EXtended use of FOsfomycin for the treatment of CYstitis in primary care

Published: 21-04-2021
Last updated: 15-05-2024

A non-inferiority/superiority trial was designed for the treatment of uncomplicated cystitis in the Dutch community, in which we compare a 1-day and 3-day regimen of FT to a 5-day regimen of nitrofurantoin to investigate the effect on time to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50944

Source
ToetsingOnline

Brief title
EXFOCY

Condition

- Bacterial infectious disorders
- Urinary tract signs and symptoms

Synonym
Cystitis, urinary tract infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW subsidie

Intervention

Keyword: Cystitis, Fosfomycin, General practitioner, Nitrofurantoin

Outcome measures

Primary outcome

* Duration of cystitis symptoms defined as *the number of days with full resolution of relevant cystitis symptoms within the period of 28 days in the absence of aggravation to pyelonephritis or urosepsis (see definition for the secondary endpoint below)*. Relevant symptoms of cystitis include:

o Dysuria

o Urgency

o Frequency of miction

o suprapubic tenderness

Secondary outcome

* Rate of clinical failure, defined as new or persisting cystitis symptoms or aggravation to pyelonephritis or urosepsis for which a new antibiotic treatment was prescribed within 28 days

* Rate of microbiological failure at day 28 (26 to 30) defined as persistence of the initial infecting organism (* 103 colony forming units (cfu) /ml)

* Rate of pyelonephritis or urosepsis, defined as the occurrence of signs or symptoms of pyelonephritis or urosepsis (fever, flank pain, or other matching symptoms) for which antibiotic treatment was prescribed*

* Rate of relapses at day 28, defined as clinical failure caused by the initial infecting organism (> 103 cfu /ml)

* Rate of reinfections at day 28, defined as clinical failure caused by another

organism than the initial infecting organism

* Rate of mortality (all-cause)

* Rate of hospital admission (all-cause)

* Duration of adverse events symptoms (including diarrhea, nausea, abdominal cramps, increased vaginal discharge or other).

* Incidence and nature of severe adverse events, see chapter 9 for definitions

* Rate of complete self-reported therapy adherence after 7 days

* Satisfaction with the treatment received after 28 days on a scale of 5

* The rate of emergence of antibiotic resistance to fosfomycin and nitrofurantoin

* Correlation between in vivo and in vitro activity for the different antibiotic arms

* The number of days of absenteeism:

o education

o (voluntary) work

Study description

Background summary

Cystitis is the most common problem in primary care in the Netherlands for women (3.7% of all consultations in women). Women are disproportionally affected with about 70/1000 new lower urinary tract infections (UTIs) per year, compared to 10/1000 new UTIs per year for men. In the Netherlands this implies more than 600,000 women suffer from a UTI every year.

Empiric treatment of lower urinary tract infection (UTI) targets Enterobacterales and in particular E.coli, the most prevalent causative pathogen. In the Netherlands, the current first choice treatment for uncomplicated cystitis is nitrofurantoin for 5 days (four times daily 50mg or

twice daily 100mg in slow release form, mainly depending on availability at the pharmacy), the second choice is fosfomycin-trometamol (FT) in a single dose and the third choice is trimethoprim for 3 days.FT is increasingly prescribed, probably because it is easy to administer, well tolerated and patient friendly due to its shorter treatment duration. In a large database of prescribed drugs in primary care (Utrecht region) there is a clear increase in FT use since (in 2013). FT became 2nd choice for the treatment of uncomplicated cystitis, at the expense of nitrofurantoin (NIT) (now 1st choice) and trimethoprim (now 3rd choice). FT as a second choice is much more frequently used than trimethoprim as a second choice in 2013.

In two randomized controlled trials, performed more than 20 years ago, efficacy (based on participant reported symptoms) between a single gift of FT compared to nitrofurantoin four times 50mg or twice daily 100mg for 7 days did not differ statistically significant. Yet, one of these studies did not meet the necessary number of inclusions and was thus underpowered and the other was performed in a population in which causative pathogens had higher levels of resistance to nitrofurantoin than is usual in the Netherlands.

A recent open-label randomized controlled trial suggests that a single gift of FT is less effective compared to thrice daily 100mg nitrofurantoin for 5 days for uncomplicated cystitis in non-pregnant women. Compared to the Dutch recommendation they applied a higher dose of nitrofurantoin, reported nitrofurantoin adherence was very high, and the study also included hospitalized patients (7,4% of study population) whereas in the Netherlands nitrofurantoin for uncomplicated cystitis is almost exclusively prescribed to outpatients. This implies that the findings of this study may not be fully generalizable to the Dutch situation, and call for a reevaluation and possible optimization of fosfomycin treatment for UTI.

Although usually prescribed in a single dose, the optimal dose of FT for cystitis is still unknown. The pharmacodynamic parameter most strongly linked to effectiveness is the area under the curve / minimal inhibitory concentration (AUC/MIC) ratio. High inter-individual variability in urinary FT concentrations in healthy female volunteers were observed after a single-gift FT with fosfomycin concentrations in urine below the EUCAST breakpoint in two-thirds of the volunteers after 72 hours. Moreover, in vitro bladder models have shown that a single dose of oral FT 3000mg is insufficient to kill E.coli strains with a minimal inhibitory concentration (MIC)>4mg/L in urine. Consequently, a single dose FT may be insufficient and it is suspected that extended dosing of FT improves outcomes.

Besides, in vitro activity of a single dose of FT for cystitis correlates badly to in vivo bacteriological efficacy, even when using agar dilution, a reference standard for susceptibility testing.3,9 For that reason, dose-finding studies in clinical patients such as in our trial are indispensable for cystitis.

In summary, the current recommendation for Dutch GPs is to treat uncomplicated cystitis with a 5-day course of nitrofurantoin (2x100mg or 4x50mg daily). It is unknown whether a single dosage might be equally effective and if the efficacy of FT could be improved by an additional dosage on day 3. Efficacy reflects the rapidity in which complaints disappear and the likelihood of not developing a relapse or recurrence cystitis or pyelonephritis within 28 days.

We, therefore, designed a non-inferiority/superiority trial for the treatment of uncomplicated cystitis in the Dutch community, in which we compare a 1-day and 3-day regimen of FT to a 5-day regimen of nitrofurantoin to investigate the effect on time to resolution of symptoms and the occurrence of recurrence/relapse within 28 days.

Study objective

A non-inferiority/superiority trial was designed for the treatment of uncomplicated cystitis in the Dutch community, in which we compare a 1-day and 3-day regimen of FT to a 5-day regimen of nitrofurantoin to investigate the effect on time to resolution of symptoms and the occurrence of recurrence/relapse within 28 days.

We will test the following hypotheses related to the primary objective:
1) FT in a single dose is non-inferior to nitrofurantoin,
2) FTin two dosages on day 1 and 3 is non-inferior to nitrofurantoin
3) FT in two dosages on day 1 and 3 is superior to fosfomycin in a single dose.

Study design

An open-label non-inferiority/superiority randomized clinical trial. Patients will be randomized in a 1:1:1 ratio to either of:

A) FT in a single dose on day one (FT1)
B) Extended use of FT during three days with a dose given on day one and three (FT1+3);
C) Nitrofurantoin for 5 consecutive days (2 times daily 100mg in slow release form (Furabid®) (NIT1-5)*

Intervention

I. Fosfomycin-trometamol (FT)
o Single dose scheme: 3000mg taken orally once (arm A)
o Extended dosing scheme: 3000mg taken orally on day 1 and day 3 (arm B)

II. Nitrofurantoin
o 100mg b.i.d. in slow release form (Furabid) taken orally for 5 days (arm C).
Only in case the slow-release formulation is not available, participants

receive 4 times 50mg normal release nitrofurantoin as an alternative (Furadantine®).

Study burden and risks

All study arms have particular benefits and possible disadvantages.
FT1: Based on PK/PD studies a single dose FT may be insufficient. The pharmacodynamic parameter most strongly linked to effectiveness is the area under the curve / minimal inhibitory concentration (AUC/MIC) ratio. For this reason it is possible that extended or higher dosing of FT improves outcomes. Additionally, high inter-individual variability in urinary FT concentrations in healthy female volunteers were observed after a single-gift FT with fosfomycin concentrations in urine below the EUCAST breakpoint in two-thirds of the volunteers after 72 hours. It is however a very patient friendly due to its simple dosing and limited side-effects which might explain why FT is increasingly used for treatment of uncomplicated UTI.
FT1+3: An extended dose of fosfomycin could have a higher efficacy than a single dose of FT for above mentioned reason, but also have a higher chance of side-effects.
NIT1-5: Is the 1st choice and possibly has the highest efficacy, but it is also the longest treatment with most pills.
Resistance rates for fosfomycin and nitrofurantoin are similar and low (1% and 2% resistance rate in primary care in 2018) and does not favour fosfomycin nor nitrofurantoin.
In summary, the current recommendation for Dutch GPs is to treat uncomplicated cystitis with a 5-day course of nitrofurantoin (at least 10 pills), and it is unknown whether a single dosage or 2 dosages of FT in 3 days might be equally effective.

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

-Adult women (><=18 years of age) with a diagnosis of uncomplicated cystitis in primary care
- Cystitis diagnosis is according to the flow diagram in the Dutch NHG-guideline. In line with the NHG guideline 2020, recognition of symptoms should always be accompanied with either a positive nitrite test or leucocyte and dipslide test

Exclusion criteria

-Pregnancy or nursing
-Diabetes Mellitus
-Immunocompromised state
o Untreated infection with human immunodeficiency virus (hiv)
o Use of high-dose systemic corticosteroids
o Use of other immunosuppressive medication (specified in protocol)
-Presence of an indwelling urinary catheter
-History of abnormalities in urinary tract or kidneys
-Neurogenic bladder dysfunction
-UTI in past 28 days before inclusion
-Antibiotic prophylaxis in past 28 days with nitrofurantoin or fosfomycin
-Known GFR <30mL/min
-Contra-indication for nitrofurantoin or fosfomycin use (e.g. allergic reactions, lung or liver reaction or peripheral neuropathy after previous use in clinical history, acute porphyria, G6PD deficiency)
-Current use of an antibiotic for any reason

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-10-2021
Enrollment:	777
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Furabid
Generic name:	Nitrofurantoin - slow-release
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Monuril
Generic name:	Fosfomycin-trometamol
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-04-2021
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-07-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-10-2021
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25501
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-005337-33-NL
CCMO	NL75841.041.20
OMON	NL-OMON25501