Effectiveness and safety of nitrofurantoin in outpatient male veterans

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Ther Adv Urol

2015, Vol. 7(4) 186–193

DOI: 10.1177/

1756287215581556

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Abstract

Objectives: The aim of the study was to assess both the safety and the effectiveness of nitrofurantoin in male veterans treated for urinary tract infections (UTIs) with varying degrees of renal impairment in the outpatient setting. Nitrofurantoin is an important oral option for treating UTIs given increasing resistance to commonly used agents. Nitrofurantoin is currently contraindicated in patients with a creatinine clearance (CrCl) of < 60 ml/min, but the reason for this threshold has not been well documented.

Methods: Data were collected through a retrospective chart review from January 2004 to July 2013 of men who had received nitrofurantoin. Bivariate analyses followed by multivariate analyses were performed between patients experiencing clinical cure and those who did not, to determine factors significantly impacting effectiveness.

Results: The Gram stain of the organism causing the UTI and CrCl were significant factors impacting effectiveness. For every 1 ml/min increase in CrCl, the odds of clinical cure increased by 1.3%. Patients with Gram-negative UTIs predictably had 80% cure rates with CrCl around 60 ml/min. Patients with Gram-positive UTIs required higher CrCl, nearing 100 ml/min, to establish an 80% cure rate. Adverse effects did not vary with CrCl.

Conclusions: The odds of clinical cure varied with CrCl and with the type of organism causing the UTI, while adverse events did not differ based on renal function. A minimum CrCl of 60 ml/min is suggested for men to achieve an 80% cure rate for UTIs with the most common urinary pathogens.

Keywords: effectiveness, nitrofurantoin, safety, urinary tract infection

Introduction

Urinary tract infections (UTIs) are amongst the most common types of infections in older patients [Mouton *et al.* 2001]. They appear most commonly in otherwise healthy women, while those infections that occur in men are usually the result of a structural or neurological abnormality [Coyle and Prince, 2008]. As adults age, the incidence of UTIs increases, and the difference in rates between genders decreases [Coyle and Prince, 2008]. These structural or neurological abnormalities can be associated with several clinical factors including the use of catheters, neurogenic-ity of the bladder, and prostate enlargement in men [Mouton *et al.* 2001]. This study focuses on the effectiveness and safety of nitrofurantoin treatment of complicated UTIs in older men. Treatment of uncomplicated UTIs and pyelone-phritis in men is a pressing topic, however

guidelines, such as those published by the Infectious Disease Society of America, are exclu-sive to women. Nitrofurantoin is recommended as first-line treatment for uncomplicated UTIs in women, however efficacy data in men are lacking [Gupta *et al.* 2011]. Antibiotic resistance is forc-ing clinicians to use nitrofurantoin in the male population, despite lack of randomized controlled trials and guidelines to support its use in this population.

Antibiotic resistance among Gram-negative uri-nary pathogens is increasing. Agents commonly used to treat UTIs in the USA include quinolo-nes, trimethoprim/sulfamethoxazole, and nitro-furantoin. The most prevalent pathogen implicated in UTIs is *Escherichia coli* [Hooton *et al.* 2010; Gupta *et al.* 2011]. One study meas-ured the change in antimicrobial resistance to

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outpatient urinary isolates of *E. coli* in the USA between 2000 and 2010. Steady increases in resistance were seen for most of the antibiotics tested. Trimethoprim/sulfamethoxazole resistance increased from 17.9% to 24.2%, and ciprofloxacin resistance increased from 3.0% to 17.1%. Resistance to nitrofurantoin rose from 0.8% in 2000 to 1.6% in 2010, but remained low relative to other agents [Sanchez *et al.* 2012]. Given the relative stability of *E. coli* susceptibilities to nitrofurantoin, and low rates of resistance, nitrofurantoin is becoming an important therapeutic option for treating outpatient UTIs in the USA. Nitrofurantoin is a bactericidal drug that inhibits bacterial protein synthesis by attacking ribosomes. It is reduced by bacterial flavoproteins to reactive intermediates that nonspecifically inactivate ribosomal proteins leading to inhibition of protein synthesis. Nitrofurantoin's bactericidal nature, nonspecific molecular target, and limited exposure outside the urinary tract may have contributed to the lack of large increases in resistance seen with this drug [McOsker and Fitzpatrick, 1994].

The urinary recovery of nitrofurantoin is linearly correlated with creatinine clearance (CrCl) according to Sachs and colleagues. They studied a group of patients with uremia and found little or no drug in the urine during the 10-h collection period (CrCl 0.2–29 ml/min equated to a 10-h urinary recovery of nitrofurantoin of < 1.0–13.3 mg). Conversely, patients with CrCl > 60 ml/min, had urinary recovery of up to 48 mg in a 10-h period [Sachs *et al.* 1968]. In the USA, nitrofurantoin is currently contraindicated in those patients with a CrCl of < 60 ml/min *via* the Cockcroft–Gault equation [Macrobid, 2009]. Historically, nitrofurantoin has been contraindicated in patients with a CrCl of < 40 ml/min [Oplinger and Andrews, 2013]. The reason for this change in threshold is unknown, but several small studies, such as those done by Sachs and colleagues have shown little drug recovery in the urine of those patients with CrCl of < 60 ml/min [Sachs *et al.* 1968]. In a recent review, the literature supporting a nitrofurantoin contraindication for CrCl of < 60 ml/min was evaluated and it was determined that the evidence was insufficient to support a contraindication at this threshold [Oplinger and Andrews, 2013]. These authors concluded that with limited data available, using a cutoff of 40 ml/min could be considered in the appropriate patient, defined as an uncomplicated

UTI, when susceptibility data support its use and when the duration is less than 1 week. Their conclusion was based primarily on the fact that the change in threshold for CrCl from 40 ml/min to 60 ml/min was based on pharmacokinetic drug concentration studies rather than clinical trials evaluating treatment success [Oplinger and Andrews, 2013]. A retrospective review of predominantly women, assessed the effectiveness and safety of nitrofurantoin in renally impaired inpatients finding similar cure rates in patients with glomerular filtration rate (GFR) $\leq$ 50 ml/min compared with patients with GFR > 50 ml/min [Bains *et al.* 2009]. This study focuses on men to determine if the anatomical differences in the urinary tract affect the effectiveness of nitrofurantoin in men with varying renal function.

Since nitrofurantoin was introduced into the market in 1953, several serious adverse drug events (ADEs) have been reported, including hepatitis, neuropathy, blood dyscrasias, renal failure, pulmonary fibrosis, and inflammatory response syndrome [Bottiger and Westerholm, 1973; Goemaere *et al.* 2008; Forster *et al.* 2009; Namagondlu *et al.* 2010; Czaja, 2011; Tan *et al.* 2012]. Loughridge found serum levels of 5.1–6.5 μ g/ml in a patient with uremia, which was attributed with toxicity [Loughridge, 1962]. Due to the serious nature of these reactions, nitrofurantoin effects should be monitored. Pulmonary reactions occur more frequently in patients with lower CrCl according to one reference [Geerts *et al.* 2013].

Rising rates of resistance have led to limited options for the treatment of UTIs. Ciprofloxacin and trimethoprim/sulfamethoxazole are no longer reliable first-line agents for Gram-negative infections. The purpose of this retrospective study is to assess the safety and effectiveness of nitrofurantoin in outpatient men being treated for UTIs. Prostate infections were excluded from efficacy analysis because of the poor prostatic fluid levels of nitrofurantoin resulting in subtherapeutic levels of $\leq$ 1 μ g/ml [Dunn and Stamey, 1967; Fowler, 2002]. This study aimed to determine a CrCl threshold to achieve an 80% cure rate. It also sought to determine a difference if the patient had a UTI with Gram-positive *versus* Gram-negative or mixed infection. With these results, treatment decisions can be made early, generally within 24 h of culture specimen collection, allowing for effective care in a timely fashion.

Materials and methods

Study setting

The Veteran Affairs (VA) Western New York Healthcare System consists of two healthcare facilities in Buffalo and Batavia, as well as community-based outpatient clinics in Dunkirk, Jamestown, Lackawanna, Lockport, Niagara Falls, Olean, and Springville. The institutional review board and research and development committee have approved this study. Susceptibilities for urine cultures were tracked on a duplicate-suppressed urine-specific antibiogram. *E. coli* susceptibilities during the time period were as follows: ciprofloxacin (64–78%), trimethoprim/sulfamethoxazole (70–83%), nitrofurantoin (97–100%), and aminoglycosides (85–93%). Approximately 10–12% of the *E. coli* isolates produced extended spectrum beta-lactamases. *Enterococcus faecalis* susceptibilities for ciprofloxacin were 38–42% and 98–100% for nitrofurantoin. *E. faecium* susceptibilities for nitrofurantoin were 56–71%.

Study design

This was a retrospective study of male veterans who were dispensed a prescription of nitrofurantoin dating from 1 January 2004 to 31 July 2013. Male patients over the age of 18 years who sought care in the VA Western New York Healthcare System and received nitrofurantoin for the treatment of a UTI in the outpatient setting were included. Patients were included if they had signs and symptoms of cystitis or an infection in the lower urinary tract. Patients with a catheter-associated UTI were also included. Cultures were collected for all patients; however, lack of cultures did not lead to exclusion. Patients were excluded from the study if they received concurrent antibiotics in addition to nitrofurantoin. Patients were excluded from the effectiveness analysis if they were prescribed nitrofurantoin for chronic suppressive therapy, prophylaxis, posturological procedure, prostatitis, pyelonephritis, had resistant urinary isolates (resistant cultures or known non-susceptibility to nitrofurantoin), or did not have clear signs and symptoms of a UTI (defined as dysuria, urinary frequency, fever, rigors, flank pain, or nausea). Patients with an indwelling catheter could also have symptoms including suprapubic pain, urgency, rigors, or an acute mental status change with no alternative diagnosis. Patients with an adverse reaction clearly related to another medication were excluded from the safety analysis.

Study endpoints

The purpose of this retrospective study was to assess the safety and effectiveness (clinical cure) of nitrofurantoin in outpatient men being treated for UTIs. This study aimed to determine a CrCl threshold to achieve an 80% cure rate. It also sought to determine a difference if a patient had a UTI with a Gram-positive *versus* Gram-negative or mixed infection. Clinical cure was defined as no signs or symptoms of a UTI for 14 days after stopping nitrofurantoin, without other antibiotic use. If a second antibiotic was prescribed subsequently during this time period for a UTI, treatment with nitrofurantoin was considered a failure.

The secondary endpoint was the occurrence of ADEs related to nitrofurantoin therapy. Patients were divided into three groups based on their CrCl, that is, CrCl < 40 ml/min, CrCl 40–59 ml/min, and CrCl ≥ 60 ml/min, to determine the presence of ADEs with various levels of renal function. ADEs included gastrointestinal distress, headache, peripheral neuropathy, rash, acute pulmonary reaction, hepatotoxicity, hemolytic reaction, or miscellaneous. Patients were followed for ADEs for 7 days after completion of nitrofurantoin.

Data collection

Medical and laboratory data were collected by chart review from the VA's computerized patient record system. Data collected included age, height, weight, serum creatinine, liver function enzymes (aspartate aminotransferase, alanine transaminase), reported signs and symptoms of UTIs, comorbidities, presence of a catheter, type of catheter if applicable, pH of the urine, type of bacteria isolated with susceptibilities, and the formulation of nitrofurantoin dispensed as well as the directions and duration of treatment. Demographics and laboratory data were collected closest to the date that the nitrofurantoin prescription was written, but no greater than 6 months apart from the infection.

Statistical analysis

All statistical analyses were performed using JMP version 10. Using an estimated cure rate of 80%, 400 patients were needed for 80% power with a 95% confidence interval (CI) [Bains *et al.* 2009]. A bivariate analysis was performed between those who experienced clinical cure and those who

Table 1. Demographics and comorbidities: bivariate analysis of patients included in the effectiveness analysis.

Characteristic	Total cohort	No clinical cure <i>n</i> = 110	Clinical cure <i>n</i> = 375	<i>p</i> value
Age (years)	73.32 ± 11.30	75.37 ± 12.37	72.71 ± 10.91	0.028
Height (m)	1.75 ± 0.08	1.75 ± 0.09	1.76 ± 0.07	0.37
Weight (kg)	86.82 ± 20.79	82.23 ± 17.23	88.18 ± 21.55	0.0074
Serum creatinine (μmol/L)	98.12 ± 37.12	107.00 ± 44.20	94.58 ± 35.36	0.0056
Creatine clearance (ml/min)	66.11 ± 26.78	59.90 ± 27.54	67.93 ± 26.31	0.0037
Aspartate aminotransferase (units/L)	23.02 ± 16.02	23.62 ± 18.22	22.83 ± 15.27	0.66
Alanine transaminase (units/L)	26.13 ± 19.34	26.27 ± 24.03	26.08 ± 17.68	0.93
Postherpetic neuralgia	0.62% (<i>n</i> = 3)	0.9% (<i>n</i> = 1)	0.5% (<i>n</i> = 2)	0.66
Neuropathy	17.94% (<i>n</i> = 87)	15.5% (<i>n</i> = 17)	18.7% (<i>n</i> = 70)	0.44
Prior pulmonary reaction	0.41% (<i>n</i> = 2)	0.9% (<i>n</i> = 1)	0.4% (<i>n</i> = 1)	0.36
Chronic obstructive pulmonary disease	21.65% (<i>n</i> = 105)	15.5% (<i>n</i> = 17)	23.5% (<i>n</i> = 88)	0.073
Liver dysfunction	5.57% (<i>n</i> = 27)	4.6% (<i>n</i> = 5)	5.9% (<i>n</i> = 22)	0.60
Diabetes mellitus	37.32% (<i>n</i> = 181)	38.2% (<i>n</i> = 42)	37.1% (<i>n</i> = 139)	0.83

failed therapy to determine which factors significantly impacted effectiveness. For continuous data, an independent sample student's *t*-test was used to determine significance and for categorical data, a chi-square test was used.

All values from the multivariate with a *p* ≤ 0.05 were included in the multivariate logistic regression analysis. Variables were eliminated in a backwards fashion, with the least significant variable eliminated and a new model created in a stepwise fashion. Models were built controlling for significant factors to determine a CrCl threshold to achieve an 80% clinical cure rate for Gram-positive, Gram-negative, and mixed infections.

Analysis of variance was used to determine any significant difference in ADEs across the three CrCl groups.

Results

In total, 1551 patients had a prescription dispensed for nitrofurantoin within the study time period. The inclusion criteria were met by 801

patients for the safety analysis, and 485 for the effectiveness analysis. The majority of patients, 571, were prescribed Macrobid 100 mg twice daily, 164 patients received macrocrystals (50–100 mg four times/day), six patients received the suspension, and 60 patients received Macrochantin (50–100 mg four times/day).

Baseline characteristics and comorbidities are shown in Table 1. Age, weight, and CrCl were determined to be significant in the bivariate analysis for clinical cure. The patients in the group experiencing clinical cure were of younger age (72.71 ± 10.91 *versus* 75.37 ± 12.37, *p* = 0.028), heavier (88.15 kg ± 21.55 *versus* 82.23 kg ± 17.23, *p* = 0.0074), and higher CrCl (67.93 ml/min ± 26.31 *versus* 59.90 ml/min ± 27.54, *p* = 0.0037). There was no difference between cure rates in patients who had the following comorbidities: postherpetic neuralgia, neuropathy, prior pulmonary reaction, chronic obstructive pulmonary disease, liver dysfunction, or diabetes. The Charlson comorbidity index also did not vary between the groups (*p* = 0.19). The average score for patients experiencing cure was 3.84 ± 2.89 *versus* 4.65 ± 3.20 in those failing nitrofurantoin.

Of the UTI signs and symptoms that were reported to be diagnostic of UTI, only dysuria demonstrated significance in the bivariate analysis. Of the total cohort, 21% experienced dysuria, 16% had frequency, 2% had fever, rigors, or nausea, and 5% experienced flank pain or nocturia. Of those who experienced a clinical cure, 18.4% experienced dysuria *versus* 30.9%, who did not experience a cure ($p = 0.0030$). There was no significant difference in urine pH between the two groups (6.14 ± 0.75 *versus* 6.13 ± 0.69 , $p = 0.90$). Patients were treated for approximately the same duration of treatment between the success and failure groups; 8.58 ± 3.57 days *versus* 9.26 ± 6.92 days ($p = 0.28$).

Approximately 32% of the population had a catheter at the time nitrofurantoin was prescribed. There was a significant difference between the different types of catheters and those with an uninstrumented urinary tract ($p = 0.014$), with higher rates of failure in those with a Foley catheter (28% failed treatment). Of the total cohort, condom catheters were used by 2.89%, Foley catheters by 17.32%, intermittent catheters by 6.80%, and suprapubic catheters by 4.54%. There was no statistical difference when comparing cure rates with the presence *versus* absence of a catheter ($p = 0.089$). Of those who experienced clinical cure with nitrofurantoin, 29.6% had a catheter of any type *versus* 70.4% who had no catheter. For clinical failure, 38.2% had a catheter and 61.8% did not have a catheter ($p = 0.089$).

Significant factors in the effectiveness analysis, including age, weight, CrCl and Gram stain, were built into a multivariate logistic regression model to determine factors impacting the success of treatment with nitrofurantoin. A backwards elimination of the least significant factors was performed to provide a stable model. Age ($p = 0.96$) and then weight ($p = 0.051$) were eliminated leaving individual CrCl ($p = 0.030$) and Gram stain of urine culture ($p = 0.0013$) to be included in the final model. The model was rebuilt with Gram stain ($p = 0.0004$) and individual CrCl ($p = 0.0032$). In this final model, the unit odds ratio for CrCl was 1.013 (95% CI 1.004–1.023), indicating that for every 1 ml/min increase in CrCl, the odds of clinical cure also increased by 1.3%; this was a linear relationship.

Individual prediction profiles were built to determine what CrCl breakpoint would be required to establish a cure rate of 80% for the Gram stain in

the urine culture. For urine cultures with only Gram-negative organisms, primarily composed of *E.coli* in our patient population, the minimum CrCl required to achieve at least an 80% cure rate was 58 ml/min. For cultures with only Gram-positive organisms (predominately *Staphylococcus aureus* or *Enterococcus*), a CrCl of at least 98 ml/min was needed. The cutoff for mixed Gram positive and Gram negatives was > 100 ml/min, for negative cultures 63 ml/min, and for patients who did not get a urine culture 32 ml/min.

Of the patients who had a recurrence or reinfection, 123 patients had repeat urine cultures. A total of 74 patients had infection with the same bacteria with which they were infected prior to the nitrofurantoin treatment. When percentage failure was analyzed by CrCl groups, 9 failed (12.12%) in CrCl ≤ 40 ml/min, 27 failed (36.49%) in the CrCl group of 40–59 ml/min, and 51.35% failed in those with CrCl ≥ 60 ml/min ($p = 0.70$).

Of the 801 patients included in the safety analysis, gastrointestinal distress was experienced by seven patients, peripheral neuropathy by four patients, rash by two patients, acute pulmonary reaction by three patients, hepatotoxicity by four patients, and hemolytic reaction by one patient. The incidence of ADEs across the different CrCl categories is documented in Table 2. Renal function did not affect the incidence of ADEs. Statistical significance was not demonstrated for any of the reported ADEs across the different CrCl categories.

Discussion

The use of nitrofurantoin is expanding to previously unstudied populations, such as men, due to rising resistance amongst bacteria against conventionally used antibiotics such as ciprofloxacin and trimethoprim/sulfamethoxazole. This study examined the safety and efficacy of nitrofurantoin in the treatment of UTIs and catheter-associated UTIs in men. Nitrofurantoin should not be used in pyelonephritis or prostatitis, thus these subpopulations were excluded from the efficacy analysis. This study demonstrates the importance of CrCl and type of urinary microorganism in achieving a clinical cure of UTIs in outpatient men treated with nitrofurantoin. Our data suggest that using a CrCl cutoff of 60 ml/min is reasonable to achieve effectiveness in men with UTIs. Nitrofurantoin is primarily used to treat Gram-negative UTIs,

Table 2. Impact of creatine clearance on adverse drug events rate: percentage of total adverse drug events.

Event	Total cohort <i>n</i> = 801	CrCl < 40 ml/min	CrCl 40–59 ml/min	CrCl ≥ 60 ml/min	<i>p</i> value
Gastrointestinal distress	0.87% (<i>n</i> = 7)	0.12% (<i>n</i> = 1)	0.25% (<i>n</i> = 2)	0.5% (<i>n</i> = 4)	0.90
Peripheral neuropathy	0.50% (<i>n</i> = 4)	0.25% (<i>n</i> = 2)	0.12% (<i>n</i> = 1)	0.12% (<i>n</i> = 1)	0.54
Rash	0.25% (<i>n</i> = 2)	0.00% (<i>n</i> = 0)	0.00% (<i>n</i> = 0)	0.25% (<i>n</i> = 2)	0.50
Acute pulmonary reaction	0.38% (<i>n</i> = 3)	0.00% (<i>n</i> = 0)	0.25% (<i>n</i> = 2)	0.12% (<i>n</i> = 1)	0.53
Hepatotoxicity	0.50% (<i>n</i> = 4)	0.00% (<i>n</i> = 0)	0.25% (<i>n</i> = 2)	0.25% (<i>n</i> = 2)	0.67
Hemolytic reaction	0.13% (<i>n</i> = 1)	0.00% (<i>n</i> = 0)	0.00% (<i>n</i> = 0)	0.12% (<i>n</i> = 1)	0.75
Other	2.75% (<i>n</i> = 22)	0.25% (<i>n</i> = 2)	0.75% (<i>n</i> = 6)	1.75% (<i>n</i> = 14)	0.87
CrCl, creatinine clearance.					

particularly those caused by *E. coli*, and our models showed that a CrCl around 58 ml/min or above is needed to achieve a cure rate of at least 80%. The positive correlation of clinical cure rates with CrCl suggests that limiting the use of nitrofurantoin to patients with better renal function is appropriate to ensure adequate cure rates. The mechanism behind this correlation is unclear, but may be related to the lower urinary concentrations of nitrofurantoin in patients with reduced CrCl that have been demonstrated in other studies [Sachs *et al.* 1968].

Patients with no growth in their urine cultures also required a CrCl in the same range as Gram-negative cultures (63 ml/min) to achieve 80% clinical cure. It is unclear if these patients had no growth in their cultures because they did not have a bacterial UTI, or if negative cultures were a result of poor urine collection technique or undocumented pretreatment with antibiotics before the culture was obtained.

UTIs caused by Gram-positive organisms or mixed Gram-positive and Gram-negative organisms required a much higher CrCl (around 100 ml/min or higher) to achieve similar rates of clinical cure. This suggests that nitrofurantoin may not be as effective in this group of organisms, requiring higher urinary concentrations to achieve clinical cure. Another possibility is that these patients had UTIs that were more complicated, potentially leading to lower cure rates regardless of treatment. When Gram-positive infections were further analyzed, 24% of catheterized patients had a Gram-positive infection. In the Gram-positive group 36.42% had an enterococcal infection, and 54.31% had a staphylococcal infection. It seems that most of the failure was driven by the

staphylococcal isolates (25% of total failures) and enterococcal isolates (15.45% of total failures). Further studies would be needed to evaluate the specific etiological factors impacting clinical cure in these patients.

There was also a significant group of patients in our study who were treated empirically for UTIs without obtaining a urine culture. This group appears to be less affected by lower CrCl, maintaining 80% or greater cure rates to a CrCl of 32 ml/min. The exact reasons for this are unclear, but it could be due to selection bias in determining from which patients to obtain urine cultures. It is plausible that the providers may have been more apt to obtain pretreatment cultures on sicker patients, or those with greater likelihood of failure, such as those with recurrent infections, while fewer cultures were obtained on patients who had lower risk of failure with empirical treatment. This could have made the group without urine cultures appear more responsive to nitrofurantoin therapy.

A previous retrospective review looked at 356 patients and found similar cure rates in patients with an estimated GFR ≤ 50 ml/min (renal impairment) compared with patients with an estimated GFR > 50 ml/min (control group). Unlike our study, the effectiveness was predominantly assayed in women. The renal impairment group consisted of only 16% male patients [Bains *et al.* 2009]. Women with uncomplicated UTIs are generally more responsive to treatment, while UTIs in men are, by definition, complicated [Gupta *et al.* 2011]. Complicated UTIs are more often associated with anatomic abnormalities or instrumentation, and are typically more difficult to treat. These differences could have contributed to

the study failing to find a difference in cure rate with decreased renal function. Thus, patients with UTIs that are easier to treat may be able to obtain clinical cure even with lower CrCl, while those with more complicated infections require better renal function to achieve adequate therapeutic levels of nitrofurantoin in the urinary tract.

CrCl did not have a significant impact on the rate of ADEs with nitrofurantoin. However, the number of ADEs that was reported in our study was small. This is in contrast to an earlier report conducted in women, suggesting an increased rate of pulmonary reactions in patients with lower CrCl [Hooton *et al.* 2010]. Another study, similar in size to our study, indicated no difference in ADEs with different CrCl groups (GFR $\leq$ 50 ml/min *versus* $>$ 50 ml/min) [Bains *et al.* 2009]. While there is a potential for increased accumulation of nitrofurantoin with lower CrCl, this has not been shown to be significant in our study from a safety standpoint.

One of the limitations of this study is that it is a retrospective chart review in a primarily White male veteran population, which may limit external validity. The study was retrospective thus there is potential for a lack of documentation of administration of the drug, reporting for ADEs, and early discontinuation of therapy by the patient. The timing of the urine culture relative to the initiation of therapy was not recorded, which could have implications, particularly for the group of patients with no growth in their urine culture, as it may be possible that the patient took his first dose of antibiotic before submitting a urine culture. All calculations of CrCl were performed using the Cockcroft–Gault equation. Somewhat different results may be seen if other measures of renal function are utilized.

Conclusion

In conclusion, our data support a CrCl cutoff of 60 ml/min for the use of nitrofurantoin to treat outpatient UTIs in men, based on the lower rates of clinical cure seen below this threshold for Gram-negative infections. Prospective studies may be appropriate to better evaluate the effect of CrCl on ADEs associated with nitrofurantoin, as some of these events may not have been captured due to the retrospective nature of this analysis.

Acknowledgements

This material is the result of work supported with resources and the use of facilities at the VA

Western New York Healthcare System. The contents of this manuscript are not intended to represent the views of the Department of Veterans Affairs or the US Government.

Funding

This study received no financial support.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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