Low-Dose Ketamine Helps Resistant Depression

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A single intravenous infusion of low-dose ketamine relieved treatment-resistant depression within 2 hours, and the "robust" response persisted for 1 week in a preliminary study of 18 patients, reported Dr. Carlos A. Zarate Jr. and his associates at the National Institute of Mental Health, Bethesda, Md.

"To our knowledge, there has never been a report of any other drug or somatic treatment (i.e., sleep deprivation, thyrotropin-releasing hormone, antidepressant, dexamethasone, or [electroconvulsive therapy]) that results in such a dramatic, rapid, and prolonged response with a single administration," the researchers noted.

Previous trials of antidepressants have yielded response rates of 62% for bupropion, 63% for selective serotonin reuptake inhibitors, and 65% for venlafaxine (Effexor) at 8 weeks. In dramatic contrast, the response rate was 71% within 1 day in this trial of patients who were refractory to an average of six previous treatments, Dr. Zarate and his associates said (Arch. Gen. Psychiatry 2006;63:856-64).

Ketamine, which directly targets the *N*-methyl-D-aspartate receptor complex, is known to produce adverse effects at higher doses or when used for a prolonged time, so it is unlikely to be used widely in clinical settings. But these findings should lead to development of other, safer agents that similarly target the NMDA system.

In what they described as one of the first studies examining ketamine's antidepressant effects in humans, Dr. Zarate and his associates recruited 12 female and 6 male inpatients who were in good physical health but had recurrent major depressive disorder without psychotic features. The mean patient age was 47 years, the mean length of depressive illness was 24 years, the mean duration of the current depressive episode was 34 months, and the mean number of lifetime episodes of depression was 7.

Eleven patients (61%) had a lifetime comorbid diagnosis of anxiety, and 39% had a comorbid diagnosis of substance abuse or dependence but were certified to be free of drugs or alcohol for at least the preceding 30 days. All had a score of 18 or higher on the 21-item Hamilton Depression Rating Scale.

The subjects were randomly assigned to receive intravenous infusions of either ketamine dissolved in saline or a saline placebo, then were crossed over to the other infusion 1 week later. Outcomes were assessed before infusion and at 40, 80, 100, and 230 minutes afterward, as well as at 1, 2, 3, and 7 days afterward.

Clinical response was defined as a 50% or greater decrease in Hamilton score, and remission was defined as a Hamilton score of 7 or lower. One patient dropped out of the study for medical reasons after a placebo infusion.

A robust treatment response was noted within 110 minutes, and persisted for 7 days or more in 6 of 17 patients (35%). Remission occurred in 5 patients (29%). In contrast, there were no responses or remissions with the placebo infusion.

The prolonged effect was remarkable considering ketamine's short, approximately 2-hour half-life, the researchers said.

There were no serious adverse effects, but patients did report transient perceptual disturbances, confusion, euphoria, and dizziness. Most such effects resolved within 80 minutes of infusion.

Initially, the study was meant to include 22 patients to adequately detect a treatment response. But interim data analysis showed a very large treatment effect with the first 18 patients that would have persisted even if no further responses occurred, so the trial was stopped at that point.

Although the sample size in this preliminary trial was relatively small, three different types of data analysis using five symptom measures (the Hamilton scale, the Beck Depression Inventory, the Brief Psychiatric Rating Scale, the Young Mania Rating Scale, and a visual analog scale) amply demonstrated the significance of the treatment effect, "and the effect sizes were very large at day 1 and moderate to large at day 7," Dr. Zarate and his associates noted.

In a statement accompanying the publication of this report, Dr. Elias A. Zerhouni, director of the National Institutes of Health, said, "The public health implications of being able to treat major depression this quickly would be enormous.

"These new findings demonstrate the importance of developing new classes of antidepressants," he added. ■