Letters to the Editor

Ketamine Infusion Successful in Some Patients

To the Editor:

We read with interest the observational report of Kapural et al (1) titled "Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements." While we do not disagree that in some patients the pain-relieving effect of intravenous ketamine can be short-lived, we do disagree with the authors' conclusion that this is not a feasible option for pain relief in this chronic pain population. The statement implying that the infusion was not successful is unfortunately misleading and misses the more obvious and important clinical and scientific questions of why some patients responded and others did not. Despite the lack of internal validity in their study design, there was still improved analgesia in some patients for up to 6 months, similar to our experience with low and moderate dose infusion of ketamine in the CRPS population (2,3).

We would like to briefly discuss some of the critical aspects relating to this study:

The study is a retrospective analysis, of a non-homogenous population with multiple diagnoses, and lacks a true matched control population. The studies quoted, specifically those of Koffler et al (4), Goldberg et al (2), and Sigtermans et al (5) all deal with a single group of patients, those with a diagnosis of CRPS. The authors regrettably fail to mention the placebo controlled trial of Schwartzman et al (6) that reported significant decreases in multiple pain measures after a 10-day ketamine infusion in patients with CRPS who had failed all other therapies. Also significant in Kapural et al's study (1) was the fact that 6 months post treatment, almost 50% (5/11) of the subjects maintained their opioid use at less than 50% of their baseline. In our opinion this seems to represent a clinically significant improvement.

The notion of expense outweighing benefit cannot be supported by the study of Kapural et al (1). The low dose outpatient infusion is performed similarly to blood transfusions and is covered by insurance in most cases. The moderate dose 5-day infusion in the inpatient setting is performed with telemetry monitoring and is often covered by insurance in our practice. The high dose therapy is not performed in the United States and does require ICU admission and intensive monitoring. This is a recommended treatment to reduce opioid load in the chronic pain patient, but is reserved only for the most refractory cases of CRPS.

Finally, we have recently reported the results from an initial study of the plasma concentrations of ketamine and norketamine, and other major ketamine metabolites in CRPS patients (7). The data indicate that the ketamine metabolites, other than norketamine, were the predominant circulating metabolites and suggest that these compounds play a role in ketamine-related pain relief. Thus, it is likely that metabolic differences based upon pharmacogenetic factors play a role in the determination of responder and non-responder populations. Once these factors are identified, it will be possible to preselect candidates for treatment with ketamine and to individualize their treatment.

We therefore continue to support a role for ketamine and/or its metabolites in the treatment of chronic pain in the patients with CRPS.

MIchael E. Goldberg, MD
Professor and Chief
Department of Anesthesiology
Cooper University Hospital
UMDNJ
Newark, NJ
E-mail: goldberg-Mike@cooperhealth.edu

Robert J. Schwartzman, MD
Professor and Chairman
Department of Neurology
Drexel University College of Medicine
Philadelphia, PA

Marc C. Torjman, PhD
Professor
Department of Anesthesiology
Cooper University Hospital
UMDNJ
Newark, NJ

Irving W. Wainer, PhD
Senior Scientist
The Laboratory of Clinical Investigation
National institute on Aging
Intramural Research Program, NIH
Baltimore, MD

References

1. Kapural L, Kapural M, Bensitel T, Sessler, DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. *Pain Physician* 2010; 13:389-394.
2. Goldberg ME, Domsky R, Scaringe D, Hirsh R, Dotson J, Sharaf I, Torjman MC, Schwartzman RJ. Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. *Pain Physician* 2005; 8:175-179.
3. Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. Pharmacodynamic profiles of ketamine (r-) and (s+) with five day inpatient infusion for the treatment of complex regional pain syndrome. *Pain Physician* 2010; 13:379-387.
4. Koffler SP, Hampstead BM, Irani F, Tinker J, Kiefer RT, Rohr P, Schwartzman RJ. The neurocognitive effects of 5 day anesthetic ketamine for the treatment of refractory complex regional pain syndrome. *Arch Clin Neuropsychol* 2007; 22:719-729.
5. Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain* 2009; 145:304-311.
6. Schwartzman RJ. Alexander GM. Grothusen JR. Paylor T. Reichenberger E. Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: aA double-blind placebo controlled study. *Pain* 2009; 147:107-115.
7. Moaddel, R, Venkata SL, Tanga MJ, Bupp JE, Green CE, Iyer L, Furimsky A, Goldberg ME, Torjman MC, Wainer IW. A parallel chiral-achiral liquid chromatographic method for the determination of the stereoisomers of ketamine and ketamine metabolites in the plasma and urine of patients with complex regional pain syndrome. *Talanta* 2010; In Press