

## CORRESPONDENCE

### On the Safety and Benefits of Repeated Intravenous Injections of Ketamine For Depression

To the Editor:

The rapid and robust antidepressant effect of the intravenous infusion of a subanesthetic dose of ketamine in 2000 has triggered research endeavors in this novel mechanism of action (1-5). Its drug abuse potential and early reports of neuronal toxicity in rats are likely contributing to slowing the clinical progress (6).

Ketamine is a dissociative anesthetic agent used routinely for more than 40 years in human anesthesiology (7). It is particularly useful in conditions in which cardiovascular and respiratory monitoring is not available because it does not depress such parameters and its anesthetic effect rapidly subsides. For instance, six trained nurses used a median dose of 2 mg/kg of ketamine, its usual anesthetic dose given in a bolus, for 191 procedures in rural Uganda in patients from 1 week to 78 years old (8). Only minor adverse events occurred: hypoxemia in 22 cases and vomiting in nine. The procedures were carried out at an altitude of 5000 feet, which likely contributed to the former side effect.

The true extent of the effectiveness of ketamine in depression nevertheless remains to be established in adequately blinded studies because patients detect its mild psychotomimetic effects. The use of saline as a placebo is not adequate. In addition, much work has to be done to better characterize its clinical benefits, the optimal doses and routes of administration, and the patient population likely to benefit most and to prolong its effects. Three concerns also remain: the level of physiologic monitoring that should be implemented, its potential neurotoxicity, and its dependence potential.

There must be cardiovascular and oxygen saturation monitoring when using ketamine infusions for the treatment of depression. Indeed, depressed patients may be on medications that could synergize with ketamine and produce respiratory depression or changes of blood pressure. Specifically, sedatives and opiates could depress respirations. Consequently, an ambu bag should be available for ventilation.

The main problem with ketamine is that its antidepressant effects are transient, even when administered in the presence of antidepressants and/or augmentation strategies. There is obviously no concern about a potential neurotoxic effect of a single dose of ketamine, given its established safety record in anesthesia. Indeed, a single dose in rats showed that up to 20 mg/kg (subcutaneously) of ketamine did not exert neuronal toxicity (6). It is noteworthy that the metabolism of ketamine is faster in rats than in humans. Nevertheless, in 35-day-old monkeys, there was no neurotoxicity of a single dose of ketamine producing plasma levels 5-10 times higher than achieved in human anesthesia (9). Multiple dosing remains an issue, but given the short half-life of ketamine (3 hours) (10), theoretically there should not be concerns about neurotoxicity with repeated injections of subanesthetic doses when carried out after complete elimination of the drug (11). Furthermore, studies have documented a neurotrophic effect of ketamine in rats with 3 mg/kg, intraperitoneally, in particular an increase in spine density and synaptic function on the dendritic tree of pyramidal neurons in the frontal cortex that is dependent on the brain-derived neurotrophic factor (12), the opposite to the synaptic deficits that result from exposure to stress. Such changes lead to antidepressant-like effects in rats (5,13).

In chronic pain, both anesthetic and subanesthetic doses have been used in multiple-injection protocols (14,15). Cognitive functions have nevertheless not been monitored in these patients. It

would thus seem prudent to do so in patients with depression who would need repeated injections. The following case illustrates some features of multiple injections of intravenous ketamine.

Mrs. A is now a 44-year-old woman who had her first episode of unipolar depression in 1995. She remitted to a first course of electroconvulsive therapy (ECT) but did not respond to a subsequent course. She also responded to tranylcypromine, but it was discontinued because of orthostatic hypotension. She responded to venlafaxine (300 mg/day) plus mirtazapine (45 mg/day) but gained 65 pounds over the course of 8 months. Other antidepressants from all classes both alone and in combination did not help. The first side effect she reported 5 minutes after starting the ketamine infusion (0.5 mg/kg over 40 min) was a metallic taste. She then had mild derealization, which disappeared within 10 minutes after the end of the infusion. She reported about a 50% decrease of her dysphoria and anxiety within an hour. These benefits, while on antidepressants and augmentation strategies, lasted only about 36 hours. Upon giving her two injections a few days apart, the benefits would last about 3-4 days. Holding lorazepam from the night before enhanced the benefits of ketamine, and the 0.5 mg/kg infusion was also more effective than a 0.2 mg/kg bolus. After 14 injections, she scored 28/30 on the Montreal cognitive assessment test (16). Two months later after a further 17 infusions, she scored 30 and 6 weeks later after another 10 infusions, 28. She now remains symptomatic with ongoing infusions but is currently able to do some chores at home rather than staying in bed most of the time crying. She has been referred for deep brain stimulation.

The final concern about the repeated use of ketamine infusion is the development of dependence. We have not observed this problem so far with repeated administration. It is important, however, that none of our patients have had a history of drug abuse or dependence. When infusions are withheld, patients are not insistent to get an additional one. Patients tell us that what they appreciate from the infusions is the improvement of depressive symptoms and that they would rather not receive the infusions if the benefits were otherwise maintained.

In our research unit, ketamine is offered only to outpatients in distress that we have been following up for a long time. They are required to sign an informed consent. In other words, we currently use it as an urgent procedure as we would ECT. In this regard, it will be interesting to compare ketamine with ECT and to their combination. Finally, we deem it could be hazardous to use ketamine in the emergency room in suicidal patients without adequate subsequent monitoring, given its transient action.

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