

Intravenous ketamine therapy in a patient with a treatment-resistant major depression

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Summary

Background: Recently, reports from North America have indicated that the intravenous infusion of ketamine hydrochloride (an N-methyl-d-aspartate receptor antagonist) results in a sudden and robust improvement of depression symptoms.

Objective: To corroborate antidepressant effectiveness of IV ketamine in a patient with a co-occurring substance use disorder for the first time in a European clinical setting.

Design: Open label trial

Methods: A 55-year-old male subject with a treatment-resistant major depression and a co-occurring alcohol and benzodiazepine dependence received an intravenous infusion of 0.5 mg/kg ketamine over a period of 50 minutes. Effects were assessed by means of a clinical interview, the 21-item Hamilton Depression Rating scale (HDRS), and the 21-item Beck Depression Inventory (BDI)

at baseline, 1 hour, 1 day, 2 days, and 7 days after intervention.

Results: Following the administration of ketamine the subject experienced a significant improvement of his symptoms peaking on the 2nd day post infusion (HDRS from 36 to 16; –56.6%, BDI from 26 to 9; –65.4%).

The subject first reported improvements 25 min. into the infusion and continued to describe positive effects throughout the subsequent 7 days.

Conclusion: Ketamine not only seems to have strong antidepressant effects but also to act very swiftly. These actions were unaffected by an alcohol or benzodiazepine dependence.

Key words: treatment-resistant major depression; N-methyl-d-aspartate receptor antagonist; ketamine

Introduction

It is widely accepted that at least 20% of all depressed patients do not respond adequately to several antidepressant drugs [1]. Recent reports from North America have suggested that an intravenous infusion of ketamine results in a fast (onset within hours) and drastic improvement of depression [2–4]. In one current trial [4] 71% of all otherwise treatment-resistant patients responded (> –50% on the HDRS) [6]. The exact mechanism for this effect is still unknown. However, modulation and dysfunction of the glutamatergic system seems to be involved in depression. Unlike monoaminergic antidepressants ketamine acts directly at the NMDA receptor and thereby may bypass long neurotrophic signalling cascades, which in turn could be the reason for the delayed effects of traditional antidepressants [4]. Ketamine is a chiral compound and a dissociative anaesthetic. Because of psychotomimetic effects induced by ketamine in

dosages necessary for anaesthesia (0.7–2 mg/kg bodyweight) its use in human medicine has decreased. For antidepressant effects a non-anaesthetic dosage of 0.5 mg/kg was needed.

Known side effects include perceptual disturbances, confusion, elevations of blood pressure, euphoria, dizziness, and increased libido. These adverse effects cease about 80–110 min after an IV infusion.

Previous to this study only subjects without a current comorbid substance use disorder were included in clinical trials with ketamine [4]. In the trial by Zarate et al. 7 out of 18 patients had a lifetime comorbid substance abuse, but were not permitted to consume for 90 days prior inclusion in the study. Since this is a rare clinical situation our objectives were to replicate and further evaluate ketamine's antidepressant effects in a substance abusing subject.

Patients and methods

For this open label trial we recruited a 55 year old male subject with a history of a treatment resistant major depression (DSM-IV). Furthermore the subject met DSM-IV criteria for a co-occurring alcohol, benzodiazepine and nicotine dependence. A SCID II interview revealed no personality disorder. There was no history of schizophrenia, schizoaffective, bipolar- or an organic mental disorder.

Between 2002 and 2006 the subject had been admitted seven times to inpatient psychiatric services with the following symptoms: restlessness, feelings of hopelessness, helplessness, feelings of guilt, sadness, anxiety, early morning awakening, loss of interest in formerly enjoyable activities, and suicidal ideation. These symptoms had developed after the commercial failure of the patient's company in 1999 and had worsened since then. Over a period of five years the subject had been treated with a wide variety of antidepressants: citalopram (40 mg/d), paroxetine (40 mg/d), mianserine (120 mg/d), mirtazapine (30 mg/d), venlafaxine (375 mg/d), trimipramine (350 mg/d), trazodone (900 mg/d), and escitalopram (20 mg/d). Augmentation therapy had comprised methylphenidate, valproic acid, lithium, olanzapine, quetiapine, bupirone, and chlorprothixene.

Throughout 2002 the subject had received cognitive behavioural therapy in a day clinic.

All psychopharmacological and psychotherapeutic interventions were tolerated well, but failed to achieve remission.

In April 2006 electroconvulsive therapy (ECT) was considered. Since benzodiazepines are known to increase seizure threshold and might thereby complicate ECT, a benzodiazepine reduction treatment was initiated [5]. However, the dosage of lorazepam could not be reduced beyond 4mg/d without strongly increasing symptoms of restlessness. Thus this option was ruled out.

By November 2006 the subject continued to be severely depressed as indicated by weekly clinical interviews, scores on the 21-item HDRS between 33 (14 days prior infusion), 35 (7 days prior infusion), and 36 (2 hours prior infusion) and a BDI [7] score of 26 (2 hours prior infusion). Throughout the study all HDRS ratings were performed by the same psychiatrist three times during the week prior infusion, as well as on day 1 and 7 post treatment.

The patient also completed the self rating question-

naire BDI two hours before treatment, as well as two hours and on days 1, 2, and 7 after treatment. Consumption of nicotine and alcohol had been stable over the course of 6 months at three packets/d and 2.5 l beer/d, respectively, while consumption of benzodiazepines had risen over the same period from 5 mg to 15 mg lorazepam/d. The subject did not consume any other legal or illegal substances as indicated by urinalysis.

Seven days before ketamine infusion, antidepressant medication with trimipramine was stopped, to allow for a wash out period.

The anaesthesiologist involved in the present study judged the concomitant medication (lorazepam) as not being dangerous for the trial.

Prior to inclusion in the study, the subject received a routine medical work up. With the exception of high blood pressure (RR 155/95 mm Hg) the subject was in good physical health. Routine laboratory evaluation revealed the following abnormalities: cholesterol 8.3 mmol/l, triglycerides 2.1 mmol/l, and γ -GT 97 U/l. A cranial MRI, an EEG, an ECG and a chest-radiography showed no pathological findings. BMI was 24.8.

On the day of infusion the subject was admitted to the inpatient unit for dual diagnosis patients in our psychiatric hospital and then, after testing, transferred to the perianaesthesia care unit of the Balgrist hospital. There, the patient received an intravenous infusion of saline solution with 0.5 mg/kg of ketamine hydrochloride (Ketalar®, Pfizer), via an infusion pump over 50 min. During administration of ketamine the subject's ECG, blood pressure, and oxygen saturation were continuously monitored.

After the infusion the patient was transferred back to the psychiatric unit. Blood pressure measurement continued on an hourly basis until the subject fell asleep.

One day after infusion the subject was discharged. Further HDRS and BDI testing was done in an outpatient setting.

Clinically the subject did not exhibit signs of impairment in respect to consciousness, orientation, and attention. Previously to this study, the subject's accountability towards the ketamine intervention was evaluated and confirmed by a psychiatrist who was neither involved in the trial nor part of our hospital.

The study procedures and possible side effects of the study medication had been carefully explained and patient's written informed consent was obtained.

Results

At baseline, two hours before intervention, depression score on the HDRS was 36 and 26 on the BDI. Two hours after the ketamine infusion the BDI score had dropped by 9 points (or 35%) to 17 and continued to decrease to 11 (–58%) one day and to 9 (–65,4%) two days after the end of the trial. Seven days later, HDRS and BDI-scores were both 14.

Two days after the intervention HDRS score was reduced to 16 (–56.6%). In the self rating questionnaire BDI remission was indicated (<9 BDI). Regression of symptoms started 25 min into the infusion, when the subject started to report dizziness and dissociative symptoms. The subject de-

scribed a feeling of being “lulled in cotton” and being “slightly agravic”. However these sensations along with the other symptoms completely vanished two hours after the end of the infusion.

With the onset of these effects the subject began to describe a reduction in restlessness, which remained blunted for the next two days and resulted in a reduced craving for lorazepam. Although encouraged to avoid withdrawal symptoms, the subject accepted only 10 mg of lorazepam on the day of infusion.

Starting the second day the subject consumed the same amount of lorazepam as prior to the intervention. Craving for nicotine and alcohol

remained the same before and after ketamine infusion. During the entire procedure the subject remained conscious and oriented. Thirty minutes after the end of treatment the subject felt entirely unimpaired and moved around freely. Immediately after the end of the infusion the subject reported feeling less depressed, exhibiting no more signs of sadness or anxiety. He started to chat candidly with hospital staff.

The subject's mood continued to improve over the next several hours; two days later, he even stated to have rediscovered sexual interest during that time.

On the day following the infusion, the subject reported an undisturbed sleep for the first time in months. However, on the 2nd day after discharge, the subject described early morning awakening.

No cardiovascular complications were observed. Forty-five minutes after the start of the infusion, blood pressure increased to 178/105 mm Hg with a heart rate of 94. Fifteen minutes after the end of the IV application of ketamine blood pressure had returned to its initial values of 153/95 mm Hg. Monitoring remained uneventful for the following night.

Discussion

In summary, we found a single infusion of 0.5 mg/kg ketamine to have a strong antidepressant effect, which was not affected by a co-morbid abuse of benzodiazepines and alcohol.

This suggests that infusion of ketamine might be a valuable treatment option for a wider range of patients than previously reported.

Our results are in accordance with the previous findings of Berman et al. [3] and Zarate et al. [4]. The former found that four out of eight patients achieved an at least 50% reduction in HDRS scores over a three day period post infusion; the latter reported to have found 71% to respond- and 29% to remit on day one. Although our patient did not reach remission in the first 24 hours, we registered an improvement of 56.6% in the HDRS score over the course of two days post infusion. Similarly to the other studies, the onset of improvements was very rapid within minutes after ending the infusion.

There is some speculation whether the presence and a certain intensity of psychomimetic ef-

fects are necessary for the antidepressant effects to occur [3]. Furthermore, it is not yet completely clear if directly targeting the NMDA receptor complex is essential for the dramatic and swift antidepressant effects.

For further research we would therefore suggest to compare different dosages, different intervals of administration and different forms of application.

In conclusion, ketamine seems to have a high potential in the treatment of refractory depression. Additional studies are certainly needed to confirm these preliminary findings.

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References

- 1 Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, et al. The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry*. 2002;63:963-71.
- 2 Check E. Depression: Comfortably numb. *Nature*. 2006;443:629-31.
- 3 Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47:351-4.
- 4 Zarate CA Jr, Singh JB, Carlson PJ, Brusche NE, Ameli R, Luckenbaugh DA, et al. A randomised trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63:856-64.
- 5 King PH, Shin C, Mannsbach HH, Chen LS, McNamara JO. Microinjection of a benzodiazepine into substantia nigra elevates kindled seizure threshold. *Brain Res*. 1987;423:261-8.
- 6 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
- 7 Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry*. 1974;7:151-69.

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