Cholestasis and biliary dilatation associated with chronic ketamine abuse: a case series

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ABSTRACT

Ketamine is a dissociative anaesthetic agent that is still widely used in veterinary and human medicine. It is increasingly being used as a recreational hallucinogenic drug. Chronic ketamine abuse is known to account for lower urinary tract symptoms and urinary bladder dysfunction. There is now emerging evidence that ketamine misuse is also associated with abnormal liver function tests and biliary tract abnormality. We report three cases of chronic ketamine misuse in three young men who all presented with obstructive jaundice and biliary tract abnormality. We also describe the clinical features, radiological findings and potential underlying mechanisms for this new entity.

Keywords: biliary dilatation, cholestasis, ketamine

INTRODUCTION

Ketamine has been used for decades as a dissociative anaesthetic agent and has consistently maintained a good safety profile. It is increasingly being used as a recreational drug. Chronic ketamine abuse is known to account for lower urinary tract symptoms of frequency, urgency, dysuria, painful haematuria, hydronephrosis and chronic kidney injury.[1] There is now emerging evidence that chronic ketamine abuse is also associated with abnormal liver function tests and biliary tract abnormality.[2] We report a case series of cholestasis and biliary tract abnormality complicating chronic ketamine misuse.

CASE REPORTS

Case 1

A 27-year-old Caucasian man was admitted with abdominal pain and shortness of breath. He had suffered an episode of frank haematuria a month earlier. Urology investigations, including computed tomography (CT) imaging of the abdomen showed bilateral hydronephrosis and a dilated biliary system. On further questioning, the patient admitted to a four-year history of intranasal ketamine use, and that for the past 12 months, he had been experiencing frequent abdominal pains following ketamine usage. Examination revealed a depressed Glasgow Coma Scale score of 13/15, hypotension (blood pressure 95/60 mmHg), tachycardia (heart rate 140 bpm, sinus rhythm) and tachypnoea (60 breaths/min). Blood tests revealed acute renal failure (urea 37.7 mmol/L, creatinine 851 μmol/L, potassium 5.4 mmol/L) and severe metabolic acidosis (pH 7.2, bicarbonate 6.4 mmol/L, pO_2 39.3 kPa, pCO_2 2.0 kPa). His liver function tests (LFTs) were abnormal (serum bilirubin 58 μmol/L, alkaline phosphatase 294 iu/L, alanine transaminanse 106 iu/L, γGT 1,045 iu/L, albumin 26 g/dL and INR 1.0). Chest radiograph revealed bilateral basal consolidation.

Despite aggressive resuscitation, the patient's condition deteriorated rapidly to the point of requiring intensive care support. He was intubated and commenced on continuous haemofiltration and broad-spectrum antibiotics. Renal ultrasonography confirmed bilateral hydronephrosis, and bilateral nephrostomies were inserted. Full liver screen, including viral, autoimmune and metabolic tests, were all negative. Toxicology screen on admission was subsequently reported as positive for ketamine. His overall condition as well as renal (urea 7.7 mmol/L, creatinine 123 μmol/L, sodium 132 mmol/L, potassium 4.2 mmol/L) and liver (bilirubin 10 μmol/L, alkaline phosphatase 296 iu/L, alanine transaminase 59 iu/L, albumin 29 g/L) function tests improved and he was eventually discharged after a total hospital stay of six weeks. Repeated imaging conducted prior to discharge revealed a total resolution of hydronephrosis and the absence of any biliary dilatation.

The patient was re-admitted six weeks later with abdominal pain in the upper right quadrant, abnormal LFTs (serum bilirubin 7 μmol/L, alkaline phosphatase 1503 iu/L, alanine transaminase 482 iu/L, γGT 561 iu/L) and deranged renal function (serum sodium 132 mmol/L, potassium 4.4 mmol/L, urea 16.7 mmol/L and creatinine 294 μmol/L). Ultrasonography showed a recurrence of common bile duct (CBD) dilatation at 1.4 cm. Urine

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Fig. 1 Abdominal radiograph taken six hours post ERCP shows contrast retained within the gallbladder and cystic duct.

Fig. 2 Abdominal radiograph taken three days post ERCP shows that the contrast had emptied from the biliary system into the distal colon.

analysis tested positive for ketamine metabolites. The patient was treated for biliary sepsis and underwent endoscopic retrograde cholangiopancreatography (ERCP). No obstructive lesion was found to account for the dilated CBD. A 10-French plastic biliary stent was placed, and the bile and contrast drainage were noted to be slow. Subsequent clinical and biochemical improvement was noted.

Within a month, the patient was re-admitted with similar symptoms post ketamine use. He was in excruciating pain and required repeated doses of intravenous opiates for pain relief. Ultrasonography showed a dilated CBD of 1.3 cm. A repeat ERCP and stent change was carried out, with improvement of symptoms and LFTs. CT imaging carried out a week later revealed total resolution of the biliary dilatation. In the following three months, the patient had two further similar admissions with biliary dilatation, each after ketamine use. The biliary stent was replaced on both occasions. On the last occasion, two biliary stents were placed to aid biliary drainage. Hepatobiliary imino-diacetic acid (HIDA) imaging was performed three weeks post ketamine use. Results showed a mildly diminished gall bladder ejection fraction of 32% (normal > 35%).

Two months later, the patient was re-admitted with similar symptoms. The right upper quadrant abdominal pain started exactly six hours after ketamine use. ERCP 96 hours post ketamine abuse demonstrated patent stents. His bile was aspirated for toxicology screen but was negative for ketamine. Abdominal radiograph performed six hours post ERCP showed contrast retained within the gallbladder and cystic duct (Fig. 1), in keeping with biliary dyskinesia. Three days later, the contrast had emptied from the biliary system into the distal colon (Fig. 2).

Case 2
A 27-year-old Caucasian man with a two-year history of ketamine misuse (6 gm daily in split doses) was referred to us by a urologist for cholestatic LFTs (bilirubin 3 μmol/L, alkaline phosphatase 178 iu/L, ALT 75 iu/L). The patient possessed a one-year history of increased urinary frequency and nocturia, and a seven-month history of macroscopic haematuria. The hallucinogenic effect that he experienced after ketamine use markedly diminished after a year and he started to suffer from colicky epigastric pain 4–5 hours after exposure to ketamine, with each episode lasting about 30 minutes. Despite discontinuing ketamine use three weeks prior to investigation, ultrasonography showed that despite the patient's sensation of urgency, the pre-void bladder volume was only 24 ml and the post-void volume was 9 ml. There was no other renal or biliary abnormality. Cystoscopy revealed red, oedematous and ulcerated bladder mucosa, which resolved four weeks later. The patient required a period of catheterisation but recovered well over the next three months. There was no history of further ketamine misuse. At this stage, HIDA imaging

revealed normal gallbladder contraction with an ejection fraction of 90%. Unfortunately, LFTs were not repeated, as the patient was lost to follow-up.

Case 3

A 26-year-old Caucasian man with a seven-year history of ketamine misuse was referred to a urologist with a nine-month history of increased urinary frequency, urgency, nocturia and haematuria. Ultrasonography of the abdomen revealed normal conditions. At cystoscopy, the bladder dome was erythematous. Multiple biopsies revealed inflammation. The patient was managed with long-term catheterisation for symptomatic relief. CT imaging and intravenous urogram (IVU) showed bilateral hydroureters and bilateral hydronephrosis. His liver and biliary tree appeared normal on ultrasonography and CT images. LFTs, however, were fluctuating and were persistently abnormal (bilirubin 6–38 μmol/L, alkaline phosphatase 701–2475 iu/L, ALT 44–266 iu/L, albumin 24–43 g/L). A full screening confirmed the exclusion of other causes of liver disease. HIDA imaging showed no appreciable filling of the gallbladder even during delayed images. Therefore, it was not possible to calculate the gallbladder ejection fraction. These findings were consistent with gallbladder dyskinesia.

DISCUSSION

Ketamine (2-[2-chlorophenyl]-2-[methylamino]-cyclohexanone) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. It was synthesised in 1962 and licensed in 1970 by the United States Food and Drug Administration for the induction and maintenance of anaesthesia.[1] Today, it is mainly used to provide anaesthesia during in-hospital and out-of-hospital emergencies, in disaster situations and in third world countries.

Ketamine is a dose-related dissociative anaesthetics with a short duration of action. It is metabolised by hepatic microsomal enzymes. The major pathway for ketamine metabolism involves N-demethylation to form norketamine, which is in turn hydroxylated to form hydroxyl-norketamines. These products are conjugated to water-soluble glucuronide derivatives, and 90% of them are excreted in the urine.[3] For medical usage in humans and animals, ketamine is mostly supplied in vials for intramuscular or intravenous injection.

With a street name of 'K', 'Special K' or 'Cat Valium', ketamine is increasingly used as a recreational hallucinogenic drug. Consumption may result in mood elevation and visual hallucinations with colourful vision and feelings of derealisation (a weightless and out-of-body experience).[4] These psychedelic experiences are usually referred to as 'trips'. There have been a growing number of reports on the use of recreational ketamine on a global scale,[5] including in the United Kingdom.[6] As a street drug, ketamine is available as a white powder and in tablet or capsule form. In these forms, ketamine is inhaled through the nasal cavity and the users experience its effects in approximately ten minutes. When ketamine is consumed orally, it can take up to 20 minutes to have an effect. The hallucinogenic effects are short-lived and last for about an hour.[1]

This case series reports the association among ketamine misuse, cholestasis and biliary dilatation in three young Caucasian patients. Our findings are similar to a recent Asian series that reported three young patients presenting with reversible dilated CBD and abnormal LFTs due to chronic ketamine abuse.[2] There is no record of single or multiple administrations in a medical setting leading to abnormalities of the biliary system. A recent study also showed that acute administration of ketamine does not seem to affect the sphincter of Oddi manometry.[7] However, recreational ketamine use could be intermittent, regular (weekly) or even daily, as in the case of our patients.

The mechanism by which daily ketamine use leads to cholestasis and biliary dilatation remains unknown. It is, however, likely due to either direct actions on the biliary smooth muscles or central action. Previous case reports[1,8] have concentrated on urinary tract abnormalities, including hydronephrosis and lower urinary tract symptoms. However, the exact mechanism has yet to be established. A recent study has shown that activation of NMDA ionotropic receptors located on smooth muscle cells is responsible for the contraction of the human ureter.[9] Therefore, at least in theory, ketamine as an NMDA antagonist can cause smooth muscle relaxation in the ureter. This may explain the occurence of hydronephrosis in these patients. The same mechanism might apply to the biliary system. Animal studies have also shown that ketamine directly dilates cerebral arteries by acting as a calcium antagonist.[10] It is possible that this effect also extends to the biliary tree smooth muscle, thus causing biliary dilatation.

The dorsal motor nucleus of vagus (DMV) has efferent fibres that project to the gall bladder,[11] and gallbladder motility is enhanced with increased level of glutamate in DMV.[12] In animal studies, injection of NMDA into the DMV increases gallbladder motility, and its effect can be abolished following the application of ketamine.[13] It is plausible, therefore, that chronic ketamine misuse may lead to gallbladder dyskinesia via

this central pathway. Radiography and HIDA imaging in our patients suggest gallbladder dyskinesia with current ketamine use, which resolves over time with abstinence. Our experience suggests that this biliary abnormality is fully reversible, and thus, we intend to avoid biliary stenting in the future, unless absolutely necessary.

A case series from the Far East[8] has suggested that abnormal LFTs without biliary dilatation might be caused by direct ketamine hepatotoxicity that were worsened by the concurrent administration of CYP34A inhibitors such as cimetidine or proton pump inhibitors. Evidence of hepatotoxicity with ketamine is lacking, as only a single animal study exists in the literature.[14] In addition, these mechanisms could not explain delayed bile clearance and biliary dilatation in the first patient.

In conclusion, we report a case series of ketamine misuse associated with cholestasis, biliary dilatation/ dyskinesia in the absence of an obstructing lesion. Therefore, ketamine misuse should be considered as a potential cause of unexplained cholestatic LFTs, with or without biliary dilatation.

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