Efficacy & Safety of Nitrofurantoin in the Treatment of Urinary Tract Infections in Patients with Renal Impairment

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Introduction

Nitrofurantoin has been used for the treatment of urinary tract infections (UTI) since 1953. The exact mechanism of action is unclear; however, it is believed that nitrofurantoin interferes with bacterial metabolism, protein synthesis, and cell wall formation. The drug is active against S. aureus, S. epidermidis, E. faecalis, E. coli, and Citrobacter. Susceptible strains rarely develop resistance as shown in the Vancouver Island Health Authority (VIHA) south island anti-biograms.

Many tertiary references include a warning stating not to use nitrofurantoin in patients with an estimated creatinine clearance of less than 50-60 mL/min. The main concerns center around the potential for treatment failure and the potential for an increase in adverse effects. This warning stems from studies done as early as 1968 dealing with less than 10 patients. Patients with renal impairment may be unable to attain a minimum inhibitory concentration of the drug in the urine. The data supporting the potential adverse effects of nitrofurantoin in renal impairment patients is currently theoretical and inconclusive.

Objectives

Primary Objective: Compare the proportion of patients cured in two categories based on renal function (less than or equal to 50 mL/min vs greater than 50 mL/min)

Definition of Cure: Treatment discontinued and no other UTI antibiotics were started within 14 days post UTI resolution and no ongoing UTI symptoms (e.g. dysuria, urinary frequency, fever, rigors, flank pain, nausea)

***Secondary Objective*:** Compare the proportion of patients who experienced adverse reactions in each of the above categories

Definition of ADR: (*see table 3*)

Methods

***Methods*:**

- patient data was populated from the VIHA Cerner® electronic database
- 519 charts were reviewed in which 356 charts met the criteria to satisfy the study objectives

Inclusion criteria:

- a prescription for nitrofurantoin for the acute treatment of an urinary tract infection
- patient must have remained as an inpatient for the duration of treatment and for fourteen days post UTI resolution

***Recording methods*:**

- VIHA Records Services provided patient charts for the reviewers (AB and NH)
- using an electronic database designed by a health database consultant in Filemaker Pro® the following information was recorded:
  - age, serum creatinine, gender
  - urinary tract infection cured or not cured
  - patient experienced adverse reaction (see table one)
  - medical conditions that may contribute to adverse reaction experienced (*see table 1*)
  - concurrent medication that may contribute to adverse reaction experienced (*see table 1*)

Results

Table 1: Patient data with respect to GFR estimation methods

	Modified Cockcroft-Gault		*Modified Cockcroft-Gault Elderly Adjusted*		*Estimated GFR (MDRD)*	
Category	**>50 ml/min**	**≤50 ml/min**	**>50 ml/min**	**≤50 ml/min**	**>50 ml/min**	**≤50 ml/min**
Patients (n)	234	122	163	193	284	72
Mean Age (years)	73 (4-96)	86 (69-103)	67 (4-89)	86 (69-103)	76 (4-98)	83 (43-103)
Male %	29	16	39	11	29	6
Mean Creatinine Clearance (mL/min)	83 (50-387)	40 (15-50)	92 (50-387)	48 (15-50)	76 (50-406)	36 (19-50)
Diabetic %	17	15	21	12	17	14
Post Herpetic Neuralgia %	0	1	0	1	0	13
Previous Neuropathy %	13	10	13	11	12	0
Previous Pulmonary Reaction %	1	0	1	0	1	0
Sulfasalazine %	0	0	0	0	0	4
Amiodarone %	3	3	1	3	1	0
Anti-Neoplastics %	2	0	1	1	1	1
Propranolol %	1	1	1	1	0	1
Hydralazine %	0	1	1	1	0	1

Figure 1: Primary Outcome With Respect To GFR Estimation Methods

Percent Cured With Respect to Different Methods of GFR Estimation

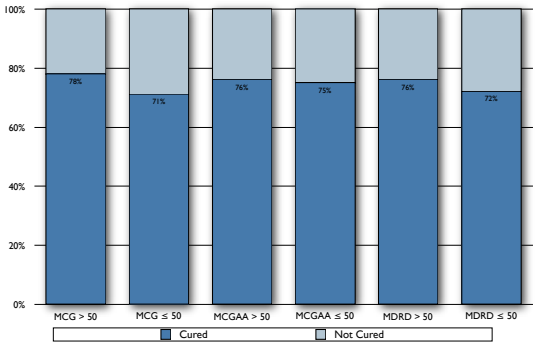

Table 2: Primary Outcome with respect to GFR estimation methods

	Modified Cockcroft-Gault		*Modified Cockcroft-Gault Elderly Adjustment*		*Estimated GFR (MDRD)*	
Category	**>50 ml/min**	**≤50 ml/min**	**>50 ml/min**	**≤50 ml/min**	**>50 ml/min**	**≤50 ml/min**
Cured (%)	78	71	76	75	76	72
Not Cured (%)	22	29	24	25	24	28

Results

Table 3: Secondary Outcomes with respect to GFR estimation methods

	Modified Cockcroft-Gault		*Modified Cockcroft-Gault Elderly Adjustment*		*Estimated GFR (MDRD)*	
Category	**>50 ml/min**	**≤50 ml/min**	**>50 ml/min**	**≤50 ml/min**	**>50 ml/min**	**≤50 ml/min**
Experienced or received treatment for a GI disturbance or headache during therapy %	8	7	9	6	7	8
Experienced or received treatment for peripheral neuropathy during or 7 days after therapy %	0.4	0	0.6	0	0.4	0
Experienced or received treatment for pulmonary reaction during or 7 days after therapy %	0	0	0	0	0	0

Discussion

Nitrofurantoin is well absorbed orally and is has a short plasma half-life of approximately 20-30 minutes. The drug reaches therapeutic concentrations within 30 minutes and maintains them for 4-5 hours. Studies as early as 1968 had demonstrated poor urine concentrations in a small number of patients with varying renal function. The results in this study for all three methods of GFR estimation showed similar results for the primary and secondary outcomes. However, the number of patients considered to be in each category differed considerably according to GFR estimation method. This proportion of patients cured and rate of adverse effects in this study is consistent with studies done in the past for both categories of renal function.

Conclusions

- The efficacy of nitrofurantoin was comparable in patients with estimated renal function greater than 50 mL/min and patients below 50 mL/min
- The safety profile of nitrofurantoin was also comparable between the two categories
- The method of estimating renal function did not effect the primary and secondary outcomes

References available on request