Neurocognitive Changes after Sustained Ketamine Administration in Children with Chronic Pain

Amy Lee Bredlau[1*], Brian T Harel[2], Michael P McDermott[3], Robert H Dworkin[4], David N Korones[5], James G Dolan[6] and Heather R Adams[7]

[1]*Department of Pediatrics, University of Rochester, Rochester, New York, USA*

[2]*Cog State, Inc. Yale University School of Medicine, Child Study Center, New Haven, USA*

[3]*Department of Biostatistics and Computational Biology, University of Rochester, Rochester, New York, USA*

[4]*Departments of Anesthesiology and Neurology, University of Rochester, Rochester, New York, USA*

[5]*Departments of Pediatrics and Palliative Care, University of Rochester, Rochester, New York, USA*

[6]*Department of Public Health Sciences, Palliative Care, University of Rochester, Rochester, New York, USA*

notable lasting neurocognitive decline after daily exposure to low-dose ketamine, it would be reasonable to assume that younger children would be similarly harmed by daily exposure to low-dose ketamine. Chronic pain could be either idiopathic or related to a known diagnosis, including but not limited to cancer, rheumatologic disease, sickle cell anemia, cystic fibrosis, pancreatitis, and neuromuscular disease. Participants were ineligible for the study if there was a known or suspected history of: drug dependence or addiction, psychiatric disorder (depression, schizophrenia, bipolar disorder), or other medical problems thought to be unsafe during ketamine exposure. Participants were referred from pediatric services including neurology, orthopedic surgery, gastroenterology, rheumatology, and palliative care for participation in this clinical trial.

Full details of the dose-escalation protocol and rationale, eligibility criteria, and preparation and delivery of oral ketamine have been previously published [4]; the current report extends this work with special focus on the intermediate-term neurocognitive safety data. The study included 4 cohorts of 3 participants each, who were given dosages of oral ketamine of 0.25, 0.5, 1, or 1.5 mg/kg/dose three times a day. Participants in each cohort completed neurocognitive testing before, immediately after and 3 months after exposure to oral ketamine. Oral ketamine was administered three times per day for 14 consecutive days.

Neurocognitive measures

The study was principally concerned with investigating safety and tolerability of ketamine, including potential cognitive effects of the drug. Therefore, participants completed a neurocognitive test battery that included assessments of attention and processing speed, memory, and executive function. The tests were selected because of prior

Sample size and follow-up

In the first two cohorts (0.25 mg/kg and 0.50 mg/kg), 100% of participants (3 per group) were present for all three neurocognitive assessments. However, there was one non-completion for the Groton Maze Chase Test (GMCT) and the International Shopping List Test (ISRL) at Baseline do to computer malfunction. In the third dosage cohort (1.0 mg/kg), one participant did not complete the Week 14 evaluation due to transportation difficulties. In the fourth cohort (1.5 mg/kg), two of three participants were not evaluated at Week 14. Unwillingness to return for evaluations was thought to be related to these participants' experience of adverse events (see below). In addition, the reliability of data obtained from one participant was deemed questionable due to motor and speech disabilities. Consequently, all data for this participant were removed from all analyses. Thus, the final sample size for neurocognitive assessment was N=11 participants (Table 1), though all 12 enrolled and treated participants are included in discussion of adverse events and pain scores.

Age (years)	
Range	11-19
Median	16
Sex	
Female	8
Male	3
Race	
African-American	1
Caucasian	9
More than One Race	1 (White and African-American)
Ethnicity	
Hispanic	1
Not Hispanic	10

Table 1: Baseline demographic characteristics of all participants contributing to neurocognitive data. (Modified with permission)

Neurocognitive assessment

Summary longitudinal data for all neurocognitive outcomes are provided in Table 2. Linear mixed model analyses indicated that there were significant main effects of time on the Executive Function Composite (F (2,18)=8.66, p=0.002) but no significant main effects of time on the Processing Speed Composite (F(2,18)=0.10, p=0.91) or the Memory Composite (F(2,18)=1.06, p=0.37). The results of the planned comparisons (Week 2 vs. Baseline and Week 14 vs. Baseline), which are summarized in Figure 1, indicate that mean composite scores at Week 2 and Week 14 were not statistically different from those at Baseline for either the Processing Speed domain (Week 2: p=0.67, d (Cohen's d)=-0.10; Week 14: p=0.84, d= -0.05) or the Memory domain (Week 2: p=0.22, d=0.45; Week 14: p=0.23, d=0.47). Significant mean improvements in the Executive Function Composite score were observed at Week 2 (p=0.001, d=0.91) and Week 14 (p=0.005, d=0.83). Improvements in Executive Function Composite scores at both Week 2 and Week 14 were noted.

Task	Measure	Cognitive Domain	Baseline (mean, SD)	Week 2 (mean, SD)	Week 14 (mean, SD)
			n=11	n=11	n=9
DET	Speed, log10ms	Processing Speed-Attention	2.46 (.06)	2.48 (.06)	2.42 (.17)
IDN	Speed, log10ms	Processing Speed-Attention	2.68 (.06)	2.70 (.08)	2.74 (.12)
GMCT	Moves per second	Processing Speed-Attention	1.38 (.40)*	1.52 (.31)	1.53 (.28)
ISLT	Total words recalled	Memory	25.90 (2.77)	28.55 (2.77)	27.89 (4.14)
ISRL	Total words recalled	Memory	9.80 (1.23)*	9.73 (1.62)	10.22 (1.56)

ONB	Speed, log10ms	Executive Function	2.93 (.06)	2.85 (.06)	2.87 (.08)
SETS	Accuracy, arcsine proportion correct				

Discussion

This article describes the neurocognitive changes in children with chronic pain who received 14 days of oral ketamine. No evidence of decline in neurocognitive abilities was observed in this small cohort of children. However, given that this was a preliminary uncontrolled study with a small sample size, it is possible that subtle neurocognitive deficits were missed. Interestingly, and unexpectedly, we observed a statistically significant improvement in executive functioning. However, when directly queried, neither any child nor their parents reported a noticeable change in the child's executive functioning.

Intuitively, it seems possible that children with chronic pain could experience decrements in neurocognitive test performance that is improved with appropriate pain control, as manifested by the increased (improved) executive function test scom1M

It is also possible that long-term neurocognitive decline may not be detectable in this study sample after only 3 months off therapy. However, given retention problems as outlined above, we thought it most reasonable to include assessments after a relatively short duration.

On the basis of prior preclinical and preliminary clinical findings, the primary concern for administering low dosage ketamine to children has been the possibility of a resulting decrement in neurocognitive function. The data presented here do not support the hypothesis that oral ketamine administered three times daily at low dosages for 14 days results in a sustained decrement in neurocognitive function, though participants did experience transient neurocognitive or neurologic adverse events while actively exposed to ketamine [4]. It is intriguing that executive function scores improved after administration of oral ketamine; however, this is in contradiction to previous data in ketamine drug abusers [8,10] and is not consistent with the preclinical data [30,31]. Data from randomized, controlled clinical trials are necessary to further characterize the impact (if any) of oral ketamine in children with chronic pain.

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Disclosures

Dr. Harel is a full time employee of CogState, a cognitive test company that provided the cognitive tests used in this study.

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