A Review of the Literature on Ketamine-Abuse-Uropathy

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Abstract

Background: From 2007 onwards reports of ketamine abuse uropathy have been reported from time to time in the medical literature but most medical practitioners and the public are not aware of the presentation, pathophysiology, investigation and management of this new entity.

Aims: To review the literature on ketamine-abuse uropathy.
To summarise the investigation and management of the disease.

Literature Review

Literature search has revealed that:
About 110 cases of Ketamine-abuse Uropathy (Ketamine-induced vesicopathy have so far been reported in the world.
The effect of ketamine abuse on the urinary bladder is universally similar and the patients present with severe irritating lower urinary tract symptoms and haematuria. The patients also develop small bladder capacities, hydronephrosis and renal impairment. Histology of the bladder biopsy specimens consistently revealed cystitis and denudation of urothelium.

Cessation of ketamine abuse before irreversible damage to the urinary tract leads to improvement or resolution of the symptoms.

A Multi-disciplinary team approach is required in the management of Ketamine abuse uropathy. Management of Ketamine abuse uropathy entails psychological support, oral medications and counselling, insertion of nephrostomy or ureteric stent, management of renal failure including the possibility of dialysis and in intractable cases operative techniques including bladder substitution or augmentation cystoplasty may be required.

A history of ketamine abuse, severe lower urinary tract symptoms and histological evidence of inflammation of a small capacity bladder in the absence of any other pathology of the urinary bladder is diagnostic of ketamine abuse uropathy (also called ketamine-induced vesicopathy).

Recommendation: There is a great need for the public to be educated about the devastating effect of Ketamine abuse on the urinary tract in order to dissuade people from abusing ketamine.

Introduction

Ketamine is a drug which has been used both in human and veterinary medicine. Ketamine hydrochloride salt is sold as Ketalar, Ketanest, and Ketaset. Pharmacologically, Ketamine is classified as N-methyl D-aspartate (NMDA) receptor antagonist. [2]

Ketamine which is a short acting anaesthetic is also being used in night clubs and dance parties as a recreational drug. Its adverse effects on lower urinary tract have been recently described by researchers. Despite sporadic reports of Ketamine Abuse Uropathy in the recent literature a number of practitioners and the public are not yet aware of the adverse effects of Ketamine abuse on the human urinary tract. In order to educate all health care workers and the public about the adverse effects of Ketamine abuse on the urinary tract, there is the need to review the literature on cases of Ketamine abuse uropathy that have so far been reported in the world literature. This paper contains a review of a number of cases of Ketamine abuse uropathy which have been reported in the literature.

Literature Review

Shahani and associates [1] described a series of 9 patients, all of whom were daily ketamine users, who presented with severe dysuria, frequency, urgency, and gross haematuria. Their investigations, included urine microscopy, culture, and cytology and in addition to CT scan, cystoscopy, and bladder biopsies, were performed to identify a relationship between recreational ketamine use and these symptoms. Shahani and associates [1] reported the following results:
* The urine cultures were sterile in all cases.
* Computed tomography revealed marked thickening of the bladder wall, a small capacity bladder, and perivesical stranding consistent with severe inflammation.
* At cystoscopy all the patients had severe ulcerative cystitis. Biopsies in 4 patients revealed epithelial denudation and inflammation with a mild eosinophilic infiltrate.
* Cessation of ketamine use, with the addition of
pentosan polysulfate, appeared to provide some symptomatic relief.

**Shahani and associates [1] concluded** that:
- This case series has described a new clinical entity of severe ulcerative cystitis as a result of chronic ketamine use.
- As illicit ketamine becomes more easily available ulcerative cystitis and potential long-term sequelae related to its use may be a more prevalent problem confronting urologists.

Christopher Ho Chee Kong and associates [3] reported a 21-year-old man who presented with a nine-month history of diurnal urinary frequency, nocturia, and supra-pubic pain. There was no history of dysuria or fever. Upon further questioning he admitted that the onset of symptoms approximately coincided with his beginning to use the recreational drug ketamine. He stated that the drug was taken in white powder form which he snorted about twice a week.

He had a number of investigations as listed below with their correspondent results:
- Urine analysis showed microscopic haematuria (10 red blood cells per high powered field).
- Serum urea level was 3.9 m-mol/L.
- Serum creatinine 79 micro-mol/L.
- The acid fast bacilli (AFB) stain for urine was negative.
- After six weeks of culture, no Mycobacterium tuberculosis was isolated from the urine.
- Urine culture also did not grow any other organism.
- Initial ultrasound scan of his renal tract showed a small, shrunken right kidney with dilated pelviccalyceal system and distal ureter; this was accompanied by compensatory left renal hypertrophy and moderate hydronephrosis. The urinary bladder was small in capacity with irregular wall thickening, especially the right lateral wall.
- Intravenous Urography (IVU) revealed left hydroureteronephrosis and a non-excreting right kidney; in the post voiding film there was evidence of a right vesico-ureteric reflux (VUR) and grossly dilated right ureter; the left collecting system was still visualised in the post-voiding film due to vesico-ureteric reflux.
- A diethylenetriamine pentaacetaeate (DTPA) renogram showed a non-functioning right kidney with severe vesico-ureteric reflux; the left kidney had good function with no evidence of obstruction.
- The normalised Gate's glomerular filtration rate was 99 mL/min/1.73 m².

Even though the right kidney was non-functioning, the left kidney was not obstructed despite evidence of the left hydronephrosis, and the renal function was normal. In view of this ureteric stenting was not done.

Christopher Chee Kong Ho and associates [3] also reported that cystoscopy revealed inflamed bladder mucosa with superficial ulcers. Histology of the patient's bladder biopsies revealed:
- Urothelial epithelium with nodular proliferation in the lamina propria;
- Dense neutrophil infiltration was seen in the urothelium as well as in the lamina propria;
- Some of the fragments were lined by granulation tissue with eosinophil infiltration; there was no granulomatous inflammation, dysplasia or malignancy;
- There was a proliferation of von Brunn's nests;
- On the whole the biopsies depicted changes consistent with severe cystitis with a proliferation of von Brunn's nests.

Pursuant to cessation of ketamine use and a one week course of antibiotics, the patient observed that his haematuria and lower urinary tract symptoms had resolved. He was asymptomatic when he was seen in the follow-up clinic 3 months after his discharge from hospital and his renal function remained normal. He refused to have any further radiological imaging of his renal tract.

Chu and associates [4] reported from Hong Kong that from 2000 to 2007, seven male and three female patients who were aged between 20 and 30 years of age (mean, 25 years) and who had all abused ketamine for 1 to 4 years came to two hospitals in Hong Kong with histories of severe lower urinary tract symptoms. All the patients presented with symptoms of dysuria, urinary frequency (voiding once every 15 minutes), urinary urgency, urge incontinence, and haematuria. None of the patients had positive urine cultures. Early morning urine specimens of all the patients were negative for acid-fast bacilli. The urine and blood toxicology profiles of some of the patients were positive for ketamine and benzodiazepam.

Evidence emanating from the voiding diaries of all the patients revealed functional vesical capacities of 30 to 100 mL only. Results obtained from available urodynamic studies of 7 of the patients were as follows: All 7 patients were found to have detrusor overactivity with urinary leakage when the bladder was filled to a capacity of 30 to 50 mL, and this was associated with bilateral vesico-ureteric reflux in one patient and unilateral vesico-ureteric reflux in two of the seven patients. Seven patients had ultrasound scan evidence of bilateral hydronephrosis at the time of diagnosis.

Four of the patients had cystoscopies and random bladder biopsies, the histology examinations of which were consistent with cystitis glandularis.

Some of the investigations done on the patients were reported as follows:
* Magnetic resonance imaging (MRI) of lumbosacral spine of 3 patients, were normal.
* Liver function tests done on all 10 patients were abnormal with raised serum alkaline and alanine aminotransferase levels.
* Ultrasound scan of renal tract and abdomen were normal in all the patients.
* Hepatitis B screen was normal in all the patients.

Clements and associates [5] as well as Malinovsky and associates [6] stated that ketamine clearance is mainly hepatic and flow dependent. Hijazi and Bouliue [7] as well as Ko and associates [8] reported that CYP3A4 is the principal microsomal enzyme involved in ketamine metabolism. Chu and associates [4] also reported that seven of their patients had complained of epigastric pain and they had oesophagogastroduodenoscopy (OGD); none of them had positive OGD findings but some of these patients had been given cimetidine or omeprazole, (which are known to be CYP34A inhibitors) for a short period and this might have contributed to the abnormal liver function in the patients.

Chu and associates [4] in addition reported that one of their patients underwent augmentation enterocystoplasty for small capacity urinary bladder with the aim of maintaining renal function and improving his quality of life. The patient continued to abuse ketamine against medical advice after his augmentation enterocystoplasty and had to be readmitted later in acute renal failure with a serum creatinine of 554 micro-mol/L and oliguria. Pursuant to ultrasound scan evidence of gross bilateral hydronephrosis bilateral percutaneous nephrostomies were inserted. The patient’s serum creatinine level improved gradually, falling to 170 micromole / L. The patient then underwent bilateral antegrade nephrostograms which revealed:
* Complete right-sided ureteric obstruction just below the pelvic-ureteric junction (PUJ).
* Markedly diminished flow of contrast in the left ureter suggestive of retroperitoneal fibrosis.

Chung and associates [9] from Taiwan in 2007 reported a 23-year-old man who presented with a one month history of gross haematuria and urinary frequency. He did not have any significant past medical history. He had been a ketamine abuser for more than one year prior to his presentation. On examination he was found to have supra-pubic tenderness, but on the whole his general and systematic examinations were unremarkable. His urinalysis revealed haematuria and pyuria. His urine culture did not grow any organism. Ultrasound scan of his renal tract was inconclusive. He was given a 7 day course of antibiotics which failed to improve his symptoms. He underwent cystoscopy under general anaesthesia which revealed three foci of whitish to yellowish ulceration on the posterior wall of the urinary bladder. Bladder biopsy was performed and after hydrodistension there was no evidence of glomeruration or petechiae. Histological examination of the biopsy from bladder ulcer revealed infiltrating eosinophils which were reported to be compatible with ketamine-associated ulcerative cystitis as reported by Shanani and associates. [1]

Chu and associates [10] retrospectively analysed the clinical presentations, pelvic pain and urgency / frequency scores, video-urodynamics studies, cystoscopy findings, histological features of bladder biopsies and radiological findings of 59 ketamine abusers who were referred to the Urology units of Princess Margaret and Tuen Mun Hospital, Hong Kong, from March 2000 to December 2007. They reported that:
* Out of the 59 patients, all had moderate to severe lower urinary tract symptoms (LUTS), i.e. Urinary frequency, urgency, dysuria, urge incontinence and occasionally haematuria.
* Forty-two (71%) patients had a cystoscopic examination which showed various degrees of epithelial inflammation similar to that seen in chronic interstitial cystitis.
* All of 12 available biopsies of urinary bladder had histological characteristics that resembled those of interstitial cystitis.
* All 47 patients who underwent urodynamics had either detrusor overactivity or decreased urinary bladder compliance with or without vesico-ureteric reflux to some degree.
* Ultrasound scan of renal tract had revealed unilateral or bilateral hydronephrosis in thirty patients (51%).
* Four patients (7%) had features suggestive of papillary necrosis on radiological imaging.
* Eight patients (14%) had a raised serum creatinine level.

They concluded that:
* A syndrome of cystitis and contracted bladder can be associated with street ketamine abuse.
* Secondary renal damage can occur in severe cases which might be irreversible, rendering patients dependent on dialysis.
* Their data did not establish the precise cause, or the incidence.
* Street-ketamine abuse is not only a drug problem, but might be associated with a serious urological condition causing a significant burden to healthcare resources.

Colebunders and Van Erps [11] from Belgium in 2008 reported the case of a 20-year-old man who presented...
with a 7-month history of diurnal urinary frequency, nocturia, urgency, supra-pubic discomfort during micturition and episodes of severe haematuria shortly after commencing weekly recreational ketamine use. He occasionally worked as a disk jockey at ‘hard style’ and ‘jump’ parties. His past medical history included asthma and nasal polyps, for which he was treated with montelukast (singulair) and fluticasone propionate in combination with salmeterol (seretide). He had never travelled outside Europe. After he had been symptomatic for 2 months he was treated with antibiotics for 5 days and anticholinergics for several weeks without any improvement. He had a number of investigations which were reported as follows: * Urine analysis was negative (normal) * Urine cytology was negative * Urine culture was sterile (no growth) * Ultrasound scan revealed a thickened bladder wall and small capacity urinary bladder but normal kidneys. He had cystoscopy which showed mild inflammatory changes, though there was no visible blood in the urine. Histological examination of bladder biopsies taken at cystoscopy was negative but they were not taken during an episode of active cystitis. He was advised to stop ketamine.

Selby and associates [12] reported a 26-year-old man who presented to the emergency department in a state of collapse. One month prior to his admission he was seen by a urologist with a history of frank haematuria which was associated with colicky abdominal pain, increased urinary frequency and dysuria. He was initially treated for urinary tract infection and he had CT scan of abdomen which revealed moderate bilateral hydronephrosis. His common bile duct was reported to be 8mm on the CT scan. He underwent cystoscopy which revealed a diffusely inflamed bladder with a reduced bladder capacity of 150 cc and both ureteric orifices looked patent without any evidence of obstruction. Bladder biopsies were taken during the cystoscopy and this revealed inflammatory change but no evidence of dysplasia or malignancy. He was discharged to be followed up in the outpatient clinic.

He was readmitted with a four days history of worsening flank pain and feeling of being unwell, drowsy, and short of breath. His initial blood pressure on readmission was low at 95/60 mmHg and an associated tachycardia with a regular heart rate of 140 beats per minute (in sinus rhythm). He was also tachypnoic with a respiratory rate of 60 breaths per minute. His assessment using Glasgow coma scale was 13/15 with no localized neurological signs. He had a number of investigations which were reported as follows: * Serum urea and electrolytes: potassium 5.4 m-mol/l, urea 36.7 m-moles/l, creatinine 851 micro-mol/l, which indicated acute renal failure. * PH 7.2, serum bicarbonate 6.4 m-mol/l, po2 39.3 kPa, pCO2 2.0 kPa which were indicative of metabolic acidosis. * Serum bilirubin 58 micro-mol/l, alkaline phosphatase 204 IU/L, alanine trans- aminase 106 IU/L, Gamma-GT - 1045 IU/L which indicated abnormal liver function with an obstructive pattern. Upon further questioning the patient stated that for a period of two years prior to his admission he had been a regular user of street ketamine intra-nasally. The patient’s condition deteriorated quickly after his initial assessment with worsening respiratory function which required intubation. His chest X-ray revealed bilateral basal consolidation consistent with aspiration. He was transferred to the intensive care unit where he was given vasopressors as part of his treatment. He also received continuous haemo-filtration (CVVH) and broad spectrum antibiotics. His blood cultures subsequently grew methicillin-sensitive staphylococcus aureus. He had a repeat ultrasound scan of the renal tract which revealed bilateral hydronephrosis in view of which bilateral nephrostomies were inserted. Gelatinous debris which was present throughout both pelvicalyceal systems and in the left ureter was aspirated from the nephrostomies. The aspirated material did not have the typical appearance of blood clots. Subsequent analysis of the material revealed the presence of ketamine metabolites, cannabandoids and lignocaine. A dilated common bile duct (CBD) was also seen on the abdominal ultrasound scan. By the second day his urine output began to return and he had bilateral nephrostomograms which showed free flow of contrast through the ureters into the urinary bladder with no evidence of obstruction. Despite this he continued to receive CVVH, then intermittent dialysis, until Day 24 when his renal function began to recover. His nephrostomies were clamped and then removed. He was then discharged. At the time of discharge his serum creatinine was 123 micromole / L. He had a follow-up ultrasound scan which confirmed that the hydronephrosis had completely resolved. His liver function tests spontaneously improved and there was ultra-sound scan evidence of resolution of his common bile duct dilatation. Pursuant to his discharge from the intensive care unit, he required nutritional support as well as several weeks of rehabilitation and at the time of his discharge from hospital he had made full recovery. Nevertheless, he was readmitted six weeks following
his discharge with right upper quadrant abdominal pain and marked derangement of his liver function tests. The results of his investigation on readmission were:

- Liver function tests: Serum bilirubin 7 micro-mol / L, alkaline phosphatise 1503 IU / L, alanine transaminase 482 IU / L, Gamma GT 561 IU / L.
- Serum creatinine had risen again to 294 micro-moles.
- A repeat ultra-sound scan had shown that the biliary tract dilatation but the renal tract appeared normal.
- His urine on analysis was positive for ketamine metabolites but negative for illicit drugs providing evidence that the patient was abusing ketamine again.

He was treated for biliary sepsis with improvement in his symptoms and he subsequently underwent endoscopic retrograde cholangiopancreatography (ERCP) which revealed no evidence of strictures or stones in the common bile duct, and a stent was inserted. He developed pancreatitis after the ERCP. Eight weeks after he had the ERCP, his liver function tests had only partially improved with the following results: Serum bilirubin 21 micro-mol / L, alkaline phosphatise 770 IU / L, alanine transaminase 326 IU / L, Gamma GT 1554 IU / L. After initial improvement, his serum creatinine had increased to 309 micro-moles / L (eGFR 21 ml/min). Another ultra-sound scan was performed which revealed no evidence of hydronephrosis, in view of this, a renal biopsy was performed. Histology of the renal biopsy revealed histological evidence of acute tubular necrosis, believed to have resulted from the sepsis and pancreatitis which the patient developed.

Mason and associates [13] described the radiological findings in a series of 23 patients, all with a history of Ketamine abuse, who presented with lower urinary tract symptoms (LUTS). The imaging techniques that were used in the investigation of the patients included: ultrasonography (US), intravenous urography (IVU), and computed tomography scan (CT scan). The aforementioned radiological investigations were reviewed in order to ascertain common imaging findings. All the patients with positive imaging findings had also undergone cystoscopy and bladder wall biopsies, which confirmed the diagnosis. The patients in this series had consented to the use of their data in the ongoing research into ketamine-induced bladder pathology. Mason and associates [13] reported the following findings: Ultrasound scan demonstrated small bladder volume and urinary bladder wall thickening. CT scan revealed the following: marked, generalized urinary bladder wall thickening; mucosal enhancement; peri-vesical inflammation; ureteric wall thickening and enhancement. In advanced cases ureteric narrowing and strictures, were identified using both CT scan and IVU. Correlation of clinical the history, radiological and pathological findings, were performed to confirm the diagnosis. Mason and associates [13] made the following conclusions: This case series illustrates the harmful effects of ketamine on the urinary tract and the associated radiological findings; delayed diagnosis can result in irreversible renal tract damage requiring surgical intervention; it is important that radiologists are aware of this emerging clinical entity as early diagnosis and treatment are essential for successful management.

Raja and associates [14] reported a 20-year-old male who presented to the urology department with a one year history of supra-pubic pain, frank haematuria, dysuria, urgency and increased urinary frequency of over twenty times a day. Abdominal examination, renal function tests, urine cultures and abdominal ultrasound were normal. He underwent cystoscopy under general anaesthesia which revealed a small capacity bladder (less than 100mls). The bladder mucosa was friable and appeared to be “tearing” with distension. Due to persistent bleeding and mucosal tearing on distension the procedure had to be abandoned and a bladder biopsy therefore was not performed. The patient was then catheterised and treated conservatively.

Based on the cystoscopic findings a bladder perforation was suspected and a post operative CT scan was performed to confirm the diagnosis. The CT scan showed free fluid and gas in the pelvis. The CT scan also showed locules of gas and extensive haematoma within the bladder suggestive of an extra-peritoneal bladder perforation. Aetiological possibilities included bladder perforation, colonic perforation or colo-vesical fistula (secondary to possible inflammatory bowel disease). The patient did not develop signs of peritonitis. A sigmoidoscopy and small bowel follow-through revealed no evidence of bowel disease or fistula. A more detailed history was taken at that point which revealed that he had been abusing ketamine intermittently as a recreational party drug (not daily usage). His weekly consumption of ketamine was variable and the patient was unable to quantify the amount used. His haematuria settled with conservative management. The catheter was left in situ for four weeks. At the time of discharge from hospital he was advised to stop ketamine abuse. After cessation of ketamine abuse and catheter removal he reported remarkable improvement in his symptoms. There was no further recurrence of haematuria. At review One year after discontinuing ketamine abuse, he had ongoing frequency which he did not find troublesome.

It was recommended that once his symptoms resolved a repeat cystoscopy and bladder biopsy under general...
anaesthesia should be performed and he should fill in and bring a frequency volume chart to assess functional bladder capacity. Nevertheless, the patient repeatedly failed to respond to the requests of the urologists to attend urology department for further evaluation. He was subsequently discharged from follow up.

Moore and associates [15] suggested that a high level of urine ketamine active metabolites might result in bladder irritation.

Ketamine has recently been gaining popularity as a party drug among dance drug users in Europe [16], [17]. Due to its short duration of action it is falsely believed that ketamine is not as harmful as some of the other drugs such as heroin or cocaine [10]. However a team of independent researchers have ranked ketamine as the sixth most harmful substance of abuse, more harmful than cannabis or ecstasy [18].

Cottrell and associates, [19] reported nine patients who presented with similar urinary symptoms and cystoscopy revealed small-volume erythematous bladders, and biopsy showed haemorrhagic cystitis with denuded urothelium. Severe reported complications included intractable symptoms, (necessitating cystectomy and neobladder formation for symptomatic relief), hydrenephrosis and chronic renal failure. From their experience, the authors felt that symptoms might improve or even reverse with ketamine cessation [19].

Chang and associates [20] reported that from November 2006 to February 2009, 20 patients visited Taipei Veterans General hospital as result of Ketamine related lower urinary tract symptoms (LUTS). They analysed the clinical presentations, daily Ketamine dose, interval between Ketamine usage to the development of LUTS, urodynamic studies, radiological image findings, cystoscopic and ureterorenoscopic findings, histological findings, urinary bladder levels, and treatment responses.

They reported that:

* Of the 20 patients, all had moderate to severe LUTS involving frequency, urgency, dysuria, and haematuria.
* The mean daily consumption of Ketamine was 3.2 ± 2.0 grams.
* The mean interval from consumption to the development of LUTS was 12.7 months (range 2 – 36 months).
* Eight patients underwent video urodynamic studies, with a mean cystoscopic capacity of 70.8 mL. Eight patients (40%) had hydrenephrosis and six underwent ureterorenoscopy. The mean bladder capacity under anaesthesia was 289.9 mL and 14 (70%) of the patients had significant symptomatic improvement after hydrodistention.

* Ten patients stopped taking Ketamine and nine (90%) experienced symptomatic relief
* The response rates of symptomatic improvement of various types of treatment were 75% (12/16) for oral pentosan polysulphate sodium with prednisolone; 40% (2/5) intravesical instillation of Xylocaine and heparin; and 0% (0/2) for intravesical instillation of hyaluronic acid.

Lee and associates [21] reported a young gentleman, with renal failure (serum creatinine > 500 m-moles / litre) and deranged liver function tests who was admitted under the joint care of nephrology and gastroenterology teams. The urologist became involved when the ultrasound scan showed thickened urinary bladder wall, bilateral hydronephrosis and hydroureter. He admitted to taking ‘K’. He was then stented and the creatinine normalised. On ultrasound scan the hydronephrosis improved. The ureteric stents were removed after a few months and within a week the kidneys became hydronephrotic again. Therefore the patient was stented again with long term stents.

Venyo and associates [22] reported a 28-year-old man who was admitted with a history of diurnal urinary frequency, urgency, nocturia and haematuria. He admitted to regular use of Ketamine for recreational purposes. He had many psychological problems. His initial investigations including Full blood count, serum urea and electrolytes and urine cytology were normal. There was no growth in his urine culture but there was evidence of sterile pyuria. His Serum C Reactive Protein level was raised. His TB Culture and Schistosoma Haematobium antibody level was normal. He had cystoscopy under general anaesthesia which revealed an inflamed urinary bladder and histology of his bladder biopsy specimen was consistent with bladder mucosal ulceration and chronic inflammation (see illustrations 1 and 2). He continued to use ketamine for recreational purposes. His urinary symptoms persisted and eventually his renal function deteriorated. Ultrasound scan of kidneys and renal tract as well as an isotope renogram confirmed bilateral hydronephrosis and bilateral ureteric obstruction. He initially had nephrostomy and bilateral antegrade ureteric stent insertion and his nephrostomy was removed. He refused to turn up for change of his ureteric stents as arranged before his discharge from hospital.

More than 2 years after his initial presentation, he eventually agreed to come to hospital when he was having worsening lower urinary tract symptoms and loin pain. He only agreed to have ureteric stents removed but refused to have either a nephrostomy or new ureteric stents.

He continued using Ketamine. His renal function and
his lower urinary tract symptoms continued to worsen. He had Isotope Renograms and ultrasound scans of the kidneys and urinary tract which confirmed worsening hydronephrosis and bilateral ureteric obstruction. Despite attempts by a multi-disciplinary team to convince him to accept to have nephrostomy and / ureteric stent he refused to have any further intervention. He was referred to be considered for dialysis because of severe renal failure.

**Discussion**

Ketamine is an N-methyl-D-aspartic acid receptor which is a commonly used anaesthetic agent in the operating theatre. Nevertheless, it is also being used in gatherings, pubs, night-clubs and at parties [1]. A number of street names have been coined for Ketamine. These include: Vitamin K, Super K, special K, K, keets, kit-kat, super acid, jet, and cat vitamins. Ketamine is usually taken for recreational purposes in powder form. Ketamine is smoked in a mixture of marijuana or tobacco, either taken orally [23] or intranasally [24].

Jansen and associates [23] stated that the psychological effects of ketamine are brief. And this usually lasts about 30 minutes. Ketamine abuse can cause psychological dissociation which results in hallucinations and subjective experience of being out of the body or states similar to near death experience. In addition to these ‘desired’ effects, ketamine abusers also commonly experience anterograde amnesia, delirium as well as confusion [24]. Ketamine abuse may also have effect on movement. These include:

- Stereotypies (persistent repetition of acts or words);
- A severe loss of coordination;
- Pronounced analgesia. [25].

A number of Ketamine abusers experienced an inability to speak, blurred vision and increased body temperature. [26]

**Other effects of Ketamine-abuse include:**

- Tachycardia;
- Palpitation;
- Hypertension;
- And respiratory depression with apnoea. [24]

Ketamine-abusers can experience “flashbacks” visual disturbances days or weeks after ingestion of ketamine [27]. A number of long term effects have been reported in ketamine-abusers. These include: long lasting impairments in episodic memory and some aspects of retrieval from semantic memory. [28]

It has been stated that long-term use of high doses of ketamine, has the potential of interfering with learning and attentional mechanisms as a result of blockade of the N-methyl-D-aspartate receptor. [23,29]. It has also been stated that some chronic ketamine abusers may become addicted and develop severe withdrawal symptoms that require detoxication. [24]

Shahani and associates [1] as well as Chu and associates [10] stated that ketamine-abusers consistently present with severe lower urinary tract symptoms including: urinary frequency and urgency and some of the patients have urinary incontinence, supra-pubic pain, haematuria and dysuria. In advanced cases of ketamine abuse bladder dysfunction the patient may need to empty his or her urinary bladder every 15 minutes. Tsai and associates [30] stated that these urinary storage symptoms usually develop after long-term ketamine abuse but the symptoms could also appear in new ketamine abusers. Lee and associates [21] stated that there is equal distribution of cases of ketamine-abuse uropathy between male and female. However, following further reports of ketamine-abuse uropathy the male to female ratio of the disease entity has now been stated to be 2.1 to 1.

Chu and associates [10] stated that the mechanism of ketamine-abuse uropathy is unknown. Nevertheless, ketamine-abuse urinary bladder dysfunction is thought to be caused by direct toxic effects of ketamine and its metabolites on the urinary bladder. This effect is thought to lead to sub-mucosal oedema, inflammation, vascular ectasia and fibrosis of the detrusor muscles. It is also thought that intrinsic microcirculation of the endothelium of the urinary bladder is compromised following ketamine abuse. In addition autoimmune reaction could play a role in causing further damage to the urinary tract [10] [21]. Chu and associates [10] suggested that whilst the exact mechanism of ketamine abuse uropathy is not clearly understood there is the need for further investigation to pinpoint the exact mechanism that leads to urinary tract damage.

In the investigation of ketamine-abuse uropathy the following investigations are used:

- The urine is sterile on culture
- Imaging studies (ultrasound scan, CT scan, or intravenous urogram) which would usually show thickened urinary bladder wall with small bladder capacity. There is usually perivesical stranding signifying severe inflammatory changes of the bladder. In severe advanced cases, hydro-uretero-nephrosis would be observed secondary to ureteric stenosis or stricture. Renal papillary necrosis had also been reported.
- Serum urea and electrolytes – renal impairment with raised serum creatinine was observed in many cases [10]
* Diuretic (Mag 3) isotope renogram – may show obstruction of the upper renal tract in severe cases and would also determine the differential renal function
* Urodynamic studies - done in specialized centres revealed detrusor over-activity and decreased bladder compliance with or without vesico-ureteric reflux [10]
* Cystoscopic examination - showed features of haemorrhagic cystitis with different degrees of severity. Biopsies of the urinary bladder revealed epithelial denudation and inflammation with oesinophilic infiltration [1], [10] [22]
**With regard to management a number of management approaches should be adopted:**
* Advise to stop ketamine-abuse - In patients with short term ketamine exposure, where there is no permanent damage to the urinary tract this measure may suffice to alleviate symptoms [30]
* Anticholinergics – could be used in the treatment of patients who do not experience symptomatic improvement on cessation of ketamine abuse; however, in long-term ketamine abusers, the symptomatic response to anticholinergics is disappointingly poor [10]
* Pentosan sulphate, given intravesically had been reported to be helpful in relieving the lower urinary tract symptoms [1]
* Oral Pentosan polysulfate sodium with prednisolone - 75% of patients treated had symptomatic improvement. [20 ]
* Moxifloxacin – it has been stated that Moxifloxacin 400 mg orally daily relieves the persistent symptoms of the urinary tract after cessation of ketamine abuse and the symptoms recurred when Moxifloxacin is discontinued. [31]
* Intravesical instillation of xylocaine and heparin - 40% of patients experienced symptomatic improvement of symptoms [20]
* Hydrodistention – significant symptomatic improvement was reported to have resulted in 70% of some cases [20]
In advanced cases with upper urinary tract obstruction and renal impairment, temporary measures to relieve the obstruction, is indicated and this could be done by means of:
* Nephrostomy insertion plus or minus antegrade ureteric stent at the same sitting or antegrade ureteric stenting subsequently
* Retrograde ureteric stenting at cystoscopy.
* Insulin glucose – may be given initially in cases of severe renal failure and hyperkalaemia to bring the serum potassium down to normal levels.
* Steroids had also been used to reduce the inflammation of the urinary tract [10]
**In cases refractory to the above measures, more drastic surgical procedures had been employed such as:**
* Bladder augmentation [10]
* Or cystectomy with construction of neobladder [19]
Nevertheless, it is worth pointing out that long-term experience with these operative interventions is limited [21]. One of the potential risks of incorporating bowel into the urinary tract in such patients (in cases of neo-bladder construction, or augmentation/clam cystoplasty), is that it could lead to re-absorption of ketamine or its metabolites. In Case the patient continues to abuse ketamine after augmentation or construction of neo-bladder, re-absorption may lead to overdose.
There is evidence in the literature that Botulinum toxin intravesical injection is ineffective in the management of intractable Ketamine-induced vesicopathy. Loeb and associates [32] reported a 25-year –old patient with a history of trans-nasal Ketamine abuse over many years who presented with severe irritating lower urinary tract symptoms. He underwent cystoscopy which showed erosive cystitis. Despite all efforts to help him stop Ketamine-abuse, he was unable to stop. He had cystoscopy and Botulinum toxin-A, injections to help improve his lower urinary tract symptoms, however, this was not effective. He therefore underwent prostate preserving cystectomy and substitution ileum neobladder.
In addition to the aforementioned treatment modalities, the role of Duloxetine in the treatment of depressed patients with Ketamine-induced lower urinary tract symptoms was reported by Jia-Yu and Hwa-An [33]. Jia-Yu and Hwa-An [33] reported a 19-year-old woman with long-term (3 years) daily ketamine abuse who had developed moderate depressive symptoms after forced cessation of ketamine use, together with severe lower urinary tract symptoms of 3 months duration. Urinary analysis and culture revealed negative results, and treatment with antibiotics was unsuccessful. Ketamine abuse-related lower urinary tract symptoms were suspected and duloxetine was prescribed at 60 mg daily. After 2 weeks, the symptoms of depression and lower urinary tract symptoms resolved. They concluded that duloxetine could be considered as one of the therapeutic drugs of choice for depressive patients with significant lower urinary tract symptoms. Middela and Pearce [34] reviewed the literature regarding the urological impact of ketamine abuse and its management. They found that approximately 110 cases of ketamine abuse uropathy (vesicopathy) were reported in the literature in the form of case series, case reports and letters. They observed that: The effect of ketamine abuse on the bladder was universally similar in all reported
cases. Presently, ketamine cessation is the only effective treatment modality to prevent deterioration of the renal function and indeed offer the possibility of symptom resolution. [34]

Multi-disciplinary team approach is necessary in the management of ketamine abusers. Deterioration in the patient's condition is attributable to failure to stop ketamine abuse. Counselling in order to deal with the problem of addiction to ketamine-abuse is vital to the management of ketamine-abusers.

Conclusions

The reports of Ketamine abuse uropathy, have come from different countries including the United Kingdom, Canada, Hong Kong and Taiwan, Malaysia and elsewhere.

There is evidence in the literature to confirm that Ketamine abuse can cause: (a) inflammation of the urinary bladder wall which leads to bladder dysfunction and small capacity urinary bladder, (b) hydroureteronephrosis and (c) renal failure.

There is evidence that if a patient with Ketamine abuse uropathy stops abusing ketamine for one year before irreversible renal tract damage occurs then the symptoms either resolve or improve [14].

The key to the successful management of ketamine abuse uropathy lies in the adoption of multi-disciplinary team approach to help the patients to stop ketamine abuse early through counselling.

References

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Illustrations

Illustration 1

H and E x 200 Magnification. The section demonstrates reactive inflammatory changes of the urothelium with underlying vascular congestion.

Illustration 2

H and Ex100 Magnification. The Section demonstrates an area of ulceration with less of then surface mucosa which has been replaced by granulation tissue. There is overlying blood and fibrin.
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