Introduction

Physicians who care for pain also must manage comorbid depression, which if not treated, may affect the outcome of pain treatment. When treating patients suffering from complex regional pain syndrome (CRPS) with a low-dose (subanesthetic) ketamine infusion [1–3], it was observed that some patients made a significant recovery from associated depression. This recovery was not formally documented, as the primary concern was the treatment of the patient’s pain. Needless to say, it was not possible to quantify to what degree depression recovery was secondary to the patient’s recovery from CRPS. Based on this result, it was thought that a low-dose (subanesthetic) infusion of ketamine was worth a trial in patients who were suffering from treatment-resistant depression without other physical or psychiatric illness. Approval for this trial was obtained from the hospital research and ethics committee.

Methods

Ketamine was infused intravenously to patients commencing at 15–20 mg/h (0.1–0.2 mg/kg/h) and the dose increased until a maximum tolerated dose was achieved. This dose was assumed to be a therapeutic dose and was maintained for 5 days. Patients were able to eat, drink, watch television, or read. They could feel inebriated and/or unsteady when walking. If hallucinations occurred, the dose was to be reduced. The patient’s normal medications were continued as it was feared that stopping them may result in a severe depressive episode.

Before and following each treatment with ketamine, at patient clinic visits, the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Score (HAMD-17) were obtained.

Results

The first two patients are described in detail:

Patient A is a 39-year-old, 101 kg woman with an 18-month history of depression. Her illness resulted in her being unable to continue her work. Patient A had been treated with Citalopram, Mirtazapine, and Venlafaxine, but these were ineffective. There was moderate but short-lived response to electroconvulsive therapy, so she was considered for the ketamine infusion trial.

The ketamine was commenced at 15 mg/h (0.15 mg/kg/h) and titrated to 27.5 mg/h (0.27 mg/kg/h). At this level, the patient was “a bit heady” but did not hallucinate. Nursing staff and family noted a positive improvement in the patient after 24 hours, particularly a decrease in fluctuation of mood. After 48 hours she began to show an interest in her pastimes and after 72 hours began cooking meals and snacks for patients and staff. She was discharged after 5 days and continued to improve for several weeks. At a follow-up visit 1 month after treatment, her 9-year-old son said “I have got my mummy back.” Twelve months after her treatment, she continues to be a bright, happy person and is participating in a “return to work” program. Current medication is Citalopram 40 mg mane.
Table 1 presents the BDI and the HAMD-17 score for patient A before her first ketamine treatment and at subsequent office visits.

Patient B is a 33-year-old, 101 kg man whose depression dated from his mid-teens and for the last 4 years had been constant. He had been treated with Fluoxetine, Nefazadone, Venlafaxine, Mirtazapine, Amisulpride, Lithium augmentation, and ECT. As all treatment modalities had been tried with only marginal but unsustained benefit, so he was considered for the ketamine trial.

Ketamine was commenced at 20 mg/h (0.2 mg/kg/h) and titrated to 30 mg/h (0.3 mg/kg/h). At this dose, the patient said he felt “a bit heady” but he did not hallucinate. After 48 hours, the patient said he felt better in his mood, and nursing staff noted that he appeared brighter and was more spontaneous in his speech and expressions. After 72 hours, he was talking positively about his future plans, interacting with staff, and initiating conversation. After 96 hours, there was some fluctuations in mood, but nursing staff reported that he was smiling and in good humor. He was discharged after 5 days of treatment.

This patient continued to improve for several weeks. He found employment at a local supermarket, initially for 12 hours/week. He was able to socialize well with people and used his spare time to attend college to have a computer course. After 2.5 months, the patient reported that his depression was returning, and this was confirmed by HAMD-17 and BDI scores. He was readmitted and a second course of ketamine at 30 mg/h (0.3 mg/kg/h) was given. Nursing staff reported improvement over the 5 days similar to that seen on the first admission. However, the patient and his mother felt that there was little change. It was about 10 days after the completion of the second infusion cycle that he reported that “the fog has lifted,” and his mood rapidly improved after that. He required a third course of treatment after another 6 months.

Twelve months after his first infusion cycle, he remains bright and happy. He has full-time employment and commenced painting his parents’ house. He is planning an overseas holiday. He has been reluctant to cease any of his medications because he “feels so well and doesn’t want to change anything.” Current medication is Lithium Carbonate 500 mg/day.

BDI and HAMD-17 score before and after ketamine treatment are presented in Table 2.

Discussion

The two patients had been managed by the psychiatric department for 18 months and 16 years, respectively, but there was no significant improvement in their depression, so the improvement observed after the infusion is unlikely to be related to their previous treatment. A synergistic action between conventional treatment and ketamine is possible.

The titration of ketamine to determine the maximum tolerated dose ensures that a significant amount of ketamine acts on the central nervous system. This method allows the dosage to be individualized for each patient and assumes that the maximum tolerated dose is a therapeutic dose for depression. The titration method makes the use of placebo controls very difficult, if not impossible, and the lack of control is an obvious disadvantage in this study. However, it is to be considered that the patients chosen are those with chronic depression who have not responded to conventional treatments, so the long-term recovery suggests that this is not a placebo effect.

A mild feeling of “headiness” or inebriation was the only side effect of ketamine observed in these patients. This was considered the end point of the titration. No sedation or hallucinations or changes in liver function were observed, and there were no changes in blood pressure or pulse. The dose of ketamine used is well below the anesthetic dose, so we believe it is safe to treat the patient in a general ward situation.

Table 1  Depression scores. Patient A

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relatives approximately 24 hours after a therapeutic dose of ketamine was achieved, and there was continued improvement for 72–96 hours. This is similar to the time required for CRPS patients to respond.

The improvement in depression being maintained for 12 months in patient A and recurrence at 2.5 months and 9 months in patient B is also consistent with the response of CRPS patients to ketamine infusion described in an earlier article [3]. This suggests that ketamine is acting in a similar manner in both depression and CRPS.

The pathology of depression is not known, but there is evidence that overactivity of the N-methyl-D-aspartate (NMDA) receptor often occurs. Sanacora et al. [4] say that many antidepressant drugs such as the tricyclics do have NMDA blocking properties. Kudoh [5] has shown that a single dose of ketamine (0.5 mg/kg) given to depressed patients having orthopaedic operations did result in improvement that lasted for several days. We suggest Kudoh’s method would have resulted in a therapeutic level of ketamine being achieved, but this level was not maintained for sufficient time to produce a long-lasting result.

The rationale for using ketamine is that it is the only noncompetitive NMDA blocking agent that is readily available for clinical use.

Our results add more evidence to the theory that NMDA overactivity is significant in some patients with chronic depression.

Conclusion

The two patients have experienced a very significant and long-lasting response to ketamine infusion.

It is likely that the ketamine infusion allows the overactive NMDA receptor to reset to normal activity and so relieve the patients’ symptoms.

References