CASE REPORT

Sustained antidepressant response to ketamine

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SUMMARY

Case series outlining the treatment of three patients with ketamine, in which two of the patients had a sustained antidepressant effect to ketamine without the need for maintenance on antidepressants. These two responders have an established diagnosis of bipolar affective disorder with a history of response to electroconvulsive therapy and lithium, both of which have an influence on the seizure threshold as has ketamine. The mechanism of action of ketamine is yet unclear and although the current focus is on the *N*-methyl-d-aspartate and alpha-amino-3-4-hydroxy-5methyl-4-isoxazoleproprionic acid receptors, we additionally recommend that its impact on the seizure threshold should be explored with a view to fully elucidating the mechanism of action.

BACKGROUND

There is at present interest in the possible antidepressant effects of ketamine a glutamate *N*-methyl-d-aspartate (NMDA) receptor antagonist. In 2000, Berman *et al*[1] reported an antidepressant effect of ketamine in a randomised placebo-controlled trial. Since then, nine other studies mainly of treatment-resistant depression with small sample sizes have yielded similar findings.[2]

The mechanism underlying ketamine's putative antidepressant effect is unclear. While the focus is on the NMDA receptor, it should be noted that ketamine has effects on other systems. The development of new compounds with an effect on the NMDA receptors has aimed at reproducing the antidepressant effect of ketamine without its dissociative or hallucinatory effects.[3 4] It is useful to exclude unnecessary properties; however, it raises an issue of what property developers should attempt to optimise in order to produce an antidepressant effect.

We report two patients with a long history of bipolar affective disorder (BPAD) who were administered ketamine. The third patient was referred to our service for electroconvulsive therapy (ECT) but the patient opted for treatment with ketamine.

The dose utilised in all the three cases was 100 mg of intramuscular ketamine. This dose typically lasts an hour and leaves a subject conscious and aware of background events but produces dissociative effects. This series highlights both remarkable responses to ketamine and a differential therapeutic effect.

CASE PRESENTATION

Case A

At the age of 18 years, case A developed BPAD against a background of a history of BPAD in her grandmother. Over a span of 25 years, she had 16 relapses and admissions, primarily for depression. She was consistently diagnosed as manic depressive throughout with no accessory diagnoses. Her depressive episodes were severe and usually included psychotic features. Over time she was tried on optimal doses of different antidepressants, antipsychotics and anticonvulsants, singly or in combination. Her antidepressants included several serotonin-specific reuptake inhibitors, several tricyclic antidepressants, reboxetine as well as phenelzine and tranylcypromine. Her antipsychotics included sulpiride, risperidone, amisulpiride, quetiapine and perphenazine. Her mood stabilisers included sodium valproate, lamotrigine and lithium. None of these helped and indeed there was a strong impression that she steadily got worse rather than better on these.

She had a range of psychotherapeutic inputs, including cognitive therapy for delusions, dialogical therapy for voices, as well as exercise and other programmes, none of which made a clear difference.

The only helpful treatment for her depression was ECT. A significant response was usually noted after the second or third ECT session and she would only require four to five sessions for a full recovery. She had 10 courses of treatment with ECT, all of which were successful.

When manic, she showed a comparably clear cut response to lithium. Within days it brought her over activity and disinhibition under control. But it seemed ineffective when given to her when she was depressed.

In late 2011, she became depressed. She was left unmedicated for 3 months in the hope that a spontaneous recovery might lead to a better long-term outcome. She developed hallucinations in two modalities as well as delusional beliefs about rotting. Finally when actively suicidal, prior to a course of ECT, which it is believed she would almost certainly have responded to, a trial of ketamine was proposed.

She had a rapid and sustained beneficial response. She described being able to view delusional beliefs that had previously been all encompassing as just a part of her. But in addition to a rapid change in perspective that psychotherapy had not been able to induce, she described being able to sleep the night after ketamine where she had been unable to sleep before, an improvement in appetite, a heightening of olfactory sensitivity and other 'physiological' effects.

Since she had ketamine case A has had no further depressive episode despite considerable stress and she has not taken an antidepressant. The only side effect she experienced on ketamine was transient motor incoordination which lasted less than 1 h after administration.

Case B

Case B also has classic manic-depressive illness. Her illness began at the age of 17. She was hospitalised

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on five occasions over a 22-year period, on each occasion for manic episodes. She showed a specific response to lithium on each occasion and remained on lithium in between episodes.

At the age of 40, she was admitted for mania in 2012. This episode was more life-disrupting than others. After discharge, she became melancholically depressed. She was psychomotor retarded, anhedonic, agitated and anxious. She had trials of quetiapine, venlafaxine and lofepramine while remaining on lithium. None made any difference and she requested ECT. Prior to ECT, she consented to a trial of ketamine.

She had an almost immediate response to ketamine. She was discharged from hospital the following day and remains euthymic 3 months later, on no treatment except lithium.

Case C

Case C was referred for ECT in her late 40s. She had had five admissions over 5 years. Her original clinician thought that her problems were primarily social but since she was very distressed and considered to be a suicide risk, she was treated with a range of antidepressants and antipsychotics. Subsequent clinical teams who took over her care had differed in their views from the original team and she was referred for two courses of ECT. She showed no convincing response to either drug treatment or ECT.

While this woman met the criteria for a major depressive disorder, she did so, on the basis of poor sleep, anxiety, hopelessness and suicidality rather than psychomotor retardation and other features predictive of a response to ECT. A measure of the confusion her case caused was that she was engaged in sustained psychotherapy sessions while these other treatments were also recommended.

We were not involved in her care until referral to ECT for a third time. At this point, she was offered ketamine.

Under the influence of ketamine she became aware of previous times of stress in her life and after the effects of the drug wore off, she reported to staff that she understood her unhappiness better. She described in detail alienation from her mother and a time in her life when she was being asked to juggle the competing demands of young children and a demanding work schedule without support. She was able to identify a link between stressors and her mood state—a connection she had previously not made in psychotherapy and this knowledge gave her more control over her mood.

This self-report appeared to make it clear that ECT was not an appropriate treatment for her and she did not proceed to ECT. But while helpful in the short term, this short-term benefit from ketamine was not maintained in this case. Ketamine was not an 'antidepressant' for this lady in the manner it had been for cases A and B. For a variety of reasons she was not able to sustain the insights she had developed. We do not know whether further treatments might have helped in this respect.

DIFFERENTIAL DIAGNOSIS

The diagnosis of bipolar affective disorder in cases A and B had been established for upward of three decades and psychosocial factors were not deemed to be a precipitant for the index depressive episode. On the other hand, differentials considered in case C included psychotic depression, severe depression without psychosis and adjustment disorder.

OUTCOME AND FOLLOW-UP

Cases A and B have been followed-up as outpatients. Case A has not had a depressive relapse inspite of not being on antidepressant for the last 16 months. Case B had an almost immediate response to ketamine. She was discharged from hospital the following day and remains euthymic 3 months later, on no treatment except lithium.

DISCUSSION

Two of the cases A and B, reveal a dramatic response to ketamine and a sustained remission. Cases A and B appeared to show a physiological response and the antidepressant action of ketamine in both patients has been optimal as well as sustained. In the history of both the cases, there is a pattern of almost exclusive response to medications and treatments which have proconvulsant properties.

In Case C ketamine appeared to lead to a development of insight into her illness more so than an alleviation of the symptoms itself. Case C would probably have shown a marked fall on Hamilton rating scale scores had these been done in the immediate aftermath of treatment with ketamine, but the response here does not appear to be physiological. It was brief, suboptimal and not sustained. She was also noted not to have the prior history of response to treatments which have proconvulsant properties which the other two patients had.

Ketamine has two effects of note. First, it acts on the reticular activating system forming the basis of its anaesthetic action. The second effect of note is a proconvulsant action. This is a property it shares with treatments such as clozapine, lithium and ECT, although it is not clear whether all four agents act through some common ionic channel to produce this proconvulsive action.

The rapid and sustained response shown by two of our cases is in keeping with the need for more trials of ketamine treatment for depressive episodes. Their previous response to treatments with proconvulsive properties highlights the need for research into identifying whether the role of the processes underlying the proconvulsive properties of some psychotropic drugs contributes to their efficacy.[5]

There is uncertainty over the duration of ketamine-linked remissions. Our cases indicate that a differential diagnosis may be important in establishing who is likely to benefit, with cases of melancholia showing a sustained and presumably physiological response while other states may show a benefit that will need further work if it is to be sustained.

Learning points

- Treatment with ketamine can result in rapid and sustained remission of depressive episodes.
- It is pertinent to fully determine the major aspects of ketamine needed to be optimised, when attempting to create novel drugs with a similar or enhanced antidepressant activity.
- The proconvulsive effects of drugs like lithium, ketamine and clozapine would be worth exploring as an additional mechanism of their antidepressant action.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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