

# Ketamine infusion induces urinary retention in a patient successfully treated by sacral neuromodulation.

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## Abstract

**Background:** Sacral neuromodulation has become an established method for treating lower urinary tract symptoms but the exact mechanisms of action remain unclear. This case report illustrates that the lack of complete knowledge of the mechanisms and (central) effects of sacral neuromodulation may elicit unexpected consequences in treating a patient for chronic pain.

**Methods:** We present a case of transient recurrent urinary and fecal retention after each administration of ketamine for chronic lumbosacral pain in a 57-year-old patient treated with sacral neuromodulation for non-obstructive urinary retention. Each episode of urinary and fecal retention appeared immediately after intravenous administration of ketamine. Spontaneous recovery occurred after a dose-dependent time (between 12 to 48 hours).

**Results:** Sacral neuromodulation may influence the (number of) NMDA-receptors in the spinal cord, thereby altering the physiological micturition and defecation reflex.

**Conclusion:** Sacral neuromodulation has a clear role in the treatment of both urinary retention and overactive bladder syndrome, but not all mechanisms of action have been discovered. We hypothesize a possible influence of sacral neuromodulation on the central presence and function of NMDA-receptors, thereby altering the physiological micturition and defecation reflexes.

**Keywords:** Sacral neuromodulation, Ketamine, Bladder syndrome, NMDA-receptors, Lumbosacral pain.

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## Introduction

Sacral neuromodulation (SNM) is an effective and increasingly used therapeutic option for various conditions such as symptoms of urgency-frequency, refractory urinary urge incontinence, pelvic pain syndrome and fecal incontinence, urinary retention and constipation. The S3 nerve is usually stimulated unilaterally with a standard frequency of 14Hz and an ideal voltage for motoric response below 3V, which is below the activation threshold of somatic muscle. This modulates the pathophysiological control of both bladder and bowel as both organ systems are innervated by the same central + peripheral nerves. However, not only are the exact mechanisms of action of neuromodulation poorly understood, the pathophysiological mechanisms of these disorders of bladder and bowel function remain unclear as well.

We want to report on a 57-year-old man, treated successfully by SNM for non-obstructive urinary retention, with transient recurrent urinary and fecal retention after each infusion of ketamine for chronic lumbosacral pain. The aim of this case report was to illustrate how the lack of understanding of the mechanisms and (central) effects of SNM may elicit unexpected consequences after treatment for chronic pain. We hypothesize on the possible (central) effects of SNM that may provoke these unexpected symptoms.

## Methods

We retrospectively reviewed the patient file and a written

informed consent was obtained from the patient for publication of this case report. A copy of the informed consent is available for review.

## Results

We present the case of a 57-year-old man initially complaining of progressive voiding difficulties not responding to an alpha-blocker. There were concomitant defecation difficulties. History reveals severe sexual abuse as a child, orchido-epididymitis for which an epididymectomy was performed in 2003), chronic prostatitis, chronic back pain, and a psychiatric history with social phobia, depression with suicide-attempt, post-traumatic stress syndrome and alcohol abuse.

A benign prostatic hyperplasia was found as well as a bladder stone. Cystoscopy excluded an urethral stenosis and in april 2008 the patient underwent a Trans Urethral Resection of the Prostate. Postoperatively he developed a persistent urinary retention. A suprapubic catheter was placed and urodynamic investigation was performed. Due to the history, transurethral placement of the measuring tubes and placement of the anal balloon were very difficult. The cystometry showed good bladder compliance, and the patient reported a sensation of urgency during an involuntary bladder contraction at 250 ml bladder filling. However, micturition was not possible: there was no detrusor contraction. MRI showed non-compressive herniation at D5-D6 and at L1-L2, L2-L3 and L5-S1. Urological EMG-SSEP showed no abnormalities.

Treatment with pelvic floor therapy and bladder training was started and the patient was taught clean intermittent catheterization. This brought no resolution of the urinary retention and due to insufficient sphincter relaxation; intermittent catheterization became more and more painful and was eventually traumatic. Furthermore, there were increasing defecation problems and there was increasing back pain.

In October 2011, the patient received sacral neuromodulation, which led to an improvement of LUTS (voluntary voiding without post-micturition residual) and to an improvement of the difficult defecation.

The chronic lumbosacral back pain was approached conservatively by the neurosurgeons and was treated by the pain department since December 2010. As pain symptoms were resistant to medical treatment (paracetamol, NSAID, tramadol, gabapentine, duloxetine, amitriptyline and baclofen) and to interventional treatment (percutaneous radiofrequency denervation), ketamine treatment was started in August 2012. In total, the patient received 40 infusions of ketamine either in day clinic (1.2 mg/kg over 4 hours) or during a 24-hour hospitalization (3.6 mg/kg over 24 hours) dependent on the pain grade and duration of pain relief. After each 24-hour hospitalization the patient developed a urinary and fecal retention with spontaneous resolution after 48 hours. After administration in day clinic (lower dose), urinary and fecal retention occurred as well but had a shorter duration of 12 hours.

## Discussion

Ketamine is an anesthetic that produces profound analgesia and amnesia, but its use in contemporary anesthesia is limited due to the occurrence of a variety of important side effects, (e.g. agitation, hallucinations and panic attacks) Although these side effects may be prevented or treated by adding benzodiazepines and/or alpha2-adrenoceptor agonists, the availability of alternatives has limited the use of ketamine in anesthesia to specific indications [1] (e.g. pediatric and trauma anesthesia). For surgical procedures, an average dose of 1-2 mg/kg can provide 5 to 10 minutes of anesthesia [2]. To our knowledge, there is no data in literature over urinary retention after perfusion of ketamine in subanesthetic doses. Bredlau [3], in a review of literature, found 6% of urinary retention with the use of ketamine, but it was not intravenously administered but intra-theal.

Neuropathic pain results from lesions of the somatosensory nervous system causing alterations in structure and function so that pain occurs spontaneously and responses to noxious and innocuous stimuli are amplified [4]. An important mechanism in this process is the phosphorylation and upregulation of the N-methyl-D-aspartate receptor (NMDAR). The NMDAR is an excitatory glutamatergic receptor present at spinal and supraspinal sites and involved in the afferent transmission of nociceptive signals. In chronic pain states, prolonged nociceptive stimulation causes activation and upregulation of the NMDAR at dorsal horn synapses resulting in enhanced and amplified trafficking of pain signals to the brain (central sensitization). Ketamine, a non-competitive inhibitor of the NMDAR, can halt

the excessive barrage of nociceptive input to the brain and is therefore an alternative to existing treatments of chronic pain syndromes [5]. The anti-hyperalgesic dose range is 0.25–0.5 mg/kg as an initial IV bolus followed by 50–500 µg/kg/h. The elimination half-life of ketamine is 2-3 hours, but the analgesic onset/offset half-time of ketamine was estimated to be 11 days [1]. The duration of the infusion determines the duration of the analgesic effect.

Additional to its effect at the NMDAR, ketamine interacts with other receptor systems as well, including muscarinic receptors [6]. Ketamine at anesthetic doses can inhibit the reflex responses to distension of the urinary bladder and has an anticholinergic effect [7,8]. Maggi et al. [9] reported that a block of the NMDA receptor with MK-801 suppressed voiding in the intact bladder in anesthetized rats and also inhibited the micturition reflex of a chronically inflamed bladder. These studies suggest that the NMDA-R plays a role in the micturition reflex and is essential to initiate bladder contractions.

SNM is an efficient treatment for both urinary retention and overactive bladder syndrome. In patients with detrusor overactivity, SNM is thought to inhibit detrusor activity without affecting urethral resistance or the strength of detrusor contractions during voiding [10]. In urinary retention, SNM has been postulated to inhibit inappropriate activation of the 'guarding reflex' (i.e., the spinally mediated reflex whereby the urethral sphincter contracts to prevent urinary incontinence on sudden increase in intravesical pressure), thus facilitating voiding by interrupting the excitatory outflow to the urethral sphincter [11,12]. In a study of 30 women with Fowler's syndrome, however, elevated maximum urethral closure pressure did not change significantly, and electromyographic abnormality persisted during SNM; the return of voiding ability seemed to be attributable to a slight increase in detrusor contractility [13]. At least in women with Fowler's syndrome, SNM seems not to restore voiding by a direct relaxant effect on the urethral sphincter, but instead by an increase in detrusor contractility that is sufficient to overcome the still overactive urethral sphincter. Furthermore, SNM reduced the sensory threshold of the bladder, but not of the urethra [14].

We could find no studies on the effect of SNM on NMDA-receptors. However, a study on intravesical electrical stimulation (IVES) in rats with spinal cord injury (SCI) showed that the increase in NMDA-receptors in rats with SCI was reversed by IVES [15].

We presented a case of a 57-year old man treated with SNM for urinary retention, who developed recurrent transient urinary and fecal retention after each intravenous administration of ketamine for chronic lumbosacral pain. When the patient presented urinary retention, we didn't try to turn off the device, in order to see if the retention would have been more significant. Indeed, we did know that the patient already had retention before neuromodulation.

In our opinion, and based on the literature above, there are different possible explanations for this phenomenon.

Our case may suggest an influence of SNM on NMDA-R

function at the central level. One of the hypotheses arising from the study by Hong et al. [15] on the effect of IVES on NMDA-R in SCI rats could be that SNM also induces a down-regulation of NMDA-R at the spinal level. We previously mentioned that the NMDA-R plays a role in the micturition reflex and is essential to initiate bladder contractions [9]. This down-regulation would lead to an increased susceptibility of the micturition reflex to the inhibitory effect of ketamine, leading to urinary retention after intravenous administration.

A second hypothesis is that chronic pelvic pain and psychosocial profile (c.f. history of abuse, chronic prostatitis, urethral dysfunction) induced an upregulation of NMDA-R at the sacral spinal level as well (next to the lumbar level due to chronic back pain). The increase in NMDA-R could lead to an habituation of the micturition reflex to this increased amount in receptors, making it reliant on more NMDA-R's to initiate the reflex. Blocking NMDA-R with ketamine could therefore more easily block the micturition reflex, leading to urinary retention.

A third possible mechanism of urinary retention in this patient is the anticholinergic effect of ketamine [7,8]. Ketamine decreases acetylcholine release [16], it profoundly inhibits muscarinic signaling and it decreases opening time of the channel coupled to the cholinergic nicotinic receptor [6]. These mechanisms inhibit the bladder peripherally, which leads to urinary retention. We consider this hypothesis less likely, as these effects have only been described at anesthetic doses of ketamine and not at analgesic doses.

The dose-dependent duration of urinary and fecal retention after ketamine administration, and the short duration compared to the analgesic effect duration, may be explained by the difference between the elimination half-life (2-3 hours) of ketamine and its analgesic half-life [1] (11 days). A higher dose would take longer to clear, leading to a prolonged urinary and fecal retention compared to a lower dose. On the other hand, ketamine is cleared relatively fast from the body compared to its analgesic effect duration, explaining the difference between the duration of its analgesic effect and the duration of urinary retention.

A final hypothesis on the cause of urinary retention after ketamine administration in this patient is a concomitant psychological inhibition of the micturition reflex due to the hospital environment, which may induce a memory of trauma in the patient (c.f. patient history). This may also lead to an increase in urethral pressure, adding an inhibitory effect to the micturition reflex along with ketamine.

## Conclusion

We presented a case of transient recurrent urinary retention after intravenous ketamine administration for chronic pain, in a 57-year old patient with SNM. SNM has a clear role in the treatment of both urinary retention and overactive bladder syndrome but not all mechanisms of action have been discovered. We hypothesize a possible influence of SNM on the central presence and function of NMDA-receptors, thereby altering the physiological micturition and defecation reflexes. This may explain the unexpected occurrence of urinary and fecal retention in this patient with a sacral neuromodulator, treated with intravenous ketamine for chronic pain.

## Original Publication

We clearly state that the paper or portion thereof have not been previously published and are not under consideration by another Journal.

## Conflicts of Interest/Disclosure Summary

François Hervé MD: None were declared.

Jacques Devulder MD, PhD: None were declared.

Michel Wyndaele MD, PhD: None were declared.

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## Ethics Approval

Informed consent from the patient is available for review.

## Author Contribution

We clearly state that authors are those who made a significant contribution to the study concept and design, acquisition of data, or analysis and interpretation of the data, drafting/revising the manuscript for important intellectual content and approval to the final version to be published have participated to the work and could publicly defend its content.

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