Cystitis and ketamine-associated bladder dysfunction☆

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KEYWORDS
Ketamine; N-methyl-D-aspartate (NMDA) receptors; Cystitis; Lower urinary tract symptoms

Abstract
Objectives: To analyze the prevalence of lower urinary tract symptoms (LUTS) in recreational ketamine users and evaluate its relationship with the consumption pattern.
Material and methods: Evaluation of 13 ketamine users. The presence of LUTS, gross hematuria and lumbar spine pain was analyzed. The ketamine usage pattern was recorded: initiation, administration route, dose in the last month, and frequency of usage.
Results: Six patients (46%) reported LUTS, with daily mean micturations every 42 min and night-time of 3 episodes, with dysuria (100%), urgency (100%), incontinence (20%), decreased flow (80%), hypogastric or perineal pain (80%), gross hematuria (80%) and bilateral lumbar spine pain (40%). Symptomatic patients described a mean intake of inhaled ketamine of 3 g/day (SD 2), 80% with a daily frequency and the asymptomatic ones of 1.03 g/day (SD 0.92) limited to weekends. The mean consumption time to the appearance of the symptoms was 31 months (SD 16.29). Intensity of the symptoms was related with the ketamine dose and improved on increasing water intake.
Conclusions: There seems to be a relationship between the picture with the dose and frequency of consumption, there being factors that reinforce the hypothesis that this action of the drug is due to the harmful effect on the urothelium. The process to identify it on time should be known, since the only known effective measure is to stop the consumption in the initial phases.
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PALABRAS CLAVE
Ketamina; Receptores N-metil-D-aspartato (NMDA); Cistitis; Síntomas del tracto urinario inferior

Cistitis y disfunción vesical asociada al consumo de ketamina

Resumen
Objetivos: Analizar la prevalencia de sintomatología del tracto urinario inferior (STUI) en consumidores de ketamina con fines recreativos y valorar su relación con el patrón de consumo.
Material y métodos: Valoración de 13 consumidores de ketamina. Se analizó la presencia de STUI, hematuria macroscópica y dolor lumbar. Se registró el patrón de consumo de ketamina: inicio, vía de administración, dosis en el último mes y frecuencia de consumo.
Resultados: Seis pacientes (46%) refirieron STUI, con un ritmo diurno medio de micciones cada 42 minutos y nocturia media de 3 episodios, con disuria (100%), urgencia (100%), incontinencia...
Introduction

Since the mid-1980s, the use of ketamine as a recreational drug has boomed. Some users of ketamine are afflicted by lower urinary tract symptoms (LUTS), such as increased urinary frequency, dysuria, hypogastric pain, urgency, and incontinence, the presence of hematuria or lumbar pain being less frequent. The exact physiopathological basis of the process is unknown, but it is believed to be due to direct injury of the urinary tract by ketamine, resulting in a bladder epithelial denudation and intense inflammation and fibrosis of the lamina propria. In more advanced cases, hydrenephrosis and renal failure have been described, and in some cases, it is necessary to proceed to puncture nephrostomies or carrying out of enterocystoplasties or cystectomies.

The available data are scarce and focus on some aspects of the diagnosis and complementary examinations of patients with the profile described. We have no data on the consumer population of ketamine or the influence that the dose or the consumption pattern can have in the appearance of the lesions and the diagnosis. Our aim in this study is to conduct a descriptive analysis of the symptoms that consumers of ketamine may present, collecting detailed information on their consumption patterns.

Material and methods

Secondary-basis cross-sectional study, using as a source users of ‘Energy Control’, ‘Psychoactivity’ and ‘Underave’, open access web pages devoted entirely to information on different types of drugs. On these digital platforms, we published a message that warned of the possible effects of ketamine on the urinary tract, with an e-mail address to arrange a visit with us. We considered as consumer of ketamine every person who admitted a minimum intake of once a week for a period of 3 months or more.

The study was conducted between April 2010 and February 2011. After the first contact, interested consumers were cited and visited in urology outpatient departments. They underwent a personal interview to quantify the consumption of ketamine and assess the presence of LUTS, hematuria, or lumbar pain. The patients implemented the Pelvic Pain and Urgency/Frequency (PUF) questionnaire, validated in the diagnosis of interstitial cystitis. We recorded the pattern of ketamine consumption: age of onset, route of administration, dose in the last month, and frequency of consumption. Sediment, urine culture and cytology, blood test, and reno-vesicoprostatic ultrasound were performed.

Results

We evaluated a total of 13 patients (8 men and 5 women), with a mean age of 26 years (standard deviation [SD] 8.52). The mean time of regular consumption of ketamine at the time of the first visit was 56 months (SD 32.21). 5 patients admitted a daily intake during the 6 months prior to the visit, and 8, a consumption at weekends only. The mean dose consumed was 1.94 g/day (SD 1.77), although many recognized modifications to the dose and frequency over time (Table 1).

Six of the patients (4 men and 2 women) had LUTS. They reported an increased urinary frequency, with an average rate of daytime urination every 42 min and average nocturia of 3 times, with dysuria (100%), urgency (100%), incontinence (20%), decreased flow (80%), and hypogastric and/or perineal pain (80%). Some were afflicted by other pains, more fickle and intermittent in time, for example, gross hematuria at least once (80%), and bilateral lumbar pain (40%). All the patients completed the PUF questionnaire; the average score was 22.5 (SD 6.98) among the symptomatic ones and 3.3 (SD 3.09) among the asymptomatic ones.

The symptomatic patients reported an average consumption of inhaled ketamine of 3 g/day (SD 2), 80% on a daily basis, and the asymptomatic ones, from 1.03 g/day (SD 0.92), limited to weekends. The average time consumption to the onset of symptoms was 31 months (SD 16.29).

The patients acknowledged the influence of the fluid intake and the dose consumed in the intensity of the symptoms. Of the 6 patients with symptoms, 4 reported a decrease in the intensity when increasing water intake and decreasing the dose of ketamine. They also described a worsening of the same over the next 24–48 h after taking a punctual high dose. Ultrasound study was performed in 4 symptomatic patients, and 3 of them showed a decreased capacity bladder, with an early feeling of repletion, but without wall thickening or dilation of the upper urinary tract (Table 2).

The patients showed poor adhesion to follow-up. Only 4 went to the subsequent tests; 3 of them had no symptoms,
Table 1 Description of the pattern of ketamine consumption in patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Dose (mg/day)</th>
<th>Frequency</th>
<th>Time of consumption (months)</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>1</td>
<td>Weekend</td>
<td>87</td>
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<tr>
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<td>43</td>
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<td>Weekend</td>
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<td>43</td>
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<tr>
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<td>23</td>
<td>3</td>
<td>Weekend</td>
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<tr>
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<td>17</td>
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<td>Weekend</td>
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</tr>
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<tr>
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<td>5</td>
<td>Daily</td>
<td>65</td>
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</table>

Table 2 Results of complementary tests performed on patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Serum Cr (mg/dl)</th>
<th>Leukocyturiaa</th>
<th>Hematuriab</th>
<th>Urine culture</th>
<th>Urine cytology</th>
<th>Ultrasound</th>
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<td>0</td>
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<td>Normal</td>
<td>Normal</td>
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<tr>
<td>2</td>
<td>0.8</td>
<td>0</td>
<td>0</td>
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<td>Normal</td>
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<td>-</td>
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<tr>
<td>5</td>
<td>0.7</td>
<td>0</td>
<td>20–50</td>
<td>Negative</td>
<td>Normal</td>
<td>Normal</td>
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<td>-</td>
<td>-</td>
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<td>0.9</td>
<td>0</td>
<td>20–50</td>
<td>Negative</td>
<td>Normal</td>
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<tr>
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<td>-</td>
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<td>Alteredc</td>
<td>-</td>
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<tr>
<td>9</td>
<td>0.9</td>
<td>20–50</td>
<td>&gt;100</td>
<td>Negative</td>
<td>Normal</td>
<td>Alteredd</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>0</td>
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</tbody>
</table>

a,bUrine sediment. Microscopic entities in 400× field.

c,d,eDecreased capacity, with a feeling of repletion at 70 ml, 35 ml and 40 ml.

and the studies performed were normal. The remaining patient, who complained of symptoms for about 3 months, showed a gradual improvement after stopping consuming. At 8 weeks, he did not show any discomfort, and the PUF questionnaire score went from 30 to 0.

Discussion

Ketamine is a non-competitive antagonist of the N-methyl-
D-aspartate (NMDA) glutamatergic receptor. Since it was
approved by the Food and Drug Administration (FDA) in 1970,
it has been used for anesthetic purposes. It induces the so-
called dissociative anesthesia, producing an intense somatic
analgesia with superficial sleep and amnesia. During the
induction and recovery, it can produce hallucinations and
dysphoria, so its use is limited.2

Ketamine is metabolized to norketamine in the liver
microsomal system, and the main enzyme involved is
CYP3A4.3 Norketamine, which has 20–30% of the activity
of the initial molecule, is hydroxylated, conjugated with glu-
curonic acid, and excreted through the kidneys. Levels of
ketamine and its metabolites can be detected in urine up to
2 weeks after consumption.4

Since the 1980s, consumption with recreational pur-
poses has experienced a great increase. The UK and
Spain are the European countries where this increase
has been greater, according to the Report by the 2010
International Narcotics Control Board (INCB). There are
commercial liquid or dried white powder preparations.
They are consumed orally, inhaled, smoked, or injected
intramuscularly.5

The first work that establishes the relation between
ketamine consumption and the occurrence of urinary symp-
toms and urinary tract injuries was published in 2007, and
it is a series of 9 patients.6 2 more series have since then
been published, of 59 and 11 patients,7,8 and some isolated
cases in different publications.10–18 The description of the
profile in patients receiving ketamine in a sustained way
as part of their treatment suggests that the effect is due
to the molecule itself and not to adulterants used in its
underground synthesis.19

The exact prevalence of this disorder among ketamine
consumers is unknown, but the data published so far place
it from 10 to 30%.8,20,21 Almost all of our patients had already
heard in their social circles about the possible occurrence of bladder injuries due to ketamine, and they even knew other consumers with symptoms, which leads us to think that these are not isolated cases. We consider that the 46% prevalence that we observed should be taken with caution, as there may be a selection bias due to the greater interest of the symptomatic patients to contact us. This point and the limitations of the small sample size may affect the external validity of our results.

The symptomatic patients described greater consumption in dose and frequency than the asymptomatic ones. The diagnosis may appear after a sustained exposure to a threshold dose to be determined. Wood et al. describe the interaction between ketamine and the bladder epithelium, experimentally observing urothelial cell death at concentrations of ketamine greater than 1 mM.

Most symptomatic patients reported a relation between the intensity of these symptoms and the ingested dose after the first complaints appeared. They also detailed a symptomatic relief by consuming plenty of water after the ingestion of ketamine, which could be explained by the greater dilution of the drug in urine. Both findings support the hypothesis that the profile may be due to the toxic effect of ketamine and/or its metabolites in the urothelium.

The improvement of the symptoms after stopping consumption has also been reported in other series, although this fact does not occur in all the patients. This difference possibly depends on the presence or absence of irreversible histological changes. The medical literature describes a denudation of the bladder epithelium. The surface area of the lamina propria shows dilation and vascular congestion, associated with infiltrates of mastocytes and lymphocytes, eosinophils predominating among the latter ones. The deep area of the lamina propria may present different grades of fibrosis. These findings may be of variable intensity and related to the dose and/or frequency of consumption.

In some of the articles published, the presence of small bladders and thick walls is described, sometimes being associated with unilateral or bilateral dilation of the excretory system. Up to 51% of the patients in the series by Chu et al. presented this dilation. Only in some series, urodynamical study was performed, showing decreased bladder capacity (lower than 150 ml in most cases), decreased accommodation, and detrusor hyperactivity at low volumes. At cystoscopy, findings suggestive of bladder inflammation are constantly described, such as hypertervascularized areas and hemorrhagic petechiae. To date, sustained consumption of ketamine has not been reported to increase the risk of urothelial cancer.

In summary, the sustained consumption of ketamine has a detrimental effect on the urinary tract. There might be a threshold of drug concentration in urine from which the described injuries occur. The dose and frequency of consumption are important in the development of the process. It seems that the injuries and symptoms are reversible in early stages and may improve after stopping use of ketamine. So far, the only effective measure is to know the process to be able to identify it on time and alert the patients before they develop irreversible lesions.

### Conflict of interest

The authors declare that they have no conflict of interest.

### Acknowledgement

To Ms. Montse Llopart, for her help to organize the visits.

### References
