http://hdl.handle.net/1765/119946

An audit of nitrofurantoin use in three Australian hospitals

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Status: paper submitted to Infection, Diseases & Health

ABSTRACT

Background: International guidelines have recommended the long-acting formulation of nitrofurantoin as first-line treatment for uncomplicated urinary tract infections (UTIs) since 2010. Australian guidelines have only recently listed nitrofurantoin as a first-line agent, but the long-acting formulation is not available. In the setting of increasing multidrug-resistance, the unavailability of the long-acting formulation of nitrofurantoin in Australia, and anecdotal perception of confusion regarding dosing, we audited nitrofurantoin use.

Methods: We performed a retrospective audit of nitrofurantoin use at Alfred Health. All patients dispensed nitrofurantoin from January 2016 to June 2018, as identified from pharmacy dispensing records, were eligible. We used a standardised case report form to extract data from medical records, including dosing regimen and indication.

Results: We included 150 patients with 151 nitrofurantoin prescriptions in the analysis, of whom 74% [111/150] were female. Nitrofurantoin was most commonly dispensed for the treatment of UTIs (68% [103/151] versus 32% [48/151] for UTI prophylaxis). For the treatment of uncomplicated UTIs, the most frequently used dose was 100 mg twice daily for five days. In male patients, the 100 mg twice daily for seven days was the most popular regimen. The prophylactic dose of 50 mg once daily was used in women but rarely in men. We did not find evidence of dose adjustment for renal impairment.

Conclusion: While treatment duration was consistent with guidelines, the dosage and frequency used was often incorrect for the formulation and was not adjusted for renal function. Nitrofurantoin use is likely to increase, so clarification regarding optimal nitrofurantoin dosing regimens may be appropriate.

Keywords: nitrofurantoin; urinary tract infections; antibiotic use; oral drugs; infectious diseases

INTRODUCTION

Nitrofurantoin is an oral antibiotic that has been recommended as first-line therapy for uncomplicated urinary tract infections (UTIs) in Europe and the United States (US) since 2010 (1, 2). First registered in 1952, nitrofurantoin has undergone a recent resurgence in popularity in parallel with the emergence of multidrug-resistance among bacteria that cause UTIs. This is because of the low prevalence of nitrofurantoin resistance and the minimal impact of nitrofurantoin on commensal microbiota in comparison with other oral treatment options, such as beta-lactams and fluoroquinolones (1, 3). Its spectrum of activity includes most uropathogens, including extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and vancomycin resistant enterococci (VRE) (4, 5).

In Australia, nitrofurantoin is only available as 50 mg and 100 mg oral capsules (Macrodantin®). The product information recommends a dose of 50-100 mg four times daily for five days (6). Internationally, nitrofurantoin is also produced as an oral suspension (Macrodantin®) and as slow-release 100 mg capsules (Macrobid®) for twice daily dosing, but these formulations are not registered in Australia (4, 5, 7). These products all contain nitrofurantoin in its macrocrystalline form, the microcrystalline containing products being less popular due to gastrointestinal side effects (8). There is substantial heterogeneity in nitrofurantoin dosing recommendations internationally, with total daily dose ranging from 150 mg to 400 mg divided in two, three or four doses per day (9). This is of concern because suboptimal nitrofurantoin dosing regimens may lead to selection of resistant isolates (1, 10).

Despite its popularity in Europe and the US, at the time of this study, the 'Therapeutic Guidelines: Antibiotic' (Version 15) recommended trimethoprim (300 mg once daily for three days), cephalexin (500 mg twice daily for five days) and amoxicillin-clavulanic acid (500/125 mg twice daily for five days) as preferable to nitrofurantoin for the treatment of uncomplicated UTIs in non-pregnant women (11). A seven-day course was recommended for male patients. Nitrofurantoin was listed as a fourth-line therapy, but with twice daily dosing, which is usually reserved for the slow-release formulation, Macrobid® (not registered in Australia). Given the differing recommendations regarding indication and dosing of this antibiotic, and the local increase in Enterobacteriaceae resistant to first-line agents (12), we performed an audit of nitrofurantoin use across three hospitals within Alfred Health, with particular focus on the indications and dosing regimens being used.

METHODS

Design, setting and population

We performed an audit of nitrofurantoin use at the three hospital campuses within Alfred Health in Melbourne, Australia; the Alfred Hospital, Caulfield Hospital and Sandringham Hospital. Any patient prescribed nitrofurantoin from 1 January 2016 to 30 June 2018 was eligible. We obtained a list of prescriptions from the pharmacy dispensing records. We reviewed how the antibiotic was used, with a specific focus on (1) the patient groups in whom this drug was used, (2) indication, and (3) variability in dosing (schedule, formulation and duration). Study data were collected and managed using REDCap electronic data capture tool hosted at Alfred Health (13).

Definitions

Uncomplicated UTIs were defined as UTIs in non-pregnant women who are not immunocompromised, have no urinary tract abnormalities, and no symptoms of tissue invasion and/or systemic infections (1). The following patients were considered to be at risk for developing a complicated UTI: male patients, pregnant women, patients with diabetes mellitus, patients with renal tract abnormalities, and patients with an impaired immune system (for example patients with transplants, Human Immunodeficiency Virus [HIV] infection, or cancer who receive immunosuppressive drugs).

Data collection and analysis

The extract from the pharmacy dispensing records included medical record number, nitrofurantoin brand name, date dispensed, and quantity dispensed. We then manually extracted data from paper-based patient medical records (including medication charts) using a standardized case report form. We recorded the laboratory accession number for relevant microbiology samples (blood/urine cultures) then extracted antimicrobial susceptibility testing results from the Alfred Health Department of Infectious Diseases microbiology database.

We used standard descriptive statistics. For most analyses, we stratified patients by nitrofurantoin indication into a therapeutic treatment group (suspected or confirmed UTI or other infection) and a prophylactic treatment group (use in asymptomatic patients to prevent UTIs). We also examined how nitrofurantoin was used in the following specific sub-groups; patients with renal impairment and patients at risk of complicated UTIs.

RESULTS

Patient characteristics

We collected information regarding 150 patients with 151 nitrofurantoin prescriptions. The majority of these prescriptions were for therapeutic use (68% [103/151]). The median age was 75 years (interquartile range [IQR] 61-84) and 74% [111/150] were female. Three patients in this cohort were pregnant. Table 1 demonstrates the patient characteristics, stratified by indication.

Therapeutic use of nitrofurantoin

Among patients prescribed nitrofurantoin for the treatment of an infection, the most common indication was uncomplicated UTI (56% [58/103]), followed by complicated UTI (22% [23/103]). The indication was not specified in 6 of the 151 prescriptions (4%). Thirty-five (34%) of the 103 patients prescribed nitrofurantoin for the treatment of an infection had documentation of an intolerance or allergy to amoxicillin-clavulanic acid.

Dosage

The most commonly prescribed dosage in this population are displayed in Table 2.

The 100 mg capsule was more commonly prescribed in the study population compared to the 50 mg capsule (72% [109/151] versus 28% [42/151] for all prescriptions and 81% [83/103] versus 17% [17/103] when used for UTI treatment). The most commonly prescribed therapeutic dose was 100 mg twice daily for five days (22% [23/103]) or seven days (18% [19/103]). The 50 mg dose was most frequently prescribed four times daily for five days (8% [8/103]). In total, 38 patients were treated with four doses per day. Only one patient was treated with three doses per day (100 mg for seven days).

There were 112 prescriptions of nitrofurantoin for female patients. The 100 mg capsule was more commonly prescribed than the 50 mg capsule (71% [79/112] versus 29% [33/112]). When stratified by indication, 100 mg twice daily for five days was the most frequently prescribed dose in female patients to treat uncomplicated UTIs (30% [21/71]) (Table 2).

There were 39 nitrofurantoin prescriptions for male patients (Table 2). The 100 mg capsule was more commonly prescribed than the 50 mg capsule (79% [31/39] versus 21% [8/39]). The most frequently prescribed dosing regimen was 100 mg twice daily for seven days (41% [13/32]) for the treatment of complicated UTI.

Pathogens

Ninety-eight microorganisms were isolated in urine samples obtained from 60 patients. *Escherichia coli* was the most frequently isolated bacteria (42% [41/98]). Six of these isolates were ESBL-producers, of which five were reported as resistant to trimethoprim,

cephalexin and amoxicillin-clavulanic acid, and one as resistant to trimethoprim and cephalexin. Additional susceptibility testing was performed for all six isolates, which were reported as susceptible to nitrofurantoin. The second most commonly isolated bacteria were *Enterococcus faecalis* (30% [29/98], of which 3 were VRE), followed by *Staphylococcus aureus* (10% [10/98], of which six were methicillin resistant). Two of the VRE isolates were also resistant to amoxicillin and were susceptible to nitrofurantoin.

Prophylactic use of nitrofurantoin

The most frequently prescribed dose of nitrofurantoin for UTI prophylaxis was 100 mg once daily (50% [24/48]), followed by the 50 mg once daily (46% [22/48]) (Table 2). No additional information was available about the duration of use. Among 41 female patients, the 50 mg once daily dose and 100 mg once daily dose were used with similar frequency (49% [20/41] and 46% [19/41]). Among the seven males prescribed nitrofurantoin for prophylaxis, 100 mg once daily was more frequently prescribed than 50 mg once daily (71% [5/7] and 29% [2/7]).

Nitrofurantoin use in patients with renal impairment

The distribution of estimated glomerular filtration rate (eGFR) in this patient population is presented in Table 1. Among patients treated for a UTI, 100 mg twice daily was the most common daily dosage regardless of renal function, when categorised into the following groups: eGFR <60 mL/min, 60-89 mL/min, and ≥90 mL/min. The most common dosages of prophylactic nitrofurantoin varied with renal function; 50 mg daily and 100 mg daily, respectively, for patients with an eGFR <89 mL/min, and ≥90 mL/min.

Nitrofurantoin dose adjustment for impaired renal function was mentioned in medical records for two female patients. The first patient was commenced on 100 mg four times daily and was changed to 100 mg twice daily in the context of an eGFR of 45 mL/min. The second patient was started on 100 mg twice daily but changed to 50 mg twice daily in the setting of an eGFR of 30 mL/min.

We identified five patients with an eGFR of less than 30 mL/min, all of whom were prescribed nitrofurantoin for UTI treatment (Table 1). Of these five patients, three were prescribed 100 mg twice daily for five days, one with 100 mg four times daily for five days, and one with 50 mg four times daily for five days. Three of these five patients had bacteria isolated from a urine sample, but none of these were multidrug-resistant.

None of the patients receiving nitrofurantoin for UTI prophylaxis had an eGFR of less than 30 mL/min.

Nitrofurantoin use in patients at risk of complicated urinary tract infections

The patients at risk of developing a complicated UTI are described in Table 1. The three pregnant women in our study were all treated for seven days. The three patients with

Table 1. Baseline patient characteristics stratified by indication for nitrofurantoin treatment.

Baseline patient characteristics	Nitrofurantoin prescriptions *(n=151)*	
	Therapeutic *(n=103)*	**Prophylactic *(n=48)***
Sex		
Female	71 (69%)	41 (85%)
Male	32 (31%)	7 (15%)
Age (years)		
Median (IQR)	72 (59-84)	77 (65-85)
Range	25 - 95	35 - 94
eGFR groups* (mL/min/1.73m^2)		
< 30	5 (5%)	0 (0%)
30-59	21 (20%)	9 (19%)
60-89	41 (40%)	25 (52%)
≥ 90	24 (23%)	8 (17%)
Unknown	12 (12%)	6 (13%)
Comorbidities/medical diagnosis		
Pregnancy	3 (3%)	0 (0%)
Immunosuppression	3 (3%)	0 (0%)
Diabetes Mellitus	13 (13%)	14 (29%)
Renal tract abnormalities		
Functional	10 (10%)	6 (13%)
Structural	16 16%)	16 (33%)
Antibiotic allergy		
Amoxicillin-clavulanic acid	35 (34%)	2 (4%)
Trimethoprim	4 (4%)	0 (0%)
Cephalexin	4 (4%)	0 (0%)
Indications for nitrofurantoin use		
UTI prophylaxis	NA	48 (100%)
Uncomplicated UTI	58 (56%)	NA
Complicated UTI	23 (22%)	
Asymptomatic bacteriuria	14 (14%)	
Prostatitis	2 (2%)	
Other infection/unknown*	6 (6%)	

eGFR = estimated glomerular filtration rate; mL/min = millilitre/minute; IQR = inter quartile range; urinary tract infection (UTI)

* therapeutic treatment course used, but indication not documented.

an impaired immune system were treated for 5 days. Among the thirteen patients with diabetes mellitus treated therapeutically with nitrofurantoin, five (56%) were treated for seven days. Six (60%) patients with functional renal tract abnormalities and nine (56%) patients with structural renal tract abnormalities were treated for seven days. Male patients were discussed above.

Table 2. The most frequently prescribed nitrofurantoin regimens, stratified by indication and sex.

	Total	Females	Males
Therapeutic use	***(n=103)***	***(n=71)***	***(n=32)***
100 mg BD 5d	23 (22%)	21 (30%)	2 (6%)
100 mg BD 7d	20 (19%)	7 (10%)	13 (41%)
100 mg QID 5d	11 (11%)	9 (13%)	2 (6%)
50 mg QID 5d	8 (8%)	8 (11%)	0
100 mg QID 7d	4 (4%)	4 (6%)	0
100 mg BD 10d	4 (4%)	4 (6%)	0
Other	33 (32%)	18 (25%)	15 (47%)
Prophylactic use	***(n=48)***	***(n=41)***	***(n=7)***
100 mg daily	24 (50%)	19 (17%)	5 (71%)
50 mg daily	22 (46%)	20 (49%)	2 (29%)
50 mg BD	2 (4%)	2 (5%)	0

Percentages in parentheses correspond to the proportion of times each regimen was used for the corresponding group (i.e. total, female, or males). d=days, BD=twice daily, QID=four times daily.

DISCUSSION

We described the use of nitrofurantoin in three hospitals within our health service. The most common therapeutic dose prescribed was 100 mg twice daily for five days. A regimen of 100 mg twice daily for seven days was also commonly used, possibly because our study population contained a relatively high number of males and patients with comorbidities, which may place the patients at risk for a complicated UTI. The duration of treatment was predominantly consistent with (international) guidelines (1, 11, 14). Nitrofurantoin was also used for the prophylaxis of UTIs despite not being recommended for this indication in 'Therapeutic Guidelines: Antibiotic' (version 15) during the study period (11).

The most common frequency used for treatment of UTIs was twice daily, a substantial departure from the Macrodantin® recommendation of four times daily (6). This difference may be explained by the fact that the 'Therapeutic Guidelines: Antibiotic' (version 15) recommended 100 mg twice daily for nitrofurantoin without specifying which for-

mulation. In contrast, the 2010 US-European guidelines also recommend 100 mg twice daily, but specified the Macrobid® (long-acting) formulation. There are pharmacokinetic differences between Macrodantin® and Macrobid®, so substituting these nitrofurantoin products may result in different antibiotic concentration profiles in the lower urinary tract (15–17). The impact of twice daily dosing of Macrodantin® on therapeutic effectiveness is unknown, however we did not observe major problems with relapse or recurrence in this study (albeit that we had limited capacity to evaluate this).

Among the patients in our cohort, the median eGFR was 74 mL/min/1.73m^2 in the treatment group and 76 mL/min/1.73m^2 in the prophylactic group, with 35 patients having an eGFR of <60 mL/min. While the Australian Macrodantin® product information leaflet lists a creatinine clearance of less than 60 mL/min as a contraindication, the United Kingdom Medicines and Products Regulatory Agency revised this to a threshold eGFR of 45 mL/min/1.73m^2, adding that short courses (5-7 days) may be used with caution in patients with an eGFR of 30 to 45 mL/min/1.73m^2 in the setting of multidrug-resistant bacteria (6). The Australian Medicines Handbook provides the same recommendation (18). Patients with impaired renal function excrete less nitrofurantoin in the urine so urinary concentrations may be sub-therapeutic, which could lead to treatment failure, the selection of nitrofurantoin-resistance, or toxicity due to higher plasma concentrations (19–21). In this study, eight patients with an eGFR between 30 and 45 mL/min were treated with nitrofurantoin, one of which had a UTI caused by multidrug-resistant bacteria. Of five patients with an eGFR <30 mL/min treated with nitrofurantoin, none had a UTI caused by a multidrug-resistant bacteria. We did not find any evidence that the prophylactic dose was changed (or discontinued) based on impaired renal function. The prophylactic use of nitrofurantoin is not mentioned in the 'Therapeutic Guidelines: Antibiotic' (Version 15) or the Australian Medicines Handbook (2019). However, it may be reasonable for a prescriber to adjust the duration of the prophylactic use because long term use of nitrofurantoin is associated with (severe) side effects (22) as side effects are more likely to occur in patients where higher plasma concentrations of nitrofurantoin can be expected due to slower excretion from the plasma to the urine compartment (16). We identified no patients with an eGFR < 30 mL/min being treated with prophylactic nitrofurantoin in this cohort.

A new version (Version 16) of the Australian 'Therapeutic Guidelines: Antibiotic' was published after the completion of this study (23). The two first-line options for treatment of uncomplicated lower UTIs are now nitrofurantoin, 100 mg four times daily for five days, and trimethoprim 300 mg once daily for three days (23). The nitrofurantoin formulation is not specified, but given Macrobid® is not available in Australia, prescribers will most likely prescribe Macrodantin®. This total daily dosage of nitrofurantoin (400 mg) is higher than recommended in all but one European national guideline

(9). A recent review of national treatments guidelines for UTIs in European countries highlighted the lack of clarity around optimal nitrofurantoin dosing, with recommendations ranging from 150 mg daily (50 mg 8-hourly in Norway and Sweden, and 75 mg 12-hourly in Finland) to the one country that recommends up to 400 mg daily (Russia). This diversity in recommendations demonstrates the need for further research on the pharmacokinetics and pharmacodynamics of nitrofurantoin, and evidence regarding efficacy of different regimens.

We acknowledge the limitations of this study. First, our cohort comes from three hospitals in one health service, and may not be generalisable to other settings in Australia. Second, we don't have information about the total number of UTIs at Alfred Health during the study period, and therefore can't calculate the relative frequency of nitrofurantoin usage for the treatment of UTIs. Finally, we were not able to systematically collect information regarding clinical or microbiological cure from this retrospective audit.

CONCLUSIONS

Nitrofurantoin is considered an important antibiotic for the treatment of UTIs in the context of increasing multi-drug resistance. In our study, while the most common indication for nitrofurantoin use (uncomplicated lower UTIs) and treatment duration were consistent with national and international guidelines, the dosage frequency used was not correct for the formulation that is available in Australia. This study and the wide range of different recommendations for nitrofurantoin dosing internationally, highlight the need for further research into optimal nitrofurantoin dosing regimens to maximise efficacy while avoiding dose-dependent toxicities and the emergence of resistance.

Ethics

The study was approved by the Human Research and Ethics Committee at Alfred Hospital [Project Number: 577/18].

Author statement

RAW, AYP and AJS designed the study. RAW, SJC and KAC obtained the data. RAW analysed the data and drafted the report. All authors critically reviewed the report and approved the final version.

Conflicts of interest

All authors have no conflicts of interest relevant to this study.

Funding

AJS is supported by an Australian National Health and Medical Research Council Early Career Fellowship (GNT1141398) and AYP is supported by an Australian National Health and Medical Research Council Practitioner Fellowship (GNT1117940).

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