Recreational ketamine use can lead to irreversible bladder damage

Daniel Eaton, Frank Kueppers

ABSTRACT

An increasing number of young patients with severe bladder overactivity syndrome potentially caused by recreational ketamine use has been treated in our department. Ketamine has become a popular and increasingly used recreational drug in New Zealand. Ketamine bladder syndrome has been reported internationally; however, local New Zealand data do not exist. It can lead to irreversible damage to the bladder, and internationally, surgical procedures like cystectomy and urinary diversion or augmentation cystoplasty have been reported as necessary treatments.

Ketamine is well recognised as a dissociative anaesthetic used primarily for the induction and maintenance of anaesthesia. It is also used in emergency medicine for procedural analgesia and acute pain management. More recently, psychiatry is using low-dose ketamine for treatment-resistant depression. Given these indications require only short-term use, the risks of long-term exposure have been unknown.

However, the dissociative and hallucinogenic effects of ketamine have led it to becoming increasingly popular as a recreational drug, a trend also observed in New Zealand. Unfortunately, we are now recognising several concerning side effects associated with this recreational use. One of these conditions is ketamine bladder syndrome. Other terminology for this condition includes ketamine (induced) cystitis or ketamine (induced) uropathy.

The purpose of this article is to raise awareness in the New Zealand medical community of this condition, given the growing popularity of recreational ketamine use. We will discuss what is known about the pathophysiology of ketamine bladder syndrome, the current data on recreational ketamine use in New Zealand and the latest literature on diagnosis and management of this condition. Finally, we will present a local case of a patient with ketamine bladder syndrome managed in our department.

Pathophysiology of ketamine and ketamine bladder syndrome

Ketamine is a N-Methyl-D-aspartic acid (NMDA) receptor antagonist, which blocks the excitatory neurotransmitter glutamate.[1] It may also interact with norepinephrine, serotonin, muscarinic and opiate receptors at central and spinal sites.[1] This induces analgesia and disrupts association pathways of the brain to produce dissociative anaesthesia.[1]

Therapeutically, ketamine is generally administered intravenously. However, since it is both water and lipid soluble it may be administered by several routes, including intramuscularly, intranasally, orally, sublingually or rectally, with varying bioavailability.[2] Once absorbed, the lipid solubility allows it to be rapidly distributed to the brain and body tissues.[2] Recreational ketamine is typically bought as a white powder and administered intranasally, with onset of effect within 15 minutes and duration up to 3 hours.[3]

Ketamine is metabolised in the liver. Ketamine and its metabolites are then excreted in the urine, largely as conjugates of hydroxylated ketamine metabolites with glucuronic acid (80%) and dehydronorketamine (16%).[2] The pathophysiology of ketamine bladder syndrome is still largely unknown, but it is hypothesised that these metabolites damage the urothelial cells, leading to disruption of the urothelial barrier.[4] Once this barrier is disrupted, a number of inflammatory cascades leads to inflammation and fibrosis, causing ketamine bladder syndrome.[4] These damages can occur in the bladder, leading to fibrosis and a poorly compliant bladder, as well as in the ureter, leading to ureteric stenosis or impaired ureteral peristalsis.[4] These changes can eventually lead to chronic kidney failure.[4]

Recreational ketamine use in New Zealand

Recreational ketamine was identified in New

Zealand as a potential concern in 2010 and added to the Misuse of Drugs order and classified as a Class C controlled drug.[5] This order immediately classifies a substance that may have a risk of harm to the public. This is the same status as drugs such as cannabis plants, barbiturates, codeine, coca leaf and benzylpiperazine. Despite this, the data available to ascertain the magnitude of recreational ketamine use remain limited.

We do know, however, that ketamine border seizure has significantly increased from 0.15kg in 2016 to 22kg in 2021.[6] Reports from Know Your Stuff NZ, a volunteer organisation that provides free clinics at events such as music festivals to test the purity of recreational drugs, show further support of increased recreational ketamine use. In 2016–2017, only four reports of ketamine use were noted, whereas in 2020–2021 this was up to 186.[7] New Zealand Police planned to introduce testing of ketamine and its metabolites in the wastewater in 2022, but in the most recent report in September 2023 it is yet to be reported.[6,8] Some concerns have been raised with possible confounding results by legal hospital and veterinary ketamine use.

Overall, these reports do suggest a serious and significant increase of recreational ketamine use in New Zealand. However, clearly data remain limited, and more objective monitoring of ketamine use is required.

Diagnosis of ketamine bladder syndrome

Ketamine bladder syndrome is a new entity, with the first reported cases in 2007.[9] Since then, with more awareness of the condition, more cases have been identified and more research into the area has occurred, leading to many studies being published. These have predominantly been case reports, rodent model trials or small retrospective studies. Over the last few years, several international systematic reviews have appraised the available literature.[4,10–12]

These have highlighted that the common symptoms of ketamine bladder syndrome are of the lower urinary tract. These include urinary frequency, urgency and nocturia, with associated dysuria or suprapubic discomfort.[4,11] In severe cases pain can be significant, and urinary incontinence or haematuria can be present.[4] The severity of the condition does appear to have a positive correlation with ketamine exposure in most studies.[4] Taking a recreational drug history is paramount.

Diagnostic investigations for this condition include urinalysis, usually with the presence of sterile pyuria, haematuria or raised eosinophils.[4] Radiological imaging may identify a small, contracted bladder with a severely thickened bladder wall, at times with disease extension into the ureter.[4,11] Ureteric dilation, vesicoureteral reflux and hydronephrosis may be present in severe disease.[11] Cystoscopy may show a thickened bladder wall with mucosal oedema and inflammation with or without ulceration.[11] As discussed previously, ketamine bladder syndrome leads to damage to urothelial lining, hence on histology epithelial denudation is seen.[11] Ulceration, petechial haemorrhage and infiltration of immune cells may be present throughout the layers of the bladder wall, with submucosal fibrosis and muscle hypertrophy also detected.[11]

The symptom profile for ketamine bladder syndrome is predominantly of bladder overactivity, and a number of differential diagnoses need to be assessed before a diagnosis of ketamine bladder syndrome is made. These include urinary infection, neurogenic bladder, diuresis conditions, stone disease and schistosomiasis. It is important to also exclude anatomical abnormality and carcinoma *in situ*, or bladder malignancy. All these conditions can be reviewed with a thorough history and examination followed by appropriate investigations, including urine analysis, radiological imaging and endoscopic procedures as required.

Treatment of ketamine bladder syndrome

Currently, there is no standardised approach to managing this condition. However, the evidence is clear that abstinence of ketamine is imperative to stop progression of this condition. This alone can be successful treatment for patients with early ketamine bladder syndrome and prevent long-term damage from this condition.[4,10,11] For patients with more severe conditions, symptoms may not fully recover, and can even progress despite abstinence.[4,11] This emphasises the importance of early diagnosis. Abstinence can be challenging for patients, and referral to support and drug services is essential.

In combination with ketamine cessation pharmacological therapy can be useful, with the aim to manage symptoms and reduce inflammation. Oral therapy, including non-steroidal anti-inflammatories such as diclofenac, and anticholinergics such as solifenacin, are used. Steroids, COX-II

inhibitors, neuropathic analgesia, and general analgesics including paracetamol and opioids, have also been trialled.[4,11] Pentosan polysulfate, used for interstitial cystitis and painful bladder syndrome, can give symptomatic relief.[4,9,11]

If symptoms are not controlled on oral therapy, then intravesical treatment can be given. This includes intravesical instillation of hyaluronic acid, which has been shown to be safe and can be effective, although a standardised regimen is not available.[4,11,13] Additionally, intravesical botulinum toxin combined with bladder hydrodistension has shown some effectiveness.[4] Several other therapies have been trialled in animal models.[4,11]

Finally, in severe conditions with significant intractable symptoms or structural abnormalities, surgical management may be required. Depending on the indication, surgical options can include urethral dilation, ureteric reimplantation, ileal conduit urinary diversion, augmentation cystoplasty with or without Mitrofanoff channels and cystectomy with neobladder.[4,11,12] These surgeries can involve high morbidity.[11,14]

Case report

Mr K is a 28-year-old Egyptian-born male, now resident in New Zealand. He presented in the community with urinary frequency, urgency, dysuria and a white urethral discharge. He received antibiotics for a presumed sexually transmitted infection. However, the presenting urine analysis returned negative for both sexually transmitted and urinary tract infections. Ongoing symptoms prompted a Urology Specialist review at Christchurch Hospital. A repeat urine analysis showed sterile pyuria and microscopic haematuria. He was commenced on oral ciprofloxacin 500mg twice daily and solifenacin 10mg once daily for overactive bladder symptoms. A travel history to Egypt was noted and schistosomiasis testing was negative. An ultrasound demonstrated no renal tract abnormality. Following completion of 3 weeks of ciprofloxacin, flexible cystoscopy was performed. Notably, very unusual erythematous patches were seen on the posterior bladder wall. This appearance raised concerns and a formal cystoscopy with biopsy under general anaesthetic was arranged. The urine cytology was sent to assess for malignancy.

Mr K presented two further times acutely due to ongoing urinary symptoms. He was not systemically unwell and urinary cultures were negative. The goals of care were symptoms' management. Variable combinations of therapies were trialled, including simple and anti-inflammatory analgesia such as paracetamol and diclofenac, opioid-based analgesia including codeine and morphine, anticholinergics including oxybutynin and solifenacin, and finally neuropathic medications including amitriptyline.

At elective cystoscopy, the findings were again notable, with numerous patchy erythematous areas on his bladder wall that bled easily on bladder filling. His bladder was generally inflamed and trabeculated. Multiple biopsies were taken, and haemostasis gained with roller ball diathermy.

The anaesthetic intra-operative notes remarked on the large opioid requirement for Mr K's anaesthesia. Post-operatively this prompted careful questioning with Mr K regarding the possibility of recreational drug use. This was the first documentation that he had been using ketamine 1g intranasally weekly for the last few years.

His biopsies demonstrated active chronic ulcerative cystitis. They showed extensively eroded and denuded lamina propria and detrusor muscle. The lamina propria was oedematous and congested containing inflammatory cells including eosinophil and had foci of fibrosis.

A diagnosis of ketamine bladder syndrome was made based on histology, in conjunction with a clear clinical history of recreational ketamine use, having excluded other differentials.

As reviewed in this article, the key to successful management of ketamine bladder syndrome is education and support to achieve long-term ketamine cessation. In the interim, given ongoing significant symptoms, Mr K was commenced on oral prednisone with an initial dose of 40mg weaned over 3 weeks. On Urology Outpatient review his urinary symptoms had significantly improved and he was only requiring simple analgesia. Importantly, Mr K self-reported ketamine abstinence. At the 6-month review, symptoms remained relatively well controlled, with only mild residual chronic pain. Unfortunately, he was now reporting intermittent ketamine use again, which highlights the difficulty with ketamine cessation. He appeared to understand the risk of cumulative bladder injury from ketamine use and was committed to continue to work on ketamine abstinence in primary care.

This local case serves to highlight several learning points we have discussed in this review. While uncommon, it does remain an important differential for a patient presenting with overactive bladder symptoms or suprapubic discomfort with

no identifiable cause. A recreational drug history is critical to raise the possibility of and then ultimately to secure the diagnosis of ketamine bladder syndrome. Furthermore, management is largely symptomatic in conjunction with long-term ketamine abstinence. This case emphasises the importance of community support for patients with the challenge of ketamine abstinence.

Learning points

Evidence suggests that recreational ketamine use in New Zealand is increasing. This increased use will be associated with more patients presenting with ketamine bladder syndrome. As such, it is important to be aware of the symptoms and signs of this condition, which include bladder overactivity and small bladder capacity. Recreational drug history is paramount, and if there is any concern for ketamine bladder syndrome, the patient should be strongly encouraged to stop using ketamine and should be referred to a drug support service and Urology. Early diagnosis and ketamine cessation are the primary management for this condition. There is currently no standardised approach for symptom control, but oral and intravesical therapies are available. Severe cases with intractable symptoms or structural abnormalities require urological review for assessment, investigation and consideration of surgical management.

COMPETING INTERESTS
Nil.

AUTHOR INFORMATION
Daniel Eaton: Urology Registrar, Urology Department, Waitaha Canterbury (CDHB), Christchurch, New Zealand.
Frank Kueppers: Dr med, Urologist, Urology Department, Waitaha Canterbury (CDHB), Christchurch, New Zealand.

CORRESPONDING AUTHOR
Daniel Eaton: Urology Registrar, Urology Department, Waitaha Canterbury (CDHB), Christchurch. Ph: 03 364 0640. E: Daniel.eaton@cdhb.health.nz.

URL
www.nzmj.org.nz/journal/vol-137-no-1593/recreational-ketamine-use-can-lead-to-irreversible-bladder-damage

REFERENCES
1. New Zealand Formulary. Ketamine [Internet]. NZ: New Zealand Formulary; 2024 [cited 2023]. Available from: https://nzf.org.nz/nzf_6903.
2. Dinis-Oliveira RJ. Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sci Res. 2017;2(1):2-10. doi: 10.1080/20961790.2017.1285219.
3. Know Your Stuff NZ. Ketamine [Internet]. NZ: Know Your Stuff NZ; 2022 [cited 2023]. Available from: https://knowyourstuff.nz/2022/01/18/ketamine-know-your-stuff-nz-with-knowyourstuffnz/.
4. Anderson DJ, Zhou J, Cao D, et al. Ketamine-Induced Cystitis: A Comprehensive Review of the Urologic Effects of This Psychoactive Drug. Health Psychol Res. 2022;10(3):38247. doi: 10.52965/001c.38247.
5. New Zealand Legislation. Misuse of Drugs (Classification of Ketamine) Order Commencement Order 2010 [Internet]. Wellington (NZ): Parliamentary Counsel Office; 2010 [cited 2023]. Available from: https://www.legislation.govt.nz/regulation/public/2010/0208/latest/versions.aspx.
6. Cornish S. Recreational ketamine use likely to surpass cocaine in popularity. Stuff News [Internet]. 2022 Mar 19 [cited 2023]. Available from: https://www.stuff.co.nz/national/crime/128069752/recreational-ketamine-use-likely-to-surpass-cocaine-in-popularity-in-new-zealand.
7. Know Your Stuff NZ. 2021-2022 Testing Report [Internet]. NZ: Know Your Stuff NZ; 2023 [cited 2023]. Available from https://knowyourstuff.nz/our-results-2/testing-results/testing-reports/2021-2022-testing-report/.
8. New Zealand Police. National Drugs Wastewater Testing Programme - Quarter 1, 2023 [Internet]. NZ: New Zealand Police; 2023 [cited 2023]. Available from: https://www.police.govt.nz/about-us/publication/national-drugs-wastewater-testing-programme-quarter-1-2023.
9. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology. 2007;69(5):810-2. doi: 10.1016/j.urology.2007.01.038.
10. Castellani D, Pirola GM, Gubbiotti M, et al. What urologists need to know about ketamine-induced uropathy: A systematic review. Neurourol Urodyn. 2020;39(4):1049-1062. doi: 10.1002/nau.24341.
11. Zhou J, Scott C, Miab ZR, Lehmann C. Current approaches for the treatment of ketamine-induced cystitis. Neurourol Urodyn. 2023;42(3):680-689. doi: 10.1002/nau.25148.
12. Vizgan G, Huamán M, Rychik K, et al. Ketamine-induced uropathy: A narrative systemic review of surgical outcomes of reconstructive surgery. BJUI Compass. 2023;4(4):377-384. doi: 10.1002/bco2.239.
13. Madurga Patuel B, González-López R, Resel Folkersma L, et al. Recommendations on the use of intravesical hyaluronic acid instillations in bladder pain syndrome. Actas Urol Esp (Engl Ed). 2022;46(3):131-137. English, Spanish. doi: 10.1016/j.acuroe.2022.02.007.
14. Sihra N, Ockrim J, Wood D. The effects of recreational ketamine cystitis on urinary tract reconstruction - a surgical challenge. BJU Int. 2018;121(3):458-465. doi: 10.1111/bju.14094.