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INTRODUCTION

Ketamine, an *N*-methyl-*D*-aspartate-receptor antagonist, provides effective nonopioid analgesia for refractory headache[1] and complex regional pain syndrome (CRPS).[2] Adverse drug effects (ADEs), including hallucinations, may still occur at subanesthetic doses,[3] but previous studies have not examined the incidence of ADEs across multiple treatments. Hepatotoxicity has also been associated with ketamine abuse and repeat infusions[4] but associations with continuous multiday infusions have not been explored. Unlike previous studies, our analysis compares ADEs in initial versus repeat ketamine infusions and describes the association between liver enzymes (LEs) and continuous multiday infusions. We hypothesized that there would be an increased rate of LE elevation in subsequent measurements compared to baseline.

METHODS

The institutional review boards of Thomas Jefferson University (TJU) and the University of Virginia (UVA) approved this study. Consecutive patient records from 2014-2018 were analyzed and patients with complete data were included. The following were collected: demographics, past medical history, medications, LEs, ADEs, and ketamine infusion details. Initial admissions were grouped separately from subsequent admissions and all admissions were analyzed. If any LE (AST, ALT, or alkaline phosphatase) was elevated the entire set was labeled "elevated." Point estimates of ADE data are presented as percentages with binomial 95% confidence intervals. Statistical analyses were performed using Systat (San Jose, CA), V13 or statpages.info. Differences in LEs between baseline and subsequent values for initial and repeated admissions were analyzed using ANOVA with repeated measures. Significance was defined by $P < 0.05$. Because this is an exploratory analysis, we did not adjust for multiple comparisons.

RESULTS

A total of 115 patients (74.7% female), including 53 with refractory headache from TJU and 62 with CRPS from UVA, underwent inpatient continuous 5-day ketamine infusions. The overall mean age was 46 years. There were 115 initial admissions and 105 repeat admissions. The mean (SD) ketamine infusion rates for the initial and repeat admissions were 39.3 (17.2) and 45.6 (21.2) mg/hour, respectively. The mean (SD) ketamine infusion duration at TJU was 100.3 (20.8) h versus 104.4 (36.1) h at UVA. Hallucinations occurred in 23.5% [16.1 – 32.3] of initial and 24.0% [16.2 – 33.4] of repeat admissions; vivid dreams occurred in 9.6% [4.9 – 16.5] of initial and 5.7% [2.1 – 12.0] of repeat admissions. Percentages of patients experiencing ADEs are shown in Figure 1.

For the primary outcome, there were no differences between baseline and subsequent LEs within initial admissions, but AST and ALT were more likely to be elevated in subsequent testing within repeat admissions (Table 1). The majority demonstrated a pattern of transaminase elevations and four patients with normal or mildly elevated baseline AST and ALT developed markedly elevated LEs (>10x normal) during treatment.[5]

DISCUSSION

Our principal finding is that elevated LEs were associated with ketamine infusions during repeat admissions. Although the overall risk of LE elevation was low, the four patients who developed markedly elevated LEs (>10 times normal) had previously documented normal or mildly elevated LEs, which raises concern for a possible effect of ketamine.[5] Although LE elevation from ketamine is not new, this study suggests closer monitoring may be in order. As a result of this study, we recommend checking follow-up LEs in all patients receiving continuous multiday ketamine infusions to monitor for significant elevations and we have made institutional changes based on these results. Because of small numbers, we cannot make definitive conclusions and these findings should be confirmed in larger studies.

Additional findings included similar rates of hallucinations and vivid dreams in patients having their first or repeat ketamine treatments. These results suggest patients do not become tolerant to these ADEs over time and continued vigilance and frequent assessment are needed.

Figure Legends

Figure 1. Adverse drug effects from ketamine in initial and repeat admissions with variance.

Liver enzyme	Baseline, median (IQR)	During infusion, median (IQR)	p-value[a]
Initial Admissions			
Alkaline phosphatase (IU/L)	71.5 (56.3-86.8)	73.0 (56.1-89.9)	0.92
Aspartate aminotransferase (U/L)	22.0 (16.8-27.3)	22.5 (11.8-33.3)	0.53
Alanine aminotransferase (U/L)	18.5 (8.5-28.5)	20 (6.25-33.8)	0.41
Repeat Admissions			
Alkaline phosphatase (IU/L)	63.0 (46.5-79.5)	72.0 (47.5-96.5)	0.12
Aspartate aminotransferase (U/L)	21.0 (15.4-26.6)	23.0 (9.8-36.3)	0.03
Alanine aminotransferase (U/L)	19.0 (10.0-28.0)	23.0 (3.8-42.3)	0.04

Abbreviations: IQR, interquartile range;
[a]Analysis of variance (ANOVA) with repeated measures was used for differences in liver enzymes between baseline and subsequent values during ketamine infusion

Table 1. Liver enzymes at baseline prior to ketamine infusion and then during the infusion

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