Study Report

Product: Mannose, lactic acid, calcium carbonate
Study code: UVIREN-01
Datum: 2016-09-02

Alternative treatment with UVIREN for recurring, uncomplicated lower urinary tract infection

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1. BACKGROUND

About half of all women receive at least one acute urinary tract infection (UTI) during their lifetime. Typical symptoms of UTIs are a recurrent feeling of urgency, painful burning and frequent urination. Acute UVI (Cystitis) is in most cases a benign condition and among approximately 30 % of those afflicted symptoms disappear after a week.

Bacteria responsible for UTIs have their origin in the bowls and do sometimes colonize the vaginal and periurethral microflora. It has shown that most women with cystitis, about 70-80 %, show a colonization of such bacteria in their urine and the first treatment of choice to shorten the time with symptoms is antibiotics.

Roughly 10% of Swedish women above the age of 18 (~ 350 000) are treated with antibiotics for at least one UTI per year. Among these, up to a third get treated for yet another or several more infections during the rest of the year.

The prevalence of resistant bacteria has dramatically increased worldwide, in large part due to extended use of antibiotics among humans as well as other animals. Antibiotic resistance is an increasing problem that inspires one to look for other effective methods to treat- and prevent UTIs.

2. UVIREN

This study has examined UVIREN, which is a two-step method for treating and easing symptoms of uncomplicated urinary tract infection. The method is meant to hinder bacterial growth and their ability to cling to the inner walls of the bladder by repeatedly shifting pH-value.

- Flushes away bacteria from the bladder every third hour, five times a day during four consecutive days.
- Changes pH-value, stressing the bacteria (their adaptation time is 5-7 days) and considerably lessening their ability to grow and multiply.

The patient should be free of harmful bacteria within four days, without any side effects or interactions with other drugs.

UVIREN is an alternative treatment/health food supplement that contains a certain blend of mannose, lactic acid, calcium- and magnesium carbonate as well as inulin.

3. INVESTIGATOR

Constantin Raduti

4. STUDY PERIOD

First trial subject's first visit: 14th of April 2015

Last trial subject's last visit: 12th of July 2016

Duration: 15 months

5. PURPOSE

The purpose of this pilot study was to investigate whether UVIREN, a method based on a principle of pH-shifting, decreases the number of harmful bacteria and gives symptom relief for uncomplicated UTIs.

5.1 Primary purpose

The primary purpose of this study was to examine the number of bacteria before- and after treatment.

Analysis: The number of bacteria post four day-treatment in comparison with number pre-treatment.

5.2 Secondary purpose

Secondary purpose was looking at self-reported symptoms before, during- and after treatment.

Analysis: Elapsed time before symptom relief.

6. ETHICS

The study was conducted according to the ICH Good Clinical Practice (GCP) guidelines. The study subjects were given written as well as oral information about the design, purpose and eventual good of the study.

7. STUDY DESIGN

This was an open, uncontrolled pilot study where active treatment was planned to be given out to 20 women, five times per day during four consecutive days. Urine samples were taken before and after the treatment period for quantitative and qualitative determination of bacteria in the urine and antibiogram for four different antibiotics. The study subjects were encouraged to self-rapport eventual symptoms during the treatment period.

Figur 1 ***Study design***

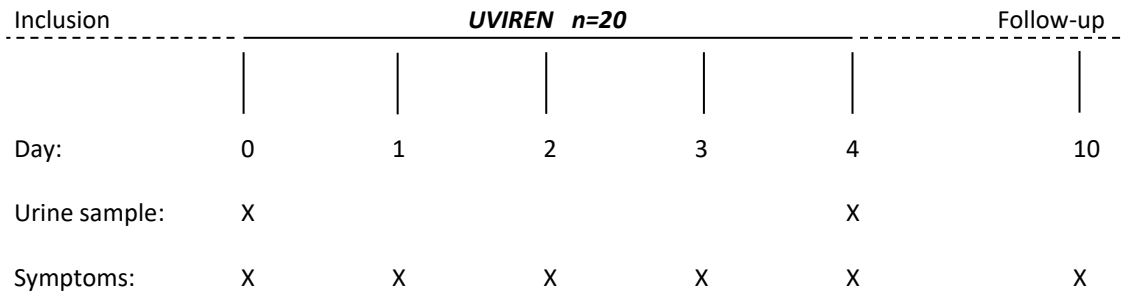

Table 1 ***Study activities***

Dag	**0**	**1**	**2**	**3**	**4**	
Information	X					
Consent	X					
Anamnesis	X					
Symptoms	X					
Urine samples	X				X	
Symptom registration		X	X	X	X	X
Study drug		X	X	X	X	

Information about the study was advertised in the local city magazine as well as the health store. The trial subjects were told to call the study investigator as soon as characteristic burning (UTI) was felt and they were then asked to come to the store. Written and oral information was provided, and consent was collected. After this the subject left a urine sample, provided that it had been at least four hours since their last urination. The sample was tested immediately with a urine stick to show levels of protein, nitrates and leukocytes. High levels of nitrites in the urine suggests an increased number of bacteria present.

If the sample was positive (higher in bacteria) the subject was included in the study. The test tube was marked, put in a sterile plastic bag and stored directly in a refrigerator or in a cool bag on ice packs and was sent together with requisition to Klinisk Mikrobiologi, Sahlgrenska

Universitetssjukhus. The sample analysis was sent back to the doctor responsible at Vårdcentralen the following day.

The test subjects were informed not to drink any sour beverages such as grapefruit juice, cranberry juice or anything containing lemon during the trial period.

Included subjects were allotted a pack of 20 UVIREN dosage bags on the first visit and started their treatment immediately. The total dosage was one bag five times a day with approximately three hours in between for the next four days. They were instructed to dissolve the contents of each dosage bag in 100 ml of water and specify time and date of every taken dose in a diary. In the diary they were also instructed to write down any symptoms by the end of the day.

8. PATIENT POPULATION

A total of 20 test subjects with recurring UTIs and a positive urine stick sample was planned to be part of the study and was ordinated UVIREN for five dosages a day during four consecutive days.

8.1 Inclusion criteria

1. Informed consent
2. Adult woman (>25 years old)
3. Recurring UTI symptoms
4. With urine stick verified Bacteriuria (high level of nitrates)

8.2 Exclusion criteria

1. Treated with antibiotics for UTI within the last 30 days
2. Hiprex for UTI within the last 30 days
3. Intake of sour beverages such as grapefruit juice or cranberry juice

9. TREATMENT

This was an open study of UVIREN. No control group was used in this pilot study.

Table 2 Contents of trial product (dosage bags)

Ingredients	Dosage, strength	Manufacturer
Mannose	1000mg	Hong Kong Biochem
Lactic acid (E-number 270)	100mg	Caldic AB
Calcium Carbonate	50mg	Ph Kalk AB
Magnesium Carbonate	50mg	Ph Kalk AB
Inulin	1000mg	Carls-Bergh
Aroma		
Energy: 15 kcal		

9.1 Preparation

Dosage bags with the contents listed in table 2 were prepared by Carls-Bergh Pharma AB.

9.1.1 Administration

The contents of the dosage bag were dissolved in 100 ml of water for oral intake.

9.1.2 Storage and labeling

20 dosage bags (2,1 g/bag) was numbered from 1-20 and put in a box marked with the study code, expiration date, handling- and dosage prescriptions, name and phone number to responsible investigator, “For testing” as well as room for the test subjects’ personal identity number.

9.2 Concurrent administration of other drugs

UVIREN is to be considered as a health food supplement and could be used in combination with medical drugs. Drugs and treatments vital to the test subject could be taken simultaneously with UVIREN.

9.3 Compliance

” Supplement counting”, meaning the test subjects returned the carton at the follow up and eventual remaining dosage bags where registered.

9.4 Follow-up

The test subjects were contacted via phone within a week after finished treatment and questions were asked about symptoms and eventually experienced side-effects. If the test subject reported remaining UTI-complications and/or fever they were asked to contact the health centre.

9.5 Measured variables

Quantitative determination of bacteria in urine was done according to required criteria at the department for Clinical Microbiology.

Table 3 Quantification of bacteria

1	Low	100-1000
2	Moderate	1000-10 000
3	High	>10 000

The difference between the number of bacteria present pre- and post-treatment was categorized as either fewer, more or unchanged.

Type and antibiogram was given according to routine for this type of question formulation.

9.6 Symptoms

The test subjects rated their symptoms by the end of each day in a diary with unchanged questions and answers. Space was given for additional commenting. The subjects rated their felt sense of burning, feeling of urgency and the number of urinations on a 4-graded scale as seen below (table 4) as well as a summarization rating of the effects of treatment.

Table 4 Grading of symptoms

1	No improvement
2	Moderate improvement
3	Large improvement
4	Considerable improvement

10. STATISTICS

The primary variable in this study was the difference between number of bacteria before- and after treatment (less bacteria, more bacteria, unchanged number).

The secondary variable was the time before alleviation of symptoms and a rating of whether symptoms had been improved, worsened or unchanged.

This was a pilot study with the purpose of investigating if UVIREN had an effect or not on treating UTIs for a limited amount of test subjects. The results and side-effects are descriptively presented below at an individual level.

11. DEVIATIONS FROM PROTOCOL

Every patient was allotted a carton of 30 dosage bags instead of the planned 20. Thus the treatment duration was increased from four to six consecutive days.

The diaries meant to track symptom development daily were removed because of low compliance. At the second visit (day 6) a summarizing question regarding symptom relief was asked and the answer was registered in CRF.

Type and antibiogram was conducted with seven anti-bacterial substances instead of the planned four.

12. DESCRIPTION OF THE PATIENT POPULATION

A total of 16 test subjects were included in the study. One subject (number two) opted out after the first visit because of pregnancy. No subjects needed to terminate their participation because of side-effects or other issues. 15 subjects completed the study.

All test subjects were women in the ages between 7-88. The average age was 61. The study was conducted during all different seasons.

Three subjects reported allergies or a sensitivity to animals, citrus or pollen. Two subjects were taking medication for high blood pressure and another one used blood-thinning drugs. One subject was on anti-depressive medication. None of the subjects were smokers.

13. EFFECTS

The primary variable in the study was the difference between number of bacteria pre- and post-treatment (less bacteria, more bacteria, unchanged number).

The secondary variable was the time before alleviation of symptoms and a rating of whether symptoms had been improved, worsened or unchanged.

Table 1 summarizes the results.

All patients were showing positive results (high nitrates) on the urine stick test at the beginning of the study, which is a sign of an ongoing UTI by the time of arrival at the laboratory was approximately four hours for every subject except for patient 13 and 17 that had a time exceeding four hours. The nitrates-test at the laboratory was positive for patient 6 and 8, but for the remaining subjects the test was negative. In common for those subjects with the existence of E.coli bacteria was a significant bacterial growth (>100.000 bacterial units/ml).

Most subjects, 12 out of 15 (80%), described the treatment after the six days as having a large or considerable effect. A single patient (nr. 12) declared she didn't notice any improvements and ended up using antibiotics after the study was conducted. Subject nr. 8 only noticed a moderate effect. Nr. 9 experienced certain relief and kept using UVIREN for yet another week.

Table 5 Patient populationen age and results from effect measures

Patient nr.	**Age**	**E.coli Bact/ml Test 1**	**E.coli Bact/ml Test 2**	**Resistance development**	**Symptom-relief**
1 (LS)	38	100.000	100.000		Large
2 (AP)	50	-	-		-
3 (ST)	49	Negative	Negative		Considerable
4 (KS)	85	Negative	100.000	Ceftibuten Mecillinam	Large
5 (KE)	74	Negative	Negative		Considerable
6 (TL)	7	100.000	100.000		Large
7	-	-	-	-	-

8 (MS)	76	100.000	100.000		Moderate
9 (RR)	50	Negative	Negative		Moderate
10 (YL)	58	Negative	Negative		Considerable
11 (AÅ)	4	Negative	-		Large
12 (MH)	75	100.000	-		None
13 (IP)	88	Negative	-		Considerable
14 (EJ)	65	10.000	Negative	Trimetoprim	Considerable
15 (MT)	75	100.000	100.000	Ciprofloxacin Trimetoprim	Large
16 (AL)	73	Negative	Negative		Considerable
17 (AE)	65	Negative	Negative		Considerable

Like previously stated, most test subjects (9 out of 15) showed negative urine samples for bacterial growth. In the cases of a positive result the difference between the number of bacteria before- and after treatment was unchanged.

Type and antibiogram was done with seven anti-bacterial drugs: Amoxicillin, Cefadroxil, Ciprofloxacin, Mecillinam, Nitrofurantoin, Tim/Sulfa och Trimetoprim. The results were presented as S = sensitive, I = intermediate or R = resistant.

Subject nr. 4 showed resistance towards Ceftibuten and Mecillinam, nr. 14 was resistant towards Trimetoprim and nr. 15 was resistant toward Ciprofloxacin och Trimetoprim.

14. SIDE EFFECTS

No side effects were reported. The subjects didn’t report any issues with the treatment. No unforeseen events were reported.

15. DISCUSSION AND CONCLUSIONS

This was a pilot study performed on a small group of individuals who were frequently bothered by acute, uncomplicated UTIs. The study was conducted in a structured way but was uncontrolled in the sense that it didn't include a control group. All people participating in the study got the same standardized treatment in controlled settings.

Frequent urgency and burning are typical symptoms of a UTI and are experienced as very troubling and painful. These symptoms weren't evaluated on a daily basis but there was a summarizing assessment of the effects of the treatment according to a 4-graded scale by the end of the treatment (no improvement, moderate improvement, large improvement or considerable improvement). Seven people out of 15 reported a considerable improvement after six days of treatment and another five rated their results as leading to a large improvement. Taken together, this clear majority showed a large or considerable improvement in their symptoms after using UVIREN for six days.

Only one person needed to seek additional medical advice through the health care system and pursue antibiotic treatment. Possibly UVIREN could be ascribed treatment benefits that might make it plausible to avoid the usage of antibiotics in certain cases where they would normally be prescribed. This needs to be examined further through controlled trials.

Regarding a correlation between lessening of symptoms and the number of bacteria in urine before- and after, no correlation was shown. It could be because the used method for quantifying bacterial growth isn't precise enough to detect smaller and possibly significant changes in numbers that would otherwise yield such a correlation with symptoms.

In summary, 80% of the test subjects showed a large to considerable improvement of symptoms after six days treatment with the health supplement UVIREN.

The study concludes that UVIREN for uncomplicated UTI may provide symptom relief.

SIGNATURES OF PERSONS RESPONSIBLE FOR THIS STUDY

I approve the terms and conditions of this study report.

Constantin Raduti	201610 05 Date (year month day)