Advantage and limitations of nitrofurantoin in multi-drug resistant Indian scenario

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Abstract

Infections caused by antibiotic resistant pathogens are of significant concern and are associated with higher mortality and morbidity. Nitrofurantoin is a broad-spectrum bactericidal antibiotic and is effectively used to treat urinary tract infections (UTIs) caused by E. coli, Klebsiella sp., Enterobacter sp., Enterococcus sp. and Staphylococcus aureus. It interferes with the synthesis of cell wall, bacterial proteins and DNA of both Gram positive and Gram negative pathogens. Nitrofurantoin has been used successfully for treatment and prophylaxis of acute lower urinary tract infections. With the emergence of antibiotic resistance, nitrofurantoin has become the choice of agent for treating UTIs caused by multi-drug resistant pathogens.

Key words: Nitrofurantoin, MDR, UTI

Introduction

Interest in nitrofurantoin, an old drug has increased as a solution to the ever increasing menace of antimicrobial resistance. This Review will highlight the potential and the limitation of this agent in the era of drug resistance, especially in India.

The major strength of nitrofurantoin is its action at multiple sites and levels. This includes inhibition of bacterial enzymes involved in carbohydrate synthesis and in higher concentration DNA, RNA, and total protein synthesis by the non-specific attack on bacterial ribosomal proteins.[1,2] This is preceded by activation of nitrofurantoin by bacterial reductases to highly reactive electrophilic intermediates, and an inverse correlation exists with the bacterial reductase activity of the bacteria and its nitrofurantoin minimum inhibitory concentration (MIC). However, this reduction of nitrofurantoin is not an absolute requirement for its antibacterial activity.[2]

Bioavailability and spectrum of activity

Nitrofurantoin formulation determine its pharmacokinetics (PK) whereas very little is known about its pharmacodynamics (PD). Different formulations of nitrofurantoin include microcrystals and macrocrystals. Macrocrystalline formulations have a slower rate of dissolution and lower bioavailability. Dual release capsules contain 25% microcrystal and 75% nitrofurantoin monohydrate, which allows sustained release and maintenance of plasma levels. Oral bioavailability is 40–50% and increases with food.[3] Very low peak plasma level of <2 µg/mL is achieved after 1–4 h of oral administration.[4,5] Nitrofurantoin is metabolised in renal tissue and rapidly excreted in the urine through both glomerular filtration, as well as tubular secretion, with a plasma half-life of 0.5–1 h. With this rapid excretion, the urinary concentration of nitrofurantoin is more than 100 µg/mL (up to 250 µg/mL).[5] High concentration achievable in urine makes it an ideal choice for treatment of urinary tract infection (UTI). There is very limited information available on PK/PD property of nitrofurantoin. As a result, the optimal dosing schedule remains uncertain and different countries follow differing regimen.

There is only one study on the PD property of nitrofurantoin. Komp Lindgren et al. demonstrated rapid and complete killing of extended spectrum beta-lactamase (ESBL) and non-ESBL strain of Escherichia coli in static time kill experiment while 99% killing was seen among vancomycin-resistant enterococcal (VRE) and non-VRE Enterococcus strains at 24 h.[6] In the dynamic time kill assay for E. coli the PK/PD index that best correlated...
with antibacterial activity was \( T > \text{MIC} \) (time duration where the drug concentration is more than the MIC of the agent). This finding suggests need for more PK/PD studies with the urinary drug level assay at differing dosing regimens, which will help in determining the optimum dosing schedule.

Nitrofurantoin is usually well tolerated. Side-effects occur at rates <0.001%,[7] Macrocryystal formulations reduce gastrointestinal effects such as nausea and vomiting. Haemolytic anaemia can occur in patients with glucose-6-phosphate deficiency. Serious adverse effects are rare and occur only with prolonged medication (>6 months).[1] This includes chronic pulmonary reactions and interstitial fibrosis, peripheral neuropathy and hepatic injury. Nitrofurantoin also has good safety profile for use in pregnancy (pregnancy category B).[9] Nitrofurantoin is contraindicated in patients with renal failure with creatinine clearance rate of 60 mL/min. However, recent studies indicate the use of nitrofurantoin can be expanded to creatinine clearance as low as 40 mL/min for infection with susceptible isolates.[9]

Nitrofurantoin is active against most common uropathogens including *E. coli*, *Citrobacter* spp., *Staphylococcus saprophyticus*, and *Enterococcus* spp. whereas, *Enterobacter* spp. and *Klebsiella* spp. are only moderately inhibited, *Proteus* spp., *Providencia* spp., *Morganella morgani*, *Serratia* spp., *Pseudomonas* spp., and *Acinetobacter* spp. are mostly resistant to nitrofurantoin.[10,11]

**Preference and recommendation of nitrofurantoin**

Table 1 gives the breakpoints prescribed by Central Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoints for nitrofurantoin are based on urinary concentration.[3] The EUCAST recommend the use of nitrofurantoin only for uncomplicated UTIs. The high urinary concentration achieved with nitrofurantoin is sufficient to eradicate the intraluminal bacteria, and the minimal intracellular invasion is possibly cleared by the innate immune response.[12] However, complicated UTIs are associated with more tissue invasion and can develop urosepsis rapidly. Thus for a complicated UTI and UTI with tissue component like pyelonephritis, the plasma concentration and the tissue concentration is also important and thus the use of nitrofurantoin cannot be recommended because of inadequate tissue concentration.[1,13] Nitrofurantoin may complement the primary therapy in urosepsis or as de-escalation choice.

Nitrofurantoin is recommended as the first choice for the treatment of uncomplicated cystitis and pyelonephritis in women by Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease.[14] Another role for nitrofurantoin use is in UTI in pregnancy. Asymptomatic bacteriuria happens in 2–10% of pregnancies and acute cystitis in 1–4%.[15] Among patients with asymptomatic bacteriuria, 20–40% eventually develops pyelonephritis later in pregnancy. Among multi-drug resistant (MDR) strains of *E. coli* causing UTI in pregnancy, resistance to nitrofurantoin is lower (7.7%) compared to ampicillin, trimethoprim-sulphamethoxazole, cephalothin or ciprofloxacin.[15] Nitrofurantoin is also recommended as preventive therapy for recurrent UTI during pregnancy.[16] However, its use is not recommended near term or during labour and delivery in patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of haemolytic anaemia.

**Dose and duration of nitrofurantoin**

Dosage schedule for nitrofurantoin varies considerably in different countries ranging from 50 to 100 \( \text{mg} \times 2–4 \) times/day [Table 2].[5] Infectious Diseases Society of America recommends a dosage of 100 mg BD for 5 days for uncomplicated cystitis and pyelonephritis in women.[14] Pallett and Hand recommend 100 mg \( \times 4 \) times daily for 7 days for uncomplicated or complicated lower UTIs.[17] For children younger than 12 years, dosage of 3–5 mg/kg body weight per oral in two divided dosage for 7–14 days is recommended.[18]
Similarly, though classically 10–14 days of therapy is recommended, the long duration compromises the compliance to treatment. Shorter duration of therapy has been investigated to overcome this limitation. Lumbiganon et al. compared the traditional 7 days regimen of nitrofurantoin to the 1-day regimen and found more treatment failure with shorter regimen though the rate of symptomatic infection and adverse pregnancy outcome was not significantly different.[19] Systematic review on UTI in children showed 2–4 days course of therapy to be as effective as 7–14 days of therapy.[20] However, Keren and Chan recommend treatment for the traditional 7–14 days as long-term therapy have fewer treatment failures in children.[21] It is important to note that these systemic meta-analyses are based on treatment with different groups of antimicrobials. Thus, a generalisation of treatment duration across different groups of antimicrobial agents may not be advisable.

**Mechanism of resistance**

Nitrofurantoin acts at multiple targets in the bacterial cell and resistance have not evolved as fast as other drugs with a single bacterial target. Resistance is developed through stepwise mutations. Sandegren et al. found the mutation frequency to be approximately 10⁻⁷/cell for E. coli.[22] Mutations in the genes encoding bacterial nitroreductase nfsA and nfsB were responsible for high-level nitrofurantoin resistance (median MIC of 96 µg/mL).[22,23] However, the growth rate of the resistant mutants was lower than susceptible strains, and at the therapeutic urinary concentration of above 200 µg/mL the selection of resistant mutants is prohibited.[22] This fitness cost conferred in resistant strains may render resistant strain with even moderately high MICs amenable to treatment with the normal dosing regimen. This may explain the lack of resistance to this drug even after 60 years of use. In patients with poor drug compliance or suboptimal dosing or PK altering condition (e.g., poor absorption) where the urinary drug concentration may be lower than expected, resistant mutants can, however, still be selected.

Though E. coli, in general, are highly susceptible to nitrofurantoin, susceptibility for ESBL producing strains are lower [Table 3]. Procop et al. in 2003 showed ESBL producing Klebsiella pneumoniae have significantly decreased susceptibility to nitrofurantoin compared to non-ESBL producer.[33] Tasbakan et al. showed modest clinical and microbial success rates of 68% and 69% respectively, with nitrofurantoin therapy for infection with ESBL producing nitrofurantoin susceptible E. coli.[32] The re-infection and relapse rates were 6.5% and 3.2%, respectively. However, 81% of the studied population had at least one complicating factors. The dosage of 50 mg 4 times/day for 14 days, may be suboptimal in this cohort with complicating factors.

Among VRE isolates, nitrofurantoin retain good activity [Table 3] and Heintz et al. recommends the use of empiric nitrofurantoin 100 mg 4 times daily for enterococcal cystitis and the first line therapy for nitrofurantoin susceptible VRE cystitis.[33]

**Nitrofurantoin resistance in India**

In India, resistance rates among E. coli range from 5% to 24.4% [Table 4][34-39] with higher resistance rate seen in in-patients. In one of the large-scale study of more than 2000 isolates, Sahni et al. reported ESBL production among 47.6% of E. coli isolates studied of which 76.8% were MDR, with corresponding nitrofurantoin resistance of 20%.[34,37] Shaifali et al. observed a resistance to third generation cephalosporin indicative of ESBL production as high as 90% among female out-patient.[36] The corresponding resistance to nitrofurantoin in this study was 13%. This finding is in contradiction with resistance rates of 1.1–1.8% in USA, Canada, and France.[7]

Among Klebsiella sp. resistance rates vary from 9% to 17%.[34,36] Shaifali et al., again reported third generation cephalosporin resistance of up to 90% among the Klebsiella spp. isolates studied with nitrofurantoin resistance of 9%. Among Enterococcus sp. the resistance rate is 6–17%.[34,37]

<table>
<thead>
<tr>
<th>Country</th>
<th>Recommended dose</th>
<th>Maximum dose schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>50 mg 4 times/day</td>
<td>100 mg 4 times/day</td>
</tr>
<tr>
<td>France</td>
<td>50 mg 3 times/day</td>
<td>50 mg 6 times/day</td>
</tr>
<tr>
<td>Netherlands</td>
<td>50 mg 4 times/day</td>
<td>100 mg 4 times/day</td>
</tr>
<tr>
<td>Germany</td>
<td>100 mg 2 times/day</td>
<td>100 mg 4 times/day</td>
</tr>
<tr>
<td>Norway</td>
<td>50 mg 3-4 times/day</td>
<td>50 mg 3-4 times/day</td>
</tr>
<tr>
<td>Sweden</td>
<td>50 mg 3 times/day</td>
<td>50 mg 3 times/day</td>
</tr>
</tbody>
</table>

**Table 3: Susceptibility to nitrofurantoin among drug resistant isolates**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Susceptible rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al., 2011[24]</td>
<td>Taiwan</td>
<td>79.1</td>
</tr>
<tr>
<td>Maina et al., 2013[25]</td>
<td>Kenya</td>
<td>88.9</td>
</tr>
<tr>
<td>Auer et al., 2010[26]</td>
<td>Austria</td>
<td>94</td>
</tr>
<tr>
<td>Puerto et al., 2006[27]</td>
<td>Spain</td>
<td>71.3</td>
</tr>
<tr>
<td>Zhanel et al., 2001[28]</td>
<td>Canada</td>
<td>-</td>
</tr>
<tr>
<td>Zhanel et al., 2003[29]</td>
<td>North America</td>
<td>-</td>
</tr>
<tr>
<td>Rahbar et al., 2007[30]</td>
<td>Iran</td>
<td>84.9</td>
</tr>
</tbody>
</table>

ESBL: Extended spectrum beta-lactamase, VRE: Vancomycin resistant enterococcal cystitis and the first line therapy for nitrofurantoin susceptible VRE cystitis.[33]
An agent is deemed unacceptable for empiric treatment where the rate of resistance exceeds 20%. Among oral agents used for out-patient therapy, high rates of resistance is seen in *E. coli* in India – 63.6–88% against aminopenicillins, 35–75% against ciprofloxacin, and 40–76% against trimethoprim-sulphamethoxazole. Biswas *et al.* reported nitrofurantoin susceptibility of 87% among ciprofloxacin-resistant isolates.

While the rate of nitrofurantoin resistance is lower than any of the other oral agents, some studies have reported high levels of resistance. In a multi-centric study, Kothari and Sagar found resistance rates of 24.4%. The highest rate of nitrofurantoin resistance was reported from Aligarh against both *E. coli* and *Klebsiella* spp. with rates of 80% and 76%. The corresponding ESBL rates was 34.4% and 27.3% in *E. coli* and *Klebsiella* spp., respectively. This wide variation in the rates of resistance may be determined by the local prescribing practices, with the resistance higher among the most commonly prescribed agents.

There is very limited data on nitrofurantoin activity against carbapenem-resistant isolates or VRE in India. With the increasing drug resistance seen in this decade, there is a need to evaluate the activity of nitrofurantoin against such extensively drug-resistant strains.

### Summary and Conclusion

To surmise, among the various oral antimicrobials available for UTI the use of aminopenicillins and trimethoprim/sulphamethoxazole for UTI is restricted by high rates of resistance. The ever increasing resistance to ciprofloxacin, its contraindication during pregnancy and significant impact on gut flora compared to nitrofurantoin has fallen out of favour as a choice for empirical therapy of UTI. While fosfomycin has good activity against *E. coli*, resistance rate is high among *Klebsiella* spp. (Chinnappan *et al.* Technical and interpretative issues of fosfomycin susceptibility testing, Indian Journal of Medical Microbiology 2015 - in the press.) Nitrofurantoin remains the only available alternative with almost equivalent activity against *E. coli* and *Klebsiella* spp. with high susceptibility rate among oral agents for UTI. To provide optimum use and to avoid misuse and overuse of this drug, culture, and susceptibility testing is the need of the time to preserve it for next generation.

### References

13. Richards WA, Riss E, Kass EH, Finland M. Nitrofurantoin; clinical and laboratory studies in urinary tract infections.