The urinary pharmacokinetics of nitrofurantoin in patients with uncomplicated urinary tract infections: interim analysis

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[Inclusion of patients in this study is still ongoing so interim data are reported in this paper.]

ABSTRACT

Background: Nitrofurantoin was registered as first-line treatment option of uncomplicated urinary tract infections in 1954, a time before a structured process of drug development was mandatory. As a consequence, nitrofurantoin is being prescribed in daily clinical practice based on limited data supporting the currently used dosing regimen. A better knowledge of the pharmacokinetic (PK) properties of nitrofurantoin would help to achieve optimal dosing regimens.

Objectives: To investigate and compare the urinary PK profile of nitrofurantoin in two commonly used dosing regimens in patients with uncomplicated urinary tract infections.

Methods: Urine samples were collected during 24 hours by 19 female patients who were prescribed nitrofurantoin in a dose of 50 mg q6h (Macrodantin®/Furadantin®) or 100 mg q12h (Macrobid®/Furabid®) by their treating general practitioner. Nitrofurantoin concentrations were quantified by UHPLC-UV. PK analysis was performed by PKSolver® using non-compartmental analysis.

Results: Mean peak concentrations of nitrofurantoin in urine after 100 mg were higher compared to those after 50 mg (104.2 mg/L ± 74.7 versus 84.7 mg/L ± 64.6), but the range in maximum concentrations was comparable (<4 mg/L to 264.8 mg/L or to 267.7 mg/L). The $AUC_{0\text{-}24h,ss}$ was higher (931.5 mg.h/L ± 672.3 versus 881.9 mg.h/L ± 347.1) after the 100 mg dosing regimen. The slow-release effect of the 100 mg capsule, demonstrated as a delayed peak concentration, but none of the PK parameters differed significantly between the dosing regimens.

Conclusion: The urinary PK of nitrofurantoin was comparable between the two studied dosing regimens and therefore independent of the administered dose and formulation. Additional PK studies, including more patients administering Macrobid®/Furabid®, are needed.

INTRODUCTION

In an era of emergence of drug resistant pathogens, there is more interest in the use of old antibiotics in the treatment of infections in daily clinical practice (1,2). Nitrofurantoin is one of those "old" drugs. It was registered in 1954 as oral antibiotic for the treatment of uncomplicated urinary tract infections (UTIs) (3). It is a synthetic agent with a broad spectrum of activity, including (vancomycin-resistant) enterococci and Extended Spectrum Beta-Lactamase (ESBL) producing Enterobacteriaceae (4–6). Its popularity is increasing as resistance rates for nitrofurantoin are still low (7), while increasing for former treatment options for uncomplicated UTIs like beta-lactam antibiotics and quinolones (2). Despite the fact that the drug has been used since its registration, little is known about its pharmacokinetic (PK) properties. The majority of published studies in which PK parameters are reported, were performed at the time of drug development and therefore different crystal sizes, formulations and patient populations were investigated. This variability complicates translation of these older PK data to the use of nitrofurantoin today. Therefore, renewed studies on the PK properties of nitrofurantoin, using clinically relevant formulations, dosages and patients with uncomplicated UTIs is needed. In this study, we investigated and compared the PK profile of nitrofurantoin in its macrocrystalline form after two commonly used dosing regimens e.g. Furadantin®/Macrodantin® (50 mg q6 hours) or Furabid®/Macrobid® (100 mg q12 hours). Furthermore, we explored the influence of different patient specific covariates on the PK of nitrofurantoin. This interim analysis presents the first findings.

METHODS

Study design and drug administration

The study was designed as a multicenter, open label study. Patients were approached to participate in the study after the treating physician prescribed nitrofurantoin for a suspected or proven uncomplicated UTI in the registered dose of 50 mg (Furadantin®/Macrodantin®) q6 hours or 100 mg (Furabid®/Macrobid®) q12 hours according to the Dutch Guidelines for general practitioners (GPs) (8). Patients were enrolled in one of the two clinical departments of the Erasmus Medical Center (EMC), e.g. neurosurgery and neurology, or at one of the four GPs after written informed consent was provided. The study was approved by the ethics committee of the EMC (MEC-2017-526).

Study population

Female patients of at least 18 years of age, who were prescribed nitrofurantoin, and with a recent (≤ one year) measurement of their creatinine clearance, were allowed to

participate in the study. The creatinine clearance was additionally measured as part of the study after consent of the patient if the latter requirement was not met. Patients were excluded from participation in this study if they were being treated with any other antibiotic within one week of the potential urine collection period, if the patient was known for porphyria or an allergy related to nitrofurantoin use or with a creatinine clearance of ≤30 mL/min, calculated using the CKD-EPI equation.

Sample collection

EMC patients collected urine samples during hospitalization with help from a nurse and GP patients self-collected urine samples in the home setting. Urine was collected during 24 hours and started on day 2, 3 or 4 of the 5-day treatment to ensure the steady state situation was reached. Patients were instructed to record date, time and total volume of each void. Volume could be accurately measured by voiding in a measuring cup. After recording the volume, ± 5 mL of urine was transferred to a small 50 mL-urine container. Urine containers were covered in aluminum foil to protect the content from daylight. The samples were stored in the freezer at approximately -20°C at the patients' home during the urine collection period of 24 hours. After the researchers collected the urine samples from the patients, samples were stored at -80°C in the EMC until the day of analysis. Stability of the samples at these two conditions was confirmed during validation of the method (9).

Quantification of nitrofurantoin in urine

Nitrofurantoin concentrations were determined using a ultra-high performance liquid chromatography (UHPLC) method with ultra violet (UV) detection at a wavelength of 369 nm (9). The method was validated according to the guidelines for bio analytical method validation of the Food and Drug Agency (FDA) (10). One-hundred microliter urine was needed for the sample preparation which consisted of liquid-liquid extraction. Linearity was confirmed over a concentration range from 4 to 200 mg/L. Samples were diluted with drug free urine if the concentration exceeded the upper end of this concentration range during the initial analysis. Concentrations below the lower limit of this concentration range were reported as '<4 mg/L'. Urine samples were found to be stable for at least seven days at 4°C and at room temperature and for 2 years at -20°C and at -80°C. Since short-term stability at 4°C for 7 days of lower concentrated urine samples could not be confirmed, all urine samples were stored in the patients' freezer (at approximately -20°C) for a maximum of 48 hours to guarantee stability.

Pharmacokinetic analysis

The following PK parameters were calculated with PKSolver® using non-compartmental analysis (11) based on the nitrofurantoin concentrations in the urine samples: maximum

concentration (C_{max}, mg/L) time to maximum concentrations (T_{max}, hours) cumulative amount excreted over 24 hours (mg), recovery expressed as percentage of the total daily dose (%), area under the concentration-time curve in steady-state calculated over 24 hours ($AUC_{0\text{-}24h,ss}$). The linear trapezoidal approach was used to calculate the AUC.

Data analysis

The mean, standard deviation (SD), range and coefficient of variation (CV, %) of the patient characteristics and the PK parameters were calculated for the total population and per dosing regimen. PK parameters were compared between the two dosing regimens using an unpaired, two-tailed t-test. P values ≤ 0.05 (two-sided) were considered statistically significant.

The influence of the following covariates on the PK parameters was investigated: renal function, demonstrated as the estimated glomerular filtration rate (eGFR) calculated with the CKD-EPI equation; urinary output, demonstrated as the total volume of urine excreted in 24 hours (mL), the number of voids, and the nitrofurantoin excretion rate (mg/h).

Effectiveness of the treatment was evaluated by asking the GP if the patient returned with UTI symptoms (e.g. dysuria with or without frequency, urgency, suprapubic pain, or hematuria) within two weeks and/or four weeks after finishing of the initial antibiotic course with nitrofurantoin (12).

Safety assessment

Safety evaluation included the collection of adverse events (AEs) and serious AEs reported by the patients to the GP.

RESULTS

Study population

A total of 20 patients were included in this interim analysis. One patient was not able to complete the 24-hour urine collection so the reported data are based on the samples of 19 patients. All patients were Caucasian with a median age of 62.5 years (range 19-84). Patient characteristics are shown in Table 1. Twelve patients were prescribed the dosing regimen of 50 mg q6 hours was and seven patients were prescribed the 100 mg q12 hours dosing regimen. Baseline patient characteristics were comparable for the two dosing groups (Table 1).

Sample collection

A total number of 201 samples were collected by the 19 patients with a mean of eleven samples per patient (± 3) (Table 1). There was a wide range in the number of samples per patient (7-16 samples), as a result of varying voiding rhythms.

Table 1. Patient characteristics demonstrated as the population mean, SD, range and CV (%) for the total population and per dosing regimen.

	mean	SD	range	CV (%)
Total population (n=19)				
Age (years)	62.5	14.9	19-84	24.0
Height (cm)	164	5.0	151-178	3.3
Weight (kg)	72.6	13.1	52.0-102.0	18.0
BMI	27.0	5.6	19.1-42.5	20.8
eGFR (mL/min/1.73m2)	78.2	17.0	50.0-114.0	20.8
Urine samples (n=201)	11	3	7-16	27
50 mg q6 hours (n=12)				
Age (years)	64.0	12.9	45-84	20.1
Height (cm)	165	5.0	159-178	3.1
Weight (kg)	71.5	13.5	52.0-102.0	18.9
BMI	26.2	4.8	19.1-36.6	18.4
eGFR (mL/min/1.73m2)	78.3	18.3	50.0-114.0	23.3
Urine samples (n=121)	10	3	7-16	29
100 mg q12 hours (n=7)				
Age (years)	59.9	18.9	19-74	31.6
Height (cm)	163	6.0	151-168	3.5
Weight (kg)	74.6	13.0	56.0-97.0	17.5
BMI	28.5	6.9	20.8-42.5	24.3
eGFR (mL/min/1.73m2)	81.3	14.1	58.0-97.0	17.3
Urine samples (n=80)	11	3	8-16	24

Pharmacokinetic analysis

The concentration-time curves of the patients receiving the 50 mg regimen and the 100 mg regimen are presented in Figures 1a and 1b respectively. Concentrations in the 50 mg dosing group ranged from <4 mg/L (LLOQ) to 267.7 mg/L, and from <4 mg/L to 264.8 mg/L in the 100 mg group. There was one patient in each dosing group with an extraordinary high urinary nitrofurantoin concentration (267.7 mg/L in the 50 mg group and 264.8 mg/L in the 100 mg group (Figure 1)).

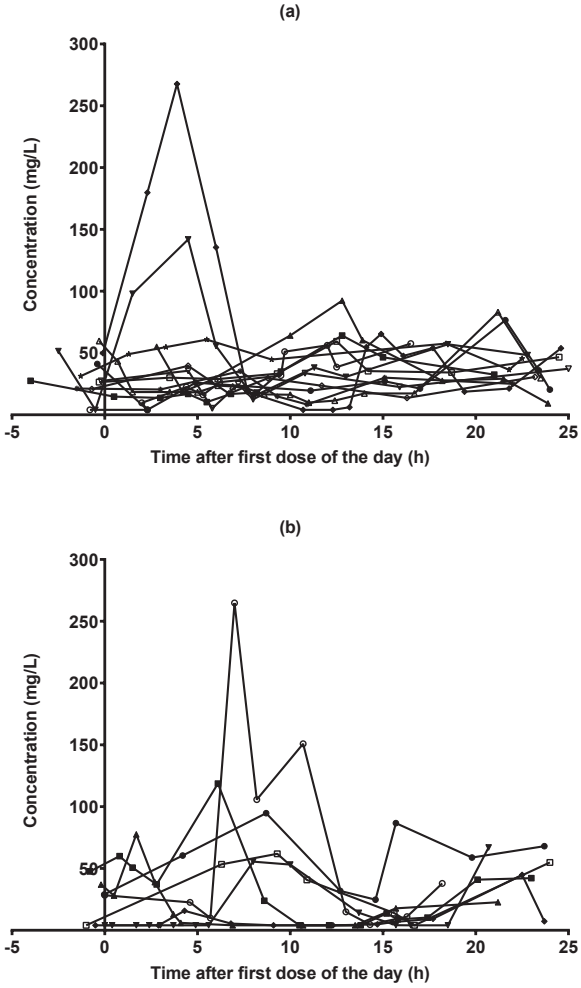

Figure 1. The individual concentration-time curves of the patients receiving a dosing regimen of 50 mg q6 hours **(a)** or 100 mg q12 hours **(b)**. Each line represents one patient.

In Table 2, the corresponding PK parameters are shown, calculated based on the individual concentration-time curves for the samples collected over 24 hours. Urinary concentrations of nitrofurantoin were highly variable between the patients, demonstrated as high SD and CV values in Table 2. Mean maximum concentrations in the 100 mg group were higher compared to those in the 50 mg group (104.2 mg/L ± 74.7 versus 84.7 mg/L ± 64.6), but the range in maximum concentrations was comparable (Table 2). The slow-release effect of the 100 mg capsule is reflected in the prolonged T_{max} (TALD) of 6.7 hours ± 6.0 compared to 4.3 hours ± 3.0 for the 50 mg dose. However, none of the PK parameters differed significantly between the two dosing regimens, probably because the range in concentrations was wide.

The higher C_{max} values found after a longer time after dose, did not result in differences in excretion and recovery values, but did result in an overall higher bladder exposure as the $AUC_{0\text{-}24h,ss}$ in patient receiving the 100 mg dose was higher compared to patients receiving the 50 mg dose (e.g. 931.5 mg.h/L ± 672.3 versus 881.9 mg.h/L ± 347.1) (Table 2).

Table 2. Pharmacokinetic parameters in urine for the two dosing regimens when the full sample collection period of 24 hours was considered.

	50 mg q6 hours (n=12)				100 mg q12 hours (n=7)				P value
	mean	SD	range	CV (%)	mean	SD	range	CV (%)	
Cmax (mg/L)	84.7	64.6	35.3-267.7	76.4	104.2	74.7	44.8-264.8	71.7	0.575
Tmax (TALD) (h)	4.3	3.0	0.02-11.3	69.7	6.7	6.0	0.3-16.6	90.1	0.354
Urinary output (mL)	2905	1065	1252-4600	36.6	2696	864	1550-3630	32.0	0.648
Cumulative recovery (%)	44.8	16.5	16.3-78.6	36.7	41.3	15.9	21.2-58.4	38.6	0.672
AUC0-24h,ss (mg.h/L)	881.9	347.1	533.4-1647.8	39.4	931.5	672.3	323.14-2217.58	72.2	0.860

TALD, time after last dose

The mean urinary output and number of voids during 24 hours was comparable between the two treatment groups (Table 1 and 2). There were three patients with a relatively high urinary output (>3700 mL in a relatively low number of voids; 7-8 voids). Despite a high recovery in these three patients (57.9 % ± 18.0), C_{max} values were low (44.8 mg/L ± 12.9) compared to those in the overall population, probably due to the high urinary output resulting in highly diluted urine and low urinary concentrations of nitrofurantoin. This is in line with the lower total bladder exposure ($AUC_{0\text{-}24h,ss}$ 679.8 mg.h/L ± 192.9). There were four patients with a relatively low urinary output (<1700 mL in a relatively high number of voids; 8-16 voids). C_{max} values and the total bladder exposure were high in these four patients compared to the overall population being 121.8 mg/L ± 98.6 and $AUC_{0\text{-}24h,ss}$ 1208.6 mg.h/L ± 868.8 respectively, but the recovery was low (28.3 % ± 12.2).

No relationship was found between the renal function of the patient and any of the following parameters: C_{max}, cumulative recovery, $AUC_{0\text{-}24h,ss}$ or the nitrofurantoin excretion rate as the graphs demonstrated a random distribution of the data points. In Figure 2, two examples of these graphs are shown. Figure 2a demonstrates the eGFR versus the nitrofurantoin clearance and Figure 2b demonstrates the eGFR versus $AUC_{0\text{-}24h,ss}$.

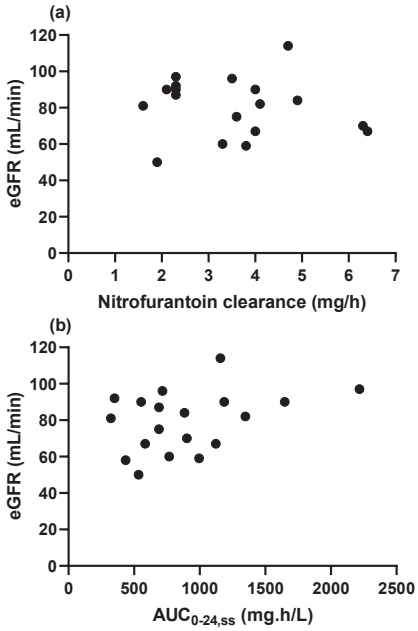

Figure 2. The renal function of the patients, demonstrated as eGFR, versus (a) nitrofurantoin clearance and (b) versus AUC0-24h,ss. The graphs demonstrated that the eGFR is not related to the nitrofurantoin clearance or the AUC0-24h,ss.

Three patients (15%) returned to their GP within two weeks with recurrent UTI symptoms (one patient had used the 50 mg dose). After four weeks, one additional patient returned to her GP with uUTI symptoms. This patient had been treated with the 50 mg dose.

DISCUSSION

The PK of macrocrystalline nitrofurantoin was studied in a group of 19 female patient with suspected or proven uUTIs, treated with 50 mg q6 hours or 100 mg q12 hours in line with the Dutch GP guidelines (8). Urinary concentrations of nitrofurantoin were studied over 24 hours and were found to be highly variable between patients, which is typical for UTI drugs, especially in studies without predefined times for urine sampling (13,14). The urinary concentrations after the 100 mg dose were slightly higher and were found after a longer time after dose compared to the 50 mg dose. This resulted in an overall bladder exposure which was slightly higher in patients being treated with the 100 mg dose. However, differences in PK parameters between the dosing regimens were small and not significant, questioning the clinical relevance of the PK differences.

The results of this interim analysis therefore point to the hypothesis that the urinary PK of nitrofurantoin is independent of the administered dose and formulation within the studied dosing regimens. The PK parameter that differed most between the dosing regimens was the T_{max} (not significant), which could be related to the slow-release formulation of the 100 mg capsule. In view of the time-dependent killing of *Escherichia coli* and *Klebsiella pneumoniae* (15), some investigators have suggested that the slow-release capsule of nitrofurantoin may lead to higher cure rates than the immediate release formulation (13). This could not be validated in our data set. More patients using Macrobid®/Furabid® should be included in the study to demonstrate this possible difference in PK.

A relationship was found between a high urinary output in a relatively low number of voids and lower C_{max} and $AUC_{0\text{-}24h,ss}$ values, but a higher urinary recovery. The opposite for patients with a low urinary output was also observed. This relationship was also found for fosfomycin (11). These observations indicate that minimizing the urinary output contributes to a higher bladder exposure and therefore a better treatment outcome. Whether patients should be advised to minimize voiding episodes is controversial since on the other hand, it is important to regularly void and thereby flush out the uropathogen together with the urine. Voiding regularly may hereby reduce the urinary antibiotic exposure, but still promote clinical cure. More research is needed to reveal how to balance between these factors (either maximizing the bladder exposure by minimizing the number of voids or clearing the uropathogen by maximizing the number of voids) in order to improve treatment outcome.

In the scarce number of publications in which the PK of nitrofurantoin after a clinically relevant dose was reported, PK results were in line with those reported in this interim analysis (16–19). The study of Huttner et al. reported the urinary PK in 12 healthy volunteers after administration of macrocrystalline nitrofurantoin (Macrodantin®/Furadantin®) in a dose of 50 mg q6 hours or 100 mg q8 hours (13). Urine samples were collected in steady state during one dose interval of 6 hours or 8 hours. Mean values of the PK parameters of this study were comparable to those found in our patients, but the variability in the PK parameters in our study was higher (Table 3). This is likely to be related to differences in patient specific factors, which can influence the urinary concentrations such as renal function, fluid intake, voiding time, urine frequency and drug absorption.

The finding that the urinary PK of nitrofurantoin based on these two studies was comparable, is interesting in the context of the administered dose and formulation. Regarding the dose, the results of the study in healthy volunteers revealed that, while

plasma concentrations are doubled when comparing the dose of 50 mg with the 100 mg, urinary concentrations are in the same order of magnitude (Table 3) (13). This points to the hypothesis that plasma concentrations are dose-dependent, but that urinary concentrations are independent of the administered dose. Regarding the formulation, the finding that the PK of 100 mg Macrodantin®/Furadantin® in volunteers is comparable with the PK of 100 mg Macrobid®/Furabid® in patients, indicates that the slow-release mechanism of nitrofurantoin from the Macrobid®/Furabid® capsule, was not reflected in higher and/or delayed urinary concentrations. Moreover, a slow-release (delayed release) effect was only observed when comparing the PK after the 50 mg dose (Macrodantin®/Furadantin®) with the PK after 100 mg Macrodantin®/Furadantin® or Macrobid®/Furabid®. Based on all the above, it became clear that the PK of nitrofurantoin is complicated and not predictable based on the administered dose and the theoretical mechanism of the Macrobid®/Furabid® nitrofurantoin formulation. Future research should focus on revealing the complete process of absorption and elimination of nitrofurantoin so this knowledge can serve as the base for treatment optimization (20). For this purpose, both plasma and urine samples must be investigated in subjects where voiding and fluid intake are standardized so that the influence of one's own voiding rhythm on the PK is minimized.

Table 3. Pharmacokinetic parameters in urine for the 50 mg dosing regimen (upper part) and for the 100 mg dosing regimen (lower part) in patients (left) and in healthy volunteers (right). The PK parameters in healthy volunteers are based on the study of Huttner et al. (13).

		Patients			Healthy volunteers		
50 mg regimen		50 mg q6 hours (n=12)			50 mg q6 hours (n=12)		
		Mean	SD	range	Mean	SD	range
	C_{max} (mg/L)	84.7	64.6	35.3-267.7	94.4	47.8	26.8-176.3
	T_{max} (TALD) (h)	4.3	3.0	0.02-11.3	5.1	0.7	3.3-5.5
	$AUC_{0\text{-}24,ss}$ (mg.h/L)	881.9	347.1	533.4-1647.8	943.5	539.6	228.2-2212.0
100 mg regimen		100 mg q12 hours (n=7)			100 mg q8 hours (n=12)		
		Mean	SD	range	Mean	SD	range
	C_{max} (mg/L)	104.2	74.7	44.8-264.8	94.1	49.9	40.1-209.4
	T_{max} (TALD) (h)	6.7	6.0	0.3-16.6	6.8	1.8	1.3-8.1
	$AUC_{0\text{-}24,ss}$ (mg.h/L)	931.5	672.3	323.1-2217.6	856.0	581.0	378.6-2098.9

TALD, time after last dose

The initial course with nitrofurantoin was not sufficient to treat the infection in four patients. The success rate of the treatment (e.g. 80% [16/20]) is comparable to what was found in a randomized clinical trial in which a clinical resolution of 70% was reported in patients through day 28 after completion of antibiotic therapy (21). Microbiological

resolution occurred in 74% of the patients (21). Because of the large interindividual variability in urinary concentrations, it is likely that urinary concentrations in some patients will be sub-therapeutic. This may explain the cases of clinical and microbiological failure, but this interim analysis was underpowered to demonstrate a difference in treatment effect for the two dosing regimens. Future research will focus on the enrollment of more patients in this ongoing study.

The small sample size is the most important limitation of the study at the time of this interim analysis. The study was underpowered to demonstrate a difference in treatment effect between the two dosing regimens and to perform a covariate analysis. The results of this interim analysis should therefore only be considered as explorative. However, the fact that the results are in line with what was found in literature about the urinary PK (13,16) and the clinical effectiveness (21), support the validity of the explorative results.

In conclusion, the urinary PK of nitrofurantoin was comparable between the two studied dosing regimens and therefore independent of the administered dose and formulation. Additional PK studies, including more patients administering Macrobid®/ Furabid®, are warranted to further investigate and compare the PK pattern of both nitrofurantoin formulations. Because of the small sample size of this interim analysis, the presented results are only explorative. The hypotheses raised in this study must be validated in additional studies with more patients.

Transparency declaration

The authors declare no conflicts of interest.

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