Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women

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SUMMARY

Background: Urinary tract infections (UTIs) are very common and have been treated with apparent success with antimicrobials for many years. However, there is a paucity of placebo-controlled clinical trials.

Aim: To measure the symptomatic and bacteriological short-term effect of nitrofurantoin treatment versus placebo, in the treatment of uncomplicated UTI in adult non-pregnant women.

Design of study: Randomised placebo-controlled trial in general practice.

Setting: Non-pregnant women, aged between 15 and 54 years old, consulting a general practitioner for symptoms suggestive of uncomplicated lower UTI and with pyuria (positive for leucocyte esterase test).

Method: A dipslide was inoculated in first-void midstream urine and sent for examination. The patients were randomised to receive nitrofurantoin 100 mg or placebo four times daily for three days. After three, seven, and 14 days a new dipslide was inoculated and symptoms of UTI were checked for the disappearance or improvement of symptoms and bacteriuria.

Results: Of 166 women consulting with symptoms suggestive for UTI, 78 had pyuria and agreed to participate in the study (the clinically suspected UTI group); of these, 40 received nitrofurantoin and 38 received placebo. The result for combined symptomatic improvement and cure after three days was 27/35 in the nitrofurantoin group and 19/35 in the placebo group (38% confidence interval [CI] = 2.3 to 79). After seven days, combined improvement and cure was observed in 30/34 and 17/33 respectively (P = 0.033, NNT = 2.7, 95% CI = 1.8 to 6.0). At inclusion, 26 women had bacteriuria of ≥10^5 CFU/ml (the bacteriologically proven UTI group). Of these, 29 received nitrofurantoin and 27 received placebo. After three days the bacteriological cure was 21/26 in the treatment group, compared with 5/25 in the placebo group (P = 0.02, NNT = 1.6, 95% CI = 1.2 to 2.6). After seven days the bacteriological cure rate was 17/23 in the intervention group and 9/22 in the placebo group (P = 0.05, NNT = 3, 95% CI = 1.7 to 17).

Conclusion: In women with bacteriologically proven UTI, nitrofurantoin was significantly more effective than placebo in achieving bacteriological cure and symptomatic relief in just three days; this was still present after seven days. In patients with clinically suspected UTI the symptomatic effect was statistically significant after seven days; after three days there was a trend towards significance.

Keywords: urinary tract infection; nitrofurantoin; placebo; randomised controlled trial.

Introduction

The advent of evidence-based medicine has confronted the medical world with many new dilemmas. One of them is the problem of universally accepted treatments for which no formal evidence exists. In contrast with the effectiveness of antimicrobials in the treatment of otitis media or acute pharyngitis, their effectiveness in the treatment of urinary tract infection (UTI) is not under debate. Nevertheless, there is a lack of placebo-controlled trials, although some have argued that it would be unethical to perform such trials in this situation.1,2 However, such an absence of evidence about a pathology affecting thousands of women each year and responsible for about 3% of the workload in general practice3 is problematic. Most trials are limited to bacteriological outcomes, despite the unclear relationship between symptoms and bacteriuria.4 Besides this, more and more patients are reluctant to use antimicrobials. Placebo-controlled trials are needed, to inform patients of the advantageous nature of the treatment. As far as could be ascertained, no such trials exist in the treatment of uncomplicated acute UTIs in general practice.

The aim of this study was to measure the symptomatic and bacteriological short-term effect of nitrofurantoin treatment versus placebo, in the treatment of clinically suspected and bacteriologically documented acute uncomplicated UTIs in adult non-pregnant women.

Method

The study took place in 17 general practices in the Ghent region of Belgium between June 1995 and December 1996. Inclusion was restricted to non-pregnant women aged between 15 and 54 years, consulting their general practitioner (GP) with symptoms suggestive of acute uncomplicated UTI (acute dysuria, urinary frequency or urgency) and with detected pyuria. This group was defined as having ‘clinically suspected UTI’ and reflects the situation in real practice: normally bacteriological cultures are not done and results are not available when treatment is begun. The ‘bacteriologically proven UTI’ group had symptoms and pyuria combined with significant bacteriuria. To avoid complicated UTI, we excluded patients with a fever, i.e. temperature above 38°C (axillary), known nephrological or urological problems, diabetes or other immunocompromising illnesses, and patients with recurrent UTI (more than three occurrences per year during the past year or a UTI in the past three months). Furthermore, women with gynaecological complaints — such as abnormal vaginal discharge, labial
irritation, intermittent vaginal bleeding, patients with symptoms present for more than seven days, patients who had taken antibiotics in the past four weeks or with known allergy to nitrofurantoin — were excluded.

The study design was a double-blind randomised placebo-controlled clinical trial in general practice. During the first consultation, and at examination three and seven days later, patients were seen by their GP and a urine specimen was taken at the surgery after instruction in the midstream technique. Two weeks after the start of treatment, another urine sample was taken. Urine samples were immediately inoculated on a ‘dipslide’ (Uricult®, Orion Diagnostics) and sent to the laboratory of bacteriology and virology at the Ghent University Hospital, where they were examined using standard techniques.

Pyuria was defined as a positive leucocyte esterase (LE) test (Nephur-test® and Leuco, Boehringer-Mannheim), with any colour change after two minutes as the criterion of positivity. Significant bacteriuria was defined as a count of 100 000 or more colony-forming units (CFU) per ml. If two species were isolated then the relative number of each species was represented semiquantitatively. Mixed cultures of more than two isolates were considered contaminated and were therefore excluded.

The patients received a diary to record symptoms on a four-item scale (‘disappearance’, ‘improvement but not completely resolved’, ‘no improvement’, and ‘worsening’) and possible adverse reactions (‘Did you experience any unusual effects since you took the medication?’).

Ethics and consent

The rules about informed consent have evolved dramatically in less than ten years. In our study, patients have given only oral informed consent: a written consent was not yet mandatory at the time the study was performed (i.e. previous to the Guidelines for Good Clinical Practice: ICH Harmonised Tripartite Guidelines, 1996). As was usual in Belgium at that time, no written information sheet was given to the patients; their own GP informed them as follows: ‘We are studying a drug that has been proven safe and is in common use. The purpose of this study is to measure its effectiveness. It does not involve a new drug.’ It was emphasised to patients that the trial could be stopped at any time, in the event of objective or subjective problems occurring. It was considered a major ethical duty to avoid potential problems for participants. The trial was approved by the ethics committee of the Ghent University Hospital.

Treatment allocation

After giving informed consent, patients were randomised to receive either a box containing capsules of nitrofurantoin (macrocrystal formulation) 100 mg or placebo capsules with the same appearance. The randomisation list was available only in the event of an emergency at the Hospital Pharmacy of the Ghent University Hospital. Patients were asked to take the capsules with some food four times a day for three days. All patients were advised to drink lots of water.

Outcome measures

Three endpoints were used: two clinical and one bacteriological. These were: ‘symptomatic cure’ (defined as ‘no more symptoms at all’), ‘improvement’ (defined as ‘few symptoms’) and a negative or non-significant culture result.

The patients and physicians were advised that they had the option to stop the trial prematurely, in the event of any side effects or aggravating symptoms. In such a case, GPs would then prescribe the treatment of their choice. These situations were recorded as ‘failures’ and treated as ‘unsuccessful’ at the third and seventh day. All other patients not attending the follow-up examinations were defined as ‘dropouts’. Relapse was defined as significant bacteriuria in patients with a negative culture at an earlier assessment.

Statistical analysis

Taking into account the ethical objections about the acceptability of a placebo-controlled trial for UTI,1,2 it was intended to limit the number of participants in the study. Limiting the numbers of patients needed in a trial can be achieved by evaluating the necessity of a two-sided test; the possibility that placebo was more active than treatment was never assumed in this study. In this situation, a one-sided test is methodologically acceptable.5,6 For the power calculation, the aim was to detect, with a 90% probability, a statistically significant difference at α = 0.05 for a one-sided test, between treatment (with an estimated cure rate of 85%) and placebo (with a cure rate of 50% or less). The calculated sample size was 26. This was the minimum size of a group. Since not all symptomatic patients with pyuria had significant bacteriuria (estimated 85%) and an estimated 10% of patients could not be evaluated, the decision was made to include 40 patients in each group.

A χ² test with Yates’ correction for 2 x 2 tables was used to test differences between the groups (SPSS 9.0 for Windows) and the number needed to treat (NNT) with a 95% confidence interval (95% CI) was calculated using Confidence Interval Analysis software. If the 95% CI included infinity (when the absolute risk reduction can be zero) the number
of patients needed to be treated for one additional patient to benefit (NNTB) and the number of patients needed to be treated for one additional patient to be harmed (NNTH) were calculated, as described by Altman.7 An intention-to-treat analysis was performed, considering each dropout as ‘unsuccessful’.

**Results**

In total, 166 women with symptoms suggestive of uncomplicated UTI were seen. Of these, 88 were not included because they declined to participate (22), did not meet the inclusion criteria (39), or had a negative LE test (27). Seventy-eight women were therefore included in the study, of whom 38 were allocated to receive placebo and 40 were allocated to receive nitrofurantoin. The baseline characteristics between both groups after randomisation did not diverge for relevant factors, owing to the very strict inclusion criteria: all complicating factors (fever, recurrent UTI, signs of sexually transmitted disease, postmenopausal atrophy) or co-morbidity (diabetes, renal or urological diseases) were excluded. The mean age was 29 years in the placebo group and 31 in the nitrofurantoin group; the median for pyuria and bacteriuria were the same in both groups (pyuria median +++ on the urine stick (LE) and bacteriuria median 100 000 CFU/ml). A flowchart describing patient participation on the different examination visits is depicted in Figure 1.

**Clinically suspected UTI group (n = 78)**

The results in all patients with symptoms and pyuria, irrespective of the result of bacterial culture, are given in Table 1. A minority of patients had no symptoms at all on the third day: 20% in the placebo group and 37% in the treatment group. In the placebo group, more than half had some improvement of their symptoms at that time. However, the effect of the treatment, although evident, was not statistically significant (P = 0.08).

With a NNT of less than three, the effect of nitrofurantoin on cure or improvement became clinically very relevant by day 7. The number and the reasons for failure are listed in Table 2.

On day 3, eight patients were lost to follow-up (dropouts) and three more patients were lost on day 7. The results of the intention-to-treat analysis are shown in Table 1.

**Bacteriologically proven UTI group**

Out of the 78 included patients, 56 had significant bacteriuria on day 1 (72%). Twenty-seven were allocated to the placebo group and 29 to the nitrofurantoin group. The results of the bacteriological and symptomatic assessment in this population after three and seven days are shown in Table 3. Significant bacteriuria had disappeared in 21/25 women after three days of nitrofurantoin, versus only 5/25 in the placebo group. This difference is statistically highly significant (P<0.001); the significance is less pronounced after seven days, mostly because of a greater proportion of spontaneous cure in the placebo group. The clinical relevance remains significant with a NNT of three. The effect on symptoms is most apparent after three days, but symptomatic improvement or cure remains significantly higher in the nitrofurantoin group after seven days. The number and the reasons for failure are listed in Table 2.

Between the day 1 and day 3 the dropout rate was 5/56; three more were lost to follow-up on day 7. The intention-to-treat analysis is shown in Table 3.
In patients who were followed up for two weeks ($n = 42$) no statistically significant differences were found between the nitrofurantoin and placebo groups in terms of bacteriology ($P = 0.31$) or symptomatology ($P = 0.29$). Eight relapses were observed at that time: five in the treatment group and three in the placebo group.

There was one clinical diagnosis of acute pyelonephritis; this patient received placebo for three days and had a bacteriuria count of $10^6$ CFU/ml on day 1. Two women in the placebo group had significant bacteriuria at each examination (one with continuing symptoms, the other symptomatically cured); there were none in the treatment group.

Table 1. Symptomatic effect of nitrofurantoin versus placebo in all women with clinically suspected UTI ($n = 78$ the first day).

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin</th>
<th>Placebo</th>
<th>Complete case analysis</th>
<th>Intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n = 40$)</td>
<td>($n = 38$)</td>
<td>$\chi^2$, NNT ($95%$ CI)</td>
<td>$\chi^2$, NNT ($95%$ CI)</td>
</tr>
<tr>
<td>Day 3 (nitrofurantoin $n = 35$, placebo $n = 35^c$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic cure</td>
<td>13 (37)</td>
<td>7 (20)</td>
<td>$P = 0.06$</td>
<td>$P = 0.2$</td>
</tr>
<tr>
<td>Symptomatic improvement</td>
<td>14 (40)</td>
<td>12 (34)</td>
<td>4.4 ($2.3$–$7.9$)</td>
<td>5.7 (NNTB 2.6–NNTH 25)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (77)</td>
<td>19 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7 (nitrofurantoin $n = 34$, placebo $n = 33$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic cure</td>
<td>24 (70)</td>
<td>14 (42)</td>
<td>$P = 0.003$</td>
<td>$P = 0.01$</td>
</tr>
<tr>
<td>Symptomatic improvement</td>
<td>6 (18)</td>
<td>3 (9)</td>
<td>2.7 ($1.8$–$6$)</td>
<td>3.3 ($2$–$10$)</td>
</tr>
<tr>
<td>Total</td>
<td>30 (88)</td>
<td>17 (51)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Complete case analysis $n = 70$ on day 3 and $n = 67$ on day 7; intention to treat analysis $n = 78$ each time. $^b$The numbers needed to treat (NNT) are given with the $95\%$ confidence interval. When the confidence interval includes infinity, the range from the NNT for one additional patient to benefit (NNTB) to the NNT for one additional patient to be harmed (NNTH) is given. $^c$Occasionally, there were a few more symptomatic data without bacteriological data available, or vice versa, which explains small differences in the denominator between this table and Figure 1.

Table 2. Reasons given by GPs for stopping treatment during the study, in patients with clinically suspected UTI (and with bacteriologically proven UTI).

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin group (clinically suspected UTI: $n = 40$; bacteriologically proven UTI: $n = 29$)</th>
<th>Placebo group (clinically suspected UTI: $n = 38$; bacteriologically proven UTI: $n = 27$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 to day 3</td>
<td>1 (1), comprising:   antimicrobial for intermittent infection</td>
<td>7 (5), comprising:   antimicrobial for intermittent infection</td>
</tr>
<tr>
<td>Day 3 to day 7</td>
<td>3 (2), comprising:   2 (1) worsening of symptoms   1 (1) antimicrobial for intermittent infection</td>
<td>6 (4), comprising:   5 (4) worsening of symptoms   1 (0) antimicrobial for intermittent infection</td>
</tr>
</tbody>
</table>

Table 3. Symptomatic and bacteriological effect of nitrofurantoin versus placebo on bacteriologically documented UTI (patients with $10^5$ CFU/ml or more on inclusion, $n = 56$).

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin</th>
<th>Placebo</th>
<th>Complete case analysis</th>
<th>Intention to treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n = 29$)</td>
<td>($n = 27$)</td>
<td>$\chi^2$, NNT ($95%$ CI)</td>
<td>$\chi^2$, NNT ($95%$ CI)</td>
</tr>
<tr>
<td>Day 3 — bacteriology: (nitrofurantoin $n = 26$, placebo $n = 25$; symptoms: nitrofurantoin $n = 25$, placebo $n = 25^c$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriological cure</td>
<td>21 (81)</td>
<td>5 (20)</td>
<td>$P &lt; 0.001$, 1.6 ($1.2$–$2.6$)</td>
<td>$P &lt; 0.001$, 1.9 ($1.3$–$3.1$)</td>
</tr>
<tr>
<td>Symptomatic cure or improvement</td>
<td>20 (80)</td>
<td>11 (44)</td>
<td>$P = 0.02$, 2.8 ($1.6$–$9$)</td>
<td>$P = 0.06$, 3.5 ($1.9$–$31$)</td>
</tr>
<tr>
<td>Day 7 — bacteriology: (nitrofurantoin $n = 23$, placebo $n = 22$; symptoms: nitrofurantoin $n = 24$, placebo $n = 24$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteriological cure</td>
<td>17 (74)</td>
<td>9 (41)</td>
<td>$P = 0.05$, 3 ($1.7$–$17$)</td>
<td>$P = 0.14$, (2–$2604$)</td>
</tr>
<tr>
<td>Symptomatic cure or improvement</td>
<td>21 (88)</td>
<td>13 (54)</td>
<td>$P = 0.03$, 3 ($1.7$–$11$)</td>
<td>$P = 0.1$, 4 (NNTB 2–NNTH 158)</td>
</tr>
</tbody>
</table>

$^c$Complete case analysis in bacteriological cure $n = 51$ on day 3 and $n = 45$ on day 7, and in symptomatic cure $n = 50$ on day 3 and $n = 48$ on day 7; intention-to-treat analysis $n = 56$ each time. $^b$The numbers needed to treat (NNT) are given with the $95\%$ confidence interval. When the confidence interval includes infinity, the range from the NNT for one additional patient to benefit (NNTB) to the NNT for one additional patient to be harmed (NNTH) is given. $^c$Occasionally, there were a few more symptomatic data without bacteriological data available, or vice versa, which explains small differences in the denominator between this table and Figure 1.

Other results

In patients who were followed up for two weeks ($n = 42$) no statistically significant differences were found between the nitrofurantoin and placebo groups in terms of bacteriology ($P = 0.31$) or symptomatology ($P = 0.29$). Eight relapses were observed at that time: five in the treatment group and three in the placebo group.

There was one clinical diagnosis of acute pyelonephritis; this patient received placebo for three days and had a bacteriuria count of $10^6$ CFU/ml on day 1. Two women in the placebo group had significant bacteriuria at each examination (one with continuing symptoms, the other symptomatically cured); there were none in the treatment group.

Nine patients in the nitrofurantoin group reported side effects, versus 10 in the placebo group — gastrointestinal problems (four versus three); headache (two versus three); dizziness/fatigue (two versus three); sleep disturbances...
(one versus zero); vaginal itching (one versus two); dermatological problems (zero versus one); and others (zero versus two), giving a total of ten versus 14. Side effects were the reason for withdrawal from the trial for only one patient (treated with placebo).

Discussion

A significant symptomatic and bacteriological short-term benefit was observed in the treatment of uncomplicated UTI with nitrofurantoin, compared with placebo. The clinical relevance of the effect is illustrated by the small numbers needing to be treated to prevent an unwanted outcome. Although this was expected, until now it has not been clearly tested. It is believed that this is the first placebo-controlled trial in uncomplicated UTI in women in general practice that meets the methodological criteria. There are three double-blind studies in the literature, but these only included patients with ‘urethral syndrome’.8-10 The controversy over urethral syndrome continues; however, even in those who consider this syndrome as a subgroup of uncomplicated UTI do not accept that the results of these studies can be extrapolated to all UTIs. In Mabeck’s study on sulfonamides in UTI a placebo arm was included; however, it was used to follow spontaneous evolution rather than the explicit comparison of drug treatment with placebo.11 A German trial in primary health care patients was performed by Asbach, which included four groups of 20 women with cystitis. It was surprising to note that 76/80 (95%) women with dysuria and pyuria had cystitis. No clear definition of cystitis, cure, blinding or randomisation was given. There was no statistical testing of results, nor was a power calculation performed. The treatment was a single dose of cefixime, ofloxacin, co-trimoxazole or placebo. The response rate (probably bacteriuria count of less than 10^3 cfu/ml) after 14 to 17 days was respectively 89.4%, 89.4%, 84.2% and 26.3%. Symptomatic relief with the presence of bacteriuria was treated as a failure, but not separately mentioned in the results.12

The last double-blind study compared a ‘placebo’ group with a single-dose treatment of amoxycillin (1 g) or co-trimoxazole (trimethoprim 480 mg) sulfamethoxazole 2400 mg in 61 adult women referred to a university polyclinic.13 A substantial number of patients with asymptomatic bacteriuria (25% [15/61]) were included; 34 women had recurrent UTI (56%). Sodium bicarbonate (2 g, four times daily) served as placebo. After seven days, 44% (8/18) of the patients in the placebo group were bacteriologically cured (less than 10^5 CFU/ml), compared with 45% (statistically non-significant) in the amoxycillin and 95% (√χ^2, P<0.001) in the co-trimoxazole group. There were no data on the evolution of symptoms. No other trials could be found.

In this study, the definition of 100 000 CFU/ml for UTI was a very conservative one. Discussion on the bacteriological cut-off point for the definition of UTI has been ongoing since the 1980s.14 Most — but not all15 — authorities in this area have accepted lower cut-off points in symptomatic women, ranging from 100 CFU/ml16 to 100017 and 10 000 CFU/ml.18 By taking the most conservative opinion and clinical suspicion, we have tried to include the full spectrum of possibilities in our data.

An important effect of nitrofurantoin treatment was observed on symptoms in those patients with significant bacteriuria after three days, though this was less marked than the bacteriological effect. After seven days the symptomatic benefit of treatment was diminished, mostly owing to a spontaneous improvement in the placebo group. Also, the failure rate in this study is a strong argument in favour of antimicrobial treatment; in those patients with bacteriologically documented UTI, eight patients in the placebo group curtailed their treatment because of symptomatology, compared with only one in the drug treatment group (√χ^2, P = 0.02).

In daily practice it is advisable only to perform bacterial culture in suspected complicated UTI.19 GPs treat patients based on symptoms, often in combination with the detection of pyuria. The symptomatic improvement in patients with clinically suspected UTI significantly favours drug treatment after seven days. Also in this group, the failure rate owing to worsening of symptoms largely favours antimicrobial treatment: 10 patients versus two had stopped participating in the trial for this reason (Table 2, √χ^2, P = 0.02).

By following our inclusion and exclusion criteria, we studied the most common UTI patient group (adult, healthy women) seen in general practice. The participating GPs were asked what factors could have interfered with inclusion of patients. They reported that selection was made only according to workload and mentioned that refusal was not linked to specific characteristics of women or illness, because the stringent exclusion criteria avoided nearly all patients at risk for complicated UTI or sexually transmitted disease.

Nitrofurantoin was used because it is an accepted and efficient antimicrobial agent for empirical treatment in general practice.20-22 The sensitivity of uropathogens for this drug is very high in Belgium23 and it is widely used by Belgian GPs.24 The three-day treatment is the current treatment of choice,17,19 this being considered the time required to effect a cure. It is surprising to have so few patients in the treated group with completely resolved symptoms after three days. Nitrofurantoin is possibly slightly less effective than co-trimoxazole in achieving short-term symptomatic relief.17 However, when using short therapies it is important to tell patients that some symptoms may persist when treatment stops, even when bacterial eradication has been successful.

Unfortunately a high number of patients dropped out between day 7 and week 2. Therefore no fully reliable conclusions for week 2 can be made. The challenge for this type of study is to persuade ambulatory patients without symptoms to return to the surgery, two weeks after a dysuria episode.

The study became slightly underpowered in the documented UTI population after seven days. The specificity of the LE test to detect UTI, based on former data, was overestimated.25,26 A large number of false-positives explains why 72%, and not the expected 85%, of the LE-positive symptomatic patients had significant bacteriuria — a disillusioning result.27 The effect in a complete case analysis was more important than in an intention-to-treat analysis. The use of an intention-to-treat analysis in this context may be discussed: the probability that women with unchanged or worse symptoms...
would be lost to follow-up, and those with relief from symp-
toms would come more frequently to the second appoint-
ment, seems very low. On the contrary, it is very likely that
women without symptoms after two days may have forgot-
ten the appointment, as they considered themselves cured.

Conclusion
We conclude that this first placebo-controlled trial in uncom-
plicated UTI confirms the clinical impression, that nitrofuranto-
in was significantly more effective than placebo in achieving
bacteriological cure (NNT = 1.6) and symptomatic relief
(NNT = 2.8) in women with documented acute uncomplicat-
ed UTI after three days’ treatment; this effect still pre-
valued after seven days. Patients should be informed about
the frequent persistence of some symptoms after three days
of nitrofurantoin treatment, despite the apparently success-
ful bacteriological eradication. In patients with clinically sus-
pected UTI, the symptomatic effect of nitrofurantoin treat-
ment was significant after seven days (NNT = 2.7); after
three days there was only a trend towards significance.

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