Ketamine cystitis: an emerging diagnostic and therapeutic challenge

Ketamine abuse is increasingly common in the UK. Ketamine-induced cystitis can cause serious damage to the urinary tract. This emerging problem presents a new diagnostic challenge and is very likely to increase in incidence over the coming years.

First described from a small case series in 2007 (Chu et al, 2007) 'ketamine ulcerative cystitis' or 'ketamine bladder syndrome', also known as 'ketamine-induced vesicopathy' (referred to onwards as ketamine cystitis), has emerged as a potentially explosive problem in countries where recreational ketamine abuse is commonplace. The syndrome consists of a small volume, scarred and painful bladder with resulting severe lower urinary tract symptoms, incontinence and haematuria. The presence of upper urinary tract disease can cause obstruction and papillary necrosis resulting in renal failure. Some patients with ketamine cystitis have required cystectomy and reconstructive surgery, others have needed nephrostomies.

This review educates and informs health-care professionals working in a hospital setting about ketamine cystitis and its presentation, investigation and treatment.

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) non-competitive receptor antagonist (Muetzelfeldt et al, 2008). It was synthesized in 1962 (Chu et al, 2008) when researchers were trying to invent new anaesthetic agents in the same arylcyclohexylamine class as phencyclidine (PCP or 'angel dust', itself a drug of abuse) which was the precursor to ketamine. Phencyclidine was found to cause undesirable side effects including postoperative thought disturbance and severe agitation (Peterson and Stillman, 1978). Ketamine was first used in humans in 1965 (Corssen and Dormino, 1966). Ketamine binds to the same NMDA receptor as phencyclidine, but with less affinity, therefore causing less adverse side effects (Muetzelfeldt et al, 2008).

Ketamine causes psychological dissociation during emergence from anaesthesia; this can cause hallucinations, vivid dreams, subjective out of body experiences and psychedelic effects such as a slowing of time and perceptions of travelling though a dark tunnel – the 'k-hole effect'.

Ketamine is metabolized in the liver to its active metabolite norketamine, which in turn is hydroxylated to hydroxynorketamine and then conjugated with glucuronate before being excreted in the urine (Moore at al, 2001).

Ketamine is still used in both human and veterinary medicine for induction and maintenance of anaesthesia and as a powerful analgesic. It is used as a battlefield anaesthetic and also in paediatric anaesthesia. Ketamine is probably most famous for its use in veterinary medicine as a horse tranquilizer. It has excellent cardiovascular stability and dissociative effects which make it suitable for conscious sedation (Mason et al, 2010). It is also used to manage neuropathic pain and for malignant pain control.

Ketamine abuse was first reported on the west coast of the USA in the early 1970s (Peterson and Stillman, 1978). Ketamine has since become a popular drug of abuse in the clubbing, dance and rave party scenes. Ketamine was classified in the UK as a class C drug by the Misuse of Drugs Act in 2006.

Ketamine has various street names (special k, 'K', cat valium, kit cat, kiddy smack, vitamin K, super K) and it is usually sold in powdered form. The street price is usually around £20/g (Coull and O'Brien, 2008), making ketamine anecdotally cheaper than a night out drinking alcohol. The usual mode of administration is snorting, the typical amount being 1 g. Oral routes of administration and intramuscular injection are favoured by some users.

A study looking at phenomenological aspects of ketamine abuse found that users liked the contentedness, increased sociability, enhanced amusement and psychedelic effects which they experienced when taking ketamine. However, users also reported negative experiences of paranoia and depression, feelings of introversion and feelings of loss of control and sensory distortion (Muetzelfeldt et al, 2008). A third of the frequent ketamine users questioned in the study reported that they suffered from 'K cramps' – a severe lower abdominal or pelvic pain associated with long-term ketamine use; a fifth reported cystitis or bladder problems (Muetzelfeldt et al, 2008). Ketamine users are usually well aware that use of ketamine could cause K cramps and urinary problems.

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Ketamine cystitis

The onset of ketamine cystitis following ketamine use is variable; there are reports of the condition developing after a few days in some users and only after years of heavy ketamine abuse in others (Wood et al, 2011). Ketamine cystitis seems to affect generally heavy ketamine users only, although the relationship between long-term use, dose and development of ketamine cystitis is variable; it seems that some people are more susceptible than others.

Ketamine cystitis was first described in a small case series of 10 patients from Hong Kong in 2007 (Chu et al, 2007), another small case series of 9 patients from Canada was published shortly afterwards (Shahani et al, 2007). The authors of both papers had noticed that heavy ketamine users were presenting with severe lower urinary tract symptoms and haematuria. Over the last 5 years the syndrome has been described in more detail and the main symptoms and signs are now understood.

Patients with ketamine cystitis usually present with a history of lower urinary tract symptoms including intract-able dysuria, intense urgency, extreme frequency and post micturition pain (Chu et al, 2008). Gross haematuria may be a feature. Suprapubic and pelvic pain are also common features. Some patients describe a jelly-like urethral discharge, which in female patients may be mistaken for vaginal discharge (*Table 1*). These symptoms can mimic interstitial cystitis, but particularly in women the presentation can be very similar to that of pelvic pain caused by pelvic inflammatory disease, ovarian cyst accident, pressure symptoms from uterine fibroids and irritable bowel syndrome. Therefore, women who have these symptoms are frequently being referred to gynaecology and urogynaecology outpatient departments (*Table 2*).

Pathophysiology of ketamine cystitis

Several commentators have questioned whether it is ketamine and/or its metabolites that actually causes ketamine cystitis; often street drugs are cut with an adulterant to reduce the cost of supplying them, and it could actually be the adulterant causing the syndrome. However, this seems unlikely as ketamine is so cheap that it is not usually mixed with anything. The adulterant used would also be likely to vary, and the same syndrome has been reported on three different continents. A Toronto-based study analysed samples of ketamine seized by the narcotics division of the Metropolitan Toronto Police Department and found them to be almost pure ketamine hydrochloride (Shahani et al, 2007).

Two mouse models using intraperitoneal injections of ketamine have demonstrated a link between ketamine and damage to the urinary tract in mice (Yeung et al, 2009; Tan et al, 2011). There are also several case reports of patients in palliative care and paediatrics developing ketamine cystitis while being treated with therapeutic doses of ketamine in a health-care setting (Gregoire et al, 2008; Storr and Quibell, 2009).

The pathophysiology of ketamine cystitis is currently unknown. There are four theories as to the mechanism of damage in ketamine cystitis, which were suggested by Chu et al (2008) (*Table 3*).

The ketamine metabolites in the urine in high concentration could cause direct toxic effects on the urothellium, resulting in a significant chronic submucosal inflammatory response (Shahani et al, 2007; Chu et al, 2008; Oxley et al, 2009). This would result in a small volume, scarred bladder. Papillary necrosis seen in the kidneys of some very heavy ketamine users could also be caused via the same mechanism, with irreversible damage caused to papillary medullary interstitial cells (Chu et al, 2008).

Another theory is that ketamine or its metabolites could cause microvascular damage to the small vessels in

Table 1. Symptoms of ketamine cystitis

Frequency
Urgency
Dysuria
Incontinence
Gross haematuria
Crampy lower abdominal pain 'K-cramp'
Suprapubic or pelvic pain
Urethral or vaginal jelly-like discharge

Table 2. Differential diagnosis of ketamine cystitis

Diagnosis of ketamine cystitis should be considered in patients presenting with symptoms of these conditions:
Interstitial cystitis
Overactive bladder
Lower urinary tract infection
Renal calculi
Carcinoma of the urinary tract: bladder cancer or kidney cancer
Renal tuberculosis
Any cause of chronic pelvic pain: pelvic inflammatory disease, uterine fibroids, ovarian cyst accident (torsion, rupture, haemorrhage), irritable bowel disease
Sexually transmitted infections, especially Chlamydia causing dysuria and discharge

Table 3. Pathophysiology of ketamine cystitis

Direct toxic effect of ketamine or its metabolites on the urinary tract
Microvascular damage to the urinary tract by ketamine or its metabolites
Autoimmune effect triggered by ketamine or its metabolites
Unrecognized bacteriuria associated with ketamine or its metabolites

From Chu et al (2008)

the bladder or kidneys (Chu et al, 2008). The presence of neovascularization in histology specimens may support this theory (Chu et al, 2008).

The theory of an autoimmune response to ketamine and its metabolites could explain the elevated erythrocyte sedimentation rate seen in ketamine cystitis sufferers. Autoimmune-mediated vascular congestion could cause submucosal oedema and scarring; this would lead to a small volume, poorly compliant bladder as seen in ketamine cystitis (Chu et al, 2008).

The fourth theory – that ketamine cystitis could be caused by an unrecognized bacteriuria – is not as plausible as the other theories. Most of the patients described in published studies had abacterial cystitis. No patients with ketamine bladder syndrome have improved in response to antibiotics alone.

It is not known whether the same disease process in ketamine cystitis causes damage to the lower urinary tract and the upper urinary tract. Upper tract disease could be caused by the presence of lower tract disease resulting in vesicoureteric reflux of urine as a result of a small bladder capacity combined with high bladder pressure from detrusor overactivity.

It is thought that upper urinary tract disease is less frequently found in ketamine cystitis sufferers because there is a longer contact time between the lower urinary tract and the ketamine and/or its metabolites in the urine than in the upper tract (Chu et al, 2008). It seems likely that upper tract disease occurs only after longstanding ketamine cystitis (Mason et al, 2010).

Investigating ketamine cystitis

The most important investigations in ketamine cystitis are computed tomography urogram and cystocopy.

The main purpose of investigations in ketamine cystitis is fourfold:

1. To exclude other potential causes of the symptoms
2. To support the diagnosis
3. To identify immediate complications such as upper tract involvement
4. For long-term surveillance of the condition (Mason et al, 2010).

Patients with ketamine cystitis normally have a negative urine culture, usually with a sterile pyuria on cytology, and urine frequency volume charts can be used to demonstrate a reduced functional voiding capacity and urinary frequency (Chu et al, 2008).

Baseline urea and electrolyte levels should always be measured and will usually be normal. If they are elevated this may be the result of upper tract obstruction and papillary necrosis causing renal failure.

Urodynamic studies in ketamine cystitis are often very poorly tolerated because of pain and may not be a very helpful investigation. A very small volume bladder, typically less than 150 ml, is usually demonstrated.

Simple ultrasonography of the renal tracts may show hydronephrosis if upper tract disease is present and will also demonstrate reduced bladder volume and bladder wall thickening. Patients with ketamine cystitis often find ultrasonography with a full bladder difficult to tolerate (Mason et al, 2010).

Intravenous urogram may demonstrate dilated upper tracts and a contracted small volume, scarred bladder (Chu et al, 2008). Ureteric strictures have also been reported in association with ketamine cystitis (Mason et al, 2010).

Computed tomography urogram is thought to be the imaging modality of choice in ketamine cystitis (Middela and Pearce, 2010) and will show diffuse bladder wall thickening with enhancement of the bladder mucosa and inflammatory changes in the surrounding perivesical fat. Upper tract changes will also be visible on computed tomography urogram (Mason et al, 2010). Again, patients found it hard to tolerate a computed tomography urogram as it involves having a full bladder.

Cystoscopy is an important investigation to exclude any other causes of haematuria and severe lower urinary tract symptoms, such as carcinoma in situ and transitional cell carcinoma. Bladder biopsies can also be obtained at the time of cystoscopy. Ketamine cystitis patients are usually unable to tolerate cystoscopy under local anaesthetic. Erythematous bladder mucosa with or without ulceration is a common finding (Mason et al, 2010).

A study from Bristol which aimed to describe the histopathological features of ketamine cystitis reviewed the histology specimens of 16 patients with the condition. Twelve of the patients had marked urothelial cell atypia with nuclear enlargement and loss of polarity, 12 of the specimens showed urothelial ulceration. Immunohistochemistry was also performed on 10 of the specimens for CK20, p53 and Ki67, markers which are all highly expressed in carcinoma in situ. High expressions of p53 and Ki67 and low expressions of CK20 were noted in the specimens. The authors concluded that the histopathological features of ketamine cystitis mimic those of carcinoma in situ apart from the negative expression of CK20; this distinguished ketamine cystitis from carcinoma in situ (Oxley et al, 2009).

Management of ketamine cystitis

While there is currently no evidence for a validated treatment regimen for ketamine cystitis, what is clear from the reported case series is that immediate and total cessation of ketamine can prevent the disease from progressing and may help it partially resolve (Shahani et al, 2007; Chu et al, 2008; Storr and Quibell, 2009).

A validated questionnaire – the Pelvic pain, Urgency and Frequency questionnaire – has been used in three published papers to evaluate symptoms of possible ketamine cystitis in ketamine users (Chu et al, 2008; Mak et al, 2011; Ng et al, 2012). The studies showed that some of those ketamine users with lower urinary tract symptoms showed spontaneous resolution of the syndrome after a year's abstinence from ketamine (Mak et al, 2011).

Ketamine is a relatively cheap drug of abuse and, as its use is not usually associated with crime, users are often seen as a low priority for rehabilitation (Wood et al, 2011).

Helping someone who has a significant history of ketamine abuse to stop using the drug can be very challenging and stands a high chance of failure. Some ketamine cystitis sufferers resort to using ketamine to treat their chronic suprapubic pain and K cramps further exacerbating the condition. A chronic pain team in Bristol has developed a regimen which uses buprenorphine patches with co-codamol and amytriptiline at night to replace the ketamine and provide adequate pain relief (Wood et al, 2011).

There are several case reports of patients with severe ketamine cystitis needing to undergo cystectomy and formation of a neobladder (Mason et al, 2010). A number of patients with severe upper tract disease have also required nephrostomies (Chu et al, 2007, 2008).

High dose antimuscarinic agents, including tolteridine 4 mg twice daily or oxybutynin 10 mg three times daily, have made no difference to the severe overactive bladder symptoms in these patients (Chu et al, 2008). A regimen using antibiotics, oral non-steroidal anti-inflammatory drugs and corticosteroids also failed to provide any benefit (Chu et al, 2008; Mak et al, 2011). Cystodistension has also proved not at all helpful in ketamine cystitis (Tsai et al, 2009).

Bladder instillations of hyaluronic acid (Cystistat) and oral Pentosan polysulphate (Elmiron) have been used in two case series to provide good symptomatic relief from ketamine cystitis. The authors have also seen it used effectively in a patient treated at the Royal Hallamshire Hospital in Sheffield.

Long-term follow up is essential for patients with ketamine cystitis. It is, as yet, unknown whether the chronic inflammatory process seen in the disease is going to predispose these patients to malignant disease of the urinary tract.

The only measure shown to help improve ketamine cystitis is cessation of ketamine; therefore good links between drug support agencies, chronic pain teams, primary care trusts and urology units is needed.

Conclusions

Ketamine users are often well aware of so-called K cramps and urinary symptoms which can occur with ketamine abuse. Publicity campaigns need to heighten awareness of ketamine cystitis and its potential severity.

Now, it is important that frontline medical staff are also aware of the major urological syndrome which ketamine causes, so that patients presenting with symptoms of ketamine cystitis are asked directly about ketamine abuse when taking a history and the appropriate investigations, management and support can be provided. BJHM

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KEY POINTS

- Ketamine abuse is prevalent in the UK, ketamine is cheap and widely available. Young people are most at risk.
- Ketamine cystitis is a major urological syndrome with potentially very damaging sequelae.
- Anyone presenting with lower urinary tract symptoms or haematuria should be asked directly about ketamine abuse.
- Women presenting with pelvic pain and vaginal discharge should also be questioned about ketamine use.
- Ketamine cessation is the only intervention shown to prevent disease progression.
- It is likely in the future that the prevalence of ketamine cystitis will increase.
- A public health campaign is needed to raise awareness among health-care professionals and to inform users about the potential long-term effects of the drug.