The Role of Flavoxate in Dysuria

Reviewed by:
Dr. Atul Goswamy
MBBS , MS - General Surgery, M.Ch – Urology (AIIMS)
Chief and Senior Consultant
Dept of Urology & Uro Oncology & Renal Transplant
Sri Balaji Action Medical Institute And Action Cancer Hospital, New Delhi

Dysuria: Clinical Insights

Dysuria is defined as pain, burning, or discomfort on urination which occurs more frequently due to UTI. It is more common in women than in men; more often in younger women, due to greater frequency of sexual activity. In men, older individuals are more likely to have dysuria because of an increased incidence of prostatic hyperplasia with accompanying inflammation and infection. Dysuria most often indicates infection or inflammation of the bladder and/or urethra. Other common causes of dysuria include prostatitis and mechanical irritation of the urethra in men, and urethrotrigonitis and vaginitis in women. Dysuria can also result from malformations of the genitourinary tract, neoplasms, neurogenic conditions, trauma, hormonal conditions, interstitial cystitis, and psychogenic disorders (Box 1).[1]

Causes of Dysuria

Infection and Inflammation

Infection is the most common cause of dysuria and presents as cystitis, prostatitis, pyelonephritis, or urethritis, depending on the area of the urogenital tract that is most affected. Evidence suggested that about two thirds of culture-proven UTIs are caused by *Escherichia coli*. Other less frequent pathogens include *Staphylococcus epidermidis*, *Proteus mirabilis*, *Staphylococcus aureus*, *Enterococcus species*, and Klebsiella species. Abnormalities in urinary anatomy or function allow more unusual, recurrent, and persistent infections. Such abnormalities include bladder diverticula, renal cysts, urethral strictures, benign prostatic hyperplasia (BPH), and neurogenic bladder. Rarely, bacteria may spread hematogenously, causing pyelonephritis. The urethra is infected preferentially by organisms such as *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Other pathogens include *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, and herpes simplex virus. Rare infectious causes of dysuria include adenovirus, herpesvirus, mumps virus, and the tropical parasite *Schistosoma haematobium*.[1]

Non-Infectious Causes

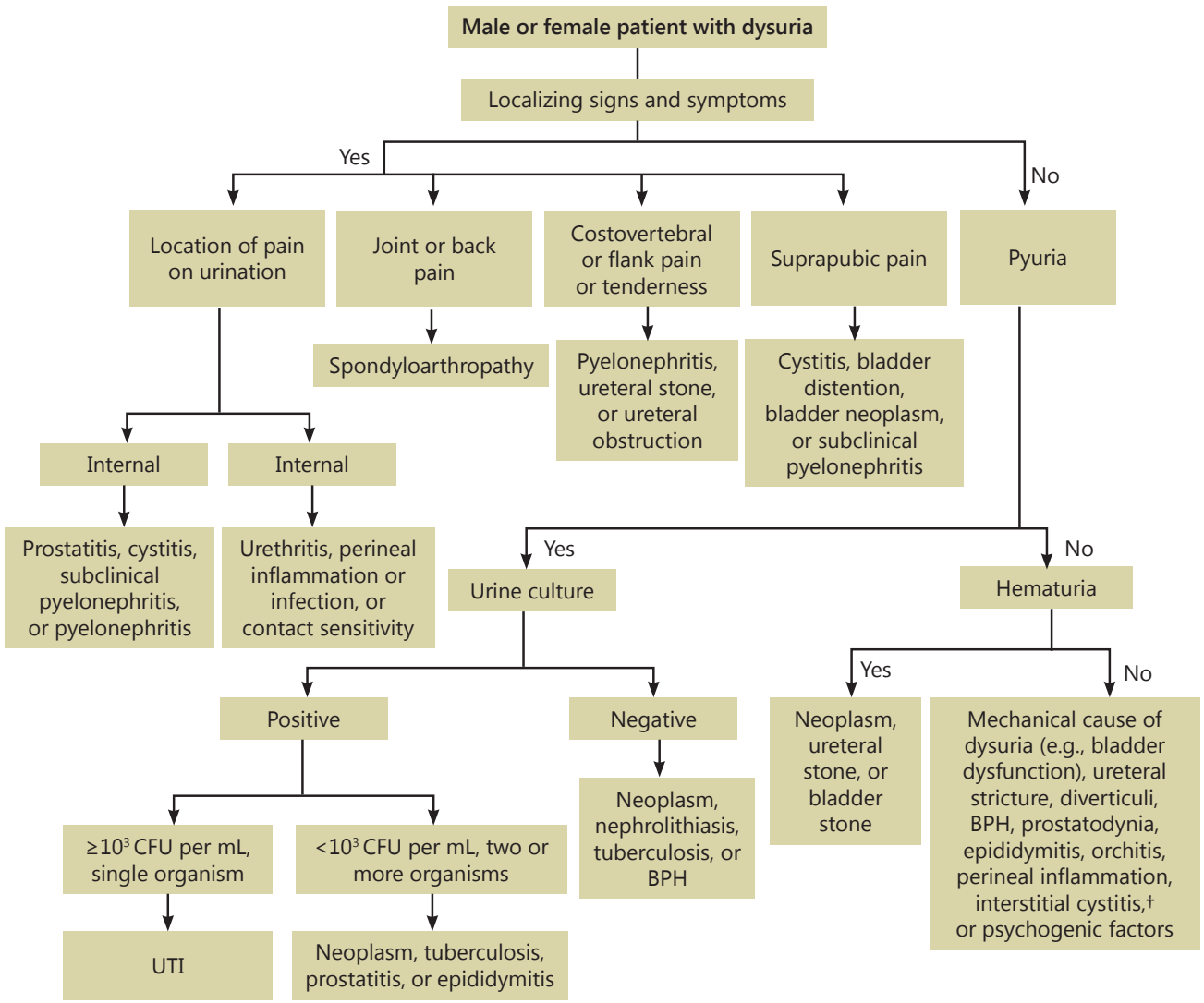
There are varied non-infectious causes of dysuria in men and women. In postmenopausal women, the marked reduction in endogenous estrogen can lead to lower urinary tract dysfunction. Atrophy, dryness, and, occasionally, inflammation of the vaginal epithelium contribute to urinary symptoms such as dysuria, frequency, and urgency. Other noninfectious causes of dysuria in women include the urethral syndrome, urethral trauma during sexual intercourse, and sensitivity to scented creams, sprays, soaps, or toilet paper. In older men, dysuria may be caused by inflammation of the distended urethral mucosa without

Box 1: Causes of Dysuria

- Infections: pyelonephritis, cystitis, prostatitis, urethritis, cervicitis, epididymo-orchitis, vulvovaginitis
- Hormonal conditions: hypoestrogenism, endometriosis
- Malformations: bladder neck obstruction (e.g., benign prostatic hyperplasia), urethral strictures or diverticula
- Neoplasms: renal cell tumor; bladder, prostate, vaginal/vulvar, and penile cancers
- Inflammatory conditions: spondyloarthropathies, drug side effects, autoimmune disorders
- Trauma: catheter placement, honeymoon cystitis
- Psychogenic conditions: somatization disorder, major depression, stress disorders or anxiety, hysteria

Source: Bremnor JD, Sadovsky R. Evaluation of dysuria in adults. *Am Fam Physician*. 2002;65(8):1589-96.

Figure 1: An algorithm for the evaluation of patients with acute dysuria



†-A minority of patients with interstitial cystitis have hematuria.

Source: Bremnor JD, Sadovsky R. Evaluation of dysuria in adults. *Am Fam Physician*. 2002;65(8):1589-96.

superimposed infection. Obstruction and dysuria can also occur because of strictures caused by gonococcal urethritis or because of urethral instrumentation or surgery. In both sexes, dysuria may be part of the clinical presentation of renal calculi and neoplasms of the bladder and renal tract. Furthermore, spondyloarthropathies can cause a general inflammatory state, including inflammation of the urothelium,that results in dysuria.[1]

Evaluation in Cases of Dysuria

A comprehensive history and physical examination can often reveal the cause of dysuria. The physical examination, especially when complicated UTI is a consideration, should include vital signs, evaluation for costovertebral angle pain, palpation for abdominal mass or tenderness, and inspection for dermatologic conditions and acute joint effusions. Furthermore, urinalysis is the most useful test in a patient with dysuria; most studies have used dipstick urinalysis. Evidence suggested that women with symptoms suggestive of a UTI have demonstrated that the presence of nitrites is highly predictive of a positive culture; dipstick showing more than trace leukocytes is nearly as predictive; and the presence of both is almost conclusive.[2]

Any patient with risk factors for a complicated UTI or whose symptoms do not respond to initial treatment should have a

urine culture and sensitivity analysis. Patients with suspected pyelonephritis should have renal function assessed with serum creatinine measurement, and electrolyte levels should be measured if there is substantial nausea and vomiting. Blood cultures are usually not necessary, but can be obtained in patients with high fever or risk of infectious complications. Urine cultures and both urethral and vaginal smears and cultures can help to identify sites of infection and causative agents. Coliform organisms, notably Escherichia coli, are the most common pathogens in urinary tract infection.[2]

Imaging is not necessary in most patients with dysuria, although it may be indicated in patients with a complicated UTI, a suspected anatomic anomaly (e.g., abnormal voiding, positive family history of genitourinary anomalies), obstruction or abscess, relapsing infection, or hematuria.[2]

An algorithm for the evaluation of patients with acute dysuria is depicted in Figure 1.[1]

Role of Flavoxate in UTI and Dysuria

In UTIs, symptoms frequently include some combination of dysuria, urinary frequency, urgency, hematuria, and suprapubic pain; all of which needs to be considered for optimal patient outcomes. Use of an anticholinergic drug may be considered for these bothersome LUTS in absence of significant post-void residual (PVR) urine volumes. However, there are concerns that these drugs may predispose to urinary retention, may be associated with anti-cholinergic side effects, and may cause drug-drug interactions, thus warranting their cautious use in carefully selected patients (Table 1). In such settings, the non-anticholinergic antispasmodics drug flavoxate, free from such concerns related to use of anticholinergics, is an obvious choice to alleviate the symptomatic burden of UTIs.[3,4]

Flavoxate is a smooth muscle relaxant with wide range of indications widely used to treat urgency and urge incontinence. In patients suffering from painful conditions of the lower urinary tract arising from inflammation and/or infection or from spasm following diagnostic or therapeutic procedures, flavoxate was shown to result in statistically significant improvement in frequency and suprapubic pain, and marked relief was afforded in dysuria, hesitancy and burning.[5]

Flavoxate possesses a direct Ca^{2+} antagonistic action on voltage-dependent L-type Ca^{2+} currents in human detrusor in addition to the actions as a modulator of the micturition centre in CNS. Thus, it seems plausible that the Ca^{2+} antagonistic actions of flavoxate are related to its spasmolytic effects on human urinary bladder.[6]

Flavoxate has been used to treat several urogenital tract disorders regardless of the etiology, though its main

Table 1: Incidence of adverse events associated with anticholinergic agents

Adverse event	Flavoxate[a]	Darifenacin	Solifenacin	Oxybutynin[b]	Tolterodine	Trospium
Dry mouth	*	20.2%–35.3%	10.9%–27.6%	29%–61%	23%	20.1%
Constipation	*	14.8%–21.3%	5.4%–13.4%	7%–13%	6%	9.6%
Upper abdominal pain	No report	2.4%–3.9%	1.2%–1.9%	<5	4%	1.5%
Dyspepsia	*	2.7%–8.4%	1.4%–3.9%	5%–7%	3%	1.2%
Nausea	*	1.5%–2.7%	1.7%–3.3%	2%–9%	*	>0.5%
Diarrhea	*	0.9%–2.1%	No report	7%–9%	*	No report
Urinary retention	*	No report	1.4%	<5%	No report	1.2%
Urinary tract infection	No report	4.5%–4.7%	2.8%–4.8%	5%	1%	1.2%
Vertigo	*	1.3%–2.1%	1.9%	4%–6%	2%	No report
Blurred vision	*	>1%	3.8%–4.8%	1%–8%	1%	>0.5%
Drowsiness	*	0.9%–2.1%	1.0%–2.1%	2%–12%	3%	1.9%
Headache	*	No report	No report	6%–10%	6%	4.2%
Dry eyes	*	1.5%–2.1%	0.3%–1.6%	3%–6%	3%	No report

[a/*] Incidence not defined. [b]Oxybutynin transdermal system adverse events also include local reactions (i.e., erythema, pruritus, rash, vesicles, or macules at the application site).

Source: Hesch K. *Proc (Bayl Univ Med Cent)* 2007;20(3):307–314.

indications have been Overactive Bladder (OAB) and urge symptomatology. This rationale could be supported by the finding that flavoxate was found to increase bladder capacity significantly, without increasing the end-residual urine volume, and required no adjustment for renal or hepatic dysfunction.[7,8] Additionally, the presence of phosphodiesterase enzymes in the prostate and the detrusor muscle of the bladder also seem to validate application of flavoxate owing to its phosphodiesterase inhibitory effects; moreover, flavoxate has local anaesthetic and analgesic action as well. Such proposed favorable use of flavoxate has indeed been shown in clinical studies also. Favourable and efficacious profile of flavoxate was corroborated by a drug utilization observation study of 1800 patients. In this study, a subgroup of 618 patients without UTI or BPH, who were treated with flavoxate only, showed a reduction of dysuria (37%), nocturia (53%), and both daytime (61%) and night-time urge (69%).[8] In another study, flavoxate was found to completely cure the symptoms of urgency/incontinence in 67% patients with urgency/incontinence of various types; patients received 200 mg drug three times daily, orally, for 2 weeks. Flavoxate was also effective in 77.4% of patients refractory to previous anticholinergic treatment.[7] Likewise, similar clinical evidence exists to support the safety of flavoxate. While Gu *et al*, in their study, documented that adverse events occurred only in 1.3% patients with urgency and urge incontinence treated with flavoxate; the drug trended to be superior even in comparative studies.[7] Flavoxate may hence be used in patients with urgency/incontinence of various causes, who do not achieve symptom relief and QOL improvement with conservative methods.

Conclusion

Dysuria most often indicates infection or inflammation of the bladder and/or urethra. It is characterized by the sensation of pain, burning, or discomfort on urination. Although dysuria may be caused by anything that leads to inflammation of the urethal mucosa, it is most often the result of urinary tract infection. In younger patients, the infectious agent is usually a sexually transmitted organism such as *Chlamydia trachomatis*. In patients over 35 years of age, coliform bacteria predominate. Infection in older men most often occurs as a result of urinary stasis secondary to benign prostatic hyperplasia.

Flavoxate hydrochloride is an antispasmodic agent which exerts an inhibition of the phosphodiesterases, a moderate calcium antagonistic activity, and a local anesthetic effect. Flavoxate treatment was associated with a significant improvement in different low urinary tract symptoms, such as diurnal and night frequency, urgency and urinary incontinence, suprapubic pain, dysuria, hesitancy and burning. The minimal side effects and high tolerability of flavoxate make it worthy of consideration for the treatment of several clinical urogynecological conditions.

References

1. Bremnor JD, Sadovsky R. Evaluation of dysuria in adults. *Am Fam Physician*. 2002;65(8):1589-96.
2. Michels TC, Sands JE. Dysuria: Evaluation and Differential Diagnosis in Adults. *Am Fam Physician*. 2015;92(9):778-86.
3. Roxburgh C, Cook J, Dublin N. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. *Cochrane Database Syst Rev.* 2007;(3):CD003190.
4. Ruffmann R, Sartani A. Flavoxate, a drug with smooth muscle relaxing activity. *Drugs Exp Clin Res.* 1987;13(1):57-62.
5. Zor M, Aydur E, Dmochowski RR. Flavoxate in urogynecology: an old drug revisited. *Int Urogynecol J*. 2014.
6. Tomoda T, Aishima M, Takano N, *et al*. The effects of flavoxate hydrochloride on voltage-dependent L-type Ca2+ currents in human urinary bladder. *Br J Pharmacol*. 2005;146(1):25-32.
7. Gu FL, Reng ZY, Shang GZ. Treatment of urgency and urge incontinence with flavoxate in the People's Republic of China. *J Int Med Res*. 1987;15(5):312-8.
8. Fehrmann-Zumpe P, Karbe K, Blessman G. Using flavoxate as primary medication for patients suffering from urge symptomatology. *Int Urogynecol J Pelvic Floor Dysfunct.* 1999;10(2):91-5