CLINICAL REVIEW

PEER-REVIEWED

A retrospective review assessing the efficacy and safety of nitrofurantoin in renal impairment

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The authors have an interest in therapeutic controversies that require research to improve patient outcomes. They noticed that clinical situations would often arise regarding use of nitrofurantoin in renal impairment, and one author (AB) studied this as a pharmacy residency project.

Les auteurs s'intéressent aux controverses touchant les soins aux patients qui nécessitent de la recherche en vue d'améliorer les résultats des patients. Ils ont remarqué que des situations cliniques surviennent souvent lorsque les patients souffrant d'une insuffisance rénale prennent de la nitrofurantoïne, ce qu'un des auteurs (AB) a étudié dans le cadre d'un projet de résidence en pharmacie.

Abstract

Background: Nitrofurantoin (NF) is an antibiotic commonly used to treat uncomplicated urinary tract infections (UTIs). Although NF is contraindicated in patients with an estimated glomerular filtration rate (GFR) of less than 60 mL/min, the evidence demonstrating its lack of efficacy and an increased rate of adverse reactions in these patients is marginal.

Methods: A retrospective chart review was conducted to determine the efficacy and safety of NF in patients with a UTI and an estimated GFR ≤50 mL/min (impaired renal function group) compared to >50 mL/min (control group).

Results: A total of 356 patients met our inclusion criteria. The Modified Cockcroft-Gault equation was used to estimate GFR. The point estimate for cure rate in the impaired renal function group was 71% (95% CI 63–79), versus 78% (95% CI 73–84) for the control group.

Conclusions: **Similar NF cure rates were observed in patients with impaired renal function (estimated GFR ≤50 mL/min) and patients in the control group (estimated GFR >50 mL/min). The occurrence of adverse events was comparable between the 2 groups.** ***Can Pharm J* 2009;142:248-252.**

Introduction

Nitrofurantoin (NF) has been used to treat urinary tract infections (UTIs) since 1953.[1] Many references include a warning not to use NF in patients with an estimated glomerular filtration rate (GFR) of less than 50–60 mL/min.[2-4] The main concerns centre on the potential for treatment failure and an increase in adverse effects. The warning stems from a study done in 1968 on fewer than 10 patients who received single 100 mg doses of NF. The author concluded that NF may not reach adequate urinary minimum inhibitory concentration (MIC) in patients with renal impairment.[5]

NF has a broad spectrum of activity against most gram-negative bacilli and many gram-positive organisms.[2] Gram-negative organisms cause approximately 90% of uncomplicated UTIs, and 80% to 90% of those gram-negative organisms are *Escherichia coli*.[2,6] NF is well absorbed orally, principally in the small intestine. The bioavailability ranges from 87% on an empty stomach to 94% when taken with food.[1] It is susceptible to enzymatic degradation; therefore, substantial tissue drug concentrations are not expected. Approximately one-third of the drug appears in the urine in its active form. It is distributed exclusively to the renal medulla and into the urine. NF is rapidly eliminated by glomerular filtration with a small amount of tubular reabsorption. In patients with renal impairment, excretion is decreased, while serum levels remain low.[1,2] The lack of distribution to tissues, and almost exclusive concentration into the urine, makes NF an ideal antimicrobial for lower UTIs, although NF is not useful for treat-

ing pyelonephritis. Conversely, patients with renal impairment may be unable to attain a MIC of the drug in the urine.

Sulfamethoxazole and trimethoprim (SMX/TMP) or TMP alone are often considered first-line therapy for uncomplicated UTIs.[6] Fluoroquinolones, such as ciprofloxacin, and sulfonamides, such as SMX/TMP, are commonly employed. However, NF is becoming an increasingly desirable option as resistance to both SMX/TMP and fluoroquinolones increases. Resistance to these standard therapies (Table 1) is a concern in the Vancouver Island Health Authority (VIHA). Resistance to NF may be limited by its restricted use, limited systemic distribution or the need for multiple genetic mutations to confer resistance.[7]

TABLE 1 ***E. coli*** **antibiotic susceptibility from VIHA antibiograms, South Island 2005**

Drug	Susceptibility (% sensitive)
Ciprofloxacin	71
SMX/TMP	79
Ampicillin	62
Gentamicin	94
Nitrofurantoin	95

The most commonly reported adverse reactions to NF are nausea (8%), headache (6%) and rash (6%).[1-3] For serious adverse events, including pulmonary, neurotoxic, hepatic and hemolytic reactions, the total incidence rate is less than 0.003%.[8] The incidence of adverse effects may increase with declining renal function as a result of decreased elimination and therefore increased serum concentration.[4] There have been no studies to clinically quantify the theoretical risk.

Many clinicians in our local health authority have observed the use of NF as a treatment for UTIs in patients with impaired renal function. Coupled with the anecdotal evidence of treatment success and a noticeable lack of adverse events, we conducted a retrospective study to compare the efficacy and safety of NF in patients with a UTI and an estimated GFR of ≤50 mL/min (impaired renal function group) versus >50 mL/min (control group).

Methods

The medical records of all patients with suspected UTI in the southern region of the VIHA who received NF between 2004 and 2008 were identified and retrospectively reviewed. Patient lists were compiled using the VIHA Cerner® software database. The a priori statistical calculation was to review 400 patients in order to have 80% power and 95% confidence interval. This was based on an estimated cure rate for NF of 80%. An 80% cure rate was estimated using data from previous UTI efficacy studies.[9]

Medical records were reviewed for clinical and microbiological evidence of cure, adverse reactions, comorbid illnesses, age, gender, serum creatinine and relevant concurrent medications. Patients had to be in the hospital for at least 14 days after antibiotic treatment was finished, and patients were excluded if treatment was stopped for any reason aside from therapy failure. Patient records were reviewed from both acute care hospitals and residential long-term care hospitals. Reviewers used clinical judgment with regard to including patients who were on concomitant antibiotics that may have had an effect on the outcomes of the study.

The primary outcome was cure — clinical and/or microbiological. Clinical cure was defined as treatment discontinuation after an appropriate course of antibiotics (between 5 and 10 days) with no other UTI antibiotics initiated within 14 days and no UTI symptoms (dysuria, urinary frequency, fever, rigors, flank pain, nausea). Microbiological cure was considered to have occurred when a repeat negative culture was documented. It was decided that 14 days would be sufficient time to rule out any failed treatments and record any acute adverse events.

The secondary outcome was adverse events. These events were recorded as minor (gastrointestinal disturbance, headache) or major (peripheral neuropathy, acute pulmonary reaction) events when experienced by the patient or if the patient received treatment for these events up to 7 days following UTI treatment. Reviewers arbitrarily chose 7 days post–UTI treatment due to limitations in the details of patient documentation. The selection of minor adverse events was based on the most common events reported in the NF monograph.[1] The major adverse events were selected based on contraindications and precautions outlined in references.[2,3]

The primary outcome was determined using the estimated creatinine clearance (an estimate of GFR) values from the Modified Cockcroft-Gault

Key points

- Nitrofurantoin is commonly used to treat urinary tract infections, though one small study from the 1960s advised against nitrofurantoin being used in patients with renal impairment.
- Bacterial resistance to conventional first-line UTI antibiotics makes the role of nitrofurantoin in renal impairment more pressing.
- Larger prospective studies are required to further study the role of nitrofurantoin in renal impairment.

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BOX 1 Formulas used[11-12]

Modified Cockcroft-Gault (MCG) equation:

CrCl [(mL/min)/70 kg] = [(140 – age) × 90]/SCr (μmol/L)
For women, multiply by 0.85.

Elderly-Adjusted MCG equation:

Same as above; however, if age is greater than or equal to 65 years, assume a serum creatinine of at least 88.4 μmol/L.

Modification of Diet in Renal Disease (MDRD) equation:

GFR ([mL/min]/1.73 m^2) =
186.3 × [SCr (μmol/L)/88.4] – 1.154 × age – 0.203
For women, multiply by 0.742.

CrCl = creatinine clearance; GFR = glomerular filtration rate; SCr = serum creatinine.

(MCG) equation. This method was chosen due to its widely accepted use in practice. Statistical analysis was conducted after the data were categorized using 3 different methods of estimating GFR (Box 1): 1) MCG (primary outcome), 2) Elderly-Adjusted MCG and 3) Modification of Diet in Renal Disease (MDRD). The MCG used the original Cockcroft-Gault equation[10] but did not include weight.[11] The Elderly-Adjusted category used the MCG equation with the assumption that those aged 65 years and older would have a minimum serum creatinine of 88.4 μmol/L (1 mg/dL).[11] The third category used the MDRD formula to estimate GFR.[12] These 3 methods of estimating GFR were used in order to look for variation in the primary and secondary outcomes. The MCG and Elderly-Adjusted MCG equations estimate creatinine clearance, which can be used as an estimate of GFR. The MDRD equation is a direct estimate of GFR. An estimated GFR of ≤50 mL/min was considered to reflect impaired renal function.

The primary outcome data were analyzed as percent cure rate (using SPSS version 16) with 95% confidence intervals. The adverse events were tabulated as actual numbers.

Results

Over 500 patient charts were reviewed, in which a total of 356 patients met our inclusion criteria. Patient demographics, estimated GFR, relevant past medical history and medications are summarized in Table 2. The portion of the total patients in each group (control and renally impaired) varied when using the 3 different estimated GFR methods. Patient characteristics used in estimating GFR (age, gender, serum creatinine) predictably demonstrated that the renally impaired group consisted of more female and elderly patients. The MDRD

TABLE 2 Patient data with respect to renal function

	MCG[11]		Elderly-Adjusted MCG[11]		MDRD[12]	
	Control*	Renal impairment	Control	Renal impairment	Control	Renal impairment
Patients, *n*	234	122	163	193	284	72
Mean age in years (range)	73 (4–96)	86 (69–103)	67 (4–89)	86 (69–103)	76 (4–98)	83 (43–103)
Male, % (*n*)	29 (67)	16 (19)	39 (64)	11 (22)	29 (82)	6 (4)
Mean creatinine clearance in mL/min (range)	83 (51–387)	40 (15–50)	92 (51–387)	48 (15–50)	76 (51–406)	36 (19–50)
Diabetic, % (*n*)	17 (40)	15 (18)	21 (34)	12 (24)	17 (48)	14 (10)
Postherpetic neuralgia, *n*	1	1	0	2	1	1
Any previous neuropathy, *n*	30	12	21	21	33	9
Any previous pulmonary reaction, *n*	2	0	2	0	2	0
Sulfasalazine, *n*	0	0	0	0	0	0
Amiodarone, *n*	2	4	1	5	3	3
Antineoplastics, *n*	4	0	2	2	4	0
Propranolol, *n*	1	1	1	1	1	1
Hydralazine, *n*	1	1	1	1	1	1

*Control group = estimated GFR >50 mL/min; renal impairment group = estimated GFR ≤50 mL/min.

equation showed fewer patients to be renally impaired (72 versus 122 and 193 for MCG and Elderly-Adjusted MCG, respectively). Comorbid diseases and concurrent medications were observationally comparable in both categories.

Based on the MCG formula, the majority of patients showed cure of their UTI (Table 3), with comparable cure rates for the impaired renal function group (71%, 95% CI 63–79) and control group (78%, 95% CI 73–84). The cure rates did not vary significantly when using the Elderly-Adjusted MCG formula (impaired renal function: 75%, 95% CI 69–81 vs control: 76%, 95% CI 69–83) or the MDRD formula (impaired renal function: 72%, 95% CI 62–83 vs control: 76%, 95% CI 71–81).

Although the rates of adverse events were comparable between the 3 methods used for estimating GFR (Table 4), no statistical tests were conducted due to the low incidence of adverse events and small sample size. Adverse event occurrences were similar to rates reported in the NF product monograph.[1]

Discussion

The estimated probability of cure (point estimate) for the proportion of patients cured was similar in all 3 estimated GFR categories. The confidence intervals grew wider as a result of the fewer than expected patients in each renal function group. The study originally aimed for 400 patients (200 in each renal function group) to demonstrate an 80% power but was only able to collect 356 eligible patients. A larger sample size would have resulted in greater power and less type II error, increasing the likelihood of the study being able to detect the inferiority of NF in renal impairment.

In examining all 3 methods of estimating GFR, NF appears to be efficacious in patients with an estimated GFR ≤50 mL/min (mean 40 mL/min); the point estimates of efficacy are similar to other trials conducted on women.[9] The recorded occurrence of adverse events was similar among the estimated GFR methods and was also comparable to the rates provided in the NF product monograph.[1]

Limitations of this study include the nature of retrospective chart reviews, in which adverse reactions and therapeutic failure may not be adequately documented. Diagnostic criteria to satisfy a microbiologically confirmed UTI versus a suspected UTI were not considered, and this is another limitation of this study. Furthermore, the study did not achieve its a priori sample size calculation. Given that the mean estimated GFR was 40 mL/min in the renal impairment group (≤50 mL/min group), few patients had severely impaired renal function, and this makes extrapolation of results to patients with severe renal impairment difficult.

Points clés

• La nitrofurantoïne est couramment utilisée pour traiter les infections urinaires; toutefois, une petite étude menée dans les années 1960 recommande de ne pas utiliser la nitrofurantoïne chez les patients atteints d'une insuffisance rénale.

• La résistance bactérienne aux antibiotiques comme traitement de première intention utilisés pour soigner les infections urinaires rend la détermination du rôle de la nitrofurantoïne dans les cas d'insuffisance rénale encore plus urgent.

• Cette question nécessite des études prospectives plus larges visant à étudier le rôle de la nitrofurantoïne dans les cas d'insuffisance rénale.

TABLE 3 Clinical cure rates with respect to renal function*

	MCG[11]		Elderly-Adjusted MCG[11]		MDRD[12]	
	Control†	Renal impairment	Control	Renal impairment	Control	Renal impairment
Cure, % (95% CI)	78 (73–84)	71 (63–79)	76 (69–83)	75 (69–81)	76 (71–81)	72 (62–83)
No cure, % (95% CI)	22 (16–27)	29 (21–37)	24 (17–31)	25 (19–31)	24 (19–29)	28 (17–38)

*Both clinical and microbiological cure rates were examined. However, evidence supporting microbiological cure was not available in most instances. †Control group = estimated GFR >50 mL/min; renal impairment group = estimated GFR ≤50 mL/min.

TABLE 4 Reported minor adverse events with respect to renal function

	MCG[11]		Elderly-Adjusted MCG[11]		MDRD[12]	
	Control*	Renal impairment	Control	Renal impairment	Control	Renal impairment
Gastrointestinal disturbance or headache,† % (no.)	8 (18)	7 (9)	9 (15)	6 (12)	7 (21)	8 (6)

*Control group = estimated GFR >50 mL/min; renal impairment group = estimated GFR ≤50 mL/min.
†Experienced or received treatment for the condition during UTI therapy.

NF remains a relatively inexpensive yet effective choice for treatment of uncomplicated UTIs. With the emergence of resistant organisms, antibiotic options may become increasingly limited in the future. This retrospective review demonstrates that in patients with an estimated GFR of 50 mL/min or less, NF appears to achieve acceptable clinical cure rates and is well tolerated. The results of this chart review allow for the possibility of conducting further research, including a prospective study examining the efficacy and safety of NF in patients with renal impairment. ■

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