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Recreational ketamine: from pleasure to pain

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Ketamine has become increasingly recognized as a drug of recreational use. Individuals using significant amounts have developed symptoms including a small painful bladder, ureteric obstruction, papillary necrosis and hepatic dysfunction. The present paper examines the current literature on the relationship between ketamine use and these symptoms. Our own clinical experience and the data available clarify the causal relationship, and further data help to elucidate the mechanism of damage. On the basis of continued work and development with patients who are ketamine users we suggest an assessment and treatment regime that includes cessation of ketamine use and adequate analgesia to overcome symptoms. In conclusion, it is important for medical practitioners who encounter patients with these symptoms to ask about recreational drug use. Ketamine remains a safe and effective drug to use under appropriate medical supervision. Patients identified as suffering from this syndrome will need to be referred to a urological unit with an interest in the treatment of the condition.

What's known on the subject? and What does the study add?

There is a very limited literature on the syndrome described in this review. The largest series comes from Hong Kong and includes 59 patients – this was largely a description of the presenting problems and established the link between these symptoms and ketamine. Prior to this much smaller case series (including one from the same group) were all that exists.

An increasing number of UK urologists are reporting seeing these patients and we have formed a collaboration interested in understanding the pathology and establishing an effective treatment pathway for these patients. This paper aims to consolidate this knowledge.

KEYWORDS

ketamine, painful bladder syndrome, lower urinary tract symptoms

INTRODUCTION

Ketamine is a 'dissociative anaesthetic' that acts as a glutamatergic N-methyl-d-aspartate antagonist. It was first synthesized in 1964 and it has had an excellent track record in anaesthesia and analgesia across both human medical and veterinary fields [1,2]. In clinical practice, patients coming round from ketamine-based anaesthesia have reported a variety of strange effects including 'out of body' and 'near-death' experiences, delirium, confusion, delusions and hallucinations. This dissociative sensation (the 'K Hole') is pleasurable to some and, combined with its ready availability and low price (annecdotally 'cheaper than a night on alcohol'), has led to ketamine gaining in popularity as a recreational drug. Some 'middle-class' social circles use ketamine regularly at weekends, and the drug has been adopted by the party scene worldwide, leading to the emergence of a mixed pattern of intermittent, daily and extremely high-dose users [3]. The highest dose noted in the series of patients encountered by our group is 20 g per day. The present review focuses on the urological issues associated with sustained ketamine use and presents evidence to establish a causal relationship between ketamine toxicity and the symptoms/clinical findings described in patients.

Ketamine misuse is already a major problem in Asia where significant quantities are manufactured by the generics pharmaceutical industry, providing a ready supply. Internet searches and anecdotal discussions with users indicate a number of perceived advantages, including low rates of physical or psychological addiction and minimal side effects. However, there is evidence of cognitive impairment and long-term psychological effects as a result of prolonged heavy use [4]. In addition, we have identified a cohort of patients who have developed a major urological syndrome that was originally reported in small case series [5,6].

The clinical syndrome includes a small, very painful bladder, incontinence, upper tract obstruction, papillary necrosis and hepatic dysfunction [7,8]. Before recognition of the syndrome, many patients had been treated empirically for recurrent UTIs or painful bladder syndrome and a lack of specific enquiry relating to substance abuse has contributed to treatment failure. Cystoscopic inspection of the bladder frequently shows a denuded urothelium, which in the most severe cases may slough off as intact sheets of cells. The mechanism of damage from ketamine is not yet clear, but the effects, which are not specific to the bladder, are most likely to result from direct toxicity of ketamine or its metabolites. This is supported by a rudimentary mouse model based on intraperitoneal ketamine injections [9] and by a few cases where patients given therapeutic ketamine have experienced identical symptoms to those described by recreational users. In addition, laboratory research from our group has shown a

specific interaction between ketamine and differentiated human urothelium *in vitro*, thus providing a direct link between ketamine and the clinical syndrome [Baker *et al.*, own unpublished data].

Because of the illegal nature of the drug, we may never know how many people use ketamine, or the precise correlation between chronic high-dose intake and symptoms. Previous studies have suggested that 20% of users may develop symptoms but there is no consistent safe level or time frame for regular users [10]. Although it is difficult to obtain accurate data regarding the epidemiology of ketamine use, in 2007/2008, 0.9% of 16–24 year olds questioned in the UK admitted to ketamine use in the preceding year [11]. This figure rises in selected populations (e.g. police detainees in Taiwan) to 2% [12] and up to 70% of 'party drug' users in Australia [3]. David Nutt recently stated that Class C 'may be the wrong class' for ketamine, suggesting the need for its status to be reviewed. Additionally, in 2009, the Home Office suggested that the classification of ketamine should be reviewed after consideration of its pathological effects on the urinary tract (http://news.bbc.co.uk/newsbeat/10003110 (checked 31/12/10)).

PATIENTS

Among the three clinical centres involved in our collaboration, we have seen approximately 60 patients; the majority are young (17–45 years at presentation) and almost all are recreational users. We have developed four principal questions:

1. Is there a true causal relationship between ketamine and the LUTS?
2. What is the mechanism(s) of damage?
3. What is an effective and appropriate treatment regime for such patients?
4. What support exists from other agencies to educate about the harmful effects and to reduce use?

CAUSAL RELATIONSHIP

A reasonable question that has been raised in both written and verbal discussion is whether it is ketamine itself that causes the symptoms. It could be that other substances taken in conjunction with ketamine, either knowingly or as an adulterant, are responsible or that there is another unrecognized disease process. We have considered the possibility that another substance is responsible for the major bladder damage, but that the sensation is masked by the anaesthetic properties of the ketamine. Upon consideration, an adulterant effect seems highly unlikely for the following reasons:

1. As the use of adulterants would be expected to vary, ketamine appears to be the common factor. Although there is some variation in the detailed pattern of disease between different racial groups (e.g. emphasis on upper tract manifestations in Asia [7]), there is consistency in the use of ketamine and the development of symptoms.
2. The low cost of ketamine mitigates against the need for, or regular use of adulterants.
3. An animal model suggests a causal link [9].
4. There are case reports in adult and paediatric patients using therapeutic ketamine [13,14].
5. There is both a dose and time relationship [15].

On the basis of these considerations, we are convinced of the causal link between ketamine use and damage to the urinary tract; however, the possibility of a synergistic effect between either an adulterant or other substances taken in tandem (e.g. alcohol, tobacco or other drugs) does need to be considered.

MECHANISM OF DAMAGE

The possible mechanisms suggested by Chu *et al.* [7] for damage to the urinary tract can be summarized as follows:

1. Direct toxic damage to the urinary tract by ketamine and/or its metabolites.
2. Microvascular damage by ketamine and/or its metabolites.
3. Autoimmunity triggered by either circulating or urinary ketamine.
4. Unrecognized bacteriuria.

In vitro studies carried out by the scientists in our collaboration have shown compelling evidence of a direct interaction between ketamine and the bladder urothelium, with cell death observed at concentrations ≥1 mM, but with evidence of an intriguing receptor-mediated component [Baker *et al.*, own unpublished data]. The nature of the receptor activated by ketamine has yet to be identified as ketamine is renowned for its binding promiscuity [16].

There is some suspicion in the field that metabolites of ketamine could be the toxic agents responsible for LUTS; however, at the time of writing, there is no direct evidence to support this hypothesis.

As part of an audit of our histopathological assessment of patients with ketamine-induced cystitis, we have found a difference in the number of mast cells compared with equivalent tissues from patients with interstitial cystitis. This may indicate differences in the underlying aetiopathology of the two conditions and reflect the specific immune-mediated response to ketamine or its metabolites, although at present the exact mechanism remains unclear (C.White and A.Freeman, unpubl. data).

Developing our understanding of the histopathology of the disease is critical, as before the syndrome was recognized, the histological similarities to high grade dysplasia or malignant cystitis could have led to a mistaken diagnosis of carcinoma *in situ*. The absence of a pattern of cytokeratin 20 expression associated with carcinoma *in situ* [17] in patients with ketamine-induced cystitis appears to be an important distinguishing feature [18].

TREATMENT REGIME

There is no evidence for a successful treatment regime and at the outset of our collaboration, all groups were doing their best to treat patients who were presenting with a previously unseen phenomenon. The urologists amongst us have all seen young patients, at an end-stage in the disease process, who have required cystectomy and reconstruction. For those patients most severely affected, suprapubic pain has been a major issue and unfortunately many patients have resorted to self-medication with ketamine itself as the most effective means of pain relief.

After our group met initially, we wrote to the President of BAUS suggesting a strategy for evaluating these patients. We wrote:

> Early investigation must rule out UTIs and is fairly standard. Anyone who gives a history of drug abuse should be placed in contact with a local drug support service. If ketamine is identified as a factor we strongly recommend that renal function is

assessed. In addition a CT urogram is an important investigation to understand the extent of disease.

A urine culture is mandatory in our clinical practice and we routinely evaluate the upper tracts with a CT urogram to rule out ureteric stricture and use cystoscopy to assess bladder capacity.

It is clearly vital to ask the correct questions and failure to ask about recreational drug use will result in this being overlooked in many patients. We have all seen patients with symptoms compatible with these patients' complaints and many have been treated with a variety of speculative therapies. Increasing awareness of the urological effects of recreational drugs should lead to more doctors asking the questions that will help to identify and treat such syndromes [19].

Foremost in our treatment strategy is the absolute requirement for a patient to stop ketamine use. This may sound straightforward, but in a context where patients feel their only way of controlling the pain is with ketamine, it has proven to be difficult. It is not universally true, but many of this patient population have been unreliable attendees at both outpatient and investigation appointments.

Because ketamine is relatively cheap, it has little or no direct association with crime and hence drug support agencies and primary care trusts may not see ketamine users as a high priority for rehabilitation. For these reasons, expecting someone to stop ketamine use carries a significant risk of failure. In Bristol, the chronic pain team have worked closely with the urology team and developed a strategy that includes buprenorphine patches with cocodamol and amytriptiline at night. This appears to offer reasonable symptom control, allowing users to avoid ketamine.

The involvement of drug support agencies is important but can be difficult, particularly if patients are seeing a urologist out of their residential area. As support is given by residential area, it is best organized by the GP once the diagnosis has been established.

In some areas, drug support agencies have been extremely proactive in initiating contact with a local urology department. This has created a productive link both for patients and for furthering enquiry into this emerging clinical phenomenon.

In conclusion, the urological syndrome associated with ketamine use is severe. If drug cessation is achieved it may be, at least partially, reversible. The early syndrome may be present in casual or weekend users as episodes of cystitis treated empirically. Once a usage threshold is crossed, bladder pain (or other symptoms) may drive further use to suppress symptoms, leading to irreversible damage and scarring. This is a concern of ours, as the worst-affected patients have required major surgery, i.e. cystectomy and bladder reconstruction, with all its inherent risks. Such surgery should only be done after careful counselling and a sustained attempt to stop ketamine use.

Ketamine has been widely used for chronic pain and there is one report of ketamine-induced cystitis in a paediatric patient [13]. There is also a report of disabling bladder symptoms in patients receiving ketamine in the chronic pain and palliative care setting; this suggests that the effect is not uniform and some individuals may be more susceptible than others. However, most studies of ketamine used for chronic pain were of short duration and involved lower doses than seen in recreational use, so LUTS were not reported [14]. Whilst somewhat rudimentary, a mouse model has gone some way to cementing the link between ketamine and urinary tract damage [9]. Laboratory research from our group shows a clear link between ketamine and damage to the urothelium; this, coupled with disease manifestation and patterns of use, firmly establishes the causal link with ketamine.

We emphasize that, under medical supervision, ketamine remains a very safe and useful drug in anaesthetic practice. However, there are significant side effects as a result of misuse, with long-term consequences. We would urge all medical practitioners seeing patients with these symptoms to ask about recreational drug use and to consider appropriate rehabilitation and support, along with referral to a urology department with a specialized interest.

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CONFLICT OF INTEREST

None declared.

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