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Original Research Article

Relooking at Nitrofurantoin as drug of choice for empiric treatment of community acquired uncomplicated urinary tract infections: An effective and economic treatment option

Tabia Mir, Rouchelle Tellis* and Vidya Pai

Department of Microbiology, Yenepoya Medical College Hospital, Yenepoya University, Deralakatte, Mangaluru-575018, India

QR Code

***Correspondence Info:**
Dr. Rouchelle Tellis
Department of Microbiology,
Yenepoya Medical College Hospital, Yenepoya University,
Deralakatte, Mangaluru-575018,

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Abstract

Introduction: In recent times, urinary tract infections (UTI) which are more often caused by multidrug resistant bacteria has necessitated the use of broad spectrum expensive antibiotics, which tend to further enhance antibiotic pressure. In this context, it would be ideal to look at older less commonly prescribed antibiotics like nitrofurantoin and assess its sensitivity for treatment of community acquired UTIs. Nitrofurantoin has in the past been successfully used for prophylaxis and treatment of acute lower UTIs in adults, children and pregnant women.

Aim & objectives: This study aims to assess *in-vitro* sensitivity of common uropathogens to nitrofurantoin including extended spectrum beta lactamase (ESBL) producers.

Materials and methods: Urine culture and bacterial identification were done using standard laboratory tests. Antibiotic sensitivity was assessed by Kirby Bauer disc diffusion method and ESBL producers were identified by phenotypic confirmatory disc diffusion test (PCDDT).

Results: 226 (29.89%) of 756 urine samples cultured showed growth of significant bacteruria, of which 122 (53.98%) were *E. coli*, 32(14.15%) *K. pneumoniae*, 23(10.17%) *P. aeruginosa*, 14(6.19%) *Enterococcus* spp., 12(5.30%) *Acinetobacter* spp, 10(4.42%) *S. saprophyticus* and 5(2.3%) were Candida species. 108/122(88.5%) of *E. coli* were sensitive to nitrofurantoin. 37/40 (92.5%) ESBL producing *E. coli* and all isolates of *S. saprophyticus* and *Enterococcus* spp. were sensitive to nitrofurantoin.

Conclusions: Nitrofurantoin is an oral antibiotic with minimal adverse effects, showing *in-vitro* sensitivity against community acquired uro-pathogens and is also reasonably priced. Hence there is a need to re-consider nitrofurantoin as drug of choice for treatment of community acquired uncomplicated lower UTIs. This would ease the antibiotic pressure, off oral cephalosporins and fluoroquinolones which are currently overused in the community.

Keywords: Community acquired, Urinary tract infection, Nitrofurantoin.

1. Introduction

Urinary tract infections (UTIs) are the second commonest infections treated in the outpatient clinics only after respiratory tract infections. They are more common among women, with one-half of all women experiencing at least one episode of UTI during their lifetime.[1] UTIs are commonly divided into infections of the upper or lower UTI, based on the anatomic location of the infection. Pyelonephritis and pyelitis are considered infections of the upper urinary tract which can also extend to include the lower tract. Cystitis is the commonest infection of the lower urinary tract. UTIs are classified as uncomplicated or complicated based on patient co-morbidities and the presence of anatomic or physiologic abnormalities that predispose to UTI. Uncomplicated UTIs are episodes of

cystitis or pyelonephritis in premenopausal, non-pregnant women without structural or functional urinary tract abnormalities, whereas complicated UTIs occur in patients with abnormal anatomy of the urinary tract or significant medical or surgical co-morbidities such as uncontrolled diabetes mellitus, urinary tract obstruction, vesico-urethral reflux etc.[2] A majority of the cases of acute uncomplicated cystitis are caused by *Escherichia coli* (86%), followed by *Staphylococcus saprophyticus* (4%), *Klebsiella* species (3%), *Proteus* species (3%) and the rest by *Enterobacter, Citrobacter* or *Enterococcus* species. [3]

In the past decade oral antibiotics such as norfloxacin, nitrofurantoin, cefuroxime and trimethoprim-sulfamethoxazole were commonly used to treat uncomplicated UTIs. However more recently antibiogram analysis of the uropathogens reveals that close to 50% cases of community acquired UTIs are caused by multidrug resistant (MDR) bacteria, the commonest etiologic agent being MDR *Escherichia coli*. Most of these bacteria show resistance to most of the antibiotics used in clinical practice, with the exception of nitrofurantoin. Nitrofurantoin is a broad spectrum synthetic antimicrobial derived from furan by the addition of a nitro group and a side chain containing hydantoin. It was introduced into clinical practice in 1952 for treatment of acute uncomplicated UTIs and was prescribed widely for the next two decades, until its popularity decreased in 1970s with the advent of other oral antibiotics like co-trimoxazole and β-lactams. However, recently the increasing resistance to co-trimoxazole and fluoroquinolones has led to renewed interest in this old drug. With the rise in ESBL producing and carbapenem resistant bacteria, several guidelines were revised to reposition nitrofurantoin as first line therapy for uncomplicated lower UTI.[4]

2. Materials and Methods

This was a prospective study done to determine *in-vitro* sensitivity of common uropathogens to nitrofurantoin and to analyze the possibility of its use to treat UTI caused by extended spectrum beta-lactamase (ESBL) producers. Out of 756 urine samples collected from clinically suspected cases of UTI, during 3 months from May to July 2015 only those showing significant bacteruria by semi-quantitative culture according to Kass criteria were included in the study. Bacteria were identified based on their colony morphology and using standard biochemical tests.[5] Antibiotic sensitivity was assessed by Kirby-bauer disc diffusion testing and results were interpreted according to CLSI guidelines. 3-4 similar colonies of the bacterial isolate were inoculated into peptone water and incubated for 2-3 hours. The turbidity was adjusted to 0.5 McFarland standards. This inoculum was lawn cultured on the surface of cation adjusted-Mueller Hinton agar (CA-MHA) and antibiotic discs were placed including a nitrofurantoin (30µg) disc, ensuring sufficient space between individual discs to allow for proper measurement of inhibition zones. The inoculated plates were incubated for overnight at 37°C. Bacteria resistant or showing decreased susceptibility (Intermediate) to any one of the third generation cephalosporins (ceftazidime ≤22 mm, cefotaxime ≤27mm) were subjected to confirmatory test for presence of ESBL according to CLSI ESBL detection guidelines. ESBL production was confirmed by phenotypic confirmatory disc diffusion test (PCDDT) using 30µg disc of ceftazidime in combination with a ceftazidime–clavulanic acid disc (30/10ug).[6] The test was considered positive when there was an increase in the growth-inhibitory zone around either the ceftazidime disk with Clavulanic acid was 5 mm or greater of the diameter around the disk containing ceftazidime alone

3. Results

Out of the 756 urine samples received during the study period 226 (29.89%) showed significant bacterial growth of $>10^5$CFU/ml. Of these 122 (53.98%) were *E. coli* and 108 /122 (88.5%) *E. coli* isolates were sensitive to nitrofurantoin. Among 32 isolates of *Klebsiella* 26(81.3%) were found to be sensitive to nitrofurantoin. Table 1 shows the various micro-organisms isolated from urine cultures and their nitrofurantoin sensitivity. All isolates of *S. saprophyticus* and *Enterococcus spp*. were sensitive to nitrofurantoin *in-vitro.*

40 out of 122 *E. coli* isolates (32.7%) were ESBL producers, and 37 out of 40 (92.5%) ESBL producing *E. coli* were sensitive to nitrofurantoin. Table 2 shows the antibiogram of ESBL and non-ESBL producing *E. coli* and *K. pneumoniae.* 86.5% of Non ESBL producing *E. coli* and 92.5% of ESBL producing *E. coli* in this study were sensitive to nitrofurantoin whereas 84% of non-ESBL producing *K. pneumoniae* and 71.4% of ESBL producing *K. pneumoniae* were sensitive to nitrofurantoin.

Table 1: Micro-organisms isolated from urine samples and their nitrofurantoin sensitivity

Micro-organism	No. of isolates (%)	Nitrofurantoin sensitivity n (%)
Escherichia coli	122 (53.98%)	108 (88.5%)
Klebsiella pneumonia	32 (14.15%)	26 (81.3%)
Pseudomonas aeruginosa	23 (10.17%)	Naturally resistant
Enterococcus species	14 (6.19%)	14 (100%)
Acinetobacter species	12 (5.30%)	11 (91.6%)
Staphylococcus saprophyticus	10(4.42%)	10 (100%)
Candida species	5 (2.3%)	------
Enterobacter species	4 (1.76%)	4 (100%)
Trichosporon species	1 (0.44%)	------
Morganella morganii	1 (0.44%)	1 (100%)
Citrobacter species	2 (0.88%)	1 (100%)

Table 2: Antibiogram of *Escherichia coli* and *Klebsiella pneumonaie* to various antibiotics tested

Antibiotics	*E. coli (122)*		*K. pneumoniae (32)*	
	Non ESBL producers n=82 (% Sensitive)	ESBL producers n=40 (% Sensitive)	Non ESBL producers n=25 (% Sensitive)	ESBL producers n=7 (% Sensitive)
Ampicillin	26 (31.7%)	0	3 (12.0%)	0
Cefuroxime	55 (67.1%)	0	15 (60.0%)	0
Cefotaxime	57 (69.5%)	0	16 (64.0%)	0
Ceftazidime	64 (78.0%)	0	19 (76.0%)	0
Cefipime	75 (91.5%)	0	21 (84.0%)	0
Ciprofloxacin	41 (50.0%)	20 (50%)	14 (56.0%)	3 (42.8%)
Gentamicin	63 (76.8%)	14 (35%)	14 (56.0%)	3 (42.8%)
Amikacin	51 (62.2%)	26 (65%)	20 (80.0%)	4 (57.1%)
Amoxicillin + Clavulanic acid	46 (56.1%)	24 (60%)	14 (56.0%)	3 (42.8%)
Co-trimoxazole	55 (67.1%)	25 (62.5%)	13 (52%)	1 (14.3%)
Nitrofurantoin	71(86.5%)	37(92.5%)	21 (84.0%)	5 (71.4%)
Norfloxacin	32 (39.0%)	10 (25.0%)	16 (64.0%)	3 (42.8%)
Piperacillin	24 (29.2%)	8 (20.0%)	12 (48.0%)	3 (42.8%)
Piperacillin + Tazobactum	59 (71.9%)	14 (35.0%)	18 (72.0%)	5 (71.4%)
Imipenem	68 (82.9%)	30 (75.0%)	24 (96.0%)	6 (85.7%)

4. Discussion

E. coli is the most common pathogen, isolated from approximately 80% of outpatients with acute uncomplicated cystitis across India. In this study *E. coli is* the most predominant uro-pathogen isolated from 53.98% of urine samples showing significant bacteriuria followed by *K. pneumonaie* (14.15%). A similar finding of *E. coli* being the most common uro-pathogen from patients with UTIs has been reported by Kothari and Sagar (68%) in 2008 and Ganju *et al* (49.8%) in 2016.[7,8] Fluoroquinolones and cephalosporins are the most commonly used antibiotics for treatment of community acquired uncomplicated UTIs but the development of widespread resistance to these agents may result in poor clinical outcomes. Antibiogram analysis of these isolates reveals that the resistance to antibiotics such as ampicillin, fluroquinolones, 3rd and 4th generation cephalosporins and gentamicin among the ESBL producing uropathogens is quite high, whereas the resistance to nitrofurantoin is not very significant. In this study 92.5% of ESBL producing *E. coli* and 86.5% of non ESBL producing *E. coli* were sensitive to nitrofurantoin. Similar findings were reflected in a study by Babypadmini and Appalaraju from Tamilnadu in South India where in 89% of ESBL producing *E. coli* and 94% of Non ESBL *E.coli* were susceptible to nitrofurantoin.[9] A similar observation is made by Tasbakan MI *et al* who have proposed that nitrofurantoin may be used as option in the treatment of ESBL-producing *E. coli* related lower UTI.[10] In this study 71.4% and 84% ESBL producing and non ESBL producing *K. pneumonaie* were sensitive to this antibiotic which is in line with the observations by Kyabaggu *et al*.[11] Among oral agents used in out-patient therapy to treat uncomplicated lower UTIs high rates of resistance is reported from across India for amino-penicillins (63.6–88%), ciprofloxacin (35–75%) and 40–76% against trimethoprim-sulphamethoxazole.[12-14] Among the oral

antibiotics commonly used to treat uncomplicated UTIs such as co-trimoxazole, nitrofurantoin and norfloxacin, nitrofurantoin has the best sensitivity *in vitro*. The present study establishes the fact that majority of the organisms causing uncomplicated UTI are sensitive to nitrofurantoin, be it a gram positive or gram negative bacteria. Among 122 isolates of *E. coli* only 14(11.47%) were resistant to nitrofurantoin where as resistance to ciprofloxacin was seen in 61 isolates (50%). Resistance to co-trimoxazole was seen in 42 isolates (34.4%) and resistance to imepenem was seen in 24 isolates (19.7%).

Table 2 shows that ESBL producing *Klebsiella pneumoniae* having significantly decreased susceptibility to nitrofurantoin compared to non-ESBL producers, an observation similar to that reported by Procop GW *et al* in 2003.[15] By providing an effective alternative for the treatment of uncomplicated UTIs, nitrofurantoin may also contribute to a overall reduction in the use of fluoroquinolones and beta-lactams and thus help to reduce selection pressure for increased resistance to these antibiotics. In this study besides *E. coli* and *Klebsiella* nitrofurantoin showed high rates of *invitro* sensitivity to other bacteria associated with community acquired UTI such as *S. saprophyticus*, *Enterococcus* and *Enterobacter* species. Biswas D *et al* from Uttaranchal in their study of empirical therapy for acute cystitis have reported that nitrofurantoin was the most effective antibiotic not only for *E.coli* (90.7%) but also for most other bacteria isolated from cases of community acquired cystitis.[14] Therefore nitrofurantoin can be used effectively for the treatment of community acquired uropathogens as also suggested by Barry *et.al*.[16]

Based on clinical, *in vitro* and mathematical modelling studies Infectious Diseases Society of America (IDSA) recommends that an antibiotic can be used for empirical therapy only if the resistance rates for it do not exceed 20%.[17] For an antibiotic to be suitable for use as an agent for empiric therapy for treatment of community acquired non-complicated lower UTIs, it should fulfill certain criteria such as: low resistance rates against potential pathogens, ability to achieve significant urinary concentration, be cost effective and with minimal adverse effects. Nitrofurantoin is a cost effective oral antibiotic with minimal adverse drug effects thus having good patient compliance rates. Currently available macro-crystal formulation of nitrofurantoin can be given as twice daily regimen [18]. The high level of susceptibility of *E. coli* to nitrofurantoin may be due to its narrow spectrum of activity, limited clinical use and narrow tissue distribution. Therefore, Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease recommend nitrofurantoin as the agent of first choice for the treatment of uncomplicated cystitis and pyelonephritis in women.[17] However it needs to be remembered that nitrofurantoin has no activity against *Proteus spp*. or *P. aeruginosa* as both these bacteria produce the enzyme urease that raises the local pH in the urinary tract and the activity of nitrofurantoin is pH dependent and mean inhibitory concentration rises sharply with increased pH above 6.[18]

Another role for nitrofurantoin is in treatment of UTI in pregnancy, because of its safety profile in early pregnancy compared to that of ciprofloxacin and co-timoxazole. Our data supports the 2011 IDSA recommendations that nitrofurantoin be considered as first-line empirical therapy for uncomplicated UTIs. In clinical practice, antibiotic therapy for community acquired, uncomplicated cystitis is usually empiric as urine cultures are commonly not performed and treatment is more or less based upon the knowledge of local or national surveillance studies. Therefore,the best practice would be to adopt empiric antibiotic treatment based on local antibiogram patterns that need to be re-assessed periodically.

The adverse effects of nitrofurantoin are relatively uncommon and benign.[19,20] Occasional nausea may occur but is uncommon with the currently available macrocrystalline formulations. In patients with intact renal function, nitrofurantoin urinary concentrations are 50 to 300 mg/mL.[20] With creatinine clearances lower than 30 mL/min, therapeutic urinary concentrations are unlikely to be obtained, and therapeutic failure may result.[19,20] For this reason, nitrofurantoin should be avoided in patients with a creatinine clearance lower than 30 ml/min.[20,21] Acute toxicity with this drug is very rare and limited to acute or reversible migratory pulmonary infiltrates or eosinophilia. Long-term nitrofurantoin toxicity includes peripheral neuropathy, interstitial lung disease, or hepatotoxicity, which may occur in patients treated long term who have chronic renal insufficiency.[20, 22]

5. Conclusion

Nitrofurantoin is a reasonably priced oral antibiotic with a positive safety profile showing high rates of sensitivity to all the common community acquired uro-pathogens. Hence there is a need to reconsider it as the drug of choice for empiric treatment of community acquired uncomplicated cases of lower urinary tract infections and UTIs in pregnancy. This could help ease the antibiotic pressure off oral ß-lactams, cephalosporins and fluoroquinolones that are currently ineffective due to high rates of antibiotic resistance and thus helping them also to regain their lost sensitivity.

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