Irritative voiding symptoms, urinary urgency, frequency, nocturia, painful voiding, bladder discomfort or stranguria, are to the urinary tract much as a cough is to the pulmonary system, i.e., they are a nonspecific manifestation of multiple potential underlying causes. Similar to the lungs, the urinary bladder responds to a spectrum of pathologic processes with a limited repertoire of symptoms. Irritative symptoms of the lower urinary tract generally refer to urinary urgency, frequency, nocturia, painful voiding, bladder discomfort or stranguria. An Internet-based questionnaire found that 20-30% of adults >40 years reported symptoms of urgency, frequency, nocturia or urge incontinence. The study also noted that 5% of men and 8% of women reported bladder pain; painful urination was found in 3% of adults. In addition, patients with the most severe lower urinary tract symptoms (LUTS) had the greatest degree of bother, highest rates of clinical anxiety or depression, and the lowest quality-of-life.

LUTS are associated with lower urinary tract dysfunction. They can also indicate pathologies other than lower urinary tract dysfunction, such as urinary tract infection (UTI). Many patients with indwelling catheter experience catheter cramp. Irritation of the trigone causes detrusor contractions, known as bladder spasms, in these patients. Bladder spasms are a distressing complication for the patient. Placement of a ureteral stent after ureteroscopy is a common practice in urology. It has been reported that 38-80% of patients experience stent-related symptoms such as flank pain, lower abdominal discomfort, urinary urgency, urinary frequency, infection.

Anticholinergic medications provide useful beneficial symptomatic management in these patients.

**ANTICHOLINERGICS**

The anticholinergic/antispasmodic drugs are used to relieve cramps or spasms of the bladder and to reduce irritative voiding symptoms. Anticholinergic drugs reduce detrusor contractions by blocking antimuscarinic receptors in the detrusor. Since, muscarinic receptors are found in many different organs, urinary antispasmodics are associated with adverse anticholinergic effects, such as blurred vision, dry mouth, constipation, urinary retention, and central nervous system effects such as dizziness, somnolence and headaches. The elderly, so also the children, are usually more sensitive to these effects of anticholinergics.

**Flavoxate:** A tertiary-amine antimuscarinic, flavoxate is used for its antispasmodic properties in the symptomatic treatment of many urological conditions including overactive bladder and incontinence. Randomized studies and one Cochrane review have found flavoxate to be no better than placebo for urge incontinence. Given the lack of demonstrated effect of flavoxate in placebo-controlled studies it is
difficult to recommend its use and it is definitely not a first-line treatment. Bilateral acute angle closure glaucoma following flavoxate administration has been reported.\textsuperscript{11}

Briggs and associates reported essentially no effect of flavoxate in elderly patients with detrusor hyperreflexia.\textsuperscript{12}

**Oxybutynin:** Oxybutynin is a tertiary-amine with anticholinergic, antispasmodic and local anesthetic properties.\textsuperscript{13} Its usefulness is however limited by classic antimuscarinic side effects. Dry mouth is the most common and bothersome complaint, followed by constipation, blurred vision, dry eyes, urinary retention and drowsiness. These adverse effects, particularly dry mouth, are often severe enough to cause poor patient compliance, suboptimal dosing and even drug discontinuation.\textsuperscript{14}

The mean pharmacokinetic parameters (i.e., $C_{\text{max}}$ and AUC) of oxybutynin may be altered when co-administered with antibiotics like macrolides (erythromycin, clarithromycin). These drugs should therefore be used together with caution.\textsuperscript{15}

Oxybutynin was no better than placebo in patients with bladder spasm after transurethral surgery\textsuperscript{16} or for the treatment of incontinence in the presence of detrusor instability in elderly institutionalized people.\textsuperscript{17} Clinically, oxybutynin appears more potent in causing dry mouth than in inhibiting detrusor instability.\textsuperscript{14}

**ROLE OF PHENAZOPYRIDINE**

Phenazopyridine hydrochloride is an azo dye with local analgesic and anesthetic effects on the urinary tract.\textsuperscript{18} Chemically, phenazopyridine is 2,6-Pyridinediamine, 3-(phenylazo), monohydrochloride.\textsuperscript{19}

It is used as a urinary tract antiseptic and analgesic as brief adjuvant therapy for treatment of UTI. Additionally, the drug is used for many urologic problems involving dysuria.\textsuperscript{20}

**Clinical Pharmacology**

The exact mechanism of action of phenazopyridine hydrochloride is not known. It is excreted in the urine, where it exerts a topical analgesic effect on the mucosa of the urinary tract. This action helps to relieve pain, burning, urgency and frequency. Phenazopyridine has no antimicrobial actions.

Phenazopyridine exerts its clinical effect in conditions of urinary bladder hypersensitivity by direct inhibition of the mechanosensitive A$\delta$ fibers as demonstrated by Aizawa et al in their study. They evaluated the effect of phenazopyridine on afferent nerve activity by direct measurement of both A$\delta$- and C-fibers, and compared the outcome with the effects of a local anesthetic (lidocaine) and of an analgesic (acetaminophen). Intravenous administration of phenazopyridine was found to significantly decrease dose-dependently only the A$\delta$-fiber but not the C-fiber activity. Acetaminophen significantly decreased only A$\delta$-fiber activity, but it was not dose-dependently completely. Lidocaine inhibited both the A$\delta$- and C-fiber activities.\textsuperscript{21} Table 1 describes the salient pharmacokinetic properties of phenazopyridine.

**Phenazopyridine Efficacy: Clinical Evidence**

Phenazopyridine hydrochloride acts as a topical analgesic on the mucosal lining of the urinary tract and thus relieves pain, burning, urgency and frequency.\textsuperscript{19}

- Phenazopyridine relieves symptoms of urogenital infections: A study was done on 118 cases of urogenital infections with symptoms of pain on urination, burning, frequency and nocturia. The patients were administered phenazopyridine 500 mg in dose of two tablets thrice-daily. In 65 (55.1%) cases, all the characteristic symptoms of urogenital infections were relieved: Pain on urination was alleviated or abolished in 95.3%; burning on urination was relieved in 93.6%; frequency decreased in 85%, nocturia was eliminated or reduced in 83.7%, with reduction the organized sediment. In the remaining 53 cases, symptomatic relief was also observed in all but a few, although, there was no concomitant reduction in the organized urinary sediment. No toxic effects from phenazopyridine were observed during the two weeks of its administration.\textsuperscript{25}

**Table 1. Pharmacokinetics: Salient Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>7.35 hours.\textsuperscript{22}</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mainly metabolized by hydroxylation;\textsuperscript{23} the extent of azo bond cleavage is low. 5-hydroxyl PAP is the major metabolite (48.3% of the dose).\textsuperscript{24}</td>
</tr>
<tr>
<td>Excretion</td>
<td>Rapidly excreted by the kidneys directly into the urine (65% of the drug is excreted unchanged into the urine); about 40% is excreted in the bile.\textsuperscript{23} Major urinary metabolites: 4-acetylamino-phenol (NAPA) followed in order by 5,4′-dihydroxy-PAP, 5-hydroxy-PAP, 4′-hydroxy-PAP and 2′-hydroxy-PAP.\textsuperscript{24}</td>
</tr>
</tbody>
</table>

Table 1.
Phenazopyridine is very useful as adjuvant to antimicrobial therapy in uncomplicated UTIs: Phenazopyridine when administered along with antibiotics is efficacious as short-term analgesic in the treatment of uncomplicated UTIs (uUTIs) as shown in a randomized, open label study. Phenazopyridine, when given with antibiotics such as ciprofloxacin, doxycycline within 48 hours of diagnosis, resulted in marked reduction in urinary symptoms of burning micturition (91%) and pain during voiding of urine (89%).

Phenazopyridine co-administration enhances ciprofloxacin bioavailability: A study compared the pharmacokinetic behavior of ciprofloxacin administered alone versus ciprofloxacin plus phenazopyridine. While there were no differences between the two treatments in terms of peak plasma concentration (C_max) and elimination constant (ke), area under the concentration-time curve to last measurable concentration (AUC_t) and area under the concentration-time curve extrapolated to infinity (AUC_∞) were 35% and 29% higher, respectively, in the combined treatment arm. In addition, a significant delay in t_max (from 1 to 1.5 hours) and a statistical increase of 29% in mean residence time (MRT) were also observed in the combination group. The study concluded that phenazopyridine, when given together with antibiotic (ciprofloxacin) enhances its bioavailability with regard to the amount absorbed and MRT in the body, which is beneficial during treatment.

Phenazopyridine does not alter efficacy of sulfonamides against uropathogenic bacteria: Phenazopyridine is widely used as an adjunct to sulfonamides in the treatment of bacterial UTIs and has been shown not to alter the effectiveness of sulfonamides (sulfacytine, sulfisoxazole and sulfamethoxazole) against uropathogenic bacteria. The combined bacteriostatic activity of sulfonamide compounds and phenazopyridine upon Balantidium coli has also been demonstrated earlier by Neter and Loomis.

Phenazopyridine relieves pain due to bladder spasms: Indwelling urinary catheters can cause severe pain and discomfort and can impair a person’s quality-of-life. A catheter is a foreign body and its presence may trigger bladder spasm and pain. Phenazopyridine helps to relieve the pain caused by catheters.

Phenazopyridine relieves postoperative ureteral stent discomfort: Stent placement after ureteroscopy results in considerable morbidity in the form of irritative lower urinary tract symptoms. Norris et al published their findings of a small but well-conducted double-blind, placebo-controlled study comparing ER oxybutynin, phenazopyridine and placebo in patients who had a stent place after ureteroscopy. Each of 60 patients who received a unilateral stent after ureteroscopy was given a blister pack containing 21 unmarked capsules of either extended-release oxybutynin 10 mg, phenazopyridine 200 mg or placebo in a prospective, randomized and double-blinded fashion. Patients were instructed to take 1 capsule 3 times daily immediately after the procedure. Patients were given 50 tablets of oral narcotic to be taken as needed. Assessment tools included a questionnaire for stent symptoms, visual analog scale scores and requirement of narcotic medications. Results did not show differences for flank pain, suprapubic pain, urinary frequency, urgency and dysuria. The phenazopyridine group reported less hematuria on postoperative Day 1 when compared with placebo, which was statistically significant.

Phenazopyridine relieves autonomic dysreflexia associated with cystitis: Autonomic dysreflexia (AD) in individuals with spinal cord injury and other neurologic disorders is due to a genitourinary cause 81-87% of the time. Urinary bladder distension due to urinary retention, blocked catheters or of defective catheter tubing or drainage bags is the commonest precipitant. UTIs can also induce AD, albeit not as commonly as bladder distension. Phenazopyridine is useful in the management of AD associated with cystitis as documented by Paola and coauthors.

CONCLUSION

Irritative voiding symptoms occur with a high prevalence in the general population and can greatly affect patients’ quality-of-life. These symptoms can be a source of great discomfort, embarrassment and loss of confidence, causing withdrawal from social life and affecting physical and mental health. UTIs are usually associated
with irritative voiding symptoms, such as painful urination (dysuria), urinary urgency and frequency.

- Anticholinergic drugs are widely used in clinical practice to reduce irritative voiding symptoms. Anticholinergics/Antispasmodics help relieve dysuria and provide relief from bladder spasms. Optimal control is obtained if both infection and bladder spasms are treated simultaneously.

- Urinary antispasmodics such as oxybutynin and flavoxate are muscarinic receptor antagonists and exert beneficial direct relaxant effect on smooth muscle of the urinary tract. But they have high incidence of side effects, predominantly dry mouth, which is a major disadvantage leading to poor patient compliance and discontinuation of treatment.

- The lack of demonstrated effect of flavoxate in placebo-controlled studies makes it difficult to recommend the use of flavoxate and it is definitely not a first-line treatment.

- Clinically, oxybutynin appears more potent in causing dry mouth than in inhibiting detrusor instability, which precludes its use. Also, drug interactions are known to occur when co-administered with antibiotics like macrolides.

- Phenazopyridine is a urinary tract analgesic, which is used to treat symptoms of dysuria, while the patient is awaiting medical evaluation and treatment.

- When taken orally, majority of the drug enters the urine unchanged, where it acts as a topical analgesic within the bladder.

- Phenazopyridine is also frequently used for adjunctive treatment of pain associated with UTIs in addition to antibiotics aimed at the underlying microbial infection. It relieves pain and discomfort during the interval before antibiotic therapy begins to control the infection.

- Most doctors prefer to use phenazopyridine as a first choice drug in dysuria.

REFERENCES

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