Effectiveness of fosfomycin versus nitrofurantoin in Dutch risk groups with cystitis: a pilot study (Uri-weg study)

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To determine the microbiological and clinical cure rate after 14 days.

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

Summary

ID

NL-OMON45847

Source
ToetsingOnline

Brief title
Uri-weg study

Condition

- Bacterial infectious disorders

Synonym
Cystitis and uncomplicated urinary tract infection

Research involving
Human

Sponsors and support

Primary sponsor: Streeklaboratorium voor de volksgezondheid Kennemerland
Source(s) of monetary or material Support: Streeklaboratorium voor de volksgezondheid Kennemerland

Intervention

Keyword: Clinical effectiveness, Fosfomycin, Microbiological effectiveness, Nitrofurantoin

Outcome measures

Primary outcome

The microbiological effectiveness (negative follow-up sample 14 days after antibiotic treatment) of fosfomycin in reference to nitrofurantoin in Dutch risk groups with a cystitis without signs of tissue invasion.

Secondary outcome

To determine the clinical cure rate of fosfomycin and nitrofurantoin (elimination of symptoms).

To determine side effects of fosfomycin and nitrofurantoin.

To determine the prevalence of MDROs (multi-drug resistant microorganisms) in uropathogens.

To determine the resistance rates towards the following antibiotics:

Ampicillin, Amoxicillin/clavulanic acid (augmentin), Cefuroxime, Cefotaxime, Gentamicin, Tobramycin, Ciprofloxacin, Norfloxacin, Trimethoprim, Nitrofurantoin, Fosfomycin, Trimethoprim/sulfamethoxazole (co-trimoxazole)

To determine the distribution of microorganisms in uropathogens.

To determine the ease of use of fosfomycin and nitrofurantoin.

To determine the compliance of fosfomycin and nitrofurantoin.

To determine differences in risk groups between the above mentioned objectives.

Study description

Background summary

More and more urinary tract infections in general practitioner patients are caused by extended-spectrum beta lactamases (ESBLs). In 2013, 3% of all (E.coli) urine isolates reported in ISIS-AR (GP patients) was ESBL positive. Observational studies have previously shown a significant increase in ESBL (E. coli) prevalence in urine samples from GP patients with cystitis (0.1% in 2006 to 1.0% in 2009). Currently, no longer trimethoprim but nitrofurantoin is prescribed as the first choice treatment in healthy non-pregnant women (over 12 years) with cystitis (without tissue invasion). Fosfomycin and trimethoprim are now prescribed respectively as second and third choice treatment. In patients with an increased risk of complicated cystitis the first and second choice antibiotic treatment is nitrofurantoin and amoxicillin / clavulanic acid (in pregnant women) or trimethoprim (in other risk groups) respectively. Fosfomycin is not included in the empirical antibiotic policy in risk groups despite its low resistance and good cure rates, partly because there is little scientific support for risk groups. In a recent review, the effect (microbiological eradication) of fosfomycin compared to other antibiotics (including fluoroquinolones, trimethoprim, and nitrofurantoin), was already demonstrated in patients with cystitis from a non-risk group. It was shown that fosfomycin compared to nitrofurantoin (and other antibiotics) showed comparable microbiological eradication rates with fewer side effects. The same effect was seen within risk groups (including pregnant women and males). Unfortunately, the quality of these studies was low and the effect was not compared to nitrofurantoin, which is currently empirically prescribed as first antibiotic treatment in the Netherlands. To address this knowledge gap in Dutch risk groups a randomized controlled trial is necessary.

Study objective

To determine the microbiological and clinical cure rate after 14 days.

Study design

This study will be designed as a pilot study (open-label randomized clinical trial). The study population consists of patients who present to their GP with signs of a urinary tract infection without signs of tissue invasion and belong to a NHG-defined risk group. NHG risk groups are: men, pregnant women, patients with diabetes mellitus or impaired immune systems, patients with an indwelling urinary catheter and those with preexisting abnormalities of kidney or urinary tract. When these patients with symptoms of uncomplicated UTI (painful or burning urination, increased urinary frequency, false urgency, hematuria, abdominal pain) present to their general practitioner and are diagnosed with an urinary tract infection with the standard recommended procedure by the NHG (dipstick test, dip slide, (water) complaints, sediment and / or culture) will be asked to participate in the study. Three GP practices will participate in

this study (all based in one location) and asking the patient informed consent. Participating patients will be randomized into one of two treatment arms. Urinary voiding symptoms, test results and demographic data are registered by the GP (online CRF). Also a urine sample is sent to the microbiology laboratory for a classic urine culture. Patients are treated with fosfomycin (1 time daily, 3 grams) of nitrofurantoin (7 days, 2 times daily 100 mg) on the basis of the randomization results. The doctor writes this prescription and the medication is picked up at a pharmacy of choice. Over 14 days, the patients will keep a daily diary in which they describe their (voiding) symptoms and side effects. If the symptoms worsen in these 14 days, it is recommended to contact the patients GP. In the case of side effects or worsening of symptoms and in any other situation, the physician has the ability to prescribe a treatment of choice. These situations will be defined as 'failures'. After 14 days, the patient will return to general practice and urine is sent to the microbiology laboratory for a classic urine culture as control. Also a brief questionnaire about the urinary problems at that time will be performed (online CRF). During the 14 days of patient updates will be registered by the GP. The details of patients' lost-to-follow-up will also be recorded. Also is asked the practitioners to register the number of patients that decide not to participate in the study, without recording personal data. The microbiological and clinical cure of both treatment arms will be compared after 14 days.

Intervention

Fosfomycin (1 day, 1 time 3 gram) or nitrofurantoin (7 days; 2 times a day 100 mg) based on randomization

Study burden and risks

Complications can never be ruled out completely. However, both groups are treated with antibiotics that are registered for the indication (uncomplicated UTI). By setting the exclusion criteria as an attempt is made to keep the complications as small as possible.
Exclusion criteria:
Patients with known renal dysfunction(s) (MDRD< 60 ml/min).
Patient is known with an uropathogen isolated in the past 12 months with resistance towards nitrofurantoin and/or fosfomycin.
Patient is known with complications towards nitrofurantoin and/or fosfomycin such as allergic reactions, peripheral neuropathy and/or lung and liver reactions.
Patients who are known hypersensitive towards nitrofurantoin, fosfomycin and / or one of the excipients.
Patients known with Glucose-6-phosphate dehydrogenase deficiency.
Patients with known fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.
Patients with known acute porphyria.

Patients with known gout.
Patients receiving hemodialysis.
Patients using other antibiotics.
Patients using alkalizing agents.
For pregnant women:
Is in the first trimester of pregnancy (week 1 to 13).
Is in the period of delivery (after the first contractions).
Patients who refuse or are unable to give informed consent.

In addition, outside the Netherlands sufficient experience is gained with fosfomycin in risk groups (including men and pregnant women). A recent review carried out [Falagas, 2010) concluded that side effects in pregnant women were significantly lower when treated with fosfomycin relative to the comparators (including cefuroxime, pipemidic acid, ceftibuten and amoxicillin / clavulanic acid). Additionally, the latest issue of drugs in pregnancy and lactation concludes that fosfomycin can be used in all trimesters of pregnancy without harming both fetus and child, and can therefore be classified as low risk for pregnant women. In addition, the microbiological eradication is comparable in comparison with the comparators in the mentioned review.

Completing the diary and the submission of the control urine (other than standard) takes minimal time and is not seen as a major drawback for the patient. This study provides insight into the effectiveness (both clinical and microbiological) of fosfomycin. With rising resistance rates, it is important to have sufficient reserve antibiotics as well as effective first-line agents.

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

Patients presenting to their GP with symptoms of cystitis belonging to a risk group (according to the NHG standard in 2013) without signs of tissue invasion, and have an indication for antibiotic treatment according to the GP. Dutch defined risk groups are defined by males, pregnant females, patients with diabetes mellitus, impaired immunity, abnormalities of the renal or urinary tract, neurological bladder dysfunction and/or an indwelling urinary catheter.

Exclusion criteria

Patients with known renal dysfunction(s) (MDRD < 60 ml/min).
Patient is known with an uropathogen isolated in the past 12 months with resistance towards nitrofurantoin and/or fosfomycin.
Patient is known with earlier complications towards nitrofurantoin and/or fosfomycin such as allergic reactions, hypersensitivity peripheral neuropathy and/or lung and liver reactions.
Patients known with Glucose-6-phosphate dehydrogenase deficiency, fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency, acute porphyria or gout.
Patients using other antibiotics and/or using alkalizing agents.
For pregnant women: is in the first trimester of pregnancy (week 1 to 13) or in the period of delivery (after the first contractions).
Patients who refuse or are unable to give informed consent.

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:	Recruiting
Start date (anticipated):	14-10-2016
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Monuril 3000
Generic name:	Fosfomycin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nitrofurantoïne Apotex
Generic name:	Nitrofurantoin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-01-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2016

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2015-004297-14-NL
CCMO	NL55419.094.15