Substantial Elevation of Liver Enzymes During Ketamine Infusion: A Case Report

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Intravenous infusion of a subanesthetic dose of ketamine has been shown to improve neuropathic pain. However, ketamine-induced liver injury can occur. Reported here are 2 cases with substantial liver enzyme elevations less than 2 days after initiation of repeat ketamine infusion at least 7 months after the last infusion. Although their liver enzymes normalized within a few weeks, it is unclear what the long-term consequences are. Furthermore, drug-induced liver injury can cause acute liver failure. Therefore, we recommend close monitoring of liver enzymes every 1 to 2 days during ketamine infusions. (A&A Practice. 2020;14:e01239.)

GLOSSARY

ALP = alkaline phosphatase; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CRPS** = complex regional pain syndrome; **DILI** = drug-induced liver injury; **KILI** = ketamine-induced liver injury; **LLE** = left lower extremity; **RUE** = right upper extremity; **ULN** = upper limit of normal range

Intravenous infusion of an anesthetic or subanesthetic dose of ketamine has been shown to improve chronic neuropathic pain, such as complex regional pain syndrome (CRPS), thought to be mainly through N-methyl-D-aspartate receptor antagonism.¹⁻³ Recent studies suggest that the analgesic effect of ketamine is dose dependent, and prolonged and repetitive administrations of ketamine are needed to induce long-term pain relief.¹⁻³ However, it is not clear how high the safe ketamine dose is, how long ketamine infusion can be continued, or how soon ketamine infusion can be repeated. Existing literature showed that ketamine infusion for chronic pain had been administered in a wide variety of ways, with infusion rate ranging from 2.0 to 66.5 mg/h (not weight based) or 0.08 to 7.00 mg/kg/h (weight based), infusion duration from 0.75 to 28 days, and the shortest interval between infusions 12 days.^{4,5}

The use of ketamine has raised the concern of toxicity.⁶ In addition to the well-known psychotropic side effects, mild elevation in liver enzymes has been reported following ketamine anesthesia⁷ and ketamine infusion at anesthetic doses for treating chronic neuropathic pain.³ Recent evidence suggests that ketamine-induced liver injury (KILI) can occur when the ketamine infusion is repeated within a short period of time (16 days),⁵ and drug-induced liver injury (DILI) is the most common cause of acute liver failure in the United States.⁸ Reported here are 2 cases with patients who had marked elevations in liver enzymes less than 2 days

into a repeat ketamine infusion treatment at least 7 months after the last infusion.

The patients have signed a Health Insurance Portability and Accountability Act authorization to publish this case report. This article adheres to the applicable Enhancing the Quality of and Transparency of Health Research guideline.

CASE DESCRIPTION

Both patients were admitted for repeat ketamine infusion to treat pain from CRPS type 1 (Table). They had no known history of liver disease and did not take any hepatotoxic medications during their admissions. Preinfusion liver enzymes were normal: alanine aminotransferase (ALT) <55 U/L, aspartate aminotransferase (AST) <35 U/L, and alkaline phosphatase (ALP) 40–150 U/L (our institutional cutoff points). Ketamine infusion was stopped when liver enzymes were first found to be elevated. Supportive treatments were provided, and the enzymes were monitored closely until they started to decline. Then the patients were discharged home, at their requests and with approval from the hepatology service, with instructions to have liver enzymes rechecked as outpatient. Both patients' liver enzymes normalized when rechecked at their primary care doctor's office 3 weeks later (Figures 1 and 2). For patient A, during her previous infusions, liver enzymes were not monitored after a preinfusion enzyme test came back normal (Table).

Patient A is a 54-year-old woman admitted for her fourth ketamine infusion. Due to ketamine shortage, her previous most recent ketamine infusion was 3 years prior (Table). Approximately 44 hours after initiation of her infusion, her enzymes were noted to have sharply risen (Figure 1). The infusion was discontinued, and she received a total of 1254 mg of ketamine (Table). The hepatology service was consulted. The next day, her enzymes peaked to their maximum values of ALT 1160 U/L, AST 883 U/L, and ALP 294 U/L, and 21, 25, and 2 times of the upper limit of normal range (ULN), respectively (Figure 1). The patient reported mild nausea but denied other symptoms, and there were no

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Table. Details of Ketamine Infusions, Liver Enzymes, and Pain Relief of Patients A and B

Patients	Diagnosis	Infusions	Time Since Last Infusion (mo)	Infusion Duration (h)	Cumulative Ketamine Dose (mg)	Liver Enzymes		Pain Relief	
						Baseline	During Infusion	Maximum Relief (%)	Duration (mo)
Patient A	CRPS type I of LLE	First		135	3945	Normal	Not monitored	>75%	7–8
		Second	10.5	89	2466	Normal	Not monitored	75%	6
		Third	7.5	92	2622	Normal	Not monitored	>50%	4
		Fourth	34.0	45	1254	Normal	Elevated	Minimal	
Patient B	CRPS type I of RUE	First		140	5413	Normal	Normal	50%	5–6
		Second	7.0	90	3165	Normal	Normal	>50%	6
		Third	7.5	47	1858	Normal	Elevated	Minimal	

Abbreviations: CRPS, complex regional pain syndrome; LLE, left low extremity; RUE, right upper extremity.

signs of liver injury, including fever, jaundice, tenderness, or enlargement of the liver present on physical examination. She reported drinking 1 to 2 glasses of wine per night and using up to 6 g of acetaminophen per day for pain at home. A hepatitis panel was nonreactive for hepatitis A and C, and she had previously been vaccinated against hepatitis B. A right upper quadrant ultrasound was normal. DILI from ketamine was diagnosed. Around 26 hours after cessation of her ketamine infusion, her enzymes started to trend down (Figure 1). She was later discharged home with approval from hepatology and with instructions to follow up with hepatology for laboratory monitoring. She was also counseled to avoid anything potentially toxic to the liver, including alcohol, excess acetaminophen (not >2 g/d), and herbal supplements. Patient followed up with her primary care physician instead.

Patient B is a 61-year-old man with a history of 2 prior ketamine infusions with no liver enzyme elevation (Table). His most recent infusion was 7 months ago (Table). Approximately 46 hours after initiation of the infusion, his liver enzymes were noted to be elevated from its normal preinfusion baseline (Figure 2). They continued to rise to the highest of ALT 746, AST 401, and ALP 165 U/L, and 14, 11, and 1 times of the ULN, respectively, (Figure 2) despite the discontinuation of infusion 22 hours earlier. He received a total of 1858 mg of ketamine (Table). No symptoms or signs of liver injury were noted. He reported drinking 3–4

alcoholic beverages per week at home. The hepatology service was consulted. Prothrombin time and partial thromboplastin time were normal, and a hepatitis panel was nonreactive for hepatitis A, B, or C. Ultrasound of the right upper quadrant showed increased echogenicity of the liver consistent with hepatocellular dysfunction and no portal venous thrombosis. He was later discharged home when repeat serum enzymes stably trended down (Figure 2). He was instructed to avoid substances potentially toxic to the liver and have liver enzymes rechecked as outpatient.

DISCUSSION

The incidence of KILI is unknown, although it has a likelihood score of B (highly likely cause of clinically apparent biliary and hepatic injury) according to LiverTox (<https://livertox.nih.gov/Ketamine.htm>), a National Institutes of Health online database. Most studies on the use of ketamine for treating chronic pain either did not monitor or found no elevation in liver enzymes.^{1,9,10} Reports of KILI do exist, but liver enzyme elevations in those reported cases were modest³ or unspecified.^{2,11} Noppers et al⁵ reported 2 cases of grade 3 (ULN: 5–10) of 4 elevation in liver enzymes during repeat ketamine infusion 16 days after last infusion, according to a commonly used grading system in LiverTox. In this grading system, values expressed as multiples of the ULN are used to assess severity. Cases by Noppers et al⁵ suggested an increased risk of KILI when the infusion is

Liver Enzymes and Multiples of ULN

Figure 1. Liver enzymes of patient A during and following the fourth ketamine infusion. Bars, values of liver enzymes; blue line, ketamine infusion duration (45h); and yellow, red, and green lines, multiples of ULN of liver enzymes. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal range.

Liver Enzymes and Multiples of ULN

Figure 2. Liver enzymes of patient B during and following the third ketamine infusion. Bars, values of liver enzymes; blue line, ketamine infusion duration (47 h); and yellow, red, and green lines, multiples of ULN of liver enzymes. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal range.

repeated within a short time frame. In our cases, patients' last ketamine infusions were at least 7 months prior, and yet the elevations in liver enzymes were more severe (grade 4, ULN >10). The possible reasons include that ketamine infusion was started at higher doses; dose escalations were faster; and patients had more previous ketamine infusions, thus more exposures (3 or 4 vs 1 in their cases).

DILI is classified into 3 types: direct, idiosyncratic, and indirect injury, each with several phenotypes.¹² Our cases of KILI fall mainly into the phenotype acute hepatocellular hepatitis of idiosyncratic hepatotoxicity with some characteristics of direct liver injury, based on the features (short latency, unpredictable, marked abrupt ALT elevations, mild ALP elevations, fast improvement following ketamine cessation) and R value.^{8,12} R value is calculated as $R = (\text{ALT value}/\text{ALT ULN})/(\text{ALP value}/\text{ALP ULN})$, and an R value >5 indicates hepatocellular pattern of injury.^{8,12} The exact mechanism of KILI is not fully understood. It appears to have immune-mediated and nonimmune-mediated features.⁵ Possible factors include mitochondrial dysfunction, increased lipid peroxidation with the formation of free radicals, and allergic hepatitis.^{5,13,14} It is not clear why some people are more susceptible than others. Because of the immune-mediated aspect of KILI, repeat ketamine infusion treatment is likely to cause sooner and more extensive liver injury; therefore, it should be discouraged for patients who have a history of KILI. It is unknown whether patient A had KILI during previous infusions due to the lack of enzyme monitoring. Although both patients' liver enzymes normalized within a few weeks, the long-term consequences remain unclear. This further suggests the need to avoid repeat infusions in these patients to avoid repeat injuries.

In the United States, DILI is the most common cause of acute liver failure. It has an unpredictable and heterogeneous course, ranging from an asymptomatic rise in liver enzymes to acute liver failure.⁸ In our reported cases, despite significant elevations in liver enzymes, symptoms and signs of liver injury were not reported (with the exception of nausea in 1 patient). Lacking these symptoms or signs makes the diagnosis of KILI reliant on laboratory values. In addition, ketamine can cause nonspecific symptoms

like fatigue, nausea, and vomiting, confusing the diagnosis. Therefore, close monitoring of liver enzymes is strongly recommended to detect liver injury early, maybe before infusion, 24 hours after starting infusion, if normal, then every 2 days after that. The management of KILI is cessation of the ketamine infusion and supportive treatment.^{5,8} At the same time, other causes of liver injury should be ruled out. ■■

DISCLOSURES

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