

Fosfomycin Therapy for Non-Complicated Lower Urinary Tract Infections during Pregnancy: Tanta University Experience

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Abstract

Objectives: To evaluate the efficacy, compliance, safety and economic cost for Fosfomycin trometamol and Nitofurantoïn in uncomplicated lower urinary tract infections during pregnancy. **Background:** Nitofurantoïn and Fosfomycin trometamol are recommended as the first-line agents for treatment of urinary tract infections (UTIs) in the latest guidelines endorsed by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). Fosfomycin is bactericidal and inhibits bacterial cell wall biogenesis and reduces bacterial adherence to uroepithelial cells. Fosfomycin has broad antibacterial activity against both Gram-positive and Gram-negative pathogens, as *Escherichia coli*, *Escherichia faecalis*, and various Gram-negatives like *Citrobacter* and *Proteus*. Both Nitofurantoïn and Fosfomycin are category B in pregnancy. **Patients and Methods:** This study was conducted at Tanta University Hospitals in the period from June, 1, 2015 to January, 1, 2017. Patients were recruited from outpatient clinics of Obstetrics and Gynecology and Urology Departments presenting with asymptomatic bacteruria or cystitis. Patients were allocated randomly into 2 groups: group I (n = 50 cases) received Fosfomycin therapy and group II (n = 50 cases) received Nitofurantoïn therapy (n = 50 cases). After treatment, evaluation of patient symptoms, organism count, patient compliance and cost of treatment were done. **Results:** The enrolled patients were suffering from lower urinary tract infections; asymptomatic bacteruria (17 cases) or cystitis (83 cases). Ten patients were excluded. The demographic data of included patients were not significant for both groups. Complete relief (100%) of symptoms 5 days after start of treatment was noticed in Fosfomycin group while improvement of symptoms after 5 day-treatment was noticed in 86.49% in Nitofurantoïn group (p-value = 0.030). The side effects were recorded in 7 cases (18.42%) in Fosfomycin group compared to (35.14%) with significant

difference in the reported side effects, (p-value = 0.003). Compliance was 38/38 (100%) in Fosfomycin group compared to 34/37 (91.89%) in Nitrofurantoin group (p-value = 0.001). Resistance was very minimal in Fosfomycin group where 1/38 case (2.63%) reported resistance for treatment compared to 8/37 cases (21.62%) in Nitrofurantoin group (p-value = 0.001). **Conclusion:** Fosfomycin trometamine proved to be safe, effective, and has limited resistance. Moreover higher patient compliance and fewer side effects were recommending Fosfomycin to be a first choice drug for uncomplicated lower urinary tract infections during pregnancy at Tanta University.

Keywords

Fosfomycin, Nitrofurantoin, Pregnancy, UTIs, Asymptomatic Bacteruria, Cystitis

1. Introduction

Urinary tract infection (UTI) is considered the most commonly occurring bacterial infection in women [1]. Urinary tract infections (UTIs) complicate 3% to 10% of pregnancies and are among the commonest reasons for antibiotic use in obstetrics. Uncomplicated lower UTI is usually defined as acute cystitis occurring with no known abnormalities of the urological tract, and is characterized by symptoms such as dysuria, urgency, frequency, suprapubic pain and/or haematuria [1] [2].

Escherichia coli is the leading organism responsible for uncomplicated UTI (82.5%), while other entero-bacteria (e.g. *Proteus mirabilis*, *Klebsiella pneumoniae*), *Staphylococcus saprophyticus* and *Enterococcus faecalis* are also commonly implicated [3] [4].

Enterobacteriaceae has been the production of enzymes, known as beta-lactamases, capable of inactivating some members of the penicillin and cephalosporin class antibiotics, which share a similar beta-lactam chemical ring structure. Most recently extended-spectrum beta-lactamase (ESBL) enzymes have arisen, which cause resistance not only to penicillins and cephalosporins, but also additional resistance to fluoroquinolones, aminoglycosides, and sulfamethoxazole-trimethoprim, and are known as multidrug-resistant organisms (MDROs) [5] [6].

Antibiotic resistance has affected disease management in our specialty. Increased resistance of *Neisseria gonorrhoea* to penicillins and quinolones, emergence of methicillin-resistant *staphylococcus aureus* (MRSA) and resistance of Group B *Streptococcus* to erythromycin and clindamycin have led us to modify our antibiotic treatment regimens [5] [6] [7].

Fosfomycin trometamol [Monuril®] is FDA approved (category B) in numerous countries worldwide, mainly for the treatment of uncomplicated urinary tract infections (UTIs). Fosfomycin has good *in-vitro* activity against common uropathogens, including Gram positive and negative organisms such as *Escherichia coli* (including extended-spectrum β -lactamase-producing *E. coli*), *Proteus mirabilis*, *Klebsiella pneumoniae* and *Staphylococcus saprophyticus* [8] [9] [10].

Fosfomycin trometamol given in a single oral dose of 3 g achieves high concentrations in urine and is generally well tolerated. The most reported side ef-

fects were gastrointestinal (e.g. diarrhoea, nausea) and vaginitis [8] [9] [10].

Results of recent randomized trials showed that single-dose fosfomycin trometamol had similar clinical and/or bacteriological efficacy to 3-7-day regimens of ciprofloxacin, norfloxacin, cotrimoxazole or nitrofurantoin in women with uncomplicated lower UTIs [9] [10] [11]. In addition, single-dose Fosfomycin trometamol had similar bacteriological efficacy to a 7-day course of combined antibiotic regimens [11] [12] [13].

In this study, we compared the efficacy of single dose 3 g orally versus the conventional oral Nitrofurantoin in non-complicated lower urinary tract infections during pregnancy at Tanta University Hospitals.

2. Patients and Methods

2.1. Study Design

A prospective, non-blinded, randomized controlled clinical trial.

2.2. Study Settings

This study was conducted at Tanta University in both departments of Obstetrics and Gynecology and department of Urology in the period from June, 1, 2015 to January, 1, 2017.

2.3. Recruitment

Hundred patients between 12 - 36 weeks of gestation were enrolled in this study according to the following *inclusion criteria*: a) Uncomplicated lower UTIs (asymptomatic bacteruria or cyctitis); b) Patient in whom culture revealed an antibiotic contraindicated with pregnancy. The *exclusion criteria* were for patients with a) History of congenital urogenital anomalies; b) Cases associated with hydronephrosis due to any cause; c) Urinary stones; d) Diabetic and immune-compromised patients; e) Patients with high grade fever associated with flank pain and/or signs of pyelonephritis; f) Patients with severe nausea and/or vomiting and are unable to receive oral medication.

2.4. Sample Calculation

The sample was calculated by Epi info 0.7 programs with 2 sided confidence level 95% at power of 85%. H_0 postulated to denote that Fosfomycin is superior to Nitofurantoin. The estimated sample was 100 patients.

2.5. Randomization and Allocation

Patients were allocated randomly into 2 groups. Randomization was done by specific computerized program and alternate allocation for both groups. Group I (n = 50 cases): patients received oral Fosfomycin single dose therapy. Group II (n = 50 cases) received oral Nitrofurantoin.

2.6. Dosage and Administration

Fosfomycin trometamin sachet was dissolved into half a cup of water and taken

before bed time. Patients should empty their bladder, and then took the dissolved Fosfomycin before bedtime.

Nitrofurantoin 100 mg was given in capsule form three times daily for 7 days.

2.7. Methods

All patients age, parity, gestational age, and symptoms plus abdomen /pelvis ultrasonography and urine analysis, were taken at the beginning of the study. After 7 days, questionnaire for symptoms relief, compliance, and complications plus a second urine analysis for counts of organisms. Results were recorded for both groups.

Questionnaire was simply designed and specified by authors' collaboration. It was made of 3 sections: The first section, considered demographic data of participants, the second sections, considered patients' presentation, symptom relief, residual symptoms, compliance and costs of treatment. The third section evaluated the efficacy of treatment by second urine analysis findings and occurrence of side effects and specifying these side effects (**Appendix I**).

2.8. Ethical Approval

This study was obtained before the start of treatment under the code **31242/12/16** by Tanta University Ethical committee.

2.9. Statistical Analysis

It was done using SPSS version 18, USA. The statistical tests used were mean, standard deviation, Chi square (χ^2) and p-value. Significance is positive if $p \leq 0.05$.

3. Results

One hundred patients were enrolled in this study from Urology and Obstetrics and Gynecology Departments, Tanta University, Egypt. All patients were suffering either asymptomatic bacteruria (17 cases) or cystitis (83 cases). Ten patients were excluded because they were either not meeting inclusion criteria (7 cases) or declined to participate (3 cases). The flow chart of enrolled patients is demonstrated in **Figure 1**.

The mean patient's age was 28.5 ± 3.4 years in group I and 27.9 ± 4.02 years in group II. The mean gravidity was (1.2 ± 0.3 and 1.3 ± 0.4) for group I and II respectively. The mean parity was (1.7 ± 0.4 and 1.9 ± 0.9) for group I and II respectively. The mean BMI was (23.7 ± 3.2 and 22.8 ± 2.4) for group I and II respectively. The mean gestational age at presentation was (33.4 ± 1.7 and 34.01 ± 1.23) for group I and II respectively. The demographic data of included patients were not significant for both groups **Table 1**.

Efficacy of the 2 drugs Fosfomycin and Nitrofurantoin was evaluated by subjective improvement of symptoms where 38/38 (100%) were symptom-free 5 days after start of treatment in Fosfomycin group. Improvement of symptoms after 5 day-treatment was noticed in 32/37 (86.49%) in Nitrofurantoin group, (p-value = 0.030) (**Table 2**).

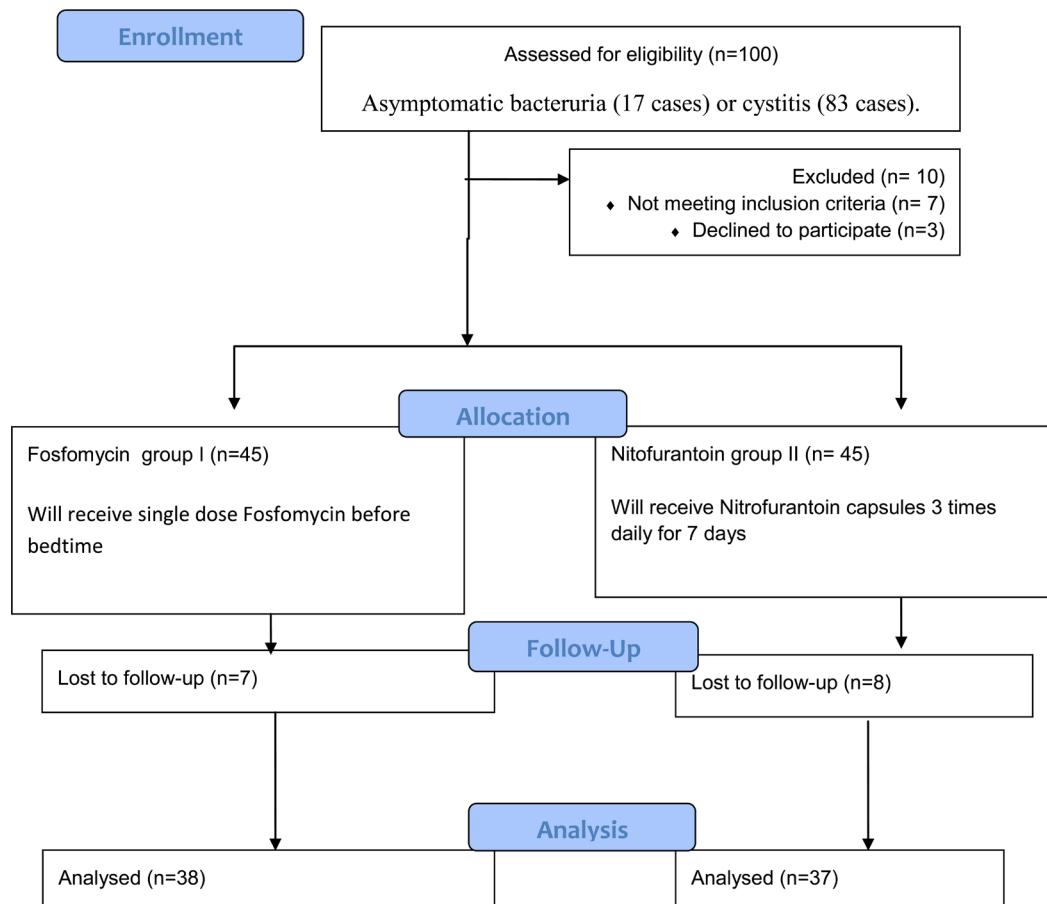


Figure 1. Flow chart of included patients and their management options.

Table 1. Demographic data and presentation of enrolled patients.

	Group I Fosfomycin (N = 38)	Group II Nitrofurantoin (n = 37)	X ²	p value
Age (years)				
Range	22.4 - 35.6	21.8 - 34.9	2.122	0.064
Mean ± SD	28.5 ± 3.4	27.9 ± 4.02		
Gravidity				
Range	1 - 5	1 - 6	1.230	0.073
Mean ± SD	1.2 ± 0.3	1.3 ± 0.4		
Parity				
Range	0 - 5	0 - 5	1.039	0.080
Mean ± SD	1.7 ± 0.4	1.9 ± 0.9		
BMI				
Range	19.34 - 27.71	20.06 - 27.12	3.124	0.120
Mean ± SD	23.7 ± 3.2	22.8 ± 2.4		
Gestational age at presentation				
Range	22.5 - 35.4	23.2 - 36.6	7.88	0.839
Mean ± SD	33.4 ± 1.7	34.01 ± 1.23		
Presentations				
Cystitis	31 (81.58%)	30 (81.08%)	11.304	0.451
Asymptomatic bacteriuria	7 (18.42%)	7 (18.92%)	2.409	0.297

A second urine sample was done 7 days after start of treatment where pus cells (0-10/HPF) was found in Fosfomycin group compared to (15 - 20 pus cells/HPF) in Nitrofurantoin group, (p-value = 0.002). Compliance was 38/38 (100%) in Fosfomycin group compared to 34/37 (91.89%) in Nitrofurantoin group, (p-value = 0.001). The common causes of incomplete compliance were multi-dosing and occurrence of side effects. The cost of therapy was slightly higher in fosfomycin group (45 LE) compared to (35 LE) in Nitrofurantoin group. This difference was not significant (p-value = 0.342) (**Table 2**).

The side effects was recorded in 7 cases (18.42%) in Fosfomycin group compared to (35.14%) with significant difference in the reported side effects, (p-value = 0.003) (**Table 2**). The most common side effects for Fosfomycin were diarrhea 11/38 (28.95%), nausea/vomiting 5/38 (13.16%) and dizziness 5/38 (13.16%). In Nitrofurantoin group the most common side effects were diarrhea 14/37 (37.84%), dyspepsia 12/37 (32.43%) followed by nausea/vomiting and dizziness in equal number of patients 7/37 (18.92%) for each side effect (**Figure 2**).

Resistance was very minimal in Fosfomycin group where 1/38 case (2.63%) reported resistance for treatment compared to 8/37 cases (21.62%) in Nitrofurantoin group, (p-value=0.001). The cure rate for Fosfomycin group was 97.37% compared to 78.38% for Nitrofurantoin group, (p-value=0.002) (**Table 2**).

4. Discussion

Urinary tract infections (UTIs) are common among females; especially pregnant ones due to associated physiological changes that favor the occurrence of UTI. Although pregnancy is a major risk factor for UTI, there are many other contributing factors like, socioeconomic state, diabetes mellitus, recurrent UTI, and other immunologic and blood diseases [14] [15].

UTIs may be presented as asymptomatic bacteruria, cystitis or pyelonephritis with systemic manifestations [16] [17]. Asymptomatic bacteruria should be treated to prevent the occurrence of symptomatic bacteruria as cystitis and pyelonephritis and to prevent its hazards on pregnancy outcomes. At the same time it should be known that asymptomatic bacteruria carries a great risk for development of pre-eclampsia, chorio-amnionitis and preterm delivery [18] [19] [20].

Moreover, repeated urinary tract infection with repeated courses of antibiotic treatment resulted in highly antibiotic resistant bacteria and multi-drug resistant organisms. In addition, the compliance of the patient to take a drug may add a hazard to drug resistant and recurrent infection. So, physicians should shift towards early efficient treatment of UTI in the pregnant females, not only for the health hazards, but also, to decrease progressive UTI during pregnancy which are the most common cause of hospital admissions during pregnancy [21] [22].

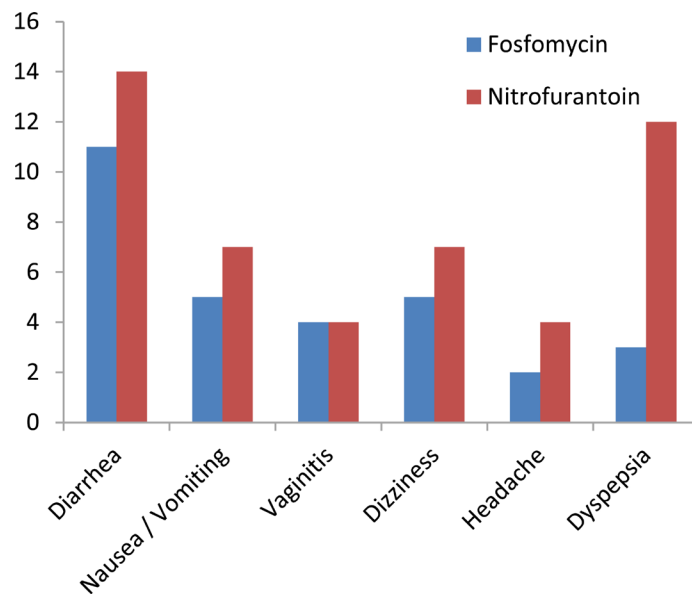
It is well known that urine cultures are time and money consuming, contaminated and sometimes antibiotic sensitivity results may be inconvenient with pregnancy; these factors motivate both urologists and obstetricians to begin empirical antibiotic therapy especially in symptomatic patients [17] [23] [24] [25].

Nitrofurantoin and Fosfomycin trometamol are considered the first line of

Table 2. Efficacy, safety, compliance and cost of treatment options for both groups.

	Group I Fosfomycin (N = 38)	Group II Nitrofurantoin (n = 37)	X ²	p value
Subjective improvement 5 days post treatment	38/38 (100%)	32/37 (86.49%)	11.390	0.030*
Second urinalysis 7 days after treatment	Pus cells 0 - 10/HPF	Pus cells 15-20/HPF	2.334	0.002*
Compliance of patients	38/38(100%)	34/37 (91.89%)	2.118	0.001*
Cost of therapy	45 LE	36 LE	2.578	0.342
Side effects of drugs	7/38 patients (18.42%)	13/37 patients (35.14%)	1.209	0.003
Resistance	1/38 case (2.63%) One case had 10 pus cells/HPF in second urine analysis due to resistance to Fosfomycin	8/37 cases (21.62%)	7.342	0.001*
Cure rate	97.37%	78.38%	2.007	0.002*

*means significant p-value.

**Figure 2.** Side effects of drugs tested in the study.

treatment in non-complicated UTI [26]. Nitrofurantoin is a category B drug during pregnancy and commonly prescribed drug for non-complicated UTI during pregnancy [27] [28]. However, there are a lot of concerns about Nitrofurantoin resistance, safety, and patient compliance [29]. Also Nitrofurantoin not used during delivery or in near term (*i.e.* >36 weeks) because of the assumed possibility of haemolytic anaemia in the newborn [30].

Fosfomycin trometamol is another category B drug used in single dose and shown stability with decreased appearance of mutant urinary strains overtime in many studies. It has higher efficacy and better compliance over Nitrofurantoin and other drugs making it a first choice drug for uncomplicated UTIs In pregnancy [10] [31] [32] [33].

Many studies compared the efficacy and safety of both drugs in uncomplicated UTIs in females but not during pregnancy. Both drugs proved to be safe.

Side effects were comparable in both groups, but drug compliance was better with Fosfomycin trometamol. Also, subjective and the resolution of infection were better and significantly different in the group of Fosfomycin trometamol [34] [35] [36].

During pregnancy Usta TA, *et al.* (2011) selected 324 pregnant women with lower urinary tract infection and allocated them randomly into 3 groups, Fosfomycin trometamol, Amoxicilin-calvulinc, and cefuroxime axetil. The treatment groups did not differ significantly in terms of demographics, clinical success rate, microbiological cure rate, or adverse effects. Significantly higher drug compliance was observed in the Fosfomycin trometamol group than in the other 2 groups ($p < 0.05$). Consequently, they suggested that treatment with a single dose of Fosfomycin trometamol is as effective as the standard course of treatment with Amoxicilin-calvulinc, or cefuroxime axetil, and Fosfomycin trometamol is preferable owing to its simpler use [37].

Liu H-Y, *et al.* (2011) and Araj GF *et al.* (2012) showed *in vitro* susceptibility to Fosfomycin of 86% - 100% more than Nitrofurantoin with comparable results between both groups [38] [39]. These results are comparable to result of this study where persistent infection was found in 1 (2.63%) case in Fosfomycin group and in 8 (21.62%) cases in Nitrofurantoin group. Similar Fosfomycin resistance of 0% - 2.2% to *E. coli* was reported by Pullukçu H, *et al.* (2004) and Ko KS, *et al.* (2007) [40] [41].

Although, Ceran N, *et al.* (2010) showed a comparable results between Fosfomycin and ciprofloxacin with disappearance of pyuria in 80% of cases, our better results (97.37% cure with Fosfomycin) could be attributed to less use of Fosfomycin in our locality with less appearance of resistant strains [42]. De Jong *et al.* (2016) compared Fosfomycin and Norofloxacin in non-pregnant women and they found that the simplified dosage regimen (single dose) and its favorable benefit/risk ratio justify the use of Fosfomycin trometamol as a treatment for uncomplicated urinary tract infections in female patients [43].

Another studies had similar comparable results with Fosfomycin single oral therapy than a longer period's therapy in pregnant females with lower urinary tract infection. Where Krcmery S *et al.* (2001) showed eradication rate of UTI in 95.2% and Bayrak *et al.* (2007) showed eradication rate of 93.2% with Fosfomycin group [44] [45].

In the present study, although both drugs were tolerable orally, complications occurred less frequently with Fosfomycin group 18.42% vs 35.14%. Diarrhea was the commonest complication in Fosfomycin group. This was comparable to other studies by Ceran N *et al.* (2010) [42], Sastry *et al.* (2015) [46], Meier *et al.* (2011) [47] and Mody *et al.* (2014). [48] The minor side effects of Fosfomycin were confirmed by Bayrak *et al.* (2007), who revealed associated minor side effects with Fosfomycin [45].

At last, the compliance of both drugs was better in Fosfomycin group 100% versus 91.8% in Nitrofurantoin group. This high compliance with Fosfomycin is greatly attributed to the single administered dose in opposite to the need of 7

days of Nitrofurantoin.

Limitations of the Study

The small sample size and the financial costs of drugs—being self-funded—were the main limitations of the study.

5. Conclusion

Owing to the higher safety, efficacy, low resistance for Fosfomycin trometamine in management of uncomplicated UTIs during pregnancy, we recommend its wide use at Tanta University Hospitals and to replace other antibiotic regimens as it is cost-effective than other drugs. Moreover, very high patient compliance, fewer side effects were observed with Fosfomycin than other drugs making it a first choice at our hospitals.

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Conflicts of Interests

No conflicts of interest of any kind do exist.

Author Contributions

Ayman Shehatadawood: Was responsible for scientific writing, revisions and submission. Abdel-Ghaffar Said Dawood: Was responsible for statistical analysis, writing and revisions. Salah Naglah: Was responsible for data collection, analysis, scientific writing and revisions. Mohamed Elbakary: Was responsible for data collection, analysis, scientific writing and revisions.

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Appendix I

Tanta University
Faculty of Medicine



Questionnaire form

Section 1: Demographic data

- Name: _____
- Age: _____
- Residence: _____
- Gravidity/Parity: _____
- BMI: _____

Section 2: Patient Presentation

- Gestational age: _____
- First Urine analysis findings: _____
- Ultrasound findings: _____
- Symptoms improvement: _____
 - Complete improvement
 - Partial improvement
 - If partial what are the residual symptoms: _____
- Compliance of patients:
 - Complete compliance
 - Incomplete compliance
 - Causes of incomplete compliance: _____
- Cost of treatment: _____

Section 3: Drug efficacy and safety assessment

- Second urine analysis findings: _____
- Side effects reported: _____

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