

Ketamine Cystitis in a Female Patient Ketamine Therapy for Treatment Resistant Depression

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Abstract

Ketamine has been shown to be a novel and exciting antidepressant medication in patients with treatment-resistant depression. A complication commonly seen in frequent and heavy recreational use of ketamine is ulcerative cystitis, which presents with lower urinary tract symptoms (LUTS) and upper renal tract damage, seen in over 25% of regular users [3,4].

Although KIC is a recognised complication in recreational use of ketamine, its occurrence in therapeutic use for depression has so far not been reported. The exact pathogenesis of ketamine induced cystitis is currently unknown, making treatment and prevention much more difficult. Early diagnosis of ketamine induced cystitis and immediate cessation of ketamine use has been shown to improve adverse urinary tract symptoms and prevent further damage.

We present a case of a 28-year-old female who was started on ketamine treatment for depression, who developed symptoms of cystitis, which was confirmed by urine microscopy, culture and analysis.

To our knowledge, this is the first reported case of ketamine-induced cystitis in a patient receiving treatment-dose ketamine for antidepressant therapy.

Introduction

Ketamine has been shown to be a very effective anti-depressant in patients with treatment-resistant depression (TRD) with up to 71% positive response rate in these cohorts [1]. It acts as an N-methyl-D-aspartate (NMDA) receptor antagonist with glutamate blocking capacity and onset of action much faster than conventional antidepressant medications [1,2]. Depending on the mode of delivery, the anti-depressant effects from ketamine administration can be seen within minutes to hours and the benefits can last for days to weeks [1,2].

Common symptoms of ketamine induced cystitis (KIC) include urinary urgency, polyuria, dysuria, incontinence and haematuria, progressing to incontinence, haematuria, ulcerative cystitis, hydronephrosis, bladder wall fibrosis and chronic kidney failure [5,6,9].

Regular ketamine use is associated with increase in LUTS by up to 3-4 times compared to healthy individuals. Urinary symptoms can occur in over 25% of those who use ketamine recreationally and this is directly correlated with dose and frequency of ketamine use [3]. If ketamine cessation occurs early, the urinary symptoms can improve and early damage can reverse [4].

We present a case of a 28-year-old female who was started on ketamine treatment for depression, who developed symptoms

of cystitis, which was confirmed by urine microscopy, culture and analysis. To our knowledge, this is the first reported case of ketamine-induced cystitis in a patient receiving treatment-dose ketamine for antidepressant therapy.

Case

A 28-year-old female presented to Maudsley Hospital with a relapse of her treatment-resistant depression. She had a past psychiatric history of severe unipolar treatment-resistant depression, which had previously been successfully treated with ECT and medications. Her past medical history also included epilepsy, for which she was taking sodium valproate 600mg with good effect.

She was already on a combination of antidepressant medications, mood stabilisers and an antipsychotic. Her medication regime included: Vortioxetine 20mg, Levothyroxine 150mcg, Lithium (Priadel) 800mg, Valproate 600mg and Quetiapine 500mg.

Up until this relapse, her mood had been stable and she had been taking her medications as prescribed.

On assessment, she was well-dressed and well-groomed. She spoke slowly and monotonously with one syllable words and appeared dysthymic in nature. On discussion, it was evident that she had negativistic cognitive distortions and ideas of

worthlessness. She was at times not fully able to engage in the assessment but was generally coherent. There were no signs of hallucinations or abnormal sensory experiences, but she did appear more depressed than previously and more easily distracted.

Due to this relapse, ketamine augmentation therapy was started on 25/10/2021 in the form of sublingual lozenges 160mg twice weekly. This was increased to three times a day on 10/01/2022 with good effect. However, she complained of nausea and vomiting from the sublingual preparation.

In September 2022, her depression began to decline again and on 27/09/2022 the treatment was switched to oral capsules 240mg and escalated to four times a week. She reported that the nausea and vomiting improved significantly.

The ketamine showed excellent anti-depressant response. However, she began to complain of symptoms of dysuria which initially began insidiously. She described this as “stinging during and after peeing”. This discomfort could occasionally last for a few hours after voiding. These usually happened 12-24 hours after taking the ketamine dose. She was managing the pain with over-the-counter paracetamol and phenazopyridine hydrochloride, which she found very helpful. She was advised to stay well hydrated whenever taking the ketamine and to continue monitoring her symptoms closely. She reported taking the ketamine exactly as prescribed.

Unfortunately, the frequency and severity of the dysuria progressively worsened. A urine microscopy, culture and stain demonstrated sterile pyuria, with positive inflammatory cells, but no growths, nitrites or blood. No intimate examinations were performed. There were no indications of a urinary tract infection or a sexually transmitted infection.

Blood tests were unremarkable and renal function was normal. This included: Na 141mmol/L, K 4.7mmol/L, urea 3.2mmol/L, creatinine 80mmol/L, GFR 89, WCC 5.2 x10⁹/L.

Due to the concerns about irreversible bladder and renal tract injury, the decision was made to withdraw the ketamine. The patient reported that within 3 weeks, the symptoms of dysuria had completely resolved, but her mood had worsened. A repeat urine test carried out yielded normal results. A decision was made to begin ECT and to rationalise her medications, which included discontinuing the ketamine.

Patient Perspective

“The ketamine was really helpful for my mood – it worked quickly and my family, friends and I all saw the difference straight away. My mood was better, I had more energy and motivation to do things, my thought processes took a more positive swing and I was actually genuinely happy to be alive again. Sadly, the urinary symptoms were horrible – they felt like a really bad urinary tract infection and the pain lingered longer each time. In the end, the urinary symptoms made me start to dread taking each dose of the ketamine, as I knew that the pain would be there for most of the day/night afterwards. As a result, making the decision to stop the ketamine was a difficult decision, but so was the idea of continuing it.”

Discussion

Over 350 million people in the world suffer from depression

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and about one third of these patients are believed to have treatment-resistant depression (TRD) [7]. TRD is often defined as failure to two antidepressant medications [8].

Ketamine has been shown to be a novel and exciting antidepressant in patients with treatment-resistant depression (TRD), with up to 71% positive response rate [1]. It acts as an N-methyl-D-aspartate (NMDA) receptor antagonist with glutamate-blocking capacity and onset of action much faster than conventional antidepressant medications [1,2]. Depending on the mode of delivery, the anti-depressant effects can be seen within minutes to hours and the benefits can last for days to weeks [1,2].

KIC typically starts with urinary symptoms, including dysuria, urgency, polyuria, nocturia and progressing to incontinence, haematuria, bladder wall fibrosis and ulcerative cystitis. Continuation of the drug can lead to involvement of the upper renal tract, including hydronephrosis and chronic kidney failure [5,6,9]. Physical examination and investigations may show suprapubic pain, sterile pyuria and increased eosinophils within the bladder wall [9].

Imaging of the bladder in severe cases may show a grossly constricted with thickened walls [9]. Cystoscopy often demonstrates a friable bladder mucosa that is prone to bleeding [9]. Microscopically, the urothelium may appear denuded, ulcerated and infiltrated by inflammatory cells, such as mast cells and eosinophils. Other findings include, submucosal fibrosis, muscle hypertrophy and collagen deposition [11].

Although the exact pathogenesis of ketamine induced cystitis is not yet fully understood, various mechanisms have been postulated and it is likely that several pathways are involved concurrently [10].

One theory is that the ketamine and its metabolites, which are largely excreted by the urinary tract, cause direct toxicity to the bladder. These disrupt the urothelial integrity of the bladder epithelium and initiate interstitial fibrosis. This has been demonstrated in animal models and the level of damage directly correlates with the dose of ketamine used [12].

Another theory is an IgE mediated response. Bladder samples in ketamine users frequently show raised inflammatory cells and messengers, including mast cells, eosinophils, COX-2 (cyclo-oxygenase-2), NOS (nitric oxide synthase) and IgE. These levels fall once the patient is in remission from ketamine use and rise again once ketamine use restarts. This suggests an inflammatory response or a hypersensitivity reaction leading to bladder damage [9,12].

Ketamine can also directly stimulate various chemicals, including adenosine triphosphate, antiproliferative factor, and oxidative stress which lead to changes in the bladder wall [9]. It has been reported that the N-methyl-D-aspartate receptor (NMDAR) and angiogenic factors can also cause microvascular injury in the bladder [9].

Other proposed theories include aberrant neurotrophic factors, protein kinase B, mTOR pathways and metadherin and MAPK pathways leading to downstream fibrosis of the bladder [9].

Early diagnosis of ketamine induced cystitis and immediate

cessation of ketamine usage has been shown to improve symptoms, reverse early disease and prevent further damage [9].

Conclusion

To our knowledge, this is the first reported case of ketamine-induced cystitis in a patient receiving treatment-dose ketamine for antidepressant therapy. Our case highlights the need to be aware and to monitor for symptoms of LUTS and KIC in all patients taking ketamine for depression, especially now that this therapy is becoming more and more widely used.

Further research is required to determine the safe frequency, dose, route and duration of antidepressant ketamine therapy to avoid ketamine induced cystitis. We also advise further research to identify individual susceptibility and risk factors that may play a significant role in determining the susceptibility to developing KIC. Furthermore, we recommend regular screening for such symptoms in all patients receiving ketamine treatment.

Declarations

Ethics approval and consent to participate

Patient consented to participation in this case report.

Ethics approval not applicable.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report.

Availability of data and materials: Not applicable.

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