



Short communication

Nitrofurantoin in the treatment of extended-spectrum β -lactamase-producing *Escherichia coli*-related lower urinary tract infection

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ABSTRACT

The aim of this study was to evaluate the effect of nitrofurantoin (NFT) in the treatment of extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli*-related lower urinary tract infection (LUTI). The hospital records of all patients aged >18 years with dysuria or problems with frequency or urgency in passing urine, >20 leukocytes/mm³ in urine microscopy and culture-proven ESBL-producing NFT-sensitive *E. coli* in the urine (>10⁵ CFU/mm³), no leukocytosis or fever and who were treated with NFT between January 2006 and May 2011 in our outpatient clinic or in the hospital were evaluated. All patients had received a NFT 50 mg capsule every 6 h for 14 days and had a control urine culture taken 7–9 days after therapy. Clinical success was defined as resolution of symptoms at the control visit, and microbiological success was defined as a sterile control urine culture. A total of 75 patients (mean \pm standard deviation age, 54 \pm 17 years; 45 females, 30 males, all but 14 with complicated LUTI) fulfilled the study inclusion criteria. Overall clinical and microbiological success rates were 69% (52/75) and 68% (51/75), respectively. Control urine culture performed 28–31 days after the end of therapy was available in 31/51 patients (61%) with microbiological success. Re-infection and relapse rates were 6.5% (2/31) and 3.2% (1/31), respectively. In conclusion, these results suggest that NFT may be an alternative in the treatment of ESBL-producing *E. coli*-related LUTI. This is the first study in which NFT was used in the treatment of LUTI due to ESBL-producing *E. coli* as well as in patients with complicated UTI.

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1. Introduction

Urinary tract infections (UTIs) are among the most common infections in inpatient and outpatient populations. The majority of these infections are uncomplicated UTIs such as acute uncomplicated cystitis. Lower UTI (LUTI) constitutes the real burden of UTIs in the primary care setting and is usually treated empirically [1].

Escherichia coli is the most common pathogen in LUTIs. Extended-spectrum β -lactamase (ESBL)-producing *E. coli*-related UTI is an emerging problem in many parts of the world. In serious cases the major treatment choices are carbapenems, which usually require hospitalisation and are associated with higher antibiotic costs [2]. Unfortunately, there are not too many treatment alternatives to carbapenems. Nitrofurantoin (NFT) is indicated in the treatment of uncomplicated LUTI. NFT is effective in vitro against *E. coli* strains, including ESBL-producers [3,4]. The aim of this study was to evaluate the effect of NFT in the treatment of ESBL-producing *E. coli*-related LUTI.

2. Materials and methods

The hospital records of patients aged >18 years with dysuria or problems with frequency or urgency in passing urine, >20 leukocytes/mm³ in urine microscopy and culture-proven ESBL-producing NFT-sensitive *E. coli* in the urine (>10⁵ CFU/mm³), no leukocytosis or fever and who were treated with empirical NFT between January 2006 and May 2011 in our outpatient clinic or in the hospital were evaluated.

Clean-catch urine samples obtained from patients were inoculated onto 5% sheep blood agar and eosin–methylene blue agar with 0.01 mL calibrated loops. Identification of *E. coli* was performed by conventional methods. Susceptibility to NFT, ciprofloxacin (CIP), trimethoprim/sulfamethoxazole (TMP/SMX), imipenem/cilastatin and meropenem was determined and interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria by means of disk diffusion susceptibility tests on Mueller–Hinton agar (Oxoid Ltd., Basingstoke, UK). ESBL detection was performed by the double-disk synergy test (Oxoid Ltd.) [5].

In the case of an indwelling urinary catheter, diabetes mellitus, neurogenic bladder, obstruction due to nephrolithiasis, tumour or fibrosis, urinary retention due to benign prostatic hypertrophy, bladder cancer or other urological anatomical abnormalities, the LUTI was considered to be complicated [6].

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Table 1
Complicating factors of patients with lower urinary tract infection.

Complicating factor	N ^a	%
None	14	18.7
Diabetes mellitus	12	16.0
Malignancy involving the urinary tract	11	14.7
Indwelling urinary catheter	11	14.7
Renal pathology (urethral anomaly, fistula, polycystic kidney disease)	9	12.0
Nephrolithiasis	9	12.0
Benign prostatic hypertrophy	5	6.7
Chronic renal failure	4	5.3
Gynaecological pathology (uterine prolapse, vaginal agenesis)	3	4.0
Renal transplantation	2	2.7

^a Five patients had more than one complicating factor.

All patients had received a NFT 50 mg capsule every 6 h (q6h) for 14 days (Piyeloseptyl 50 mg capsule; Biofarma, Istanbul, Turkey) and had a control urine culture taken 7–9 days after therapy [7].

Clinical success was defined as resolution of symptoms at the control visit, and microbiological success was defined as a sterile control urine culture performed 7–9 days after the last dose of the drug in accordance with the Infectious Diseases Society of America (IDSA) guidelines [8].

Relapse was defined as isolation of ESBL-producing *E. coli* in the control urine cultures performed 28–31 days after the end of therapy. Re-infection was defined as isolation of any pathogen in the control urine cultures performed 28–31 days after the end of therapy [6].

3. Results

A total of 75 patients (mean ± standard deviation age, 54 ± 17 years, range 19–82 years; 45 females, 30 males; 6 inpatients, 69 outpatients) fulfilled the study inclusion criteria. All pathogens were resistant to CIP and TMP/SMX and were susceptible to NFT, ertapenem, imipenem/cilastatin and meropenem. Approximately 81% of the cases had at least one complicating factor. The most common underlying problems were the presence of diabetes mellitus, malignancy involving the urinary tract and indwelling urinary catheter (Table 1).

Overall clinical and microbiological success rates were 69% (52/75) and 68% (51/75), respectively. Clinical and microbiological success rates were similar in patients without and with an underlying complicating factor [10/14 vs. 42/61 ($P > 0.05$) and 10/14 vs. 41/61 ($P > 0.05$), Fisher's exact test]. In addition, when analysed in terms of outpatients and inpatients, clinical success but not microbiological success was superior in outpatients compared with inpatients [50/69 vs. 2/6 ($P = 0.046$) and 49/69 vs. 2/6 ($P > 0.05$), Fisher's exact test]. Control urine culture performed 28–31 days after the end of therapy was available in 31/51 patients (61%) with microbiological success. Re-infection and relapse rates were 6.5% (2/31) and 3.2% (1/31), respectively. The relapse case had carcinoma of the prostate. One of the re-infection cases had a renal transplant (*Enterobacter* spp.) and the other had a renal tumour (*Proteus* spp.).

Regarding adverse events, only one case had nausea, which did not require discontinuation of therapy.

4. Discussion

Escherichia coli is the most common aetiological agent both in community-acquired and hospital-acquired UTIs. ESBL-producing *E. coli* increase the risk of morbidity and mortality in hospital-acquired infections and are associated with high antibiotic costs. Community-acquired ESBL-producing *E. coli* is an emerging problem. The increasing prevalence of infections caused by

antibiotic-resistant *E. coli* makes empirical treatment of these infections challenging [3,4].

The antibiotic of choice in ESBL-producing *E. coli*- or *Klebsiella pneumoniae*-related infections is generally carbapenems [6]. NFT, fosfomycin, tromethamine, quinolones or TMP/SMX may be alternative choices [5,6]. None of the isolates from the patients in this study were susceptible to TMP/SMX or CIP. Aminoglycosides were possibly not chosen owing to their toxic side effects. In Turkey, the drug acquisition cost of a 14-day carbapenem treatment is 349–508 times more than 50 mg × 4 of NFT (depending on the selected carbapenem, i.e. imipenem/cilastatin, ertapenem, doripenem or meropenem).

NFT is a specific antibiotic for infections of the urinary tract. It is bacteriostatic at low concentrations and bactericidal at high concentrations. The oral form of NFT is absorbed well. Approximately 60% is bound to plasma proteins and is metabolised in the liver; ca. 30–50% of the given dosage is excreted via the urine. Following oral administration, urine drug concentrations of NFT range between 50 µg/mL and 150 µg/mL. Its disadvantages include the requirement of dosing q6h and low tissue concentrations [3].

Recent surveys have found a persisting low prevalence of resistance to NFT (1.9–7.7%) among urinary *E. coli* isolates, including those resistant to TMP/SMX or CIP [3]. Resistance rates to NFT in ESBL-negative and ESBL-producing *E. coli* were reported to be 6.6% and 23.2%, respectively, from a tertiary care educational hospital in Turkey [4]. In a recent systematic review of Turkish publications involving *E. coli* strains isolated from UTI cases, NFT resistance was reported as 18.4% (624/3397 strains) in the period 2002–2007 [1]. Resistance rates of NFT reported from developing countries range between 6.6% and 31.6% [9,10]. Rates such as 6.2% from Spain and 3.7% from England are also reported [11,12]. NFT has been used for a very long time for the treatment of UTIs, however the introduction of CIP to the market has limited its consumption. The fact that NFT is effective both in vitro and in clinical studies against ESBL-producing *E. coli* suggests that it may be an important and economical treatment option in the near future [13].

In previous randomised controlled trials, 7 days of NFT was found to be superior to placebo and similar to CIP, TMP/SMX and fosfomycin in uncomplicated cystitis of females [14,15]. The dosages of NFT used in the trials ranged between 100 mg every 24 h and q6h. Microbiological efficacy 4–10 days after the end of NFT treatment ranged between 80% and 86%. The presented series comprised cases who had received NFT as empirical therapy. The dosage was 50 mg q6h, probably due to prospectus information of the drug.

The treatment duration was 14 days, probably due to the fact that the majority of the cases were complicated LUTI [7]. Despite longer treatment, the microbiological success rate 7–9 days after the end of treatment in complicated cases was 69%. The lower response rate in complicated cases was not an unexpected outcome owing to the complicated nature of the cases. However, in non-complicated cases the overall microbiological success rate was 71% (10/14). We may speculate that the ca. 10% lower success rate in the non-complicated cases may be due to the low number of treated patients. Another speculation may be the possibility of relatively high (but still in the susceptibility range of CLSI criteria) NFT minimum inhibitory concentrations (MICs) of *E. coli* in complicated cases, which may conceivably be associated with failure. However, we do not have NFT MICs of the strains.

In the present study, none of the cases had fever or leukocytosis. Hence, we cannot comment about the efficacy of NFT in that patient group. According to previous studies, patients with acute pyelonephritis respond inconsistently to NFT, and bacteraemias have occurred during NFT treatment, presumably due to inadequate serum concentrations [3]. Therefore, NFT should not be used for treatment of pyelonephritis. Although NFT is indicated in

non-complicated UTI with *E. coli*, the current data show that the drug can be effective in more than two-thirds of complicated cases without fever or leukocytosis.

Major adverse events of NFT are related to the gastrointestinal system and skin [3]. In the presented series there was only one case of nausea; there were no other adverse events. In the published trials there were few serious side effects with NFT and it was considered as a safe and effective first-line treatment in uncomplicated LUTI.

The main limitation of this study is the fact that it is a retrospective cohort study involving a relatively small number of cases but not a randomised and/or controlled study. Lack of NFT MICs, which may possibly be associated with some of the failures, is another disadvantage. In addition, since this was a retrospective study, we did not have 28–31-day control cultures of all cases. However, to our knowledge these are the first data evaluating NFT in the treatment of LUTI due to ESBL-producing *E. coli* as well as in patients with complicated UTI.

These results suggest that NFT is a suitable, effective and cheap alternative in the treatment of ESBL-producing *E. coli*-related lower UTI. A prospective randomised controlled study including MIC data could help to determine whether these retrospective findings are generalisable.

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