

Ketamine Lifted Bipolar Depression in 40 Minutes

BY ROBERT FINN

FROM ARCHIVES OF GENERAL PSYCHIATRY

A single infusion of ketamine relieved bipolar depression within 40 minutes in patients with treatment-resistant bipolar disorder, according to a randomized, placebo-controlled, double-blind, crossover study involving 18 patients.

The effect lasted at least 3 days, wrote

Dr. Nancy Diazgranados and her colleagues from the National Institute of Mental Health.

The participants in the study were an average of 48 years old, had suffered from bipolar I or bipolar II depression for an average of 28 years, and had failed an average of seven antidepressant treatments before the ketamine study. Fifty-five percent of the participants had failed to respond to electroconvulsive therapy. Two-thirds of participants were on psychiatric disability, and all but one were unemployed (Arch. Gen. Psychiatry 2010;67:793-802).

The investigators randomly assigned the patients to receive an infusion of 0.5 mg/kg of ketamine or placebo. Two weeks later, the patients who had been given ketamine were given placebo and vice versa.

Of the 17 patients who completed the ketamine phase of the study, 12 (71%) responded to ketamine. In contrast, of the 16 patients who completed the placebo phase of the study, only 1 (6%) responded to placebo.

The investigators assessed the patients at baseline using several rating scales, including the Montgomery-Åsberg Depression Rating Scale, the Hamilton Scale for Depression, and the Beck Depression Inventory.

Patients showed statistically significant improvements in depression with ketamine, compared with those who were on placebo on all three scales beginning at 40 minutes after ketamine infusion and continuing for at least 3 days. The mean scores on the rating scales did not differ from placebo on days 7, 10, and 14.

Within 40 minutes, 9 of 16 patients receiving ketamine (56%) responded and an additional 2 (13%) experienced complete remission of their depression. One day after the infusion of ketamine, 44% of the patients had responded and 31% had remitted.

None of the patients experienced serious adverse events during the study. Among the adverse events associated with ketamine and experienced by at least 10% of the patients were disassociation; feeling strange, weird, or bizarre; dry mouth; tachycardia; and increased blood pressure.

Ketamine has been used in human and veterinary medicine since 1962, most commonly for inducing and maintaining general anesthesia, sedation in intensive care, analgesia, and treatment of bronchospasm.

When used for general anesthesia, the initial dose of intravenous ketamine is typically 1.5-4.5 mg/kg, which is substantially higher than the level used in this study.

Ketamine is thought to act as a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor, which is part of the glutamergic neurotransmitter system.

Several lines of evidence have implicated the glutamergic system in bipolar disorder. ■

VITALS

Major Finding: In patients with treatment-resistant bipolar depression, an infusion of 0.5 mg/kg of ketamine significantly relieved depression within 40 minutes, an effect that lasted at least 3 days.

Data Source: Randomized, placebo-controlled, double-blind, crossover study involving 18 patients.

Disclosures: The National Institute of Mental Health and the National Alliance for Research on Schizophrenia and Depression funded the study. A patent application for the use of ketamine for depression has been submitted, listing two of the investigators among the inventors; they have assigned their rights on the patent to the U.S. government.

LANTUS®

(insulin glargine [rDNA origin] injection) solution for subcutaneous injection

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [see *Clinical Studies (14) in the full prescribing information*]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [see *Dosage and Administration (2.3) and Clinical Studies (14) in the full prescribing information*]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [See *Warnings and Precautions (5.3)*].

10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

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