CASE REPORT

Ketamine as a possible cause of cirrhosis in a patient with chronic pain

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ABSTRACT

Ketamine has been typically administered in short-term, few doses in the clinical setting of acute pain. Its hallucinogenic side effects have made it popular as a recreational drug. Reports of urological, biliary and liver abnormalities have been reported, mainly in cases of abuse. It is now increasingly used for chronic pain conditions, and here we report liver abnormalities and ultimately cirrhosis in an adult on regular ketamine for chronic facial pain. Abnormal liver function tests were detected incidentally, and with no other cause for liver disease found, liver biopsy was performed. This showed fibrosis with incomplete cirrhosis.

BACKGROUND

Ketamine, (*RS*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone, is a non-competitive *N*-methyl-D-aspartate receptor antagonist, a drug with sedative, analgesic and anaesthetic properties. It has hallucinogenic and 'out of body' side-effects that have made it increasingly popular as a recreational drug.

Ketamine has typically been administered short-term as a few repeated doses in a clinical setting; therefore, most reports of the long-term effects have primarily been reported and investigated in chronic ketamine abusers. However, it is increasingly being used in the treatment of chronic pain problems refractory to other treatments in intravenous and oral preparations.¹

Urological abnormalities such as ulcerative cystitis and hydronephrosis,² abnormal liver function tests (LFTs), and biliary dilatation have been recognised as complications of its use.

Here we report a case of chronic ketamine use in a chronic pain syndrome

refractory to other measures in which the patient developed abnormal LFTs, dilatation of the biliary tree and progression to cirrhosis.

CASE PRESENTATION

A 55-year-old woman was referred by her GP to the gastroenterology department after she was found to have abnormal LFTs during routine blood tests. She gave a long history of chronic facial pain dating back over 20 years, refractory to treatment. Attempts to control her pain had required trials of many different medications including pethidine and codeine. Ketamine was added 10 years ago achieving a degree of control that the patient was reluctant to lose. The dose of ketamine had been stable at 150 mg QDS for 8 years, in addition to pethidine and paracetamol, with no other changes to her medications over that time period. Her past medical history included asthma controlled with inhalers, montelukast and carbocysteine; gastro-oesophageal reflux disease treated with pantoprazole and as required domperidone and ondansetron; and gallstone disease for which she had an uncomplicated laparoscopic cholecystectomy 8 years previously. At the time of referral, her facial pain was controlled, and she had no abdominal symptoms to report. There was no history of blood transfusion, significant foreign travel, intravenous drug abuse or contact with hepatitis. There was a family history of alcoholic cirrhosis, but she had no personal history of excess alcohol intake or clinical features to suggest alcohol abuse. Her weight was 68 kg and height 1.61 m, giving a body mass index of 26.2 kg/m².

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INVESTIGATIONS

At referral, bilirubin was 8 $\mu\text{mol/L}$ ($<21 \mu\text{mol/L}$), alkaline phosphatase (ALP) 228 u/L (30–130 u/L), alanine transaminase (ALT) 188 u/L ($<40 \text{u/L}$), and full blood count and renal function were normal. Cholesterol was raised at 8 mmol/L . Ultrasound scan of her abdomen showed an enlarged liver, with normal outline and reflectivity. Cholecystectomy was noted, and the common bile duct (CBD) was ultrasonographically normal. Autoantibodies, viral hepatitis screen (B and C), serum ANCA, immunoglobulins, iron and copper studies, and $\alpha 1$ antitrypsin levels were all within normal limits. An ultrasound guided liver biopsy was performed. Histology showed prominent portal–portal bridging fibrosis with incomplete nodule formation and mild portal/septal inflammation. The inflammatory infiltrate was predominantly lymphocytes and macrophages and focused on bile ducts. No interface hepatitis was present, and there were only occasional focal of lobular inflammation. There was no fibrosis around individual hepatocytes, less than 5% steatosis and no Mallory bodies. There was ductular proliferation but unaccompanied arterioles were not seen. The liver parenchyma between the fibrous septae appeared to show relatively normal architecture. These features were felt to be in keeping with a chronic hepatitis with incomplete cirrhosis, with some features in keeping with a biliary aetiology, although a definite cause was not apparent.

Given the biopsy results and her history of cholelithiasis, she underwent a magnetic resonance cholangiopancreatography scan to further assess the biliary tree. This showed intrahepatic and extrahepatic biliary dilatation with the CBD measuring 10 mm in diameter but with no stricturing, tapering smoothly towards the ampulla. There were no duct filling defects and no pancreatic mass. An endoscopic ultrasound was performed at the regional tertiary liver centre, confirming a normal pancreas, pancreatic duct and ampulla. Again, the CBD was prominent, but there was no intrahepatic duct dilatation, and no filling defects or features to suggest microlithiasis.

Review of her liver biopsy by a specialist liver pathologist confirmed the findings of fibrosis in keeping with incomplete cirrhosis. It again highlighted the presence of copper associated protein accumulation and ductular reaction suggesting a possible underlying biliary disease, but with no pathognomonic features of any specific underlying aetiology.

A further ultrasound of the liver showed a slightly enlarged liver with a coarse echotexture.

Review of her LFTs over the preceding years was performed and some of the results listed in table 1. Her bilirubin levels have been normal throughout.

DISCUSSION

We report a case of cirrhosis presumed to be caused by a drug reaction to ketamine. As far as we are aware, this has not been previously reported in the literature.

Table 1 Liver function tests

ALP	ALT	AST	GGT	Events
47	NT	19	NT	Before starting ketamine (April 1999)
73	NT	33	159	Postcholecystectomy (August 2004)
50	NT	16	NT	Surgical follow-up (January 2005)
128	82	NT	1196	Prior to referral (May 2010)
228	188	106	2243	Referred to gastroenterology (August 2011)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, alanine transaminase; GGT, gamma-glutamyl transpeptidase; NT, not tested.

Ketamine is the most potent available non-competitive antagonist of the N-methyl-D-aspartate receptor, a receptor that plays an important role in the aetiology and duration of chronic pain. It has been used in anaesthesiology since the 1960s, although its tendency to cause hallucinations, delirium and confusion during recovery from anaesthesia means it is not as widely used in mainstream anaesthesia.² It is also a widely abused drug, particularly in Asia. In Hong Kong, it has been deemed the single most abused drug.³

One of the most commonly reported side effects of ketamine is that of uropathy. This is felt to be due to toxic metabolites causing direct damage to the bladder mucosa. It has been frequently reported in abusers of ‘street’ ketamine.^{4–5} Obstructive nephropathy and kidney injury have also been reported.⁶

Ketamine has long been shown to cause transient abnormalities in LFTs when used as an anaesthetic agent.⁷ The exact mechanism for injury is unknown but includes reduced hepatic oxygen delivery, and increased lipid peroxidation with free radical formation.⁸ Transient liver test abnormalities have also been reported in patients receiving intermittent infusions of ketamine for chronic pain syndromes.^{9–10} A review of 233 ketamine abusers attending emergency departments in Hong Kong identified abnormal LFTs in 16%.⁵ Average ALT and ALP levels were noted to be high in another case series of ketamine abusers presenting with abdominal pain.¹¹ Animal studies performed in response to the increasing use as a drug of abuse confirmed significant damage in livers of mice treated with ketamine.¹² They showed fatty degeneration of liver cells, fibrosis and a rise in liver enzymes, and noted that these effects were more severe if the animals were also treated with alcohol. Dilated biliary ducts have also been reported in abusers of ‘street ketamine’,^{13–15} and in combination with cholestasis.¹⁶

Most reports to date have been in Asian patients (even the report from New York is of two Chinese patients). This is one of a minority of reports in a Caucasian patient. It is also the first report of proven cirrhosis, although a letter to the editor of *The Clinical Journal of Pain* in 1995¹⁷ reports a case of abnormal liver tests and imaging showing extensive deformity short of cirrhosis, and histology describes a ‘cholestatic liver with extensive pericholeductal fibrosis compatible with drug-induced hepatitis’. These findings were in a 70-year-old man who received up

to 1600 mg per day of oral ketamine, but was also on several other concomitant drugs, and the authors admit being unable to confidently attribute his liver abnormalities purely to the ketamine. Many other case reports are also during an acute crisis—that is, during a hospital attendance due to reported symptoms.^{4 5 11 15 16} In our case, there have been no symptoms reported and the liver abnormalities have been detected incidentally. Decisions in this patient's care now need to be made with regard to how to best manage her pain without further affecting her liver.

Contributors RB wrote the manuscript. DB identified the case and contributed to the manuscript development.

Competing interests None.

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REFERENCES

- 1 Noppers I, Niesters M, Aarts L, *et al.* Ketamine for the treatment of chronic non-cancer pain. *Expert Opin Pharmacother* 2010;11:2417–29.
- 2 Morgan CJA, Curran HV. Ketamine use: a review. *Addiction* 2011;107:27–38.
- 3 Central Registry of Drug Abuse Sixtieth Report, 2001–2010. Narcotics division, Security Bureau, The Government of the Hong Kong Special Administration Region. http://www.nd.gov.hk/pdf/report/crda_60th/crda_60th_full_report.pdf
- 4 Chu PSK, Kwok SC, Lam KM, *et al.* 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007;13:311–13.
- 5 Ng SH, Tse ML, Ng HW, *et al.* Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. *Hong Kong Med J* 2010;16:6–11.
- 6 Selby NM, Anderson J, Bungay P, *et al.* Obstructive nephropathy and kidney injury associated with ketamine abuse. *NDT Plus* 2008;5:310–12.
- 7 Dundee JW, Fee JPH, Moore J, *et al.* Changes in serum enzyme levels following ketamine infusions. *Anaesthesia* 2007;35:12–16.
- 8 Sear JW. Ketamine hepato-toxicity in chronic pain management: another example of unexpected toxicity or a predicted result from previous clinical and pre-clinical data? *Pain* 2011;152:1946–7.
- 9 Noppers IM, Niesters M, Aarts LPHJ, *et al.* Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. *Pain* 2011;152:2173–8.
- 10 Cvrcek P. Side effects of ketamine in the long-term treatment of neuropathic pain. *Pain Med* 2008;9:253–7.
- 11 Poon TL, Wong KF, Chan MY, *et al.* Upper gastrointestinal problems in inhalation ketamine abusers. *J Dig Dis* 2010;11:106–10.
- 12 Wai MS, Chan WM, Zhang AQ, *et al.* Long-term ketamine and ketamine plus alcohol treatments produced damage in liver and kidney. *Hum Exp Toxicol* 2012;31:877–86.
- 13 Wong SW, Lee KF, Ng WWC, *et al.* Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. *Hong Kong Med J* 2009;15:53–6.
- 14 Ng SH, Lee HKH, Chan YC, *et al.* Letters to the editor—Dilated common bile ducts in ketamine abusers. *Hong Kong Med J* 2009;15:157.
- 15 Gutkin E, Hussain SA, Kim SH. Ketamine-induced biliary dilatation from Hong Kong to New York. *J Addict Med* 2012;6:89–91.
- 16 Lo RSC, Krishnamoorthy R, Freeman JG, *et al.* Cholestasis and biliary dilatation associated with chronic ketamine abuse: a case series. *Singapore Med J* 2011;52:e52–5.
- 17 Kato Y, Homma I, Ichiyana K. Letters to the Editor—Postherpetic neuralgia. *Clin J Pain* 1995;11:336–7.