Optimizing the treatment of cystitis using nitrofurantoin

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Primary Objective: To optimize the dosing regimen of nitrofurantoin in order to enhance the effectivity and the safety of the treatment of cystitis with orally administered nitrofurantoin in patients with suspected or proven cystitis.Secondary…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Urinary tract signs and symptoms
Study type	Observational invasive

Summary

ID

NL-OMON50420

Source
ToetsingOnline

Brief title
FIRE

Condition

- Urinary tract signs and symptoms

Synonym
Urinary tract infection; bacterial infection

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,EU 7th framework program c.q. AIDA grant

Intervention

Keyword: Elderly, Nitrofurantoin, Pharmacokinetics, Urinary tract infection

Outcome measures

Primary outcome

The main study parameter is the NF concentrations in urine. Nitrofurantoin urine levels will be analysed by means of a validated ultra high-performance liquid chromatography with UV detection (UPLC-UV) at the UMC of Maastricht.

Pharmacokinetic analysis

A classic pharmacokinetic curve will be developed through analysis of the pharmacokinetic data. Afterwards, a population PK analysis will be performed. Other covariates, such as age, weight, and creatinine clearance will be included in the analysis. Through this approach both intra- and inter-individual variability will be taken into account. The computer program NONMEM (nonlinear mixed effects modelling) will be used for this purpose, which is acknowledge by e.g. the FDA for this purpose. Results will be analyzed and the model will be validated according to internationally recommended standards. With this programm, we can simulate different dosing regimen in order to find the most optimal regimen so that treatment with nitrofurantoin will be optimized regarding its effectivity and safety.

Secondary outcome

Not applicable.

Study description

Background summary

Nitrofurantoin is an antibiotic used for the treatment of lower urinary tract infections (cystitis) for more than 50 years. There has been a recent resurgence of interest in this drug in the context of increasing multidrug resistance amongst Gram-negative bacteria causing urinary tract infections. Preliminary PK data demonstrates that urine concentrations of nitrofurantoin (Furadantin ®) are highly variable between subjects after administration of 50 mg q6 hours and 100 mg q8 hours. This will have high consequences for the effectivity of the therapy. These consequences are likely to be even higher for the often prescribed dose of 100 mg q12 hours of the slow-release formulation (Furabid ®) which is often used in the Netherlands. The question rises if this dose (which is recommended in the Dutch national guideline SWAB (Stichting Werkgroep Antbioticabeleid and the *NHG-standaard*) as first line treatment option of cystitis together with the dose of 50 mg q6 hours) is effective and indeed equivalent to the 50 mg q6 hour dose. (PK) Data to support this are lacking. Additionally, while official guidelines advise to avoid the use of nitrofurantoin in the elderly and those with moderate renal insufficiency, it appears that clinicians are frequently prescribing this antibiotic tot both populations in daily practice. These guidelines appear to be based mainly on decades-old studies. Given the resurgence of its clinical use, there is an urgent need to fill in these knowledge gaps regarding the effectivity and safety of the current treatment of cystitis with nitrofurantoin in the general patient population and/or patients with renal impairment.

Study objective

Primary Objective:
To optimize the dosing regimen of nitrofurantoin in order to enhance the effectivity and the safety of the treatment of cystitis with orally administered nitrofurantoin in patients with suspected or proven cystitis.

Secondary Objectives:
(1) To determine the pharmacokinetic (PK) profile of orally administered nitrofurantoin after administration of the normal-release formulation and the slow-release formulation;
(2) To explore the influence of different covariates (e.g. renal function, age, weight) on the this PK profile.
(3) To evaluate the effectivity of this treatment based on the minimum inhibitory concentration (MIC) of the uropathogen and the clinical targets as mentioned in guidelines by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Study design

This is a descriptive, prospective, pharmacokinetic study of nitrofurantoin in 60 female patients with suspected or proven active urinary tract infection.

This study will examine the pharmacokinetics of nitrofurantoin administered in the dosing regimen, conform the Dutch national guideline SWAB (Stichting Werkgroep Antibioticabeleid) of 50 mg four times daily (quarter in diem, qid) or 100 mg two times daily (bis in die, bid) in steady state, using urine samples.

Study burden and risks

This study will lead to an improved understanding of NFs properties and effects and assist development of optimal dosing regimens to reduce clinical failure, toxicity and emergence of resistance. The use of nitrofurantoin is standard for the treatment of urinary tract infection. In this context, there is no increased risk for the hospitalised patient. Therefore, the risk and burden of participation in this study are minimal as compared to the potential value of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients having been prescribed nitrofurantoin by treating physician because suspicion of or proven urinary tract infection.
2. Age of at least 18 years.
3. Female sex
4. Glomerular filtration rate (GFR) greater than or equal to 30 ml/min based on creatinine clearance.
5. Written informed consent by patient or legal representative

Exclusion criteria

1. Treated with any antibiotics within 1 week of potential sampling period.
2. Known porphyria
3. Known allergic reaction or anaphylactic shock as a result of the consumption of nitrofurantoin

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-03-2018
Enrollment:	60

Type:	Actual

Ethics review

Approved WMO Date:	16-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	NL46061.008.13
CCMO	NL62833.078.17