Multiorgan dysfunction related to chronic ketamine abuse

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Ketamine abuse is being increasingly reported worldwide. The drug can produce a dissociative state and hallucinations, making ketamine a favorite recreational agent among drug addicts. Chronic ketamine abuse can damage many organs, including the brain, heart, liver, gastrointestinal tract, and genitourinary system. We report a patient with chronic ketamine abuse who presented with severe cachexia, upper gastrointestinal involvement, hepatobiliary dysfunction, and acute kidney injury.

Ketamine is a general anesthetic agent commonly used in pediatric patients, especially for neurosurgery and for surgeries requiring cardiopulmonary bypass (1). Ketamine can produce a dissociative state and hallucinations and therefore is not commonly used in adult anesthetic practice. Because of the hallucinatory effects of the drug, recreational ketamine abuse has been increasingly reported in recent years. Chronic ketamine abuse can damage many body organs (1, 2). We report a patient with chronic ketamine abuse who presented with severe cachexia, upper gastrointestinal involvement, hepatobiliary dysfunction, and acute kidney injury.

CASE PRESENTATION

A 59-year-old man presented to the emergency department with vomiting, lower abdominal pain, dysuria, and urinary incontinence of 5 days duration. For several months he had a poor appetite and dyspepsia, and he had gradually lost weight. He was known to have chronic obstructive airway disease and enlarged kidneys detected by an ultrasonographic study. He had a 40 pack-year history of smoking, consumed about 20 units of alcohol (1 unit = 10 mL of pure alcohol) weekly, and inhaled ketamine powder intranasally almost every day for about 3 years. He lived alone and was not sexually active in the immediate past.

On examination he looked dehydrated and cachectic, and his sclerae were mildly icteric. His body mass index was 14.5 kg/m² and his blood pressure, 90/60 mm Hg. Biochemical and hematological laboratory results are shown in *Table 1*. The electrocardiograph and chest radiograph did not show any abnormalities. An abdominal ultrasonographic study revealed bilateral hydronephrosis and hydroureter, hypoechoic liver with periportal hyperechogenicity, and mild dilatation of the common bile duct. The urinary bladder wall was thickened with increased trabecula-

tions. A computed tomographic scan of the abdomen without contrast revealed a full distended stomach (*Figure 1a*), bilateral hydronephrosis (*Figure 1b*) and hydroureter, and a thickened urinary bladder wall (*Figure 1c*). The bladder was contracted.

The patient was initially managed with intravenous hydration, thiamine, and continuous urinary drainage through an indwelling catheter. Esophagogastroduodenoscopy showed grade 3 esophagitis and mild gastritis. The histology from the esophageal mucosa revealed only chronic inflammatory changes. A magnetic resonance cholangiopancreatography showed mild dilatation of the proximal common bile duct with narrowing of the common hepatic duct without cholelithiasis. The cisterna chyli was also dilated. There was no evidence of intraabdominal malignancy. Screening tests for viruses (HIV, hepatitis A, B, C, E, Epstein-Barr virus, and cytomegalovirus), autoimmune liver disorders (autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis), and metabolic liver diseases (hemochromatosis and Wilson's disease) were negative.

The patient was further managed with oral and intravenous hydration, a multivitamin supplement, and omeprazole. The acute kidney injury and the liver function abnormalities improved gradually (*Table 1*). He gained 3 kg body weight within a week of inpatient medical treatment.

With a diagnosis of ketamine-induced multisystem illness, he was advised to refrain from further drug abuse and was discharged to a community-based drug rehabilitation program. His general health steadily improved, and on a subsequent outpatient clinic visit 2 months later, he weighed 50 kg (a total weight gain of 8 kg). An abdominal ultrasonographic study revealed complete resolution of the hepatobiliary abnormalities, the hydronephrosis, and the hydroureter on both sides.

DISCUSSION

Ketamine is a phencyclidine derivative that is licensed for anesthetic use in humans and in veterinary medicine, especially

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Table 1. Biochemical and hematological laboratory data

Variable	Reference value	Day after admission			
		1	3	7	60
Hemoglobin (g/L)	130–170	150	120	118	132
White cell count (10 ⁹ /L)	4–11	16.8	10.8	7.3	8.4
Absolute neutrophil count (10 ⁹ /L)	3.2–7.1	14.5	8.0	4.2	5.1
Absolute lymphocyte count (10 ⁹ /L)	1.5–3.9	1.2	1.5	1.9	2.2
Absolute eosinophil count (10 ⁹ /L)	0–0.45	0.0	0.1	0.2	0.2
Absolute monocyte count (10 ⁹ /L)	0.2–0.7	0.9	1.0	0.7	0.6
Platelet count (10 ⁹ /L)	150–450	501	385	295	286
Sodium (mmol/L)	135–145	122	129	135	137
Potassium (mmol/L)	3.5–5.2	6.4	4.6	4.2	3.9
Blood urea nitrogen (mmol/L)	2.5–7.2	38.6	18.4	6.4	7.1
Serum creatinine (mmol/L)	70–120	228	77	47	64
Estimated glomerular filtration rate (mL/min)	>90	26	>90	>90	>90
Albumin (g/L)	35–50	30	20	32	42
Globulin (g/L)	20–32	20	22	26	30
Total bilirubin (μmol/L)	6–22	34	18	6	9
Alkaline phosphatase (IU/L)	33–125	970	746	420	120
Gamma glutamyl transferase (IU/L)	8–64	1796	1209	640	63
Alanine transaminase (IU/L)	8–37	46	53	35	24
Albumin corrected calcium (mmol/L)	2.20–2.59	2.31	2.24	2.40	2.38
Inorganic phosphate (mmol/L)	0.7–1.4	1.6	1.2	1.1	0.9
Magnesium (mmol/L)	0.7–1.0	0.7	0.8	0.7	0.9
Thyrotropin (μU/mL)	0.4–5.2	1.51	—	—	—
Free thyroxin (pmol/L)	9–19	17	—	—	—

in developing countries. At higher doses, ketamine produces a dreamlike state, hallucinations, distorted visual perceptions, a sensation of a near-death experience, amnesia, and delirium, making it a favorite recreational agent of drug abuse (3). “Special K,” “Vitamin K,” “K,” “kit-kat,” “keets,” “super acid,” “super K,” “cat valiums,” and “jet” are the terms used by drug abusers for recreational ketamine. The usual illicit dose ranges from 50 to 100 mg (3, 4). Acute toxic effects of ketamine include tachycardia, abdominal pain, hypertension, raised intracranial

pressure, muscle rigidity, cognitive dysfunction, and sometimes death (2, 5).

Urinary tract abnormalities are the most commonly reported chronic toxic effect related to ketamine abuse. With chronic use, the drug injures the urinary bladder, causing ulcers, cystitis, and fibrosis leading to urinary incontinence, hematuria, bladder overactivity and shrinkage, and, in the later stages, hydroureter and hydronephrosis (2, 6). The term “ketamine bladder syndrome” has been coined to describe this clinical entity. The smooth muscle relaxing property of ketamine was thought to be a pathogenic mechanism of urinary tract disease. Ketamine itself or its active metabolites were believed to cause injury to the urinary tract, although adulterants in the abused drug preparation were proposed as the cause by some authorities. Direct damage, microvascular injury, and immune mechanisms were thought to be the etiological factors (7). Recent evidence suggests that cytotoxic damage to the urinary tract by the drug is the cause for the abnormalities (8). By alteration of the epithelial cell-to-cell adhesion and cell coupling in the renal

tract, ketamine causes damage through a nonclassical profibrotic mechanism. Ketamine abuse more than three times weekly for more than 2 years has been found to be a significant risk factor for urinary tract disease (9). Although recovery is observed in most cases with an early intervention, irreversible damage may occur in chronic cases.

Cholestasis related to chronic ketamine abuse has been described recently (10, 11). The exact mechanism for cholestasis is not known. Biliary dyskinesia resulting from the direct effect of

Figure 1. A computed tomographic scan of the abdomen showing (a) a dilated and distended stomach with fluid level (arrow); (b) bilateral hydronephrosis (arrows); and (c) a contracted urinary bladder with a thickened wall (arrow).

the drug on the smooth muscles or through the vagus nerve may be the cause of cholestasis. Full recovery from the hepatobiliary disease over time has been observed with complete abstinence from ketamine abuse (10, 11).

Chronic abdominal pain is a common presenting complaint in ketamine abusers. The reported prevalence of upper gastrointestinal symptoms is up to 75% (2, 12). Gastritis has been demonstrated in 85% of those who had endoscopy (12). Complete relief of the symptoms is observed in most cases when patients abstain from the drug. Gastric dilatation and severe reflux esophagitis caused by chronic ketamine abuse has not been described in the medical literature previously. Ketamine has been shown to reduce the lower esophageal sphincter tone in nonhuman models (13). Smooth muscle relaxation in the upper gastrointestinal tract might have caused dysmotility, dilatation, and stasis of food in the stomach and chronic esophageal reflux in this patient. The severe cachexia mimicking malignant disease observed in our patient could have been related to upper gastrointestinal disease and the associated poor nutrition, although biliary dysfunction and acute kidney injury might have contributed to the pathogenesis.

1. Wang C, Zheng D, Xu J, Lam W, Yew DT. Brain damages in ketamine addicts as revealed by magnetic resonance imaging. *Front Neuroanat* 2013;7:23.
2. Yiu-Cheung C. Acute and chronic toxicity pattern in ketamine abusers in Hong Kong. *J Med Toxicol* 2012;8(3):267–270.
3. Chakraborty K, Neogi R, Basu D. Club drugs: review of the 'rave' with a note of concern for the Indian scenario. *Indian J Med Res* 2011;133:594–604.
4. Koesters SC, Rogers PD, Rajasingham CR. MDMA ('ecstasy') and other 'club drugs'. The new epidemic. *Pediatr Clin North Am* 2002;49(2):415–433.
5. Okon T. Ketamine: an introduction for the pain and palliative medicine physician. *Pain Physician* 2007;10(3):493–500.
6. Srirangam S, Mercer J. Ketamine bladder syndrome: an important differential diagnosis when assessing a patient with persistent lower urinary tract symptoms. *BMJ Case Rep* 2012;2012. doi: 10.1136/bcr-2012-006447.
7. Chu PS, Kwok SC, Lam KM, Chu TY, Chan SW, Man CW, Ma WK, Chui KL, Yiu MK, Chan YC, Tse ML, Lau FL. 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007;13(4):311–313.
8. Hills CE, Jin T, Siamantouras E, Liu IK, Jefferson KP, Squires PE. 'Special k' and a loss of cell-to-cell adhesion in proximal tubule-derived epithelial cells: modulation of the adherens junction complex by ketamine. *PLoS One* 2013;8(8):e71819.
9. Mak SK, Chan MT, Bower WF, Yip SK, Hou SS, Wu BB, Man CY. Lower urinary tract changes in young adults using ketamine. *J Urol* 2011;186(2):610–614.
10. Lo RS, Krishnamoorthy R, Freeman JG, Austin AS. Cholestasis and biliary dilatation associated with chronic ketamine abuse: a case series. *Singapore Med J* 2011;52(3):e52–e55.
11. Wong SW, Lee KF, Wong J, Ng WW, Cheung YS, Lai PB. Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. *Hong Kong Med J* 2009;15(1):53–56.
12. Poon TL, Wong KF, Chan MY, Fung KW, Chu SK, Man CW, Yiu MK, Leung SK. Upper gastrointestinal problems in inhalational ketamine abusers. *J Dig Dis* 2010;11(2):106–110.
13. Kohjitani A, Miyawaki T, Funahashi M, Higuchi H, Matsuo R, Shimada M. Ketamine and midazolam differentially inhibit nonadrenergic noncholinergic lower esophageal sphincter relaxation in rabbits: role of superoxide anion and nitric oxide synthase. *Anesthesiology* 2003;98(2):449–458.