REVIEW ARTICLE

Genitourinary toxicity of ketamine

YB Wei 魏永寶
JR Yang 楊金瑞
Z Yin 尹 焯
Q Guo 郭 瓊
BL Liang 梁波羅
KQ Zhou 周克勤

Ketamine is a relatively new recreational drug used by youngsters in recent decades. Its toxic effects on the genitourinary system were first reported in 2007, and now attract extensive attention from urologists, pharmacologists, and toxicologists all over the world. As many front-line health professionals and medical social workers are still unaware of this new clinical entity and an increasing number of the drug users seek help for urological symptoms, this mini-review aimed to summarise the clinical features and possible mechanisms of ketamine-induced genitourinary toxicity. By raising public awareness of these toxic effects, the authors hope that the contents of this review will be widely disseminated not only to medical professionals, but also to relevant government departments and the general public.

Introduction

Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDA) antagonist, is widely used as an anaesthetic agent in human and veterinary procedures after its successful development in the 1960s. Since the 1980s, it has been increasingly used by young people all over the world as a recreational agent. Ketamine was well known to induce multiple organic dysfunctions, but its toxic effects on the genitourinary system first drew public attention in 2007,[1,2] and now present a difficult challenge to urologists and experts in pharmacology and toxicology. This review presents information about the clinical features and possible mechanisms of ketamine-induced toxicity on the genitourinary system.

Urinary system

Epidemiology

Young persons constitute the vast majority of ketamine abusers. In 2007, 0.8% of individuals aged 16 to 24 years were reported to be using ketamine per year.[3] Another survey in Australian households indicated that the prevalence of ketamine use was highest among people aged 20 to 29 years.[4] A total of 233 records of ketamine users were reported in a Hong Kong survey, with ages ranging from 13 to 60 (median, 22) years and the male-to-female ratio of 2.1:1.[5] According to the recent largest study, 1285 (34%) of 3806 participants who completed the survey reported ketamine use within the last year, including 27% who admitted having lower urinary tract symptoms (LUTS).[6] The mean age of these subjects was 24 years, 95% reported intranasal use, 70% (n=869) were males, and the mean age of first ketamine use was 20 years.

Clinical features

Among the adverse consequences of ketamine misuse, LUTS, impaired consciousness, abdominal pain, and dizziness are the most common symptoms.[5] The typical clinical manifestations of LUTS after long-term ketamine abuse include severe dysuria, painful haematuria, urinary urgency, urge incontinence, frequency,[1,2,7] and nocturia.[8,9] Urine cultures including searches for acid-fast bacilli in early-morning urine samples[2,10] were negative, though individuals subsequently develop concomitant urinary tract bacterial infections that are considered to be secondary.[11] A few patients present with sterile pyuria[8,12,13] or proteinuria.[12] Enhanced bladder wall thickness and lower-than-normal urinary bladder volume, with or without upper urinary tract disorder (thickened ureteral wall and dilatation, hydronephrosis, and renal impairment) have also been described.[7] Based on the International Prostate Symptom Score and Quality of Life scores in those presenting with moderate-to-severe urinary symptoms, their quality of life is affected to a moderate or severe degree (according to our own unpublished survey results). Intractable urinary symptoms and severe impairment of their quality of life are difficult to tackle for urologists, pharmacologists, and toxicologists who manage these patients. Urine and blood toxicology profiles of some of these patients are also positive for ketamine. A

Key words
Cystitis; Hydronephrosis; Ketamine; Lower urinary tract symptoms; Toxicity

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Department of Urology, The Second Xiangya Hospital, Central South University, 139 Middle Renmin Road, Changsha 410011, Hunan, China
YB Wei, MD
JR Yang, PhD
Z Yin, MD
Q Guo, MD
BL Liang, MD
KQ Zhou, MD

Correspondence to: Dr JR Yang
Email: 2xiangya2010@gmail.com

氯胺酮對泌尿生殖系統的毒性

近數十年來，氯胺酮對於年青人來說是一種相對較新的「消遣性」藥物。自從2007年首次有關氯胺酮引發泌尿生殖系統毒性的報導，便吸引了世界各地的泌尿科、藥理學和毒理學醫生的廣泛關注。由於有許多前線醫療工作者和醫務社工仍不清楚這種藥物的臨床症狀，同時亦有越來越多氯胺酮濫用者尋求協助以解決其泌尿系統症狀，本文總結了氯胺酮引發的臨床症狀及介紹泌尿生殖毒性的可能機制。透過提高公眾對這些毒性作用的理解，筆者希望本文的內容不僅能在醫療專業人員中廣泛傳閱，亦能給予政府相關部門和廣大市民作一參考。

dose and frequency response relationship has been demonstrated between ketamine use and urinary symptoms,[6,14] and dose dependence has also been confirmed in vitro.[15]

Cessation of ketamine is the milestone of treatment, both for preventing deterioration of renal function and offering the possibility of symptom resolution.[6,7] After ketamine cessation, oral pentosan polysulfate[1,16,17] and intravesical instillation of hyaluronic acid solution[16,18] or lidocaine and heparin[17] appear to provide some symptomatic relief. Duloxetine (a well-known antidepressant) may be considered a therapy for depressed patients as it is also believed to counter LUTS to some extent.[19] Other forms of pharmacotherapy are generally regarded as unsuccessful or show no obvious effect, though very few patients may enjoy symptomatic benefit.[1,13,20-22] Regrettably, ketamine cessation is not an effective means of relieving all symptoms in every patient completely; symptoms may be partially alleviated only and impaired quality of life often persists.[1,8,23] It has been reported that after stopping of ketamine use, in about a third of cases LUTS resolve, in another third symptoms progress, and in the remainder there is no change.[24] Another large study reported a 51% improvement in urinary symptoms upon cessation, but about 4% of patients endured deteriorating symptoms even after stopping ketamine.[6]

Surgical interventions can be undertaken with the aim of maintaining renal function and/or improving severe LUTS. For symptom control, patients may be offered hydrodistension,[17] a suprapubic catheter,[25] augmentation enterocystoplasty,[11,12] or even cystoprostatectomy[21] and cystectomy with construction of an ileal neobladder.[26] In patients presenting with hydronephrosis and renal failure, early treatment with endoscopic insertion of JJ stents[11,17] or nephrostomy tubes[2,11,25,27] can preserve renal function before irreversible damage. A few patients in whom renal function has continued to deteriorate have undergone nephroureterectomy.[25] A multidisciplinary approach promoting harm reduction, cessation, and early urology referral can help combat and manage ketamine-associated urinary tract symptoms and avoid progression to severe symptoms and irreversible urological outcomes.[2,6]

Bladder

Different doses and frequencies of ketamine abuse lead to different degrees of bladder disturbance. Patients with near-normal cystometric bladder capacities who stop (or reduce) ketamine abuse may return to normal bladder function.[11] In long-term abusers of ketamine, functional bladder capacities (determined from voiding diaries) were between 30 and 100 mL only.[2] Intravenous pyelography showed a small-capacity bladder with the upper urinary tract involved[12] (Fig 1). Computed tomography (CT) revealed significant thickening of the bladder wall, a small capacity, and perivesicular inflammation,[1,13] or showed irregular bladder outline with a pseudo-diverticulum.[12]

Many patients fail to attend urodynamic testing, as they do not tolerate bladder distention or urethral catheterization during the procedure.[2,18] Patients available for urodynamic studies had detrusor overactivity[16] and poor relaxation of the external sphincter[19] or decreased bladder compliance, with or without variable vesico-ureteric reflux and

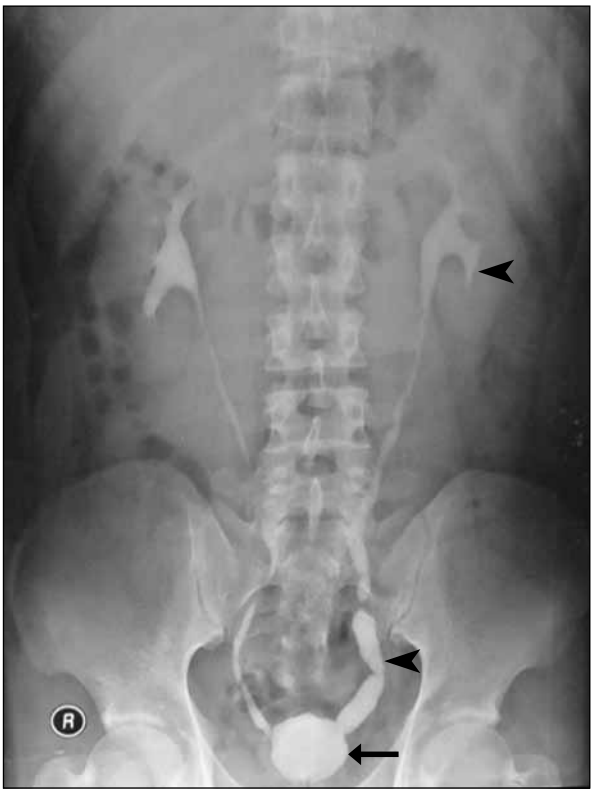

FIG 1. A 29-year-old man with severe lower urinary tract symptoms after abusing ketamine for over 2 years
Intravenous pyelography shows an irregular, small-capacity bladder with significant thickening of the bladder wall (arrow) and the upper urinary tract involvement (arrowheads)

decreased bladder capacity.[11] A bladder capacity of less than 150 mL could be regarded as a clinical threshold.[18] Urinary leakage occurred even when the bladder was filled to a capacity of 30 to 50 mL.[2] The potassium sensitivity test was positive in some patients, indicating interstitial cystitis (IC).[16]

Many patients declined cystoscopy for the same reason as for urodynamic studies,[9,11,16] though cystoscopy was usually performed either under local or general anaesthesia (based on symptom severity and patient choice).[11,16] Cystoscopic findings classically associated with IC are detailed in the Table.[1,2,7,8,10-13,16-18,20,24,26-35] They include low bladder capacity, contracted bladder, marked inflammation consistent with in-situ carcinoma or significant infection,[8] severe bladder ulceration,[1,16] multiple erythematous swelling[12,13] with necrotic mucosa,[13] various degrees of epithelial inflammation with neovascularisation and petechial haemorrhages,[11] or cystitis glandularis confirmed by biopsies only.[2] It has been noted that after cystodilation or cystoscopy on filling the bladder, there may be erythematous bladder bleeding,[21] glomerulation (bladder haemorrhages) and mucosal bleeding diffusely into the lumen,[28] and even persistent active bleeding from a bladder ulcer[16] (Fig 2).

Bladder biopsies of ketamine-induced cystitis reveal chronic inflammatory changes similar to those encountered in any form of IC.[1,11] These entail a thin epithelium with neutrophilic and lymphoplasma cell infiltration of the bladder mucosa,[16] and/or a mononuclear inflammatory cell infiltrate in submucosal tissue.[18,36] A proliferation of von Brunn's nests in the bladder has also been described.[29] Some patients with serious bladder lesions show no surface epithelium, but only smooth muscle (Fig 3), collagen and adipose tissue.[8] The bladder mucosa is typically erythematous,[26] with or without ulcerative and haemorrhagic cystitis.[1,21] Finally bladder tissue fibrosis supervenes,[12] without dysplasia or malignancy.[27] Calcification in the bladder has also been described in a few patients.[30,35] Silver staining revealed a loss of nerve fibres among the muscles of the bladder, and immunohistochemistry on choline acetyltransferase (a marker for cholinergic neurons) also yielded a decline in such cells.[36] Detailed biopsy finding in the published literature are referred to in the Table.

Bladder wall fibrosis has been demonstrated in a ketamine-treated mouse model, with loss of muscle in the bladder wall and an increase of connective tissue, which concurs with clinical findings in patients.[37] Muscular and epithelial degeneration was present, as reflected by the presence of apoptotic cells in the layers of the mouse bladder wall, and an extensive increase in fibrous tissue, mostly in the lamina propria (stained by Sirius red), but ulceration of the bladder as commonly reported was not observed.[37] Another ketamine-treated mouse model discovered transmitters changed in the urinary bladder, whereby noncholinergic contractions and P2X1 receptor expression was enhanced.[38] This indicated dysregulation of purinergic neurotransmission, possibly giving rise to detrusor overactivity and bladder dysfunction.

There was no strong bladder biopsy–based evidence that long-term ketamine use resulted in bladder tumours. Premalignant conditions such as squamous metaplasia are occasionally noted,[31,35] as is nephrogenic metaplasia in the bladder.[35] However, ketamine leading to reactive urothelial changes that mimic carcinoma in situ has been noted,

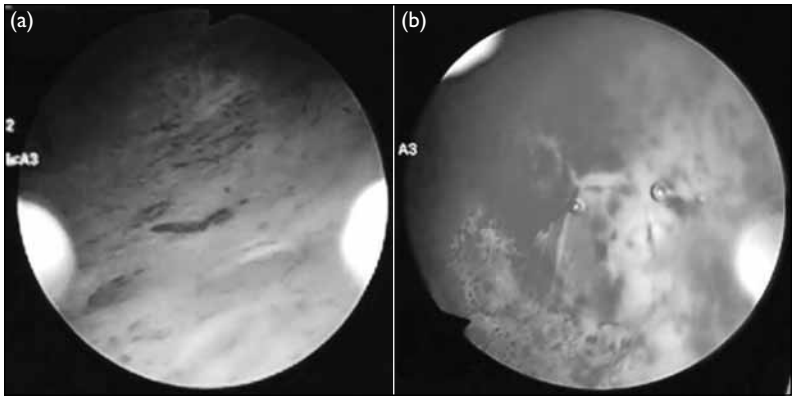

FIG 2. A 32-year-old man who abused ketamine for over 5 years was admitted with severe lower urinary tract symptoms. Cystoscopy, which had to be performed under general anaesthesia as he could not tolerate bladder distention or urethral catheterization, shows: (a) a bladder with scattered punctuate bleeding ulcers (at the beginning of the cystoscopy), and (b) diffuse bleeding and fused ulcers in the bladder

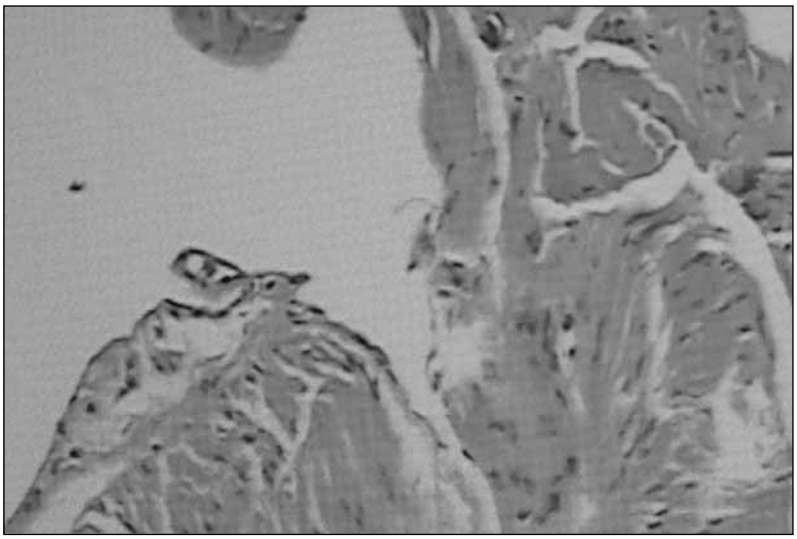

FIG 3. The patient described in the legend of Figure 2 underwent bladder biopsy in the procedure of cystoscopy, which presents no surface epithelium but yields smooth muscles in the bladder

TABLE. Published reports on cystoscopy and biopsy findings in ketamine abusers

Study	Cystoscopy	Biopsy
Shahani et al,[1] 2007	Multiple erythematous patches of the bladder wall, consistent with active cystitis	A substantially denuded urothelial mucosa, with a thin layer of reactive and regenerating epithelial cells. The superficial lamina propria was oedematous, with numerous dilated blood vessels and scattered inflammatory cells, with an overall appearance of granulation tissue. The deeper lamina propria was dense and fibrotic. Throughout the stroma, scattered lymphocytes and mast cells were identified but eosinophils predominated, mimicking the changes of chronic cystitis
Chu et al,[2] 2007	Cystitis glandularis	Cystitis glandularis
Chu et al,[11] 2008	Cystoscopy revealed various degrees of epithelial inflammation of the bladder and neovascularisation. Severe cases showed petechial haemorrhages, as classically described in patients with interstitial cystitis	Histologically, the urinary bladder epithelium was largely denuded, with a focal presence of reactive urothelium. The lamina propria showed granulation tissue and congested vessels, infiltrated predominantly by lymphocytes and a variable number of eosinophils. Ultrastructural examination by electron microscopy showed querciphylloid muscle cells (vacuoles at the periphery of muscle cells). This feature has also been found in interstitial cystitis
Tsai et al,[13] 2008	Multiple erythematous swelling and necrotic mucosa in the bladder	Multiple erythematous patches of the bladder biopsies with active cystitis were identified
Colebunders and Van Erps,[20] 2008	Mild inflammatory changes	Negative
Cottrell et al,[24] 2008	A small-capacity erythematous bladder which bled on filling	An ulcerative, haemorrhagic cystitis
Selby et al,[27] 2008	A diffusely inflamed bladder with marked reduction in capacity (150 cc) but no obstruction at the ureteric orifices	Inflammatory change but no dysplasia or malignancy
Oxley et al,[35] 2009	One specimen consisted of ulcer slough only but eosinophils were not present; the majority of the bladder was ulcerated and where the urothelium remained it showed urothelial atypia	The urothelial atypia seen in the biopsy specimens of 12 patients was marked with nuclear enlargement and loss of polarity. High expression of p53 was present in 9/10 cases, but high expression of Ki67 was present in 6/10 cases. None of the biopsy specimens showed expression of CK20 in the atypical urothelium calcification in one specimen, in another nephrogenic metaplasia and one had non-keratinising squamous metaplasia
Storr and Quibell,[8] 2009	Contracted bladder, 'marked inflammation consistent with in-situ carcinoma or significant infection', multiple telangiectasia on distension, 'bullous cystitis and scarring'	A moderate inflammatory infiltrate, denuded mucosa in places and foci of 'cystitis cystica'. There was no evidence of malignancy or granulomata, smooth muscle, collagen and adipose tissue, but no surface epithelium was obtained on either occasion
Chiew and Yang,[12] 2009	Diffuse reddish swelling of the bladder mucosa	Bladder wall ulceration, inflammation, and fibrosis
Tsai et al,[18] 2009	(Not mentioned)	Denuded urothelial mucosa and regeneration of urothelial mucosa were found. The bladder wall showed inflammatory infiltration with eosinophils and mast cells
Shahzad et al,[30] 2009	Erythematous bladder with increased vascularity	Histology showed markedly inflamed bladder wall with focal areas of ulceration and granulation tissue formation. Congo red stain failed to reveal any amyloid tissue. Areas of dystrophic calcification were evident
Middela and Pearce,[7] 2011	Diffusely inflamed bladder with a 50-mL capacity	Non-specific
Mason et al,[26] 2010	Erythematous bladder mucosa with or without ulceration was found in all cases	Histological findings included inflammatory changes with an inflammatory infiltrate containing eosinophils within the lamina propria and atypical urothelium showing increased proliferation rate and expression of p53 but no expression of cytokeratin 20
Ho et al,[29] 2010	Inflamed bladder mucosa with superficial ulcers	Biopsy revealed urothelial epithelium with nodular proliferation in the lamina propria. The cells lining the cyst were characteristic of multilayered urothelial epithelium. Dense neutrophil infiltration was seen within the epithelium and lamina propria. Some of the fragments were composed of granulation tissue with eosinophil infiltration. No granuloma, dysplasia, or malignancy was seen. On the whole, the biopsies showed changes consistent with severe cystitis with a proliferation of von Brunn's nests
Noorzurani et al,[33] 2010	A contracted and inflamed bladder	Histological changes consistent with interstitial cystitis
Chen et al,[16] 2011	Bladder ulceration, severe post-dilation haemorrhage, and low bladder capacity	Neutrophilic and lymphoplasma cell infiltration in bladder mucosa, which was consistent with chronic inflammation
Nomiya et al,[28] 2011	Mild glomerulation and mucosal bleeding appeared diffusely in the bladder mucosal lumen, indicating a diagnosis compatible with interstitial cystitis	Not performed
Lai et al,[10] 2012	A small-capacity bladder with erythematous lesions throughout the bladder	Changes of chronic cystitis
Chang et al,[17] 2012	Diffuse neovascularisation, glomerulation and multiple erythematous patches in 19 patients	Acute or chronic inflammation with denudation of the urothelium
Jalil and Gupta,[31] 2012	Features of ulcerative cystitis with small bladder capacity	Biopsy confirmed extensive ulcerative cystitis, one of which also showed squamous metaplasia
Ng et al,[32] 2012	Cystitis	(Not mentioned)
Venyo and Benatar,[34] 2012	A small-capacity inflamed bladder and both ureteric orifices looked normal	Histological examination of the biopsy specimens showed an unremarkable overlying urothelium, while the underlying lamina propria showed areas of ulceration and fibrin deposition, with granulation tissue formation. There was diffuse moderate chronic inflammation. There was no obvious atypia or malignancy. The features of the biopsy specimens were consistent with ulceration and chronic inflammation

with high p53 immunoreactivity but negative for cytokeratin 20,[26,35] and with moderate-to-high levels of immunohistochemical Ki67 reactivity.[35] These findings are important, as cytokeratin 20 has been associated with urothelial dysplasia and raises the suspicion of malignancy.

Ureter and kidney

Besides bladder lesions, the subsequent condition of the upper urinary tract (ureters and kidneys) of ketamine abusers is also noteworthy. According to the published reports, Chu et al[11] found that 51% of patients with ketamine-induced urinary symptoms had unilateral or bilateral hydronephrosis revealed by ultrasonography. Another patient with no ultrasonographic abnormality had bilateral vesico-ureteral reflux. Based on CT, no cause for hydronephrosis was evident in such patients, in particular there were no calculi.[27] Abdominal CT was performed in another patient, and mild bilateral hydroureters were evident but no hydronephrosis was mentioned.[16] Most often hydronephrosis was accompanied by varying degrees of ureteral lesions, ureteral wall thickening, ureteral stenosis, or vesico-ureteric reflux. A unilateral abnormality of the distal ureter was revealed by intravenous urography.[21] A diethylenetriamine pentaacetate scan showed that the right kidney was not functioning and there was severe vesico-ureteric reflux.[29] Chiew and Yang[12] utilised intravenous pyelography which showed narrowing of the bilateral ureterovesical junction with bilateral hydronephrosis and hydroureters. Chu et al[2] reported that one patient who continued to abuse ketamine ended up with gross bilateral hydronephrosis and acute renal failure. A subsequent antegrade nephrostogram revealed complete right-sided ureteric obstruction just below the pelvic-ureteric junction and a markedly diminished flow of contrast in the left ureter suggestive of retroperitoneal fibrosis.[2] According to a mercaptoacetyltriglycine nuclear medicine scan, one patient's right kidney contributed to only 11% of overall renal function, indicating right kidney dysfunction.[25] Subsequent nephrostograms also showed bilateral diffuse ureteric narrowing, without any extrinsic cause of ureteric obstruction demonstrated by CT, raising the suspicion of retroperitoneal fibrosis.[25] According to the published reports, in several patients the upper urinary tract is involved, while about half of them have unilateral or bilateral vesico-ureteral reflux. Chu et al[11] even found four patients with acute papillary necrosis. It was recognised that papillary necrosis could cause complete ureteric obstruction by migration of a sloughed papilla into the ureter and hence hydronephrosis.

Ketamine-induced kidney damage has also been revealed in two animal models. Yeung et al[36] found that starting from 1 month, all addicted mice showed invasion of mononuclear white cells, either surrounding the glomerulus or kidney tubules, and that aggregation of these cells extended all the way to the pelvis and ureter. Wai et al[39] observed hydropic degeneration of the kidney tubules as early as 6 weeks into ketamine treatment of mice. Long-term ketamine administration (28 weeks) led to atresia of renal glomeruli in mice, which was more severe when the animals were treated with both ketamine and alcohol.[39]

Biopsies of the ureteric wall yielded non-specific chronic inflammatory changes. Bladder biopsies in patients with ketamine cystitis showed fibrotic ureteric tissue with mucosal ulceration and residually attenuated urothelium with nuclear enlargement, pleomorphism, and occasional hyperchromasia.[25] These patients also had oedematous lamina propria infiltrated by neutrophils, plasma cells, macrophages, and eosinophils. Such inflammatory infiltrates extended through the ureteric wall with prominent regions of periureteric fibrosis.[25] Chang et al[17] described two patients in whom ureteral wall tissue (seen by ureterorenoscopy) yielded chronic inflammation with reactive changes of the urothelium and formation of granulation tissue with inflammatory exudates.

Whether chronic ketamine abuse gives rise to ureteric or kidney tumours is still unknown. Hopcroft et al[25] considered that an extension of intestinal mucosa from the ileal conduit was possible, as they found focal intestinal metaplasia extending several centimetres up the ureter and originating from the ileal conduit margin.

Reproductive system

Jang et al[40] discovered that with the exception of sexual desire, sexual dysfunction due to ketamine abuse was common in all domains (arousal, lubrication, orgasm, satisfaction, pain), and that like ketamine-induced cystitis, it too severely impacted the quality of life. Notably, there was also a statistically significant reduction in sperm motility as studied in ketamine-treated male ICR (Imprinting Control Region) mice compared with controls, and that longer durations of treatment amplified this effect.[37] Collectively, these effects suggest reduced fertility possibly associated with chronic ketamine intake.

Possible mechanisms

The underlying pathophysiological mechanism for the destruction of the urinary tract by ketamine is unknown. Further investigations to determine the exact cause of ketamine-induced pathology are necessary. Epidemiological studies as well as clinical and animal research may be helpful in assessing the

actual scope of the problem and could yield clues to aetiology. Whether damage to the lower and upper urinary tract is caused by the same factor is uncertain. Why the lower urinary tract is affected more frequently is also unknown. As the upper urinary tract appears to be involved later and less frequently, this could be a secondary phenomenon. Whatever the reason, several hypotheses for the relationship between ketamine use and the urinary tract damage have been proposed.

Direct toxic effects

The high concentration of ketamine and its metabolites (norketamine and hydroxy norketamine) in urine might be directly toxic to the lower urinary tract mucosa.[1,2] It appears plausible that these chemicals accumulating in urine induce significant bladder irritation and cause cystitis due to prolonged contact.[1] The presence of papillary necrosis in some chronic high-dose ketamine abusers might be due to irreversible toxic effects on interstitial cells in the papilla, leading to interstitial fibrosis, structural damage, and chronic renal insufficiency.[11] Ketamine and its metabolites appear to cause a disordered urine-tissue interface in the bladder, thus leading to penetration of toxic urinary compounds into the bladder wall.[18] Strong evidence implicates ketamine abuse as a cause of irritative symptoms. For example, abusers experience symptom relief after intravesical instillation hyaluronic acid,[18] thus implicating ketamine and its metabolites in the urine as a causal factor. However, it is still unknown whether it is their presence in urine that has an important role on urinary system damage.

Loss of bladder wall muscle tissue and an increase of connective tissue have been observed in mice models.[37] Muscular and epithelial degeneration, an extensive increase of fibrous tissue mostly evident in the lamina propria, and fibrosis in the muscular layer along with thinning of muscle are the main findings. Wai et al[39] proposed that ketamine induces fibrosis in liver lobes and necrotic cells in the kidney, and the resulting accumulation of its metabolites (including hydroquinone) would directly fragment the DNA of cells. These researchers found fibrosis at the tips of liver lobes in ketamine-treated animals by 16 weeks, while in controls the corresponding areas of the liver were relatively clear. The fibrosis had spread into the parenchyma of the liver by 28 weeks of ketamine treatment. They also reported that the extent of fibrosis was more abundant in the livers of ketamine-treated animals and that such animals exhibited glomerular atresia (<10%) but as much as 20% in animals that also received alcohol. This suggested that ketamine-plus-alcohol treatment induced more proliferation of nuclei than ketamine alone.

Microvasculature toxicity

Shahani et al[1] considered that ketamine and its metabolites inflicted damage to the microvasculature of the bladder, potentially leading to ischaemia and fibrosis. Chu et al[11] thought that such toxic effects on microvasculature were also applicable to the kidney. They proposed that some patients may be prone to papillary necrosis from micro-angiopathy or capillary sclerosis in the renal medulla causing papillary hypoperfusion and bladder ischaemia, and give rise to severe suprapubic pain and dysuria during bladder filling.

Neural and neurotransmitter toxic effects

Yeung et al[36] hypothesised that ketamine-induced chronic inflammation in the urinary system of the mouse was probably not a direct effect of the ketamine, but secondary to indirect pathophysiological changes. They inferred there was a change in neuromuscular activity or a possible decrease of nerve fibres, there being a decrease in silver-stainable fibres in the muscles of the mouse urinary bladder, suggesting that ketamine caused degeneration of neuromuscular junctions and/or proprioceptive sensory fibres in the course of chronic addiction. Others demonstrated that nociceptive responses induced by substance P were enhanced by NMDA antagonists in the presence of ketamine, which suggested facilitation of neurogenic inflammation as a cause of cystitis.[16] A slight disturbance in the peripheral C-fibre function did not lead to increased bladder volumes, but in schizophrenic patients detrusor hyperreflexia has been observed.[41] Thus, Meng et al[38] utilised mice treated with ketamine, which showed enhanced noncholinergic contractions and P2X1 receptor expression in the bladder, indicating dysregulation of purinergic neurotransmission possibly underlying detrusor overactivity in ketamine-induced bladder dysfunction.

Autoimmune pathogenesis

An autoimmune reaction was postulated as a cause of IC,[1] which might explain the raised erythrocyte sedimentation rate and C3/C4 found in some patients.[11,16,19]

Bacteriuria

Although most ketamine users presented with sterile urine and showed no improvement after antibiotic treatment, Chu et al[11] regarded positive bacterial culture in subsequent urine specimens of two patients might be secondary infections not responsible for the initial urinary symptoms. Yeung et al[36] considered that prolonged ketamine addiction resulted in animals becoming prone to

urinary infection. Shahani et al[1] also believed that secondary bacterial infection led to long-term renal tract damage.

Discussion

The non-medical use of ketamine has been illegal in the UK since it was classified as a class C drug in 2006, and the injection of ketamine in China was classified among the first-class psychotropic drugs in 2004. However, more and more youths fall into this recreational fraternity. Starting from the mid-1980s, ketamine has gained popularity as one of the recreational 'club' drugs used by young adults in 'rave' and other party settings. In the first half of 2007, 'street ketamine' was the most commonly abused drug among persons aged <21 years in Hong Kong.[42] In 2007, 0.8% of the individuals aged 16 to 24 years in the UK were reported to have used ketamine in the last year.[3] Between November 2009 and January 2010, 3806 participants all over the world completed surveys, of which 1285 (33.8%) reported ketamine use within the last year.[6] Reports of symptoms with ketamine abuse have come from Canada, Belgium, Hong Kong, Taiwan, Mainland China, Japan, Malaysia, the UK, and the US. Ketamine abuse has become a worldwide problem.

Commonly identified LUTS include urgency (92%), frequency (84%), nocturia (88%), dysuria (86%), and haematuria (68%).[32] These symptoms were much more frequent than in the report by Winstock et al,[6] most likely due to the severity of ketamine-induced urinary symptoms. Use of ketamine 3 or more times a week was associated with measurable dysfunction in terms of LUTS, which could persist for up to 1 year after drug cessation, whilst contracted, thick-walled, and painful bladders often developed after the onset of frequency and urgency.[43] Upper tract involvement was thought to be due to long-term decrease in bladder capacity, but this conclusion is now challenged. Ketamine users tended to be experienced poly-drug users; 80% of subjects reporting such poly-use, and two thirds of them said they also consumed alcohol when they took ketamine.[43] According to a large population survey published in 2012,[6] 98% ketamine users were reported to be concomitant with alcohol use, 96% with 3,4-methylenedioxymethamphetamine (MDMA), 92% with cannabis, 79% with cocaine, 78% with tobacco, 67% with mephedrone, 32% with amphetamine, and 28% with isopropyl nitrate.

Early urology referral for comprehensive investigation and management may help combat this new form of urinary tract disease. However, ketamine dependence has now gained more attention, as management of the dependence seems more difficult than treatment of ketamine-associated bladder dysfunction.[44] Besides LUTS from upper urinary tract involvement, disorders of the genital system, including sexual dysfunction and decrease in sperm quality, have also been reported and constitute a new cause of subfertility.

Conclusion

Many front-line health professionals and medical social workers are still unaware of this new clinical entity. The key to effective management of ketamine-induced genitourinary pathology is early diagnosis and abstinence from further use. Consultations with psychiatrists, assistance from social workers, and support of drug rehabilitation centres are also needed. In patients presenting with severe LUTS in the absence of proven infection, ketamine-related pathology should always be considered. Early referral and assessment could help reduce detrimental effects on abusers as well as health care costs to society. With the increase in popularity of ketamine as a recreational drug, a rise in the numbers of individuals seeking help for urological symptoms and drug dependence is to be expected. However, substance misuse is not just a professional issue but a public health problem as well. Therefore, multidisciplinary care within a biopsychosocial model may be helpful in the management of these patients. The important information presented in this review should be widely shared not only among medical professionals, but also by relevant government departments and the general public.

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Declaration

No conflicts of interest were declared by authors.

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