermore, the absence of R-enantiomers excludes the metabolic interaction discussed above. Intravenous induction dose of S-ketamine is 0.5-1.0 mg/kg, and maintenance is achieved by repeated 0.25-0.5 mg/kg bolus dosing or a constant infusion of 0.5-3.0 mg/kg/h. For analgesic purposes, lower bolus doses of 0.1-0.25 mg/kg followed by an infusion of 0.2-1.0 mg/kg/h may be appropriate. When racemic ketamine is used, these doses should be doubled (induction dose 1-2 mg/ml, range 1-2 to 4.5 mg/kg).

7.2 Oral ketamine

The poor bioavailability of ketamine limits its oral use in a clinical setting. Ketamine has an extensive first-pass metabolism, and only 17-24% of oral racemic ketamine and 8-11% of oral S-ketamine reach the systemic circulation [7,10–12,14,42]. The maximum plasma concentrations of ketamine appear about 40-55 minutes after ingestion and metabolites of ketamine can be measured after 10-30 minutes [1,15,42]. Recent study demonstrated that S-norketamine AUC was 16.5 times higher than that of S-ketamine after oral S-ketamine dosing reflecting the extensive first-pass metabolism of ketamine (Fig.5) [14]. Similarly, S-norketamine elimination half-life was slightly prolonged compared to S-ketamine [15,42]. Steady state concentrations of oral S-ketamine are achieved after the third dose and S-ketamine or its metabolites do not cumulate when S-ketamine is ingested twice daily [14]. Based on animal studies, S-Norketamine is weaker analgesic than S-ketamine [17], and it has been estimated that 2.4 times larger dose of oral S-ketamine is required to produce the same area under the concentration-time curve than intravenous ketamine in humans, because the oral bioavailability of S-ketamine is poor and as S-norketamine's analgesic potency is less than that of S-ketamine [14].

7.3 Intramuscular ketamine

Following an intramuscular dose of 2-4 mg/kg, ketamine is rapidly absorbed and bioavailability is approximately 93% [10,11]. Terminal plasma elimination half-life of intramuscular ketamine does not differ significantly from intravenous ketamine [11]. Ketamine can be detected in plasma after 4 minutes and the plasma concentrations peak within 5-30 minutes after injection [87]. The first effects of ketamine appear in 1-5 minutes after intramuscular injection [4]. Fast onset of action makes intramuscular ketamine valuable when sedating patients with challenging intravenous access.

7.4 Sublingual ketamine

Sublingual wafer and oral lozenge formulations of ketamine have been developed for easy to use third line treatment options for pain patients [7]. Oral and sublingual ketamine share poor (24-30%)

bioavailability, but norketamine formation is diminished after sublingual intake compared to oral route [7,12,150]. Maximum plasma concentrations of ketamine are similar compared to oral and sublingual routes, but time to maximum concentration is shorter (0.5 vs 2 hours) after sublingual administration [7]. Sublingual wafer formulations of ketamine show lower inter-subject variability in bioavailability compared to lozenge and tablet formulations, which may reflect a more controlled release of drug into the sublingual space [12,150]. Sublingual route may be preferable to oral when fast clinical effects are desired as in treating acute or breakthrough cancer pain.

7.5 Nasal ketamine

Like sublingual administration, intranasal route of ketamine bypasses the first-pass metabolism by the liver and intestine. The bioavailability of the nasal spray is approximately 45%, which is slightly larger compared to sublingual, rectal and especially oral route [8,12]. Because of a weak first-pass metabolism, norketamine exposure remains low [12]. Peak plasma concentrations of ketamine appear rapidly (10-17 min) after nasal spray, and the onset of action of intranasal ketamine seems to be superior to oral, rectal and sublingual routes [8,12]. Pharmacokinetic profile of nasal atomizer of ketamine is suitable for the treatment of breakthrough pain, but the exact dosing of ketamine is difficult to control [151,152].

7.6. Rectal ketamine

Rectal bioavailability of ketamine (approximately 30%) and AUC of norketamine are very similar to those of a sublingual tablet [12]. Pharmacokinetics of rectal ketamine have been studied in adults and children during general anesthesia [12,153]. Suppository may be a treatment option for a patient who cannot swallow a tablet and for whom a ketamine injection is not a feasible choice.

8. Side-effects and limitations

Ketamine increases blood pressure and heart rate *via* sympathetic activation and preserves respiratory activity, thus making a lethal overdose unlikely. However, the safety profile of ketamine in the long-term use is unclear. Chronic administration of ketamine is linked to severe and

persistent urinary diseases such as cystitis, contracted bladder and bladder wall thickening [154]. The exact mechanism is unclear but it may involve many different pathways [155]. Cognitive disturbances may manifest in color perception, memory, attention, reaction time, sense of time and psychological addiction in chronic ketamine users [156,157]. Ketamine is a substance of abuse producing euphoria and dream-like hallucinations in a dose dependent manner [154]. Hepatic dysfunction has been reported in chronic ketamine abuse [157]. One further inconvenient, but clinically rather minor adverse effect is hypersalivation, which can be treated by concomitant anticholinergic administration [158].

9. Summary

Phencyclidine derivative ketamine antagonizes the NMDA excitatory receptors and produces dissociative anesthesia. The low-dose use of intravenous ketamine is increasing in various pain conditions. S-ketamine has higher affinity for the NMDA receptor and is a two times more effective anesthetic and analgesic than the racemate. S-ketamine produces fewer psychomimetic adverse effects compared with R-ketamine and racemate. Ketamine is demethylated mainly to norketamine, the analgesic potency of which has been estimated to be from one-third to one-fifth of ketamine's potency in animal models. After oral ketamine, plasma concentrations of norketamine are much higher than that of the parent drug ketamine. Oral bioavailability is only 8 – 24 % and oral dosing is very challenging, since concomitant use of drugs that interfere with CYP3A and 2B6 mediated metabolism, modulate oral bioavailability. Other drug formulations show better bioavailability and norketamine is produced less than after oral dosing.

Due to the central sympathetic stimulation, ketamine produces hemodynamically stable anesthesia. Animal studies indicate that ketamine has neuroprotective properties, but may be neurotoxic in immature brains in a dose dependent manner. Cerebral blood flow is increased after ketamine administration in specific brain structures, but ketamine does not raise ICP in traumatic brain injury or with other neurological patients, when patients are sedated and under mechanical ventilation. Ketamine has a rapid antidepressant effect, which could be utilized during ECT

therapy. Low-dose perioperative ketamine may reduce opioid consumption and postoperative pain after specific surgical procedures. Ketamine has a short-term analgesic effect in some chronic pain conditions but long-term analgesic effects are less well documented. Current evidence is insufficient to recommend ketamine as routine adjuvant therapy in cancer related pain. Ketamine may prevent opioid-induced hyperalgesia in some patient groups. The safety profile of clinical long-term use of ketamine is unclear.

10. Conclusions

The primary mechanism of action of ketamine, NMDA-mediated antagonism, is unique among the anesthetics and analgesics. Psychosomatic side effects limited its use, but availability of S(+)-enantiomer and subanesthetic dosing schemes have increased its use during recent years. Ketamine reduces effectively postoperative pain and opioid consumption after painful surgical procedures and some studies suggest that low-dose perioperative ketamine may reduce chronic postsurgical pain. However, long-term analgesic effects of ketamine in chronic pain are not well known. Ketamine may cease prolonged status epilepticus and has fast acting antidepressant action, thus several new indications are emerging in emergency care, neurology and psychiatry. In addition to intravenous dosing, new administration modalities have been developed to surpass parenteral dosing and diminish extensive cytochrome P50-mediated metabolism of ketamine.

Compliance with Ethical Standards

No funding has been received for the conduct of this study. Peltoniemi, Marko A; Hagelberg, Nora M; Olkkola, Klaus T and Saari, Teijo I have no conflicts of interest that are directly relevant to the content of this study.

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