Introduction

Recurrent urinary infections in women are not uncommon and may cause great distress to the patient. Experience over the past 30 years has shown that this condition is readily amenable to control by means of long-term prophylaxis. Prophylaxis was recognized in the pre-antibiotic era (e.g. the use of the formaldehyde-producing compound methenamine, and advocacy for the ‘ketogenic diet’). Cranberry juice, which produces hippuric acid and thus exerts a weak antibacterial effect in the urine, showed some success in controlling recurrence and, more recently, trimethoprim, co-trimoxazole, oral first-generation cephalosporins and fluoroquinolones have been effective. However, topical antiseptics applied to the perineum and urethral meatus have generally proved disappointing.

The ideal prophylactic agent should be absorbed by the oral route, mainly excreted in the urine, active against putative pathogens (bearing in mind local resistance patterns), well-tolerated, lacking side-effects and toxicity, and inexpensive. Nitrofurantoin, especially the macrocrystalline formulation, Macrodantin, has given consistently good results, and so has often been used as comparator in clinical trials of the prevention of recurrent urinary infections in adult women and children.

In the present paper we analyse data obtained over 18 years at The Royal Free Hospital using nitrofurantoin.
prophylactically in women liable to recurrent urinary infections. Results of four previous comparative clinical trials involving 173 patients have been combined, added to data from 46 other patients given long-term nitrofurantoin but not in a trial, and reanalysed. Thus, sub-groups of interest (e.g. the elderly, those allergic to antibiotics, those with congenital or acquired radiological abnormalities) have been enlarged.

As the trials were carried out in a homogeneous but shifting patient group, in a single centre under the same circumstances and using virtually identical protocols, this is not a meta-analysis of the usual kind.

**Patients and methods**

The types of patient, the workings of the Urinary Infection Clinic and the way in which prophylaxis was administered have been described previously. All patient data were recorded on special Clinical Record Forms (CRFs). Forty-three patients took one 50 mg tablet of the micro-crystalline formulation every 12 h, 110 took one 100 mg capsule of Macrodantin at bedtime, and 66 took one 50 mg capsule of Macrodantin at bedtime. Patients were advised to take the medication with a snack or with milk. The recommended course was 12 months. Prophylaxis was not started until a midstream specimen of urine (MSU) had been shown to be sterile.

**Microbiological methods**

These were as described previously. A urinary infection was defined as an MSU growing \( \geq 10^6 \) mL of one bacterial species together with pyuria (\( \geq 10 \) polymorphs/\( \mu \)L). In most patients, bacteriuria was \( \geq 10^5 \) mL.

Rectal swabs or faeces were plated on MacConkey agar, and discs (200 \( \mu \)g) of nitrofurantoin were placed on the pool and spread areas. After overnight incubation any colonies growing within the zone of inhibition around the discs were subcultured, identified and their resistance to nitrofurantoin confirmed on IsoSensitest agar.

**Analysis of data**

As the efficacy of long-term prophylaxis cannot be assessed by a simple ‘cure/fail’ analysis, we used different methods. Cumulation of data. The total length of time for which prophylaxis was taken by all assessable patients was divided by the total number of symptomatic attacks during that time, giving the mean number of episodes during prophylaxis. This was compared with the figure obtained, using the same process, for the year before the start of prophylaxis.

Results in individual patients. The numbers of patients experiencing no symptomatic attacks, and of those having no bacteriuric episodes, during prophylaxis were calculated. The progress of each patient during and after the period of prophylaxis was compared with their immediate pre-history. Each patient was scored—separately for the two periods—as ‘improved’, ‘no improvement’ or ‘not calculable’, in terms of whether the frequency of symptomatic episodes had decreased during, and after, prophylaxis.

**Results**

**Patient entry**

CRFs from all 219 patients were assessed for adverse events. Forty-six patients were not assessable for clinical efficacy, as they had completed <3 months’ prophylaxis, usually as a result of withdrawal by reason of an adverse event (67%) or non-compliance.

**Patient characteristics**

Age. The overall pattern (Figure 1) was the same for all the patients entered (219) as for those who were assessable.
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for clinical efficacy (173). The age range was 9–89 years (median 31–35 years, mode 26–30 years). Most patients were <40 years of age (61%), 26% were in the middle age groups (41–65 years) and 14% were aged >65 years.

Incidence of recurrence. The incidence of symptomatic episodes during the 12 months immediately before entry is shown in Figure 2. The range was 1–12, with a median of 6 and a mode of 4. The one patient who had only one infection had recently undergone a renal transplant and was given prophylaxis in view of the potentially serious consequences of another infection. Taking an arbitrary value of 15 for any figures of >12, there was a total of 1191 episodes, giving a mean of 6.9 attacks/year/patient before prophylaxis.

Nature of most recent infecting organism. In 139 of the patients (80.3%) the organism causing their most recent infection had been identified, usually by our laboratory. Eighty-two percent of these infections had been caused by Escherichia coli, 6.5% by Klebsiella pneumoniae and the remainder by nine other bacterial species.

Allergies to antibiotics. Twenty-five patients (14.4%) were allergic to an antimicrobial agent, most commonly a β-lactam (6.4%) or an anti-folate (6%). Radiological findings. More than 90% of the patients (157) had been investigated by means of an intravenous pyelogram, and many by another form of imaging in addition. At least one abnormality was found in 37 (23.6%); see Table I.

Results of prophylaxis

A diverse events. Eighty-one patients (40%) reported some form of adverse event. The incidence, especially for nausea, differed between the three dosage groups (Table II). Nausea was most common with the microcrystalline form; halving the dose of Macrodantin did not further reduce the incidence. For ‘all adverse events’, there was a clear trend indicating the lowest incidence with 50 mg Macrodantin od, intermediate with 100 mg Macrodantin od and highest with 50 mg microcrystalline bd. The only statistically significant difference was between 50 mg Macrodantin od and 50 mg microcrystalline nitrofurantoin bd. A diverse events relating to the gastro-intestinal tract were most common, with the genito-urinary tract second, skin third and then ‘others’ (Table III).

No adverse event was of the ‘serious’ type reported for nitrofurantoin,26 i.e. pneumonitis, liver damage, etc. No eosinophilia was found. One patient reported a peripheral neuritis (tingling of the finger tips) after 12 months’ prophylaxis with 100 mg od (c.37 g), but this disappeared soon after stopping treatment. Any changes in biochemical or haematological parameters could be explained fully by concomitant conditions.

Older patients were not more likely to experience an adverse event than younger ones. The incidence of ‘all

### Table I. Prophylaxis with long-term nitrofurantoin: radiological findings in 157 assessable patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>120 (76.4%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>37 (23.6%)</td>
</tr>
<tr>
<td>duplex system</td>
<td>11</td>
</tr>
<tr>
<td>chronic pyelonephritis</td>
<td>5</td>
</tr>
<tr>
<td>clubbing of calyces</td>
<td>4</td>
</tr>
<tr>
<td>nephrectomy/transplant</td>
<td>3</td>
</tr>
<tr>
<td>dilated system</td>
<td>2</td>
</tr>
<tr>
<td>kidney cyst</td>
<td>2</td>
</tr>
<tr>
<td>trabeculation of bladder</td>
<td>2</td>
</tr>
<tr>
<td>other*</td>
<td>8</td>
</tr>
</tbody>
</table>

*One each of: filling defect, reflux nephropathy, hydronephrosis, cortical loss, horseshoe kidney, small kidney, kidney opacity, bladder prolapse.

Figure 2. Numbers of symptomatic episodes during the year before starting long-term prophylaxis.
adverse events’ in patients >65 years was 29% (9/31), as compared with 38.2% (72/188) in those ≤65 years (difference not significant).

Almost all (89%) of those who stopped treatment because of nausea did so within the first month. For those who persisted, and in the minority (c.25%) of patients who reported nausea later, nausea virtually disappeared after the third month. Thus, patients who experience nausea should be encouraged to carry on taking the medication. Only five patients reported vomiting.

Length of time taking prophylaxis. The following data refer to the 173 clinically assessable patients only.

The mean period of prophylaxis was 9.9 months (range 3–12 months, median and mode 12 months), 106 patients (61.3%) completing the full 12 month course (Figure 3). The reasons for patients not completing the prescribed course are largely unknown; several patients moved away, and a few became pregnant and decided or were advised (not by the clinic staff) to stop taking the medication.

However, in most cases patients failed to keep a scheduled appointment and did not attend the clinic again, despite three follow-up letters.

Outcome of prophylaxis. (i) Symptomatic episodes. Half the patients (50.3%) had no symptomatic episodes while taking prophylaxis (Figure 4; range 0–8, median and mode 0). In all, 184 episodes were recorded, giving a mean of 1.06 episodes/patient/period of prophylaxis. As the latter parameter was 9.9 months (see above), the mean per year is 1.28 episodes/patient, compared with a pre-prophylaxis figure of 6.9 (see above). Thus, prophylaxis caused a reduction in the mean incidence of symptomatic episodes of 5.4-fold. In a small number of patients prophylaxis failed, accounting for a disproportionately large number of episodes; for example, nine patients (5.2%) experienced a total of 52 episodes (28.3%).

(ii) Bacteriuric episodes. One hundred and forty-six patients (84.4%) remained infection-free while taking prophylaxis. There were 43 infections: 16 patients had one

Table II. Adverse events in patients taking long-term nitrofurantoin: incidence according to regimen

<table>
<thead>
<tr>
<th>Daily dose (mg)</th>
<th>Nausea reported</th>
<th>treatment stopped</th>
<th>All adverse events reported</th>
<th>treatment stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>100*a</td>
<td>20/43*</td>
<td>11</td>
<td>21*c</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(46.5%)</td>
<td>(25.6%)</td>
<td>(48%)</td>
<td>(25.6%)</td>
</tr>
<tr>
<td>100*b</td>
<td>15/110**</td>
<td>5</td>
<td>42*d</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(13.6%)</td>
<td>(4.5%)</td>
<td>(38.2%)</td>
<td>(14.5%)</td>
</tr>
<tr>
<td>50*b</td>
<td>8/66**</td>
<td>3</td>
<td>18*e</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(12.1%)</td>
<td>(4.5%)</td>
<td>(27.2%)</td>
<td>(10.6%)</td>
</tr>
</tbody>
</table>

*a50 mg microcrystalline, bd.
*bMacrocrystalline, od.
* vs **: P < 0.001; c vs d: NS; c vs e: P < 0.05.

Figure 3. Period of time for which patients took prophylactic nitrofurantoin.

Figure 4. Numbers of symptomatic episodes during period of prophylaxis.
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Inappropriate use of prophylactic antibiotics is unhelpful to patients and encourages emergence of resistance. However, prophylaxis with a carefully chosen drug can be justified for recurrent urinary infections. For prophylactic use, the effective daily dosage is about one-quarter of that used therapeutically.

Understanding the pathogenesis of urinary infection allows alternative and complementary strategies for prophylaxis to be used. Thus, potential pathogens may be targeted, and prophylaxis tailored to the individual patient.

### Discussion

The pattern of organisms causing breakthrough infection, eight had two, two had three and one had five.

- **E. coli** was less common as a breakthrough pathogen (59% vs 82%; \( P < 0.01 \)). Only nine of the strains causing breakthrough infections (21%) were resistant to nitrofurantoin.
- Patients were scored as 'improved' or 'not improved', as described in 'Patients and clinical methods'. Three patients (e.g. those with few attacks in the previous year, and who did not complete a full 12 month course) could not be assessed in this way. There were no clear differences between treatment groups, so results were pooled. One hundred and forty-three patients (84%) were scored as having 'improved'. There were no differences in outcomes between those with and those without a radiological abnormality.
- Nitrofurantoin-sensitive coliforms were present in almost all patients. The effective daily dosage is about one-quarter of that used therapeutically.

Understanding the pathogenesis of urinary infection allows alternative and complementary strategies for prophylaxis to be used. Thus, potential pathogens may be targeted, and prophylaxis tailored to the individual patient.

### Table III. Adverse events in patients taking long-term nitrofurantoin: details

<table>
<thead>
<tr>
<th>Daily dose (mg)</th>
<th>GI tract</th>
<th>UG tract</th>
<th>skin</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ( ^a )</td>
<td>nausea, 20 (11)</td>
<td>thrush, 6</td>
<td>rash, 8 (3); sweating, 1 (1); tingling, 2 (1)</td>
<td>faintness, 1 (1); headache, 1 (1); faintness, 1 (1); headache, 2 (2); Antabuse effect, 1; fever, 1 (1); loin pain, 1 (1); lethargy, 2 (1)</td>
</tr>
<tr>
<td>100 ( ^b )</td>
<td>nausea, 15 (5); abdominal pain, 4 (2); dry mouth, 1 (1)</td>
<td>rash, 2 (1); itch, 1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 ( ^c )</td>
<td>nausea, 8 (3); abdominal pain, 1; bad taste, 1 (1)</td>
<td>thrust, 6; sore vagina, 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52 (23)</td>
<td>13</td>
<td>11 (5)</td>
<td>16 (11)</td>
</tr>
</tbody>
</table>

\( ^a \)Micronutrient 50 mg bd.

\( ^b \)Macrodantin, od.

\( ^c \)Four of these patients (26%) had a history of allergy to an antibiotic (three to a /lactam, one to an anti-folate).
removed from the bowel flora, peri-urethral colonization discouraged, and a barrier of antibacterial urine maintained (Table V).

Methenamine salts generate formaldehyde in an acid urine, and so inhibit bacterial growth. However, clinical results have been less than optimal, and some patients find the large tablets difficult to swallow. Topical antiseptics (e.g. povidone iodine wash or cream) applied to the perineal area have proved disappointing. It is difficult to remove colonizing bacteria in this way, and the importance of the peri-urethral flora has been overemphasized, making this an unsuitable target. Trimethoprim, alone or in co-trimoxazole, acts in three ways, and initially gave excellent results. However, as plasmid-mediated resistance became more common, from 1980 onwards patients given these agents rapidly became colonized with resistant coliforms, and the prophylactic efficacy of these agents decreased rapidly. Fluoroquinolones behave in a similar way to trimethoprim. Their long half-lives and high intrinsic activities mean that one dose daily will ensure a permanently antibacterial urine for as long as the drug is given. These agents should remain effective until resistance emerges in *E. coli*, but they are unsuitable for women trying to become pregnant. First-generation oral cephalosporins do not affect the faecal or peri-urethral flora, and a single low dose (e.g. 250 mg) will render the urine antibacterial for only part of the day. These compounds have a short half-life (c.1 h), but giving them at bedtime considerably lengthens their period of residence in the urine, due to the nocturnal production of anti-diuretic hormone and the lack of fluid intake during sleep. This accounts for the good results that have been obtained.

**Table IV.** Prophylaxis with long-term nitrofurantoin: aetiology of breakthrough infections

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Number (%) of cases</th>
<th>Susceptibility to nitrofurantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em> a</td>
<td>26 (59%)</td>
<td>24 sensitive 2 resistant</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>8 (18.2%)</td>
<td>5 sensitive 3 resistant</td>
</tr>
<tr>
<td><em>Enterococci</em> b</td>
<td>5</td>
<td>5 sensitive 0 resistant</td>
</tr>
<tr>
<td>Others b</td>
<td>5</td>
<td>1 sensitive 4 resistant</td>
</tr>
</tbody>
</table>

a One mixed infection, *E. coli* + enterococci.
b Two *P. vulgaris*, one each *S. epidermidis, A cinetobacter sp.*,  *P. aeruginosa*.

**Table V.** Properties of prophylactic agents in preventing urinary infections, by modulation of putative pathogenetic factors

<table>
<thead>
<tr>
<th>Removing potential pathogens from</th>
<th>bowel flora</th>
<th>peri-urethral area</th>
<th>Creating antibacterial urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methenamine salts</td>
<td>- a</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Topical antiseptics</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Oral cephalosporins</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

a, no effect; +, an effect that would be expected to be advantageous to a prophylactic action, i.e. coliforms eliminated or reduced in number, or an antibacterial urine established.

The type of patient seen in our clinic remained homogeneous over the years; a large and steady turnover ensured that our studies did not involve the same patients being enrolled time and time again. Patients discharged from the clinic when their condition improved could return without formality if necessary. 

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patients actually returned, suggesting that a successful
course of prophylaxis had cured their problem of
recurrent infection.

The procedure for managing a patient on nitrofurantoin
prophylaxis involves: (i) explaining what is to happen and
why, in order to obtain the patient’s cooperation; (ii)
starting prophylaxis as soon as an MSU is shown to be free
of infection; (iii) withholding prophylaxis during treatment
for any breakthrough infections, and starting again imme-
diately the acute treatment has stopped; (iv) dispensing
antibiotic at intervals rather than giving a year’s supply
at once, as a check on compliance; (v) encouraging
patients experiencing nausea during the initial phases to
persevere, as this adverse event usually disappears after a
few weeks. The macrocrystalline formulation caused less
nausea than did the microcrystalline preparation.

This management plan can be initiated and supervised
by a family doctor. Patients with a radiological abnor-
mality benefited as much from prophylaxis as did those
with no such findings, showing that this investigation is
unnecessary in patients for whom long-term prophylaxis is
contemplated. However, failure of prophylaxis to control
recurrence may be an indication for radiological and other
investigations.

Our results show that prophylaxis should continue for
12 months, as this gives a better result than a shorter period.\textsuperscript{8,10,11,32} Most patients had a reduced recurrence rate
while taking prophylactic nitrofurantoin for 1 year, and
often maintained this improvement after prophylaxis was
stopped.

About 15% of patients did not respond to nitro-
furantoin or to other prophylactic antibiotics. The reasons
for this are unknown, and such patients did not show
any particular characteristics that enabled them to be
recognized. Breakthrough infection with resistant bacteria
was not a problem. Possibly some members of this
sub-group suffer from attacks of symptoms in the absence
of bacteriuria (the ‘urethral syndrome’,\textsuperscript{33}) in which
case antibiotic treatment could not be expected to be
effective.

Nitrofurantoin has been used for almost 40 years, and
it is remarkable that there has been hardly any increase in
resistance during that time (Table VI; see also Grüneberg\textsuperscript{34}
and Winstanley et al.,\textsuperscript{35}) in contrast to other antibiotics.

Long-term use of nitrofurantoin did not select for
resistant organisms in the intestinal flora, and intrinsically
resistant species such as Proteus spp. and Pseudomonas
spp. caused only four of the 43 (9%) breakthrough
infections recorded. The incidence of Proteus spp. as
urinary tract pathogens has declined significantly over the
past 20 years, a finding also made by Grüneberg.\textsuperscript{34} The
reasons for this decline are not known.

The continuous use of a drug for a period of 12 months
represents a very stern test, especially in terms of patient
compliance. We did not attempt any formal check on
compliance by ‘pill counting’ (which is notoriously
unreliable),\textsuperscript{36} but found that our policy of issuing medici-
nation in the clinic at planned intervals allowed us a certain
degree of control. Some patients readily admitted to
occasional ‘drug holidays’, but because many patients
commented favourably on the regimen we felt that
compliance was good in most patients. It can only be
speculated as to how often breakthrough infections by
nitrofurantoin-sensitive bacteria (Table IV) were due to
non-compliance.

In conclusion, our experience over 18 years, involving
142 patient-years of treatment, shows nitrofurantoin to be
an inexpensive, effective and acceptable means by which
to control recurrent urinary infections. We recommend a
dose of 50 mg Macrodantin at night for a period of 12
months; the drug cost\textsuperscript{30} of a year’s prophylaxis (£37.11)
compares favourably with the cost of treating the
predicted numbers of acute episodes had prophylaxis not
been given.

Acknowledgements

We thank all our colleagues who helped in the clinic
and/or laboratory. The four clinical trials\textsuperscript{12,14,16,18} were
sponsored in part by, respectively, Riker Laboratories,
Wellcome Foundation, Merck Sharp and Dohme, and

Table VI. Sensitivity to various antibiotics of infecting organisms isolated at Royal Free Hospital
Clinic, 1985–1992

<table>
<thead>
<tr>
<th>Species (n)</th>
<th>ampicillin</th>
<th>cefaclor</th>
<th>sulphamethoxazole</th>
<th>nitrofurantoin</th>
<th>trimethoprim</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli (527)</td>
<td>41</td>
<td>6</td>
<td>44</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Enterococci (85)</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>K. pneumoniae (69)</td>
<td>100</td>
<td>9</td>
<td>26</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>P. mirabilis (35)</td>
<td>3</td>
<td>11</td>
<td>33</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>S. epidermidis (15)</td>
<td>6</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Total (731)</td>
<td>39</td>
<td>18</td>
<td>48</td>
<td>8</td>
<td>22</td>
</tr>
</tbody>
</table>
Lilly Industries, who also supplied the nitrofurantoin used as comparator. The data analysis in the present study was sponsored in part by Procter & Gamble Pharmaceuticals UK Ltd.

References


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