REVIEW ARTICLE

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Drug-Induced Urinary Retention
Incidence, Management and Prevention

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Abstract

Urinary retention is a condition in which impaired emptying of the bladder results in postvoidal residual urine. It is generally classified into 'acute' or 'chronic' urinary retention. Because of the complex mechanism of micturition, many drugs can interact with the micturition pathway, all via different modes of action. Although the incidence of urinary retention, in particular acute urinary retention, has been well studied in observational studies and randomized controlled trials, data on the incidence of drug-induced urinary retention are scarce. Data from observational studies suggest that up to 10% of episodes might be attributable to the use of concomitant medication. Urinary retention has been described with the use of drugs with anticholinergic activity (e.g. antipsychotic drugs, antidepressant agents and anticholinergic respiratory agents), opioids and anaesthetics, α-adrenoceptor agonists, benzodiazepines, NSAIDs, detrusor relaxants and calcium channel antagonists. Elderly patients are at higher risk for developing drug-induced urinary retention, because of existing co-morbidities such as benign prostatic hyperplasia and the use of other concomitant medication that could reinforce the impairing effect on micturition. Drug-induced urinary retention is generally treated by urinary catheterization, especially if acute, in combination with discontinuation or a reduction in dose of the causal drug. Studies have been carried out examining the effects of preventive measures for anaesthesia-related urinary retention, both during and after surgery, particularly into the effect of using opioids in combination with non-opioid analgesic drugs on the incidence of postoperative urinary retention. Although combination therapy reduces the opioid-related adverse events, the effect on urinary retention yields contradictory results. This article reviews the literature on drug-induced urinary retention and focuses on its incidence, the different classes of drugs that have been associated with it, and options for its management and prevention.

Urinary retention is a condition in which impaired emptying of the bladder results the retention of residual urine. It can be categorized into 'acute' or 'chronic' urinary retention. Chronic urinary retention develops over a long period with development of a painless, palpable bladder due to a postvoid residual volume.[1] Complications include storage symptoms (frequency, nocturia, urgency and urge incontinence), dilatation of the upper urinary tract and eventually impaired renal function.[2] Risk factors are detrusor hypocontractility, chronic bladder outlet obstruction or neurological bladder dysfunction.

Acute urinary retention is defined as the sudden inability to micturate.[1] The onset is acute, the retention itself is often painful and it requires treatment by urinary catheterization. Risk factors are increasing age (particularly in men) and urological conditions such as benign prostatic hyperplasia (BPH), prostate cancer, urethral stricture, medical conditions such as constipation and diabetes mellitus, bed-rest, surgery and the use of certain medications.[3]

This article reviews the literature on drug-induced urinary retention and focuses on its incidence, the different classes of drugs that have been associated with it and, finally, options for its management and prevention.

A MEDLINE (via PubMed) search was done using the following search criteria: 'urinary retention' AND 'incidence'; 'drug-induced urinary retention'; 'bladder' AND 'innervation'; 'urinary retention' AND 'management'. Publications up until 31 December 2006 were included and only articles published in English were reviewed. Articles on *in vitro* data or non-human *in vivo* data were not con-

sidered in this review. The majority of papers that were available on MEDLINE considered acute urinary retention and its potential association with drug intake.

1. Incidence of Urinary Retention

Because of its sudden onset with clear symptoms, the incidence of acute urinary retention has been more widely studied than chronic urinary retention, particularly in men. Two large population-based studies in the US found an overall incidence in men of 4.5 per 1000 person-years (the Health Professionals Follow-up Study) and 6.8 per 1000 person-years (the Olmsted County Study).[4,5] The incidence of acute urinary retention among men in Europe was reported to be somewhat lower, with a range of 2.2–3.1 per 1000 person-years.[6-8] The differences in the incidence of acute urinary retention between the different geographic regions might reflect a true difference in incidence, but is more likely to be explained by differences in methodology such as case ascertainment (i.e. self-reporting vs medical records-based), different calendar time periods or potential selection bias. As BPH is one of the major risk factors for acute urinary retention, the incidence is much higher in men with BPH, with an incidence varying from 3.7 to 130 per 1000 person-years.[9]

Acute urinary retention is less common in women, and few data are available on the incidence and prevalence in this population group. The incidence of acute urinary retention in females has been estimated at around 0.07 per 1000 females.[10] It is most likely to occur in women following childbirth, especially in combination with epidural analgesia – the cumulative incidence of postpartum urinary retention ranges from 0.2% to 17.9% of all deliveries.[11,12] Apart from obstetric and gynaecological conditions, acute urinary retention in women can develop after surgery or secondary to cystitis and insufficient detrusor function. Neurogenic and psychogenic disorders might also be involved in its development in women.[13]

Although the association between the use of certain medications and the occurrence of acute urinary retention is well established, the association is poorly quantified.[14] Meigs et al.[4] studied risk factors for acute urinary retention in a general male population aged ≥45 years and found that the use of calcium channel antagonists and anticholinergic drugs doubled and tripled the risk of acute urinary retention, respectively. In an uncontrolled study,[15] all presumed aetiologies of acute urinary retention occurring in 310 men who were admitted to a teaching hospital during a 2-year period were studied and it was found that approximately 2% of cases of acute urinary retention could be attributed to the use of concomitant medication. Gatti et al.[16] reviewed all records of cases of urinary retention in children over a 6-year period. Of the 53 episodes of acute urinary retention, 13% could be attributed to the use of concomitant medication – it was noteworthy that 85% of the children with drug-related urinary retention were male. As children were the focus of this study, it is unlikely that BPH was the predisposing factor. According to the authors, the high incidence of drug-induced urinary retention in young boys might reflect the delicate autonomic balance between the bladder and the prostatic urethra.[16] Kurasawa et al.[17] studied the underlying causes of chronic urinary retention in 100 consecutive patients who were referred to a hospital from February 2002 to August 2004: 12% had chronic urinary retention attributable to the adverse effects of various concomitant medications, namely propiverine, amitriptyline, oxybutynin, eperisone and medications for the common cold.

2. Physiology of Micturition

The act of micturition follows a very complex mechanism. The lower urinary tract consists of the bladder and the urethra. The bladder serves as a reservoir for urine and expands as it fills. There are two sphincters (the internal and external urethral sphincters) in the urethral wall that prevent urine loss as the bladder fills. A variety of afferent and efferent neural pathways, reflexes and central and peripheral neurotransmitters are involved in urine storage and bladder emptying. Three nerves provide primary control of the bladder, namely the hypogastric nerve (sympathetic nervous system), the pelvic

nerve (parasympathetic nervous system) and the pudendal nerve (somatic nervous system). These nerves serve as lower motor neurons and are under the control of upper motor neurons in the brain stem and the cerebral cortex.

The storage phase of micturition is mainly mediated through stimulation of β_3-adrenergic receptors (sympathetic pathway), the α-adrenergic receptors of the urethral internal sphincter (sympathetic pathway) and the urethral external sphincter (somatic nervous system).[18-20] The external sphincter striated muscle is controlled by the neurons in Onuf's nucleus, located within the S2–4 sacral segments of the spinal cord.[21]

Stimulation of the β_3-receptors of the detrusor causes relaxation, whereas stimulation of the α_1-receptors of the internal sphincter causes constriction. The external sphincter consists of striated muscle and, like skeletal muscle, is under voluntary control. Sphincter motor neurons located in Onuf's nucleus send their axons into the pudendal nerve and stimulate the striated muscle to contract via the release of acetylcholine and binding to postjunctional nicotinic receptors. Both α-receptors and serotonin 5-HT_2 receptors are located in Onuf's nucleus and they facilitate the storage reflex.

During storage, the distension of the smooth muscle fibres and the urothelium evoke afferent activity. Myelinated Aδ sensory fibres respond to passive distension. Unmyelinated C-sensory fibres have a high mechanical threshold and respond to a variety of neurotransmitters. These neurotransmitters include adenosine triphosphate (ATP), tachykinins, nitric oxide and prostanoids (figure 1).[18,22] These neurotransmitters bind to specific receptors and stimulate or inhibit micturition. In normal urological conditions, afferent activity is stimulated mainly by the Aδ sensory fibres. In conditions such as overactive bladder or urinary tract infection, afferent activity is also generated by the C-sensory fibres, lowering the threshold for bladder contraction and provoking symptoms such as urgency, frequency and urinary incontinence.

The afferent impulses, stimulated during bladder filling, reach specific regions in the CNS involved in micturition control. In humans, these areas are mainly the pons, the periaqueductal grey and the prefrontal cortex. This central micturition control is in part mediated via central neurotransmitters such as serotonin and dopamine. The serotonergic activity facilitates urine storage by enhancing the sympathetic reflex pathway and inhibiting the parasympathetic voiding pathway. Dopaminergic pathways may exert both inhibitory and facilitatory effects on voiding. Dopamine D_1 receptors appear to have a role in suppressing bladder activity, whereas D_2 receptors appear to facilitate voiding.[18]

With the initiation of normal urination, urethral resistance decreases via relaxation of the internal and the external urethral sphincter, and a phasic contraction of the detrusor muscle empties the bladder. Bladder contraction in humans is mediated through stimulation of muscarinic receptors in the detrusor muscle (parasympathetic pathway). The detrusor smooth muscle contains both muscarinic M_2 and M_3 receptors. The principal receptors involved in bladder contraction are the M_3 receptors. Bladder contraction is caused by binding of acetylcholine to these receptors (figure 1).

3. Drugs that Have Been Associated with Urinary Retention

Numerous drugs have been associated with urinary retention. The association between concomitant drug use and acute urinary retention has received most attention in the medical literature, as the acute nature of its onset makes it relatively easy to study. Table I provides an overview of the different drug classes that have been associated with urinary retention. As micturition is such a complex mechanism, these drug classes all have different modes of action.

3.1 Drugs with Anticholinergic Activities

Acute urinary retention has been associated with the use of drugs that possess anticholinergic effects. This anticholinergic effect is caused by a blockade of the parasympathetic pathway, which can impair the contraction of the detrusor muscle. Numerous drugs have anticholinergic activities; they will be discussed in detail by therapeutic indication.

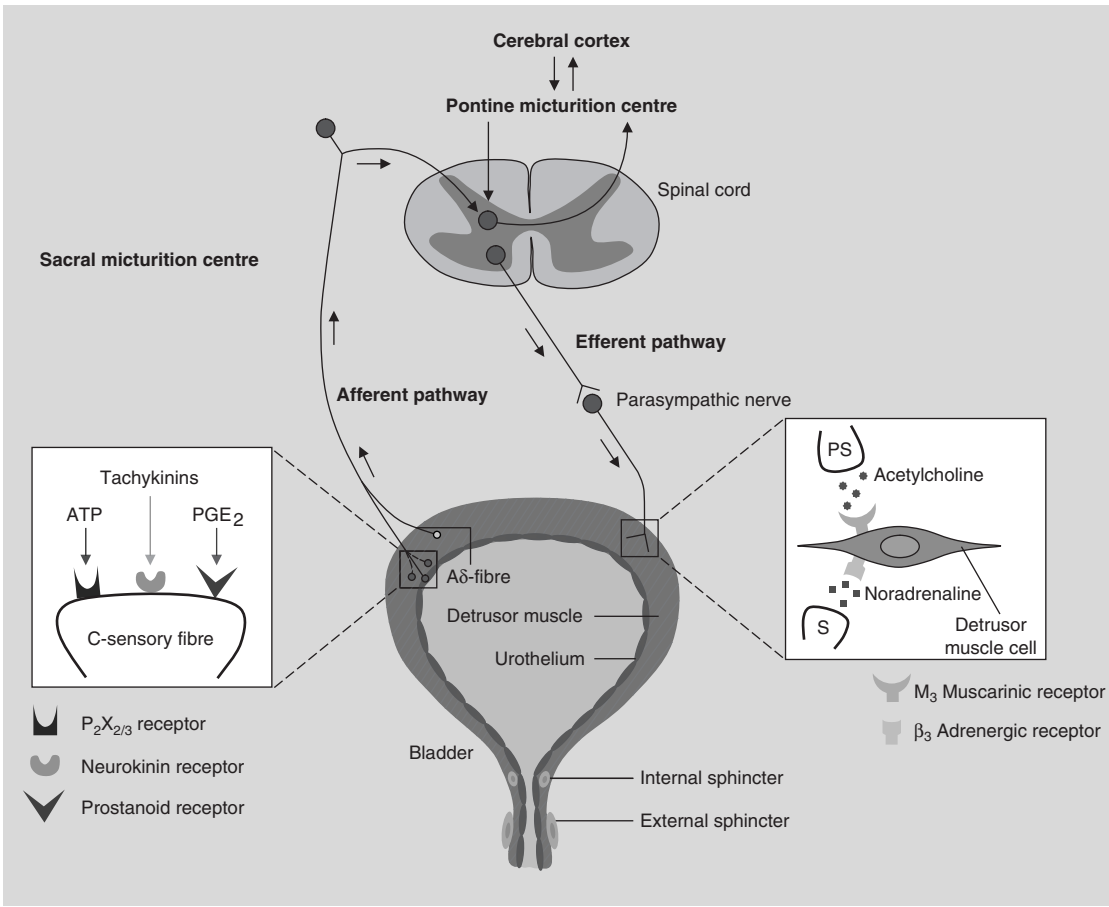

Fig. 1. The storage function of the bladder is controlled by the sympathetic nervous system inducing bladder relaxation by the binding of noradrenaline (norepinephrine) to the β_3-adrenergic receptors on the detrusor smooth muscle cells and internal sphincter contraction by stimulating α_1-receptors on the internal sphincter. The external sphincter is controlled by Onuf's nucleus in the sacral spinal cord (somatic nervous system). When the bladder fills, the distension of the detrusor smooth muscle cells and the urothelium evoke afferent activity. Myelinated Aδ sensory fibres respond to passive distension. Unmyelinated C-sensory fibres have a high mechanical threshold and respond to a variety of neurotransmitters, i.e. adenosine triphosphate (ATP), tachykinins, nitric oxide and prostanoids. These neurotransmitters bind to specific receptors on the C-sensory fibres. Under normal urological conditions, afferent activity is induced mainly by the myelinated Aδ sensory fibres, whereas in pathological conditions such as urinary tract infections or overactive bladder, afferent activity is also evoked by the C-sensory fibres. The afferent impulses reach the pontine micturition centre via passage through the spinal cord. The pontine micturition centre sends impulses via descending tracts to inhibit micturition via stimulation of the sympathetic and the somatic nervous system. When the bladder volume reaches a certain capacity, the impulses reach the cerebral cortex, and the desire to micturate is perceived. With the decision to void, both the internal and external sphincter relax and the bladder detrusor muscle contracts. Bladder contraction is a result of the binding of acetylcholine to muscarinic M_3 receptors on the detrusor smooth muscle cell: this bladder contraction is under control of the parasympathetic nervous system. **$P_2X_{2/3}$** = purinergic receptor; **PGE_2** = prostaglandin E_2; **PS** = parasympathetic pathway; **S** = sympathetic pathway.

3.1.1 Antipsychotic Drugs

Antipsychotic drugs possess varying levels of anticholinergic activity: phenothiazines (mainly chlorpromazine and thioridazine) and thioxanthenes (mainly chlorprotixen) have the strongest anticholinergic effects.[23,24] Among the atypical antipsychotics, anticholinergic adverse effects have been described for clozapine.[25] Acute urinary retention has been described for risperidone (in combination with fluoxetine) and ziprasidone. Both risperidone

Table I. Drugs associated with urinary retention

Drugs with anticholinergic effects
antipsychotics
tricyclic and tetracyclic antidepressants
class I antiarrhythmics
antispasmodics
antiparkinsonian agents
atropine
histamine H_1 receptor antagonists
anticholinergic drugs given for the treatment of COPD or asthma
anticholinergics for treatment of OAB in patients with bladder outlet obstruction
Analgesic drugs
α-Adrenoceptor agonists
NSAIDs
Benzodiazepines
Detrusor relaxants
Calcium channel antagonists
Antidepressants, excluding tricyclic antidepressants
Antiparkinsonian agents, excluding those agents with anticholinergic activity

COPD = chronic obstructive pulmonary disease; **OAB** = overactive bladder.

and ziprasidone are atypical antipsychotic agents with potent 5-HT_2 receptor and D_2 receptor antagonist effect. In addition, both risperidone and ziprasidone have a moderate affinity for adrenergic receptors. Urinary retention is the result of the central serotoninergic mechanism in combination with central D_2 blockade and peripheral stimulation of the α_1-receptors of the urinary tract.[26,27]

Although the association between the use of antipsychotic drugs and urinary retention has been described, particularly in combination with other drugs, this association is not straightforward.[27-32] Some cases and studies (both *in vitro* and *in vivo*) have reported on the occurrence of urinary incontinence as opposed to acute urinary retention in patients on antipsychotic treatment, namely involving the use of clozapine.[33-36] In addition, psychosis itself can be a direct cause of urinary incontinence. The mechanism behind the use of antipsychotic drugs and urinary incontinence is via the inhibition of the dopaminergic (central) and α-adrenergic (peripheral) receptors.[34-36] Antipsychotic drugs may thus stimulate as well as inhibit micturition.

As antipsychotic drugs are often given in combination with other drugs with activity on the CNS such as antidepressants or benzodiazepines, extra caution is warranted.[37] Antipsychotic drugs are metabolized via the cytochrome P450 (CYP) pathway, especially CYP 2D6, and this metabolism is inhibited by drugs such as selective serotonin receptor inhibitors (SSRIs), which may result in higher serum levels of the antipsychotic drugs and a higher risk of adverse effects.[27-30,38,39]

3.1.2 Class I Antiarrhythmic Drugs

Disopyramide is an antiarrhythmic agent used for the treatment of supraventricular and ventricular arrhythmias. Urinary retention is reported to occur in up to 2% of all treated patients, especially men. Disopyramide inhibits detrusor muscle contraction by its specific antagonistic effect on cholinergic receptors of the detrusor smooth muscle cells.[40]

Flecainide has also been associated with acute urinary retention but the exact mechanism for this is unclear. Since >80% of the drug is excreted unmetabolized in the urine, acute urinary retention could be caused by a local anaesthetic effect on the bladder mucosa or by an anticholinergic effect such as described for disopyramide.[41]

3.1.3 Antispasmodics

Antispasmodics, such as hyoscine butylbromide (scopolamine butylbromide), are prescribed for the treatment of abdominal pain with a spastic component, such as irritable bowel syndrome. They inhibit the parasympathetic controlled contraction of the smooth muscle cells of the gastrointestinal tract. This anticholinergic effect is not only restricted to the smooth muscle cells of the gastrointestinal system, but also involves the urogenital system, impairing the contraction of the bladder detrusor, which might result in voiding difficulties.

3.1.4 Antiparkinsonian Agents

Symptomatic pharmacotherapy of Parkinson's disease consists of anticholinergics, amantadine, monoamine oxidase B inhibitors, catechol-*O*-methyltransferase inhibitors, levodopa and dopamine agonists. The anticholinergic antiparkinsonian agents (e.g. biperiden and dexetimide) are the

oldest but their clinical use has been limited by their adverse reaction profiles and contraindications. Neuropsychiatric as well as anticholinergic adverse effects are clearly associated with the use of these drugs. These adverse effects limit their use in older patients. Anticholinergics for the treatment of Parkinson's disease are typically used in patients aged <70 years with disabling resting tremor and preserved cognitive function.[42-44]

The adverse effects of amantadine are much milder than for the anticholinergic drugs, but urinary retention has been reported, which might be associated with its anticholinergic effect.[44]

3.1.5 Atropine

Atropine is a classical anticholinergic drug with a variety of indications such as pre-medication prior to surgery to prevent hypersalivation and vomiting during recovery, and as stabilizing treatment for major atrioventricular rhythm disturbances. Atropine is also used to induce mydriasis for access to the eye fundus or to relieve symptoms of inflammatory processes of the eye such as uveitis or keratitis. Other anticholinergic drugs used in mydriatic eye drops are cyclopentolate, homatropine and tropicamide. Urinary retention has been described with both the systemic and topical use of atropine. It has been estimated that only 1–5% of the active drug in eye drops penetrates the eye, meaning that 80% of the active ingredient might reach the general circulation mainly via the tear drainage system. Elderly men are especially at risk, and it is advisable to avoid the simultaneous use of other anticholinergic drugs in these patient populations.[45]

3.1.6 Histamine H_1 Receptor Antagonists

Histamine H_1 receptor antagonists are used for the treatment of a variety of allergic disorders, namely urticaria and allergic rhinitis. Antihistamines are classified as first-generation H_1-receptor antagonists (diphenhydramine, chlorphenamine, hydroxyzine, doxepin and promethazine) and second-generation H_1-receptor antagonists (acrivastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine and mizolastine). The first-generation antihistamines cross the blood-brain barrier and may provoke sedation. In addition, these agents bind to the muscarinic receptors causing anticholinergic adverse effects, including urinary retention.[46] The second-generation antihistamines are much larger molecules and therefore do not pass the blood-brain barrier.[46-48] Although second-generation H_1 antagonists do not bind to muscarinic receptors and therefore do not have anticholinergic adverse effects, two cases of urinary retention in association with astemizole have been published in a report.[49] Urinary retention has not only been reported in association with systemic administration of antihistamines, but there is also the potential of urinary retention when these agents are topically administered.[50]

3.1.7 Anticholinergics Used for the Treatment of Chronic Airway Disease

Anticholinergic drugs act on muscarinic receptors causing bronchodilation and are used in the treatment of chronic obstructive pulmonary disease and asthma. The principal goals of bronchodilator therapy are to alleviate dyspnoea and respiratory symptoms and to improve exercise performance. In addition to bronchodilation, these agents also reduce mucus secretion.[51]

Currently, there are two types of anticholinergic agents on the market; short-acting (ipratropium and oxitropium) and long-acting (tiotropium). Both the short- and long-acting anticholinergic drugs are administered via inhalation.[52] Although the systemic effect is low, as these drugs are poorly absorbed, anticholinergic adverse effects have been described with the use of these drugs, mainly dry mouth. In addition, case reports, case series and clinical trials have reported on the occurrence of urinary retention or urinary outflow obstruction in association with short-acting and long-acting anticholinergic bronchodilators.[53-55] It should be noted that the incidence of urinary retention in the clinical trials with tiotropium bromide, the newest anticholinergic agent to be used as a bronchodilator, is probably underestimated, as patients with a history of bladder outflow obstruction were excluded from participation in the trials.[56]

3.1.8 Anticholinergics as Treatment of Overactive Bladder in Patients with Bladder Outlet Obstruction

Irritative lower urinary tract symptoms such as frequency, urgency and urinary incontinence may occur in up to 50% of patients with bladder outlet obstruction caused by BPH. Within BPH, patients have storage or voiding symptoms. In particular, storage symptoms impair the patient's quality of life, and treatment with an α-receptor antagonist in combination with an anticholinergic agent might be considered. Physicians are reluctant to prescribe anticholinergic agents in patients with BPH for fear of acute urinary retention. A recent systematic review[57] studied the efficacy and safety of anticholinergic drugs (propiverine or tolterodine) in patients with bladder outlet obstruction. Only four randomized controlled trials published in peer-reviewed journals were identified. In these trials, the incidence of acute urinary retention was not significantly higher for those patients treated with an anticholinergic agent in combination with an α_1-antagonist than in the control group of patients, who were treated with an α_1-receptor antagonist or placebo.[57]

Kaplan et al.[58] recently published the results from a randomized controlled trial on the efficacy and safety of tolterodine and tamsulosin (an α_1-receptor antagonist) for the treatment of lower urinary tract symptoms in patients with overactive bladder and BPH. A total of 879 patients were randomly assigned to treatment with placebo, tolterodine, tamsulosin or the combination of tolterodine and tamsulosin for 12 weeks. The overall incidence of acute urinary retention was low and no differences in incidence rate among the different treatment groups could be observed.[58]

Novara et al.[57] explained the safety of the anticholinergic agents in patients with overactive bladder by the fact that these drugs act mainly during the storage phase of the bladder by blocking the afferent activity, resulting in decreased urge feelings and an increased bladder capacity. During voiding, the action of these anticholinergic agents is reduced by a massive release of acetylcholine.

3.2 Antidepressants

Of the antidepressants associated with acute urinary retention, the agents more frequently associated are the older antidepressants, in particular the tricyclic antidepressants. However, case reports have also been published[28,39,59-65] on both urinary incontinence and urinary retention, in relation to the newer generations of antidepressants. These drugs are discussed separately below, as their mode of action on urinary function and the potential to precipitate acute urinary retention act via different mechanisms.

3.2.1 Tricyclic and Tetracyclic Antidepressant Agents

Tricyclic antidepressants are competitive antagonists of muscarinic acetylcholine receptors. The most common adverse effects of tricyclic antidepressants (dry mouth, blurred vision, constipation and urinary retention) are related to the anticholinergic activity of these drugs.[66,67] A systematic review on the benefits and risks of pharmacotherapy for dysthymia showed that patients treated with tricyclic antidepressants were more likely to report adverse drug reactions, including urinary retention, compared with placebo or SSRIs.[68]

Although tetracyclic antidepressant agents have a lower affinity for muscarinic receptors, thus suggesting fewer anticholinergic adverse effects, urinary retention with the use of these agents has also been described.[69]

3.2.2 Selective Serotonin Reuptake Inhibitors

A report on 299 cases of acute poisoning with the SSRI fluvoxamine was published in 1993.[63] Apart from symptoms such as drowsiness, tremor, nausea, vomiting, abdominal pain and bradycardia, anticholinergic effects including acute urinary retention were also reported. However, it should be noted that other agents – mainly benzodiazepines, antipsychotics and other antidepressants – were taken in approximately 80% of these cases of poisoning.[63] Similar to this report, the use of fluoxetine an SSRI in combination with other psychotropic drugs and/or benzodiazepines has been associated with urinary retention.[28,39]

In a recent case report, urinary retention in a patient taking the SSRI citalopram in combination with aripiprazole (an atypical antipsychotic drug) was reported.[59]

The mechanism by which the association between urinary retention and the use of SSRIs is explained as follows: in humans, serotonin is one of the neurotransmitters involved in the central control of micturition.[59] Serotonin facilitates urine storage by enhancing the sympathetic reflex pathway and inhibiting the parasympathetic voiding pathway.[18] In addition, Onuf's nucleus contains a high number of α-receptors and 5-HT_2 receptors. SSRIs inhibit the uptake of serotonin around the motor neurons of Onuf's nucleus, resulting in increased external sphincter activity.[60]

3.2.3 Selective Noradrenaline Reuptake Inhibitors

Reboxetine is a novel selective noradrenaline (norepinephrine) reuptake inhibitor with proven efficacy in a wide range of patients with major depressive disorders. Reboxetine is generally well tolerated, with a profile different to that of the tricyclic antidepressants and the SSRIs. Although reboxetine is devoid of anticholinergic effects, urinary hesitancy/retention has been reported in a small number of male patients. Urinary retention is linked to the peripheral noradrenergic activation of the α_1-adrenoceptors of the internal urethral sphincter and the α-adrenoceptors of Onuf's nucleus.[61,62]

3.3 Benzodiazepines

Urinary retention following use of benzodiazepines (clonazepam and diazepam) has been reported.[30,70,71] It is probably caused by muscle relaxation, thus micturition following the ingestion of benzodiazepines is impaired. In contrast, other authors have suggested that the anxiolytic and skeletal muscle-relaxing properties of benzodiazepines may be helpful in treating or preventing acute urinary retention.[72]

3.4 Analgesic Drugs

Overdistension of the bladder is an important risk factor for acute urinary retention, and is commonly encountered after an operation performed under general or regional anaesthesia. In the postoperative period, treatment of pain with opiates or opioid analogues decreases the sensation of bladder fullness by partially inhibiting the parasympathetic nerves that innervate the bladder.[73] In addition, they have been shown to increase the tonus of the sphincter of the urinary bladder via sympathetic overstimulation, which leads to increased resistance in the outflow tract of the bladder.[74] This, in combination with the use of concomitant therapy, results in acute urinary retention.

Observational studies have estimated that postoperative urinary retention occurs in 6–50% of patients.[75] The risk of acute urinary retention is associated with perioperative factors such as the type of anaesthesia used, the duration and location of surgery, postoperative use of opioid analgesia, and the administration of large volumes (>500 mL) of perioperative or postoperative intravenous fluid.[76] A recent systematic review[77] studied the occurrence of adverse effects (nausea, vomiting, sedation, pruritus and urinary retention) related to postoperative pain management. Three analgesic techniques were compared; intramuscular analgesia, patient-controlled analgesia and epidural analgesia. Overall, urinary retention occurred in 23% of all patients and frequency was the highest for epidural analgesia (29%).[77]

Urinary retention during the use of opioids or opioid analogues not only occurs after surgery but may also occur in patients during normal conditions, even when opioids are taken orally or sublingually.[74,78] Animal and human studies[79] have shown that intravenous morphine directly binds to spinal opioid receptors and causes total bladder relaxation rather than having targeted effects on the detrusor alone, as has been reported with epidural anaesthesia.[75]

3.5 α-Adrenoceptor Agonists

One of the indications for adrenergic agents is the treatment of postural hypotension. The adrenergic agents bind to receptors on the vascular wall and result in a higher tonus of the blood vessels. The

vascular wall has an abundance of α_{1B}-receptors, especially in the elderly, whereas the proximal urethra has an abundance of $\alpha_{1A/D}$-receptors. Non-selective adrenergic agents given for the treatment of postural hypotension not only bind to the α_{1B}-receptors on the vascular wall but also on the $\alpha_{1A/D}$-receptors of the internal sphincter of the urethra, causing a higher tonus of the internal sphincter. This higher tonus may exacerbate voiding difficulties and eventually lead to urinary retention.[80-82]

Adrenergic agents are also used for the symptomatic relief of rhinosinusitis because of their local decongestive effect on the nasal mucosa. Cold preparations often consist of a mixture of adrenergic agents in combination with anticholinergic antihistamines, which increase the risk of urinary retention. Particular caution is warranted with the use of these drugs as they are available as over-the-counter products.[83]

The use of 'ecstasy' (3, 4-methylenedioxymethamphetamine) has also been associated with urinary retention.[84,85] Ecstasy stimulates the release of the monoamine neurotransmitters (serotonin, noradrenaline and, to a lesser extent, dopamine). Noradrenaline is the predominant α-adrenergic neurotransmitter, and this α-adrenergic stimulation causes internal sphincter contraction, thus preventing voiding. This explains the urinary retention after ecstasy ingestion.

3.6 NSAIDs

Prostaglandins, especially prostaglandin E_2 (PGE_2), play an important role in genitourinary function. Prostaglandin synthesis in the bladder works via cyclo-oxygenase (COX)-2 and is up-regulated by a number of stimuli such as inflammation, trauma and over-distension. PGE_2 stimulates micturition by releasing tachykinins, which in turn initiate the micturition reflex by stimulating neurokinin receptors on afferent nerves and detrusor smooth muscle.[22] As NSAIDs have a direct effect on prostaglandin synthesis, they have been tested in clinical trials for the treatment of detrusor instability.[18,86] Gruenenfelder et al.[87] reported three cases of acute urinary retention that occurred within 1 week of starting COX-2 inhibitors. Our group studied the association between NSAIDs and acute urinary retention and found that the risk of acute urinary retention was doubled for current users of NSAIDs and that the risk increased with higher dosages.[88]

3.7 Detrusor Relaxants

In theory, all drugs that are given for the treatment of detrusor overactivity could also induce urinary retention, especially in high-risk patients. Drugs that are currently registered for the treatment of overactive bladder include anticholinergic drugs, musculotropic agents, tricyclic antidepressants, NSAIDs, calcium channel antagonists, estrogen and botulinum toxin A.[89-92] Clinical trials with some of these agents have shown that the incidence of urinary retention was higher in the treatment groups compared with groups receiving placebo.[90]

3.8 Calcium Channel Antagonists

In the Health Professionals cohort study, the risk for acute urinary retention was 2.2-fold higher in patients using calcium channel antagonists than in non-users.[4,83] In addition, several cases of urinary retention after the use of calcium channel antagonists have been reported.[93] Calcium channel antagonists reduce smooth muscle contractility in the bladder via the inhibition of calcium influx, and can occasionally cause urinary retention. Based on this mode of action, flunarizine, a calcium channel antagonist with direct smooth muscle relaxant effect, is used for the treatment of urinary incontinence.[90]

3.9 Antiparkinsonian Agents without Anticholinergic Activity

Studies have shown that, irrespective of the type of antiparkinsonian treatment, lower urinary tract symptoms (LUTS) – mainly nocturia, frequency and urgency – occur in approximately 30% of patients with Parkinson's disease. The cause may be decreased inhibitory innervation of the micturition centre.

These irritative LUTS symptoms are relieved by administration of selective D_1 receptor agonists, as

they reduce the detrusor overactivity, whereas D_2 receptor agonists, e.g. pramipeole and agonists of both and D_1- and D_2-type receptors reduce the volume threshold of micturition. The inhibitory effect on the detrusor by D_1 receptor agonists, however, might result in urinary retention.[94]

In one case report, levodopa, which acts via conversion to dopamine, has been associated with urinary retention, but the exact mechanism is unclear.[95]

3.10 Other Drugs

There have been anecdotal reports of urinary retention with a variety of different drug treatments. Because of the specific conditions surrounding the event, the low incidence, and the often unclear mechanism, they are only listed in this review. This does not imply that further research on the potential mechanism and the frequency of occurrence would not be warranted.

Sensory neuropathy resulting in urinary retention has been reported for intrathecal chemotherapy with methotrexate, cytosine arabinoside and prednisolone, and chemotherapy with oxaliplatin or cisplatin and etoposide.[96-98]

In addition, urinary retention has been associated with the use of the following drugs for the following specific conditions:[4,92,99-110]

- topical administration of imiquimod 5% cream for the treatment of genital warts;
- topical administration of isotretinoin 1 mg/kg daily for 3 months for the treatment of severe acne;
- urethral inflammation from a vaginal contraceptive suppository containing the spermicide nonoxinol-9;
- intrathecal baclofen for spastic hypertonia;
- gonadotropin-releasing hormone for the treatment of leiomyomata uteri;
- anti-dopaminergic antiemetic agents;
- carbamazepine for the treatment of neuropathic pain;
- dantrolene for treatment of diffuse spasticity;
- theophylline for the treatment of chronic obstructive pulmonary disease;
- levonantradol for the treatment of chemotherapy-induced emesis.

It is also interesting to note that the Health Professional cohort study reported a 2-fold increased risk of acute urinary retention in patients using β-receptor antagonists.[4]

4. Management of Drug-Induced Urinary Retention

Acute urinary retention is a painful event requiring immediate intervention. Treatment consists of urinary catheterization with the eventual need for additional pharmacotherapy or, in those patients with BPH, surgery (prostatectomy). It is evident that if the association between the (acute) urinary retention and the use of concomitant medication is unequivocal, drug discontinuation or eventually dose reduction should be considered.

4.1 Urinary Catheterization

The initial management of acute urinary retention is prompt relief of retention and pain by catheterization of the bladder. In most cases, this catheterization is conducted via the urethra because it is quick and can be easily performed by all healthcare professionals. An alternative to urethral catheterization is suprapubic catheterization, which might reduce the risk of urinary tract infections. The duration of catheterization, the need for hospital admission and eventual surgery will depend on the type of underlying co-morbidity, e.g. the presence of BPH.

4.2 Pharmacotherapy

4.2.1 α-Adrenoceptor Antagonists and 5α-Reductase Inhibitors for the Treatment of Benign Prostatic Hyperplasia

Urinary retention, even when drug-induced, can be one of the first signs of BPH. In these patients, treatment with α-receptor antagonists and 5-α reductase inhibitors can be used to relieve LUTS suggestive of BPH, and in the longer term to prevent recurrence of acute urinary retention. Data from randomized controlled trials have shown that α-receptor antagonists in combination with a 5α-re-

ductase inhibitor not only improve the urinary symptoms but also reduce the risk of acute urinary retention in patients with BPH.[111]

4.2.2 Cholinesterase Inhibitors

Distigmine bromide is a long-acting cholinesterase inhibitor that enhances detrusor contractility by inactivating cholinesterase and thus increasing the action of acetylcholine. In the past it has been used for the treatment of urinary retention (e.g. post-surgery). However, due to its poor safety profile, i.e. the potential for cholinergic crisis, it is no longer used.[112]

4.2.3 Cholinergic Agents

Peripheral cholinergic agents, such as bethanechol chloride, have been used for the treatment of urinary hesitancy caused by the peripheral anticholinergic adverse effects of other concomitant drugs.[67] A recent systematic review studied the use of cholinergic agents (bethanechol or carbachol) or cholinesterase inhibitors for the treatment of urinary bladder underactivity and found little evidence to support the use of these drugs for this medical condition.[113]

4.2.4 Morphine Antidotes

Naloxone, an antidote to morphine and its analogues, has been tested for the treatment of urinary retention after epidural and intrathecal anaesthesia. Although naloxone was found to be very effective in reversing urinary retention, it also reversed the analgesic effect and thus is not indicated for the treatment of postoperative urinary retention.[114,115] Nalbuphine is another antidote of morphine and there is one case report of its use in the treatment of postoperative urinary retention.[116] Nalbuphine was shown to be effective in reversing the urinary retention with sustained analgesic effect; however this should be investigated further in randomized controlled trials.

5. Prevention of Drug-Induced Urinary Retention

When prescribing a drug to a patient, a thorough knowledge of its mode of action, adverse effects and potential drug interactions is important in preventing drug-induced urinary retention. In high-risk populations in particular, such as elderly men, a thorough anamnesis and physical examination for identification of risk factors, a careful review of the use of other medications, and use of the lowest effective dose might reduce the risk of developing urinary retention.

In the field of postoperative urinary retention, research has been done to study the effects of preventive measures. Systemic opioids are regarded as the gold standard in the relief of severe postoperative pain, but morphine administration after surgery carries a high risk of adverse effects such as nausea, vomiting, pruritus, urinary retention and apnoea.[117] The multimodal or 'balanced' analgesic approach, developed by Kehlet and Dahl,[118] suggests that the use of small doses of opioids in combination with non-opioid analgesic drugs may not only improve postoperative pain control but also lower analgesic doses, and consequently reduce the number of adverse events. This approach has been tested in numerous randomized clinical trials combining opioids with other types of analgesic drugs such as paracetamol (acetaminophen) and NSAIDs.[119-122] Although most of the trials demonstrated a significant opioid-sparing effect, the prevention of opioid-related adverse events yields contradictory results. The meta-analysis from Remy et al.[119] indeed showed that combining paracetamol with morphine after surgery significantly reduced the morphine consumption, but with no effect on the incidence of morphine-related effects, including urinary retention. Another trial studied the effect of gabapentin as premedication for spinal surgery in 50 patients and showed that both morphine consumption and morphine-related adverse effects, i.e. vomiting and urinary retention, were reduced in those patients treated with gabapentin.[120]

In a meta-analysis, Marret et al.[121] studied whether adding NSAIDs to the conventional patient-controlled analgesia consisting of opioid-like drugs reduced the incidence of morphine-related adverse effects. The study showed that the incidence of nausea and vomiting was decreased in combination with NSAIDs but urinary retention, as well as

pruritus and respiratory depression, was not significantly reduced by NSAIDs. A similar study was conducted by Romsing et al.[122] who studied the reduction of opioid-related adverse events using opioid-sparing analgesia with COX-2 inhibitors. This study showed a reduction of approximately 35% in opioid consumption and a reduction in vomiting, constipation and pruritus, but no reduction in acute urinary retention. However, it should be noted that reporting of adverse events was not always properly documented in the clinical trials.

Although benzodiazepines by themselves might provoke acute urinary retention, they have been tested for the prevention of postoperative acute urinary retention, through relaxation of reflectory muscular spasms, with disappointing results.[72,123,124]

In case studies, α_{1A}-receptor antagonists, commonly used for the treatment of lower urinary tract symptoms suggestive of BPH, have been used to prevent or treat reboxetine-induced urinary hesitancy.[62,125] The results were promising, but the efficacy of these drugs was not tested by means of a randomized controlled trial.

6. Conclusion

Because of the complex micturition mechanism, the potential of drug-induced urinary retention is substantial, and it can be induced via different pathways. Although the occurrence of urinary retention in association with the use of drugs is generally well accepted, this association is poorly quantified in the scientific literature. The information on drug-induced urinary retention originates mainly from case reports, case series, a few cohort studies and, for the newer registered drugs, from clinical trials. We would like to plead for a better reporting of drug-induced urinary retention in observational research and clinical trials, even for drugs that have long been associated with it, in order to derive an accurate estimate of the proportion of urinary retention that is drug induced.

The elderly male is particularly at risk for urinary retention, first of all because of the high prevalence of BPH, probably the main risk factor for its occurrence in men. Secondly, the drugs most frequently associated with urinary retention are prescribed to the elderly population, often in combination with other drugs. And finally, elderly patients often have other co-morbidities such as constipation, lack of mobility, diabetes mellitus, dementia and malignancy which further facilitate the development of urinary retention. Also, patients requiring anaesthesia in the perioperative or postoperative setting are at risk of acute episodes, as urinary retention occurs in up to 50% of these patients. Current research in this field focuses on the addition of non-opioid analgesics to standard postoperative analgesia with the ultimate goal of reducing both opioid consumption and the related adverse effects of opioids.

In this review, we have aimed to provide a complete and comprehensive overview of drug-induced urinary retention and the underlying mechanisms. We believe that a thorough knowledge and understanding of the micturition pathway and the drugs that affect micturition might be the best tool in preventing drug-induced urinary retention.

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