S-ketamine for the treatment of depression

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Abstract

Ketamine infusion has been reported to rapidly relieve depressive symptoms and suicidal ideation in patients with treatment-resistant depression (TRD). It has also been tested in electroconvulsive therapy (ECT) anaesthesia and has been suggested to enhance the response to ECT. S-ketamine is less studied than a racemic mixture or R-enantiomer in these patients. S-ketamine is more potent as an anaesthetic and might thus also have a better antidepressive effect. In this article we present recent data concerning the antidepressive and adverse effects of S-ketamine compared with racemic and R-ketamine in major depressive disorder (MDD), especially in TRD. Based on recent literature, it is obvious that S-ketamine also possesses antidepressive properties. In ECT anaesthesia, S-ketamine might enhance the antidepressive effect of this treatment. S-ketamine may also be preferable when compared with other anaesthetics regarding adverse cognitive effects. Its adverse psychotomimetic effects may be avoidable when used in anaesthetic doses. Although the data on S-ketamine at the moment is only based on case reports and expert opinions rather than adequate prospective randomized studies, it still may offer an important option when treating severe and resistant depression.

Introduction

Ketamine is an analgesic and anaesthetic agent, a non-selective, non-competitive and high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist. Racemic ketamine has been reported to rapidly relieve depressive symptoms in major depressive disorder (MDD), in treatment-resistant depression (TRD) (1-4) and in patients with bipolar depression (5, 6) or suicidal ideation (7, 8). Racemic ketamine has also been studied in anaesthesia of electroconvulsive therapy (ECT) and has been reported to improve the therapeutic effects of ECT (9-18).

NMDA receptor antagonists like ketamine facilitate glutamatergic neurotransmission through blocking the NMDA receptors resulting in increased glutamate in the frontal lobe (19). Glutamate is the most common excitatory neurotransmitter in the Central Nervous System, both in cortical and subcortical areas. It is synthesized from glutamine via glutaminase and released from presynaptic vesicles mainly via voltage-gated Ca2+ channels (20). Glutamic acid decarboxylase transforms glutamate into inhibitory neurotransmitter gamma-aminobutyric acid (GABA), while glutamine synthetase degrades glutamate to glutamine. The effects of synaptic glutamate are regulated by glutamate transporter proteins. Extracellular lack of glutamate impairs synaptic plasticity and excess causes oxidative damage and excitotoxicity through excessive accumulation of intracellular calcium (21). Postsynaptically, signals are transmitted by ionotropic receptors: NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) and kainate receptors and by metabotropic receptors (mGluR1 - mGluR8) (20). Glutamate is involved in cognition and regulation of emotions, as prototypic forms of synaptic plasticity at glutamate synapses are long-term potentiation (LTP) and depression (LTD), in hippocampus, amygdala and prefrontal cortex (22), and presumably also in the neurobiology of schizophrenia (23). In addition to glutamatergic effects, ketamine is also involved in several other neurotransmitter systems, like striatal and nucleus accumbens dopamine release, dopamine, serotonin and noradrenaline transporter proteins and GABAergic activity. It has been reported to have neuroplastic effects through activation of trophic factors like nerve growth factor (NGF) (24).

Racemic ketamine consists of two enantiomers, R(-) and S(+) ketamine. The S(+) enantiomer has a 4-fold affinity to NMDA receptors and 3-fold anaesthetic potency, compared with the R(-) ketamine (25, 26). The S-ketamine has been found to specifically bind to phencyclidine (PCP) sites of the NMDA receptors, whereas R-ketamine also binds to sigma sites (27). Both racemic and S-ketamine seem to increase cerebral blood flow (CBF) dose-dependently. Sub-anaesthetic doses of S-ketamine increased the whole brain CBF by 14%, and anaesthetic doses further extended the effect to 36% (28, 29). In healthy individuals, S-ketamine increased brain metabolism in several cortical areas and in the thalamus in positron emission tomography, but R-ketamine had the opposite effect in corresponding areas of the brain (30).

Pharmacology of S-ketamine related to depression

Ketamine has been in clinical anaesthetic use since 1970. It produces dose-dependent unconsciousness and analgesia. The anaesthetic state has been called dissociative, as the term dissociation was thought to best describe the effect of ketamine (31). The patient appears to be fully awake, though is unaware of the vicinity and remains non-reactive to surgical stimulation. Due to unpleasant physical side effects, ketamine has not gained wide popularity. However, it maintains blood pressure and circulation better than other anaesthetics in hypovolemic patients, and possesses strong analgesic effect. It has been previously used in war surgery and emergency medicine. Recently, ketamine has gained some increased interest, mainly due to its efficacy in chronic pain states and favourable profile in treatment of opioid tolerance and hyperalgesia (32).

The pharmacokinetics of ketamine depends on the route of administration. Typically, the intravenous or intramuscular way is used. Intramuscular administration leads to 90% bioavailability, while the bioavailability after oral use is only 20% (33). It is initially distributed to highly perfused tissues like the brain, where the concentration rises four to five times greater than in plasma (34); thereafter redistributed within minutes, and finally eliminated (35). Elimination half-life of racemic ketamine is 2.17 hours (35). Ketamine metabolism takes place in the liver. It is mainly N-demethylated to norketamine by cytochrome P450 enzymes, mainly CYP3A4 as well as CYP2B6 and CYP2C9 (36). Norketamine is an active metabolite, owing 1/5 to 1/3 of the potency of ketamine (37). After biotransformation, ketamine and its metabolites are mainly secreted in urine (37).

After a 1-2 mg/kg intravenous bolus dose of racemic ketamine, unconsciousness lasts for 5-10 min. Full recovery is reported to occur within 2 hours (31). The enantiomers do not differ pharmacokinetically from each other (38), although the elimination clearance and distribution volume of S-ketamine appears to be higher (39), and its ability to suppress EEG activity is stronger than with a racemic mixture of ketamine (40).

Because ketamine possesses unique properties, compared to other conventional anaesthetics, it has gained a small but important role in anaesthesiology. Side effects are most common in adults (compared to adolescents younger than 16 years of age), females and those with history of personality disorders (37). Concomitant use of benzodiazepines has been reported to decrease the incidence of untoward side effects of ketamine anaesthesia (41).

Clinical efficacy of S-ketamine in major depression

Until now no randomized, blinded, placebo-controlled studies with either racemic ketamine or S-ketamine in depressive disorders have been published. There are also no head-to-head comparisons between racemic ketamine and S-ketamine in MDD. Reports concerning the use of S-ketamine in these patients are far less than those with racemic ketamine. In a recent preclinical study, S-ketamine was reported to have a poorer and shorter antidepressant effect than R-ketamine in mice (42). The authors suggested that R-ketamine may be a more potent antidepressant, relative to S-ketamine, and that R-ketamine may also have less psychotomimetic side effects. In another clinical report, however, S-ketamine caused less adverse psychotomimetic effects compared to racemic ketamine in two patients having MDD, although showing a similar antidepressive effect (43). In addition, oral S-ketamine of 1.25 mg/kg as an add-on medication to standard antidepressants was studied in four TRD patients (44). Two patients had an early response and stayed in remission in two weeks follow-up. Oral S-ketamine was well tolerated in these patients. In a recent sample (six patients) of Segmiller and co-authors, repeated S-ketamine infusions resulted in improvement of depressive symptoms in three patients with TRD and in remission in two patients in four weeks treatment (45). The most potent antidepressant effect was seen after the first infusion of S-ketamine.

In our recent report on S-ketamine in ECT anaesthesia as subanaesthetic adjuvant dose (in combination with propofol), S-ketamine did not show any extra advantage compared with conventional ECT in patients with TRD (46). However, in a retrospective study by Hoyer and co-workers, S-ketamine anaesthesia during ECT sessions was associated with higher quality seizures compared to thiopental and propofol anaesthesia (47). In another retrospective study in TRD patients, S-ketamine anaesthesia in ECT resulted in fewer ECT sessions compared to thiopental anaesthesia and also in better treatment response in the Hamilton Depression Rating Scale (13). This suggests that S-ketamine enhances the antidepressive effect of ECT. A difference was also noticed in the Mini-Mental State Examination (MMSE) score in favour of S-ketamine compared to thiopental. Moreover, ketamine has been shown to be preferable to thiopental (13), methohexital (48) and etomidate (49) regarding cognitive deficits after ECT. Ketamine's favourable effect on cognition may be related to NMDA receptors.

Adverse effects of S-ketamine

Derealisation and hallucinations are commonly reported adverse effects associated with racemic ketamine (50). The incidence of psychiatric symptoms after ketamine has varied between 5 and over 30 per cent (51, 52). These side effects have been characterized as alterations in mood state and body image, dissociative or extracorporeal experiences, sensations of floating, vivid dreams, illusions, and delirium. Flashbacks occurring several weeks after ketamine have also been described (37).

S-ketamine has been reported to induce more psychotic symptoms, loss of interest and emotional withdrawal compared with R-ketamine in healthy volunteers (30). In a study of ten healthy volunteers receiving R- or S-ketamine, the incidence of subjective side effects was low, but more frequently associated with R- than S-ketamine (38). The most common symptoms were drowsiness, dizziness, drunkenness, sensation of floating, distorted body experience and distorted vision/hearing (38). In repeated S-ketamine infusions in six TRD patient samples, two patients reported pronounced dissociative symptoms (45). Contrarily, S-ketamine has been reported to be better tolerated with fewer adverse psychotomimetic effects than R-ketamine in two depressive patients (43). Dissociative symptoms caused by S-ketamine may be dose-dependent and appear at low, subanaesthetic doses. In ECT anaesthesia, the preferable dosage level of S-ketamine would be around 0.8-1.2 mg/kg IV. to avoid these adverse effects (47). Even in patients with schizophrenia and schizoaffective disorder, no worsening of psychotic symptoms occurred with ketamine anaesthesia in ECT (53).

It has been suggested that propofol in combination with racemic ketamine in ECT anaesthesia may relieve adverse psychotomimetic effects compared to racemic ketamine alone (54). In our recent study as well as in recent meta-analysis, patients having S-ketamine as an anaesthetic adjuvant during ECT still had more post-treatment disorientation than the patients receiving propofol alone (46, 55).

S-ketamine anaesthesia in ECT resulted in a temporary rise of blood pressure, which could be managed with application of intravenous urapidil (47). Hypertension and autonomic activation associated with S-ketamine, especially during ECT, should be noted in patients with cardiovascular disease.

Conclusions

The Vast majority of human ketamine data comes from volunteer studies or general patient series, and is therefore poorly generalized to the treatment of MDD and the practice of ECT. The suggested advantages of S-ketamine are not based on adequate prospective, randomized studies, but merely few case reports and expert opinions. Weak evidence of efficacy and tolerability of S- and R-ketamine points in both directions. Therefore, it is fair to conclude that the antidepressive and adverse effects of S-ketamine in relation to racemic ketamine or R-ketamine are highly unknown. However, the binding site somewhat differs with S-ketamine from R-ketamine in NMDA receptors, resulting in variations in activation of several cortical areas and thalamus between S- and R-ketamine. Thus, S-ketamine being more potent than R-ketamine as an anaesthetic might also indicate better antidepressive properties. In ECT anaesthesia, an enhancing effect may be possible. S-ketamine may also be preferable when compared with other anaesthetics regarding adverse cognitive effects of ECT. Its adverse psychotomimetic effects are dose-dependent and may thus be avoidable. S-ketamine may offer an important option when treating severe and resistant depression. Adequately powered studies focusing both on the efficacy and the post-treatment side effects of these medications should be performed. Larger studies revealing differences might also add knowledge on the architectural functionality of the NMDA-receptors in addition to the biology of severe depression.

S-ketamine may be a preferable anaesthetic in ECT treatment, where it should be used at maximal anaesthetic doses to avoid adverse psychotomimetic effects.

The data about S-ketamine is still sparse and adequately powered studies focusing both on the efficacy and adverse effects in treatment of depression should be performed in the future.

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