

## Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women

### BACKGROUND:

- Fosfomycin and nitrofurantoin usage has increased since recent urinary tract infection guidelines released in 2010 that indicated them as first-line therapies. Uncertainties exist regarding the clinical efficacy of both drug regimens, especially single dose fosfomycin.
- Fosfomycin may have decreased efficacy due to increased resistance and the drug's highly variable concentrations in urine. The efficacy of fosfomycin has been compared to nitrofurantoin in only a few clinical trials.

### OBJECTIVE:

- To assess the efficacy of 5-day nitrofurantoin compared to a single dose of fosfomycin for clinical resolution of uncomplicated urinary tract infections.

### METHODS

- **Design:** Multicenter, open-label/analyst-blinded, randomized parallel trial.
- **Inclusion Criteria:** Female gender, age  $\geq 18$  years, written informed consent, urine dipstick test positive for either nitrites or leukocyte esterase, and at least one of four key UTI symptoms that could be attributed to an uncomplicated UTI: dysuria, urgency, frequency, suprapubic tenderness.
- **Exclusion Criteria:** Pregnancy or planned pregnancy, symptoms of UTI in the preceding 4 weeks, active upper UTI, indwelling catheter, immunosuppression, and renal insufficiency.
- **Primary Outcome:** Clinical response in the 28 days following completion of therapy
- **Secondary Outcomes:** Bacteriologic response at 14 and 28 days after therapy completion, clinical response at 14 days after therapy completion, duration of symptoms after treatment initiation, incidence of progression to pyelonephritis or urosepsis, lost days of work, incidence of severe adverse effects, incidence of confirmed UTI at baseline, incidence of baseline resistance, and emergence of phenotypic bacterial resistance.
- 513 patients were randomized: 255 received nitrofurantoin 100 mg three times a day for five days and 258 received a single dose of fosfomycin 3 g.
- To obtain a power of 90%, clinical superiority by 10%, and a 5% level of significance, 300 patients per group were needed. 513 were enrolled, ensuring 80% power for the primary outcome.
- Data were analyzed for both intent-to-treat and per-protocol.

### RESULTS

- 244 nitrofurantoin patients and 241 fosfomycin patients were included in the primary analysis. 237 in each group were included in the per-protocol analysis.
- **Primary Outcome Measures:** There was a statistically significant difference in clinical response at 28 days after therapy completion between nitrofurantoin (70%) and fosfomycin (58%);  $p=0.004$ .
- **Secondary Outcome Measures:** The following secondary outcomes were statistically significant (nitrofurantoin arm, fosfomycin arm; p value): clinical response at 14 days

after completion (75%, 66%; 0.03), bacteriological success at day 14 (82%, 73%; 0.04) and at day 28 (74%, 63%; 0.04).

- **Author's Conclusion:** 5-day nitrofurantoin, compared with single-dose fosfomycin, resulted in significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion in women with uncomplicated urinary tract infections.

#### STRENGTHS

- Inclusion and exclusion criteria allow for extrapolation to the population that UTIs are most commonly diagnosed in.
- Conducted and reported post-hoc analyses to show worst and best case scenarios with regard to the data handling.

#### LIMITATIONS

- Open-label
- Laboratory analyses not centralized
- Does not follow IDSA guidelines for nitrofurantoin dosing
- Increased resistance to nitrofurantoin in Poland
- Only about 77% of the participants had a positive urine culture at baseline

#### CONCLUSIONS

- The study concluded that 5-day nitrofurantoin is superior to single-dose fosfomycin for the treatment of urinary tract infection among women. There are some concerning limitations to the study. The largest concern was the dosing of nitrofurantoin, IDSA guidelines recommend twice a day and three times a day were used. This increase in dosage could have significantly impacted the results of the study. The results found in the study would be difficult to extrapolate to practice in the United States, as most places utilize the IDSA guidelines.
- Future research:
  - Future research in the area should focus on comparing the recommended dosages in the IDSA guidelines, since those are the guidelines most used in the United States. Also, future research should be double-blinded to reduce bias in the study and a better methods to identify and report adherence should be used. Lastly, controlled laboratory measures and a more similar population base would be preferred for studies moving forward.

**Reference:** Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, Kosiek K, Martinez de Tejada B, Roux X, Shiber S, Theuretzbacher U, von Dach E, Yahav D, Leibovici L, Godycki-Cwirko M, Mouton JW, Harbarth S. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. *JAMA*. 2018 May 1;319(17):1781-1789. doi: 10.1001/jama.2018.3627.

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