Ketamine pharmacology revisited

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Chapter 3

Inhaled ketamine: evaluation of safety and efficacy in healthy volunteers

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3.1 Introduction

The *N*-methyl-D-aspartate receptor antagonist ketamine is, apart from being a potent anesthetic and painkiller, a rapid-acting antidepressant.[1-3] It is currently administered to patients with therapy-resistant depression but requires multiple sessions to maintain its antidepressant effects.[3] Since ketamine is predominantly delivered intravenously, treatment is restricted to the clinical setting. This is often cumbersome and expensive. In order to circumvent the intravenous route, we explored the possibility of the deliverance of ketamine by inhalation. There are various advantages of drug inhalation with rapid delivery and absorption into the systemic circulation.[4] Additionally, inhalation is easily performed and may be achieved at home in a more comfortable setting for the patient. There are just few preliminary human data on nebulized ketamine.[5,6] In these studies, nebulized ketamine was successfully administered to postoperative adult patients to relief sore throat[5] and in preoperative pediatric patients to induce sedation.[6]

To understand the feasibility and impact of inhaled ketamine, we performed an exploratory study on increasing doses of inhaled esketamine (0.35, 0.5 and 0.7 mg kg^{-1}) followed by a single intravenous dose (0.3 mg kg^{-1}) in a small group of adult healthy volunteers. The main end-point of our study was the safety of the procedure with special emphasis on respiratory, hemodynamic and central (psychedelic) adverse events. The secondary end-point of the study was the assessment of inhalation efficacy as measured by esketamine and esnorketamine concentrations in plasma and to assess whether inhalation is equivalent to intravenous administration in terms of plasma concentration profiles and bioavailability.

3.2 Methods and materials

ETHICS

We performed a study on the safety, feasibility, pharmacokinetics and pharmacodynamics of inhaled ketamine in ten healthy volunteers from August 1, 2015 until January 1, 2016. The local Institutional Review Board and the Central Committee on Research Involving Human Subjects (CCMO) in The Hague approved the study. All subjects gave written informed consent prior to enrollment in the study. The study was registered at the Dutch trial registry under number NTR 5358.

PARTICIPANTS

Subjects of either sex, aged 18-39 years and with a body mass index <30 kg m^{-2} were eligible to participate in the study. An independent physician screened all subjects prior to enrollment. Exclusion criteria included a positive drug screen on the day of screening or on the day of testing, presence or history of any medical, neurological or psychiatric disease,

pregnancy/lactation in women, a history of illicit drug use or weekly alcohol intake >21 units/week, participation in another trial in the three months prior to enrollment, current use of any medication and abnormalities observed during physical examination. The subjects were asked to refrain from food and drinks for at least 8 hours before the inhalation of ketamine started. In addition, participants were not allowed to consume caffeinated drinks such as coffee, black tea or cola-drinks, energy drinks and chocolate for the 24 hours prior to the study. Finally, all subjects were requested to refrain from tonic and grapefruit-containing food or beverages during the 7 days preceding the study day.

STUDY DESIGN

Esketamine inhalation In this open-label feasibility and safety phase 1 study, subjects inhaled preservative-free (benzethoniumchloride) esketamine (concentration 5 mg ml^{-1}; Eurocept BV, Ankeveen, the Netherlands). We specifically used a preservative-free form of esketamine to avoid possible interaction of the preservative with lung tissue. To administer the drug, we used a nebulizer system (Aerogen Ultra, Medicare Uitgeest BV, Uitgeest, The Netherlands), which uses a palladium high-frequency vibrating mesh (Aerogen Solo Nebulizer) to aerosolize the liquid ketamine and deliver a pre-set quantity of drug to the spontaneously breathing subject. The system allows for supplemental oxygen delivery during inhalation. We attached the outlet of the device to the main venting system of the laboratory. Since the system uses a mouthpiece to deliver the aerosol, we placed a clip on the nose during inhalations to prevent nose breathing. All experiments started at 8 AM.

Drug administration and blood sampling The experiments started at 8 AM. All subjects inhaled three subsequent doses of undiluted esketamine, 0.35 (Low), 0.5 (Intermediate) and 0.7 mg kg^{-1} (High), *i.e.* 25, 37.5 and 50 mg in a 70 kg participant, with a pause of 60 minutes in between inhalations followed after another 60 minutes by a single intravenous infusion of 0.30 mg kg^{-1} (20 mg in a 70 kg participant). Using the specifications of the manufacturer (aerosol production from 0.5 ml fluid per min) we aimed at inhalation times of 10, 15 and 20 minutes. Blood samples from a 22-gauge arterial line, placed in the left or right radial artery, were drawn both during inhalation (4-5 samples, depending on the duration of inhalation) and following inhalation (6-7 samples). During the intravenous administration samples were obtained at times 2, 4, 8, 10, 15 and 20 minute and following administration at times 2, 4, 10, 20 40, 60 and 100 minute. Five ml blood was collected per sample. The analysis has been described previously.[7] In brief, the samples were centrifuged at a speed of 1,500 rpm for 15 minutes; 2 ml plasma was separated within 30 minutes of blood collection and stored at -25°C until analysis. For the construction of esketamine and esnorketamine calibration lines, solid substances were obtained from Parke-Davis (Dallas, TX) and Tocris (St. Louis, MO), respectively. After extraction from the

specific sample, esketamine and esnorketamine were determined by high-performance liquid chromatography on a Gemini C18 column (Phenomenex, Utrecht, The Netherlands) at 40°C. The mobile phase was a mixture of phosphate buffer 0.03 N:Acetonitril (92:8) at pH 2.25. Monitoring of the eluent was performed at 195 nm with a photodiode array detector (PDA 100, Dionex, Amsterdam, The Netherlands). The lower limit of quantitation was 10 ng ml^{-1}; none of the samples had esketamine or esnorketamine concentrations of less than 10 ng ml^{-1}.

Measurements The electrocardiogram, blood pressure and oxygen concentrations were continuously monitored using the Datex Cardiocap monitor (Datex, Finland), Vigileo monitor (Edwards Lifescience, Irvine, CA), and finger pulse oximeter (Masimo, Irvine, CA, USA), respectively. To quantify psychedelic side effects the Bowdle[8] questionnaire was taken upon termination of inhalation and infusion and every 20 minutes until the next inhalation or infusion. The Bowdle questionnaire has thirteen visual analogue scales (VAS) that describe the effect of ketamine on internal and external perception as well as the intensity of ketamine-induce drug-high.[9] Internal perception relates to the integrity of the inner self, external perception relates the integrity of the outer world. The Bowdle VAS were scored on a 100 mm scale ranging from 0 (= not at all) to 100 (= very much so). The complete set of thirteen questions is given in Supplementary Table S1. Additionally, to get an indication of the effect of esketamine inhalation on alertness, mood and calmness, the Bond and Lader questionnaire was taken.[10] Increased scores on 100 mm visual analogue scales indicate enhanced subjective feelings of alertness, contentedness (in general) and calmness.[9]

OUTCOME MEASURES AND DATA ANALYSIS

The primary end-point of the study was the safety of the procedure. To that end, we collected adverse events (*e.g.* low oxygen saturation, wheezing, difficulty breathing, nausea/vomiting, high blood pressure, cardiac rhythm disturbances, sedation) during esketamine inhalation and infusion. Additional adverse effects were related to esketamine-induced psychedelic symptoms and mood-related effects. The secondary end-point of the study was efficacy, which was assessed by the measurement of esketamine and esnorketamine plasma concentrations and calculation of bioavailability. A concentration above the minimum effective concentration of 100 ng ml^{-1} was considered adequate for therapeutic purposes.[11,12]

All data were summarized by mean ± SD or median (interquartile range) unless otherwise stated. Since the purpose of the study was purely descriptive and exploratory no comparative analyses were performed.

3.3 Results

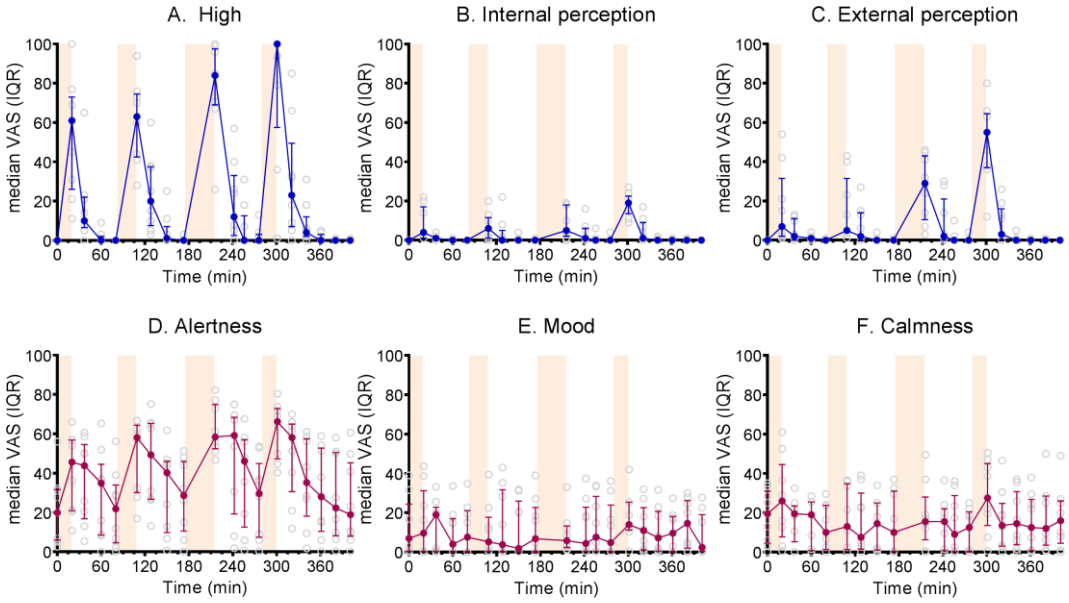
Eleven volunteers were recruited and participated in the trial. None experienced any serious adverse event. One subject did not complete the study due to persistent nausea and vomiting, which began at the start of the third inhalation. She was replaced by another female volunteer according to protocol and her data were discarded. Due to failure of the nebulizer in one subject, we report the data from the remaining nine subjects. These nine subjects (5 men, 4 women) were 24 ± 3 years of age and had a body mass index of 22.6 ± 1.6 kg m^{-2} (mean weight 71.4 ± 9.7 kg, mean height 178 ± 8 cm). All subjects indicated that inhalation from the nebulizer was tolerable and easy to perform. None of the subjects were incapacitated or sedated by the esketamine inhalation to a level that prevented the use of the nebulizer. The actual duration of inhalation for the complete uptake of esketamine took longer than initially expected. Mean inhalation times were 22 min (range 19-40 min), 33 min (24-51 min) and 41 min (30-54 min) for 0.35, 0.5 and 0.7 mg kg^{-1} esketamine, respectively.

The inhalant tasted mildly bitter. There were no incidences of oropharyngeal irritation, hypersalivation, stridor, laryngospasm, cough, dry mouth, hoarseness, dyspnea, tachypnea, aspiration or desaturations during or following the esketamine administrations. Additionally, there were no cardiac dysrhythmias. None of the subjects required supplemental oxygen during the study. Adverse events were limited to mild hypertension (*n* = 9), nausea (*n* = 2), vomiting (*n* = 1), the occurrence drug high (*n* = 9) and psychedelic side effects (*n* = 9). Mean arterial blood pressure increased dose-independently from 91 ± 6.9 mmHg (baseline) to 105 ± 11.7 mmHg (0.35 mg kg^{-1} inhaled esketamine), 104 ± 10.2 mmHg (0.5 mg kg^{-1} inhaled esketamine), 103 ± 7.2 mmHg (0.7 mg kg^{-1} inhaled esketamine) and 110 ± 9.0 mmHg (0.3 mg kg^{-1} intravenous esketamine). Blood pressure values dropped rapidly after the termination of esketamine administration to reach baseline values before the next administration. Nausea occurred in two subjects of which one vomited after completion of all esketamine administrations. The latter subject was successfully treated with intravenous ondansentron 4 mg.

The three factors of psychedelic effects (drug high, internal and external perception) derived from the Bowdle questionnaire are given in Figure 1; the response to the individual questions are shown in Supplementary Figure S1. The most prominent psychedelic adverse event was drug high that occurred during all three inhalation episodes in a dose-dependent fashion (Figure 1A). At the highest inhaled esketamine dose the VAS for drug high reached 84 (60-98) mm (median (IQR)) *versus* 100 (58-100) mm for the intravenous administration. Internal perception was mildly affected by inhaled esketamine irrespective of dose. Of the five scales that make up this composite score, item REALITY (item D of Supplementary Table S1 and Supplementary Figure S1D) was the

only contributor to the changes noted during esketamine inhalation. External perception scores were higher than scores for internal perception by about a factor of 2 with a peak score at the highest inhalation dose of 29 (11-43) mm *versus* intravenous esketamine 55 (37-65) mm. All six scales contributed equally to the esketamine-induced changes in the composite score (Supplementary Figure S1). The level of sedation during esketamine administration as determined from item K (DROWSY) of the Bond and Lader questionnaire (Supplementary Figure S3) was relatively mild to moderate and increased dose-dependently from 45 (14-63) mm (0.35 mg kg^{-1} inhaled esketamine) to 67 (37-91) mm (0.7 mg kg^{-1} inhaled esketamine) and 70 (35-75) mm (0.3 mg kg^{-1} intravenous esketamine). Neither sedation nor the psychedelic symptoms affected the inhalation of the esketamine.

Figure 1. Effect of esketamine administration on the composite scores of the Bowdle (**A**, **B** and **C**)



and Bond and Lader (**D**, **E** and **F**) questionnaires. Bowdle questionnaire: the scales describe the effect of ketamine on drug high (A), internal perception (**B**) and external perception (**C**). Bond and Lader questionnaire: the scales describe the effect of ketamine on alertness (**D**), mood (**E**) and calmness (**F**). The orange bars indicate the administration of esketamine (first administration is 0.35 mg kg^{-1} inhaled esketamine, the second 0.5 mg kg^{-1} inhaled esketamine, the third 0.7 mg kg^{-1} inhaled esketamine and the fourth 0.3 mg kg^{-1} intravenous esketamine). Values are median (interquartile range).

Esketamine had no effect on composite scales mood and calmness, as derived from the Bond and Lader questionnaire (Figure 1). In contrast the subjective feeling of alertness increased similarly during inhalation and intravenous administrations (peak VAS 59 (52-75)

mm and 66 (47-73) mm for 0.7 mg kg^{-1} inhaled and 0.3 mg kg^{-1} intravenous esketamine, respectively).

Esketamine and esnorketamine concentrations in plasma are shown in Supplementary Figure S2; pharmacokinetic parameters are given in Table 1. During all three esketamine inhalation episodes of a plateau in esketamine concentrations was observed, while esnorketamine concentrations steadily increased during inhalation. Esketamine C_{MAX} values increased dose dependently by 77% from the lowest to the highest inhalation dose; the intravenous esketamine C_{MAX} was 40% higher than that of the highest inhalation dose. Esnorketamine C_{MAX} values were about half of those of esketamine. Interestingly, the variability in plasma concentrations was in the same range during inhalational and intravenous esketamine administrations although the lowest variability was achieved at the highest inhalation dose (% coefficient of variation 16% *vs.* 25% for intravenous esketamine). Bioavailability of inhaled esketamine was 50%, indicative that just half of the administered esketamine reached the systemic circulation. Despite the higher C_{MAX} value, the intravenous dose of 0.3 mg kg^{-1} therefore corresponds best with the dose of the third and highest inhalation (0.7 mg kg^{-1}) in terms of total drug dose administered.

Table 1. Pharmacokinetic data of the inhalation and infusion of esketamine

Parameter	First inhalation	Second inhalation	Third inhalation
Dose (mg kg^{-1})	0.35	0.5	0.7
Duration of inhalation (min)	22 (7.2)	33 (8.4)	41 (6.6)
Esketamine			
C_{MAX} (ng ml^{-1})	128 (3)	180 (39)	227 (36)
Range (ng ml^{-1})	80-165	107-224	158-277
T_{MAX} (min)	22 (6.9)	15 (0)	25 (0)
CV (%)	26	22	16
Esnorketamine			
C_{MAX} (ng ml^{-1})	52 (15)	97 (21)	153 (27)
Range (ng ml^{-1})	40-81	68-126	75-219
T_{MAX} (min)	63 (7)	48 (7)	41 (7)
CV (%)	27	22	20

Values are mean (SD), except where indicated. C_{MAX}, maximal concentration during or following inhalation or infusion; CV, coefficient of variation; T_{MAX}, time of C_{MAX} from the initiation of inhalation or infusion.

3.4 Discussion

Traditionally ketamine is dissolved in saline and administered intravenously or intramuscularly. However, a dozen alternative routes, such as oral, nasal and rectal administration, have been described in the need of a less resource-consuming and painless administration.[13] Inhalation of nebulized ketamine is a relatively new route of ketamine administration. In this small study we explored the feasibility of esketamine inhalation in a group of young and healthy adult volunteers with special emphasis on safety and the plasma concentration range of esketamine and its major metabolite esnorketamine that is reached during inhalation.

Safety In order to reduce the probability of pulmonary toxicity we used preservative-free esketamine. Some effect of direct tissue exposure by (preservative-free) ketamine could not be excluded *a priori*, however.[14] We observed no respiratory adverse events during or after esketamine inhalation. This suggests that the procedure as applied by us is without clinical pulmonary toxicity but further studies with more prolonged exposures are necessary to come to more definite conclusions. Some mild hypertension was observed which was restricted to the period of administration only. This effect is directly related to the sympathomimetic effects of esketamine.[15] Psychedelic effects as measured by the composite scores on internal and external perception of the Bowdle questionnaire were lower during esketamine inhalation than during intravenous administration, although between-subject variability was high. The lower scores are probably related to the lower plasma concentrations during inhalation. Drug high seemed independent on esketamine dose and route of administration. Finally, mood and calmness remained unaffected by esketamine, while alertness was reduced due the occurrence of sedation. Still, this did not reduce the participant's ability to operate the inhaler system. Given these results, we conclude that inhalation of preservative-free esketamine at a concentration of 5 mg ml^{-1} is feasible and safe for up to 40 minutes with minimal psychedelic effects or mood related changes.

Efficacy Inhalation times were about twice as long as initially expected: 22 *vs.* 10 min for the first inhalation, 33 *vs.* 15 min for the second inhalation and 41 *vs.* 20 min for the third inhalation. These initial expectations were based on the information provided by the manufacturer that stated that 0.5 ml fluid (or 2.5 mg of esketamine) would be nebulized per minute. Our results indicate that just 1.25 mg of esketamine from the solution of 5 mg ml^{-1} esketamine was nebulized per minute. We relate this to the higher viscosity of the esketamine. Ketamine's poise is three to four times greater than that of water. From the concentration profiles we estimated that the bioavailability of inhaled esketamine was 50%. This indicates that just half of the delivered esketamine reached the systemic circulation. Possibly due to esketamine's adhesiveness some drug got retained in the

nebulizer and mouthpiece. Additionally, some drug may have been swallowed or exhaled by the participants. This should be taken into account when designing a dose scheme for studies or patients. We are currently examining whether other types of inhaler have improved esketamine delivery profiles with less influence of esketamine's viscosity and adhesiveness.

During all three inhalations a steady state in esketamine plasma concentration was reached well above the minimal effective concentration of 100 ng ml^{-1}. This concentration threshold was exceeded within 10 minutes of inhalation. The chosen minimum effective concentration is based on previous studies which showed that both acute and chronic neuropathic pain relief is achieved at concentrations above 100 ng ml^{-1}. [11,12] For the treatment of depression the minimum effective concentration or therapeutic concentration range has not been defined as yet. A recent study by Singh *et al.*[3] showed that, in terms of dose, effective antidepressant effects are achieved at an intravenous esketamine dose of 0.2 mg kg^{-1}. This dose is equivalent to the inhalation of 0.4 mg kg^{-1} esketamine with the current inhalation system. The duration of inhalation will be about 27 minutes and our current results indicate that this procedure is associated will tolerable side effects.

In this study we restricted the pharmacokinetic measurements to esnorketamine and its parent esketamine. Recent studies show that the downstream metabolite hydroxynor-ketamine is possibly the major contributor to ketamine's antidepressant effects.[16] In future studies we will address the issue of hydroxynorketamine contribution to inhaled ketamine's effects on symptoms of depression.

3.5 Conclusion

In this small exploratory observational study we show that inhalation of preservative-free esketamine rapidly produces steady-state esketamine plasma concentrations in the therapeutic concentration range without clinical signs of toxicity. The observed adverse events were mild and well accepted by the participants and did not interfere with the operating of the inhalation device. Inhalation of ketamine seems a valid alternative to intravenous ketamine administration without the need for an intravenous access line. Inhalation may be administered outside the hospital setting for a variety of indications including depression, chronic neuropathic pain, pain in the palliative setting and treatment of post-traumatic stress disorder.

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Appendix A. Supplementary data

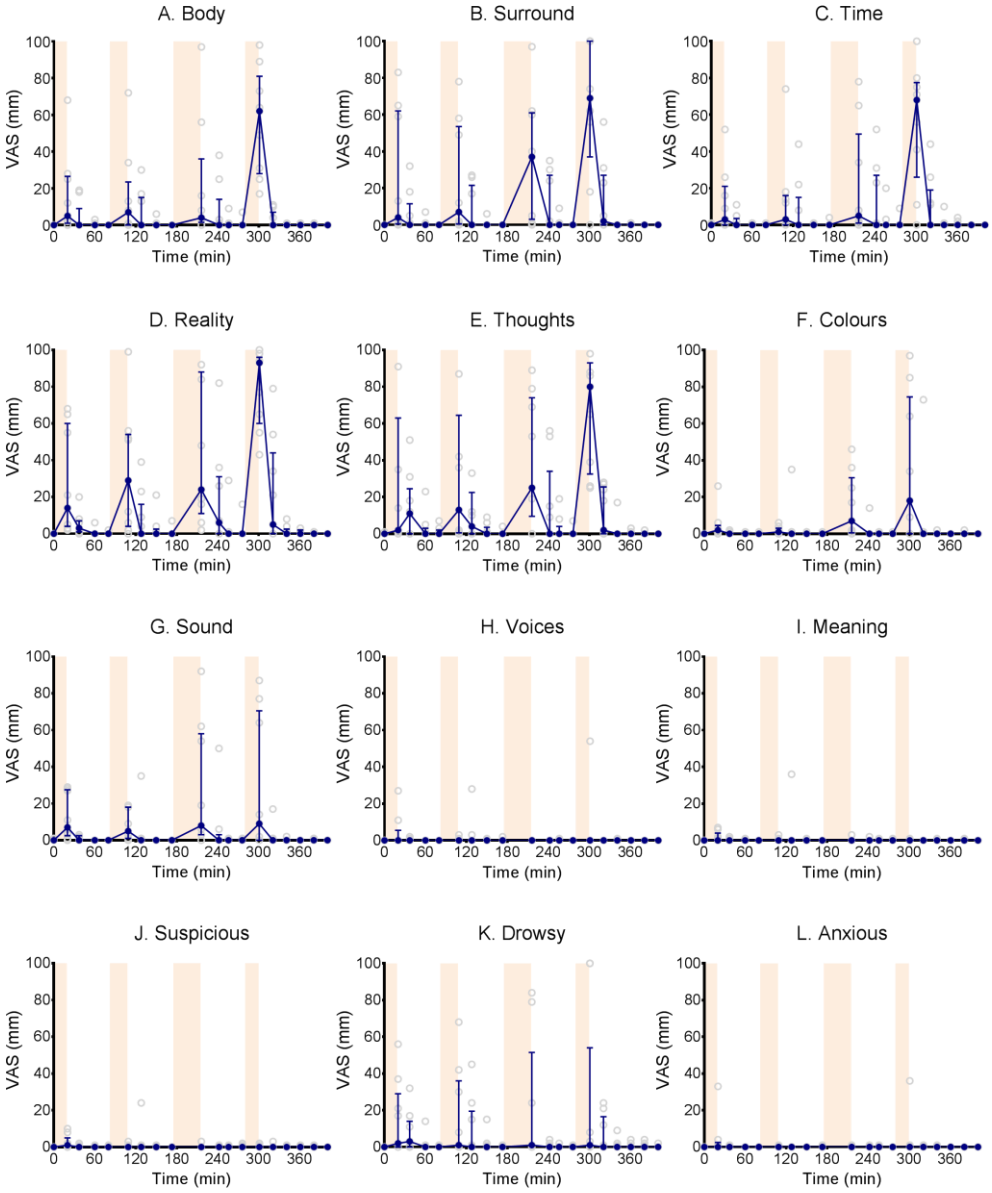

Figure S1. The effect of esketamine on 12 of the 13 scales of the Bowdle questionnaire. External perception is derived from items (**A-C,E-G**). Internal perception is derived from items (**D,H-J,L**). The effect of ketamine on HIGH is given in Figure 1**A**. Item **K** (DROWSY) does not contribute to the composite scales. See Supplementary Table S1 for the description of the different scales. Values are median (interquartile range).

Table S1. The Bowdle scales[8]

A. My body parts seemed to change their shape or position (BODY)
B. My surroundings seemed to change in size, depth, or shape (SURROUNDINGS)
C. The passing of time was altered (TIME)
D. I had feelings of unreality (REALITY)
E. It was difficult to control my thoughts (THOUGHTS)
F. The intensity of colors change (COLORS)
G. The intensity of sound changes (SOUND)
H. I heard voices and sounds that were not real (VOICES)
I. I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING)
J. I had suspicious ideas or the belief that others were against me (SUSPICIOUS)
K. I felt high (HIGH)
L. I felt drowsy (DROWSY)
M. I felt anxious (ANXIOUS)

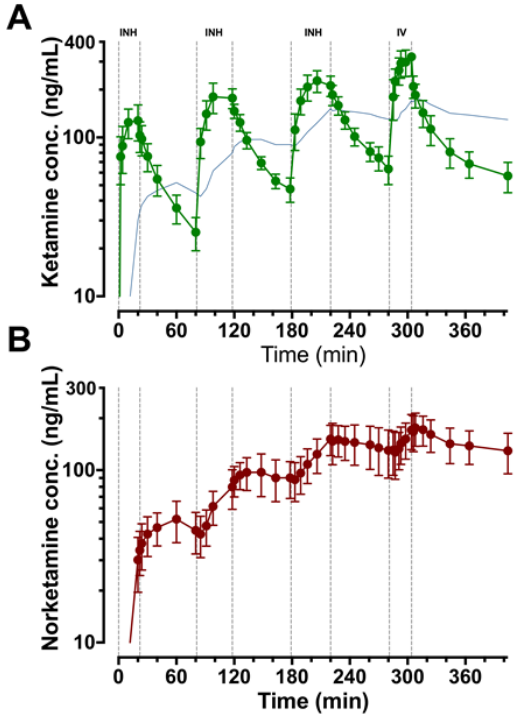

Figure S2. Measured esketamine (**A**) and esnorketamine (**B**) concentrations. The grey broken horizontal lines indicate the administration periods (INH inhalation, IV intravenous). The continuous blue line in (**A)** depicts the esnorketamine concentration. Values are mean (SD).

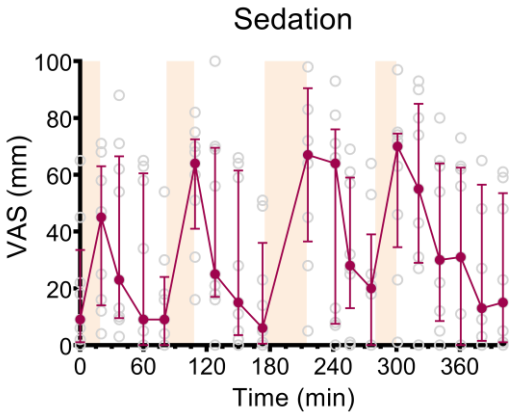

Figure S3. Sedation as derived from the Bond & Lader questionnaire (item DROWSY). Values are median (interquartile range).