Retrospective Review on the Safety and Efficacy of Nitrofurantoin for the Treatment of Cystitis in the Veteran Population With or Without Renal Impairment

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Abstract

Background Nitrofurantoin has been used to treat cystitis in women; however, data supporting its use in men is lacking. In addition, recent retrospective studies have challenged the manufacturer's recommendation to avoid nitrofurantoin with creatinine clearances (CrCl) < 60 mL/min. The purpose of this study is to compare the efficacy and safety of nitrofurantoin for the treatment of acute cystitis in male and female veterans with variable degrees of renal dysfunction.

Methods A retrospective chart review was conducted in adult patients who received nitrofurantoin for acute cystitis in the outpatient setting between May 1, 2018 and May 1, 2019. The primary outcomes were rates of clinical cure as compared between males and females, and across various renal function groups (CrCl > 60 mL/min, 30 to 60 mL/min, and < 30 mL/min) following treatment with nitrofurantoin. The secondary outcome was adverse event rates.

Results A total of 446 patients were included with 278 females and 168 males. Overall clinical cure rate was 86.5% (n=386). Clinical cure rate did not vary between genders (p=0.085) or CrCl ranges (p=1.0) as shown in the figures. Benign prostatic hyperplasia (BPH) was associated with decreased odds of clinical cure (odds ratio [OR] 0.50 [95% confidence interval (CI) 0.26-0.99], p=0.045) in addition to cirrhosis (OR 0.21 [95% CI 0.05-0.82], p=0.025). Adverse events occurred in 2% of patients and did not vary based on gender or renal function.

Conclusion There was no statistically significant difference in clinical cure with nitrofurantoin between genders and various renal impairments. However, history of BPH and cirrhosis were associated with decreased efficacy. Subgroup analysis also revealed lower efficacy in males with CrCl greater than 60 mL/min versus females with similar renal function. This study adds to the growing body of literature suggesting that renal dysfunction with CrCl of 30 to 60 mL/min may not carry the risk of treatment failure and adverse effects previously associated with nitrofurantoin, but large randomized trials are needed to confirm these results.

Background

- The 2010 Infectious Diseases Society of America (IDSA) guidelines for treatment of uncomplicated cystitis in females recommends nitrofurantoin as a first line agent, but evidence is lacking for the safety and efficacy of nitrofurantoin in males.[1]
- Manufacturer labeling recommends avoiding nitrofurantoin in patients with CrCl < 60 mL/min; however, in 2015 the American Geriatrics Society Beers Criteria revised their recommendation to avoid nitrofurantoin in patients with CrCl < 30 mL/min based on the findings of two retrospective studies.[2,3]
- Previous retrospective studies report conflicting results regarding the efficacy and safety of nitrofurantoin in the treatment of urinary infections in males and/or patients with impaired renal function.[4,5]

Methods

Study Design: Retrospective chart review

Population: Adult patients (age ≥ 18 years old) prescribed nitrofurantoin for the treatment of acute cystitis from May 1, 2018 to May 1, 2019 from the Michael E DeBakey Veterans Affairs Medical Center

Exclusion: Asymptomatic bacteriuria; prostatitis; pyelonephritis; culture isolates resistant to nitrofurantoin; concomitant antibiotics other than nitrofurantoin during treatment; nitrofurantoin prescribed < 5 days or > 14 days; nitrofurantoin for chronic suppressive therapy or prophylaxis

Primary Outcome: Clinical cure defined by both of the following:
- Treatment discontinuation after 5-14 days of nitrofurantoin at an appropriate dose and frequency
- No antibiotics initiated and no signs or symptoms of a urinary tract infection within 14 days of treatment completion

Secondary Outcome: Adverse drug effects identified during and up to 7 days following nitrofurantoin therapy

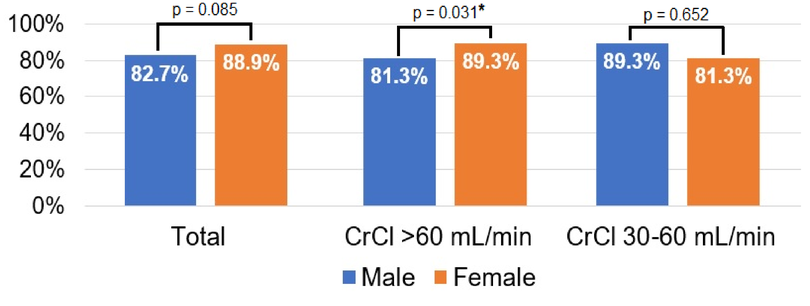
Results

Table 1. Baseline characteristics

Baseline characteristic	Total (n = 446)	Male (n = 168)	Female (n = 278)	p value (Male vs. Female)
Age (years)	58.0 (26.5)	69.0 (13.0)	48.0 (24.0)	<0.001*
CrCl (mL/min)	91.4 (40.5)	82.2 (37.0)	96.4 (41.2)	<0.001*
Treatment duration (days)‡	7.5 ± 1.9	8.4 ± 2.4	7.0 ± 1.4	<0.001*
CrCl range (mL/min)				
>60	401 (89.9%)	139 (82.7%)	262 (94.2%)	
30-60	44 (9.9%)	28 (16.7%)	16 (5.8%)	
<30	1 (0.2%)	1 (0.6%)	0 (0%)	
Urinary catheter use	25 (5.6%)	24 (14.3%)	1 (0.4%)	<0.001*
Urine culture growth	289 (83.0%)	112 (83.5%)	177 (82.7%)	0.359
Culture organism ¥				
E. coli	170 (48.8%)	74 (55.2%)	96 (44.9%)	
E. coli (ESBL-producing)	16 (4.6%)	14 (10.4%)	2 (0.9%)	
Streptococcus sp.	16 (4.6%)	6 (4.5%)	10 (4.7%)	
Staphylococcus sp.	10 (2.9%)	4 (3.0%)	6 (2.8%)	
Enterococcus sp.	12 (3.4%)	9 (6.7%)	3 (1.4%)	
Klebsiella sp.	14 (4.0%)	5 (3.7%)	9 (4.2%)	
Other sp.†	62 (13.9%)	19 (14.2%)	43 (15.5%)	

Data are presented as median with interquartile range in parenthesis (except as indicated), or as number of patients with percentage in parenthesis; ‡ Data presented as the mean ± standard deviation; ¥ Percent calculated out of total number of cultures; † Gram-positive organisms, lactose-negative/positive gram-negative rods, *Candida sp., Lactobacillus sp., Aerococcus urinae, Proteus sp. Citrobacter sp., Gardnerella vaginallis*; P values were calculated using Wilcoxon rank sum tests or student's t-test for continuous variables and Chi-square or Fisher's exact tests for nominal variables, where appropriate; CrCl = creatinine clearance; ESBL = extended-spectrum beta-lactamase; *p < 0.05

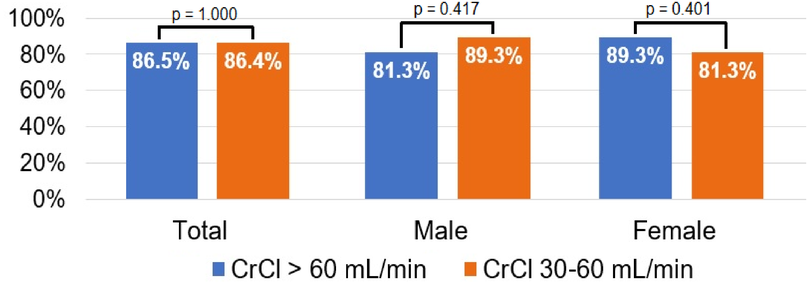
Figure 1. Rates of clinical cure by gender



- Clinical cure rate did not vary between genders (OR 0.60 [95% CI 0.35, 1.04]; p=0.085)

Results

Figure 2. Rates of clinical cure by renal function



- Clinical cure rate did not vary between CrCl > 60 mL/min and CrCl 30-60 mL/min (OR 1.01 [95% CI 0.40, 2.44]; p=1)

Table 2. Rates of adverse events by gender and renal function

Adverse events [# AE/total (%)]		OR (95% CI)	p value
Male	Female		
4/168 (2.4%)	5/278 (1.8%)	1.33 (0.35, 5.00)	0.734
CrCl > 60 mL/min	CrCl 30-60 mL/min		
7/401 (1.8%)	2/44 (4.6%)	0.37 (0.075,1.85)	0.221

P values were calculated using logistic regression; CrCl = creatinine clearance; OR = odds ratio; CI = confidence interval

- BPH was associated with decreased odds of clinical cure (OR 0.50 [95% CI 0.26, 0.99]; p=0.045)
- Cirrhosis was associated with decreased odds of clinical cure (OR 0.21 [95% CI 0.06, 0.82]; p=0.025)

Conclusions

- No difference in clinical cure with nitrofurantoin between genders or various levels of renal function
- Subgroup analysis revealed lower efficacy in males with CrCl > 60 mL/min versus females with similar renal function
- History of cirrhosis or BPH associated with decreased rates of clinical cure

References

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