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Soluble Nitrofurans in Recurrent Urinary Tract Infections: Unexpected Findings from 2014 Latvian Study

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Abstract

Antimicrobial resistance is one of the major global burdens and challenging the advancements in biomedical research. Urinary Tract Infection (UTI) is one of that kind, which is caused by bacteria, fungi and or virus. The treatment options also vary based on the cause, antibiotics are recommended for bacterial UTI whereas antivirals are effective against fungal/viral UTI. The recent findings uncovered the side effects of fluoroquinolones in empiric UTI treatment. Hence, re-evaluation of efficacy profiles of current empiric UTI treatment with nitrofuran derivates (NFD) is necessary.

Keywords: UTI; Adults; Empiric; Nitrofuran derivate; Furamags; Soluble nitrofuran

Introduction

In this study, we aimed to present an additional analysis to the original study comprised in July-November 2014, in which Latvian physicians submitted the anonymous patient data on recurrent UTI treatment in their practice. The study included 2 groups (patients with no urine culture growth group and with NFD-resistant cultures group) and a soluble nitrofuran derivate (Furaginum soluble=potassium N-(5′-nitro-2′-furilalliliden)-1-aminogidantoin with magnesium carbonate) was used. The results showed that the soluble nitrofuran derivate was clinically effective in culture-negative or NFD-resistant patients. There was not a single case without any improvement in controlled parameters. It was clinically effective in all cases, including pyelonephritis, even against the seemingly resistant flora.

In summary, soluble NDF is safe, well tolerated and effective first-line choice to treat empiric UTI (including cystitis, pyelonephritis, and recurrent UTI). However, further investigations need to be done to compare the outcomes of standard non-soluble NFD (e.g. Nitrofurantoin).

Background

Antimicrobial resistance, a leading global burden and mounting rapidly, which results in a significant gap between the infections caused by multidrug resistant bacteria and the available antibiotics. According to the data from the European organizations, resistant *Escherichia coli* strains annually account to 32,500 cases with 5,100 deaths and 358,000 hospitalization days [1,2]. The urinary tract infection is one of this kind and the available treatment options are limited. Fluoroquinolones are a class of antibiotics that act as either bactericidal and or bacteriostatic that are significant in the treatment of infections. However, a safety review by US FDA found remarkable side effects (disabling side effects), hence further use of fluoroquinolones in UTI treatment prohibited [3-6].

In Latvia, as an alternative, first line treatment option, a soluble Nitrofuran Derivate (NFD) Furamags® (Furaginum solubile=potassium N-(5′-nitro-2′-furilalliliden)-1-aminogidantoin with magnesium carbonate) is recommended for use. Nitrofuran derivates are specific due to the presence of a furan ring in the structure, thus, it is believed that all NFDs are similar in antimicrobial activity but may/may not identical in bioavailability [7,8]. The cross resistance of NFDs is well studied in *E. coli* and allow the commercial use of NFDs in diagnosis and treatment [9,10].

In Latvia, Furamags® was first synthesized in 1979 and since then there were no remarkable side effects observed. Moreover, it is 3 times less toxic than Nitrofurantoin and higher bioavailability than Furazidin, therefore, it has been explored in pediatric treatment [11,12].

Objectives

To evaluate the efficacy of the currently recommended empiric UTI treatment with Furaginum solubile against UTI patients with NFD-resistant floras.

Study design

A study conducted in Latvia in between July-14 to Nov-14, the Latvian family physicians were asked to submit data of patients with UTI in their practice. Over the study period, a total of 113 anonymous patients [103 female (91.15%) and 10 male (8.85%)] electronic data files were received and analyzed. The data were extracted and recorded as follows:

First visit: Age and sex documentation, complaints documentation, obtaining and documenting urinalysis, obtaining and documenting urine culture (clean catch), empiric treatment initiation with Furamags® 50 mg twice daily, continued towards the second visit with a minimum of a seven full days.

Second visit: After a minimum of a seven full days of empiric therapy: complaints documentation, obtaining and documenting urinalysis, side effects documentation.

Inclusion criteria

Anonymous outpatient medical records, patients age over 18 years, patients with recurrent UTI defined as three UTI episodes per year or two UTI episodes with interval of 6 months or shorter. UTI was defined as a combination diagnosis based primarily on complains (symptoms) and confirmed by positive laboratory tests (urinalysis and/or culture) as further described.

Methods and Documentation

Complains were documented as: Disuria (present/absent), flank, abdominal or back pain (present/absent), fewer (present/absent).

Urinalysis was documented: White Blood Cell (WBC) count below 25 WBC/mcl as negative, proteinuria with values below 0.25 g/l as negative, nitrite test results as positive/negative, pH within values 5 to 7 as normal.

Urine cultures (BACTEC system) were documented as: positive/no growth, flora identification, CFU count, where values 5 × 104 and above accounted as positive, flora sensitivity against NFD (sensitive/resistant), using standard commercially available Nitrofurantoin disks.

McNemar' test was used for evaluating categorical variables. IBM SPSS software (v.21) was used for data analysis. All results below are statistically significant.

Results

The main results were already reported previously. Further analyzed are only two groups of patients: those with NFD-resistant flora and those with negative urine culture. Flora resistance against NFDs was found in 27 patients (24%), and there were 19 culture-negative patients (17%).

Culture-negative patients

First visit: Disuria was present in 18 (94.74%) cases, abdominal and flank pain was present in 13 (68.42%) cases, fewer were present in 7 (36.84%) cases. First urinalysis showed WBC count over 25 WBC/mcl in 15 (78.95%) cases, proteinuria was positive in 3 (15.79%) cases, nitrite test was positive in 6 (31.58%) cases.

Second visit: Disuria was absent in all cases, abdominal and flank pain was present in 2 (10.53%) cases, fewer was absent in all cases. Second urinalysis showed WBC count over 25 WBC/mcl in 2 (10.53%) cases, proteinuria was absent in all cases, nitrite test was positive in 4 (21.05%) cases (Figures 1 and 2).

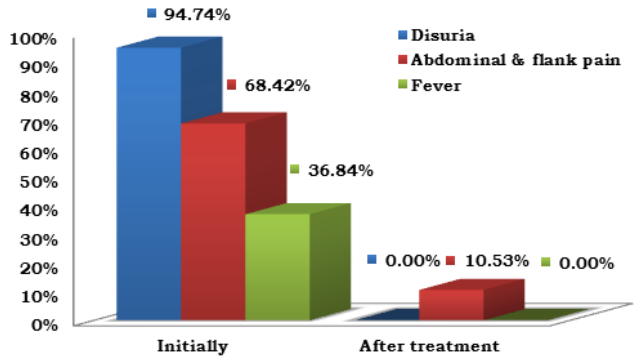

Figure 1: Complaints in culture-negative patients.

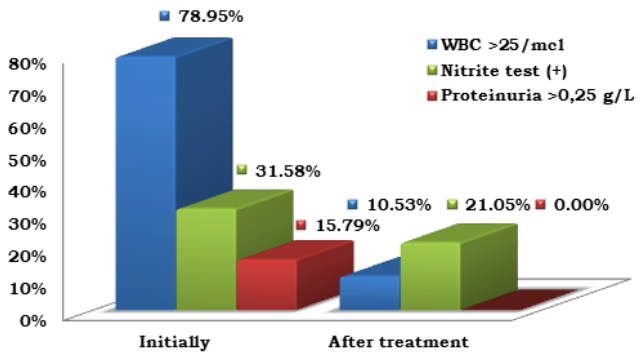

Figure 2: Urinalysis in culture-negative patients.

NFD-resistant patients

First visit: Disuria was present in 25 (92.59%) cases, abdominal and flank pain was present in 22 (81.48%) cases, fewer was present in 5 (18.52%) cases. First urinalysis showed WBC count over 25 WBC/mcl in 16 (59.26%) cases, proteinuria was positive in 7 (25.93%) cases, nitrite test was positive in 8 (29.63%) cases.

Second visit: Disuria was present in 2 (7.41%) cases, abdominal and flank pain was present in 2 (7.41%) cases, fewer was absent in all cases. Second urinalysis showed WBC count over 25 WBC/mcl in 2 (7.41%) cases, proteinuria was absent in all cases, nitrite test was positive in 2 (7.41%) cases (Figures 3 and 4).

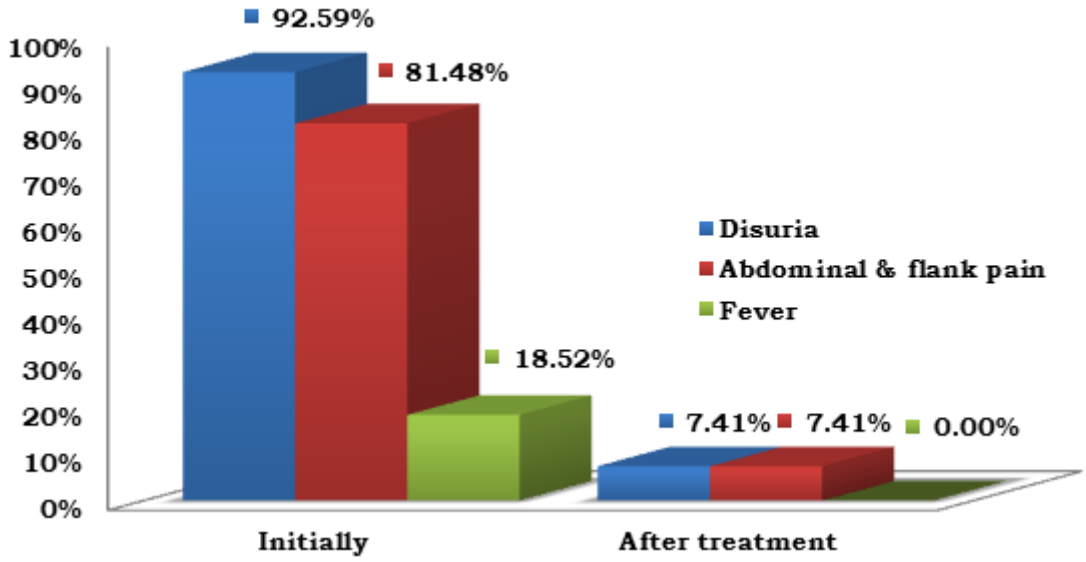

Figure 3: Complaints in NFD-resistant patients.

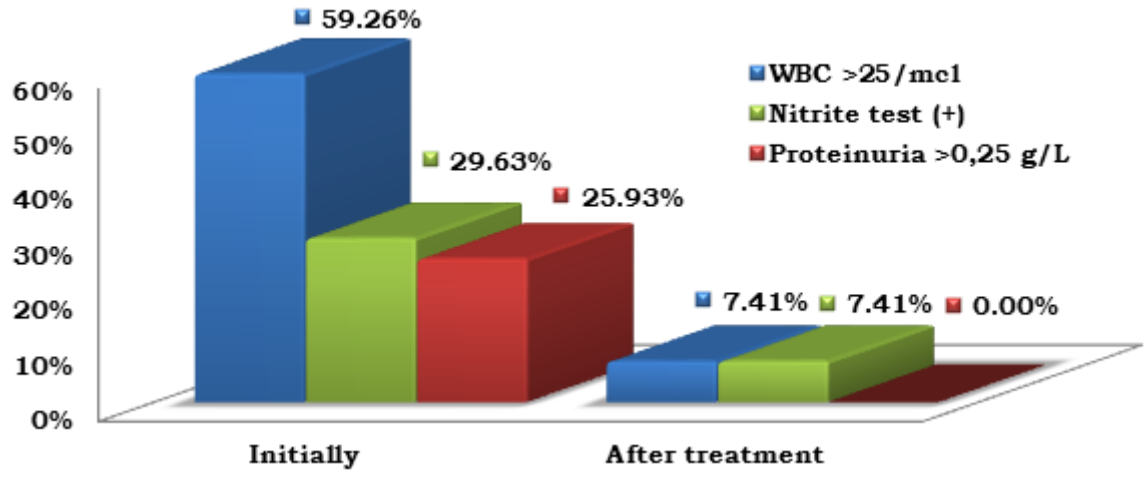

Figure 4: Urinalysis in NFD-resistant patients.

Discussion and Conclusion

In the last few years, the resistance to the first-line antimicrobial agents has been increased, particularly, resistances to fluoroquinolones have been observed in *E. coli*. As there are significant adverse effects associated with fluoroquinolones, co-trimoxazole, or cephalosporins, etc., therefore, it is important to regularly update the bacterial flora spectrum data and local drug recommendations. Nitrofuran derivates and fosfomycin are highly recommended as front-line treatment options for UTI and uncomplicated community-acquired cystitis treatment [13-17].

The laboratory finds suggested that there are no expected benefits of soluble nitrofuran derivates (Furamags® in particular) due to resistance to the flora or unknown flora, however, clinical effectiveness observed in all patients. This indicates that the bioavailability of the soluble NFD is better than expected, on the other hand, there might be a failure in BACTEC system. Moreover, in traditional practices, the usage of NFDs believed to be not suitable to treat pyelonephritis, however, the much better bioavailability of soluble NFDs overruns the obstacle and the previous pediatric studies proved the effectiveness and clinical outcomes of NFDs. The mechanism of action of NFDs is multifactorial that provide a unique of antibacterial activity against known/unknown resistant flora. NFDs could actively inhibit important cellular and molecular events involved in protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis and cell-wall synthesis, further results in better patient outcomes [18,19]. Reports suggested

that the tolerance of Furamags® is remarkable and the side effects rate is significantly lower when compared with earlier studies. In comparison, up to 34%, gastrointestinal intolerance for the Nitrofurantoin crystalline form and up to 13% for the Nitrofurantoin macrocrystalline form was reported [20].

In conclusion, Furamags® is a safe, well tolerated and effective front-line treatment choice across many infections including cystitis, pyelonephritis, and recurrent UTI. However, further research with large sample sizes and more national cohorts is required to advocate the clinical effectiveness, safety and efficacy profiles of standard non-soluble NFD (Nitrofurantoin).

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