ARTICLE

Nitrofurantoin and fosfomycin for resistant urinary tract infections: old drugs for emerging problems

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SUMMARY

Uncomplicated urinary tract infection is one of the most common indications for antibiotic use in the community. However, the Gram-negative organisms that can cause the infection are becoming more resistant to antibiotics.

Many multidrug resistant organisms retain susceptibility to two old antibiotics, nitrofurantoin and fosfomycin. Advantages over newer drugs include their high urinary concentrations and minimal toxicity.

Fosfomycin is a potential treatment option for patients with uncomplicated urinary tract infection due to resistant organisms. Nitrofurantoin may be more effective and can be used for urinary infections in pregnant women.

Introduction

Antimicrobial resistance is increasing worldwide, resulting in infections that are more difficult to treat and associated with higher mortality, morbidity and cost.[1-3] In Australia, multidrug resistant Gram-negative bacilli are responsible for a rising proportion of community-acquired uncomplicated urinary tract infections. Consequently, empiric therapy is more likely to fail. This has resulted in increasing numbers of patients with uncomplicated urinary tract infections requiring hospitalisation for intravenous antibiotics because there are no oral treatment options.

Limited Australian data are available for antimicrobial resistance rates in community-onset urinary tract infections.[4,5] One large national survey of urinary isolates from 2015 found resistance rates in *Escherichia coli* of 43% for ampicillin, 9% for amoxicillin with clavulanic acid, 16% for cefazolin, 22% for trimethoprim, and 7% for ciprofloxacin.[6] It is likely that resistance rates have continued to rise since then.

There are few new antibiotics on the horizon and those that have been recently approved are mostly for intravenous use, so older 'forgotten' drugs are being re-explored for the treatment of cystitis.[7-10] Nitrofurantoin and fosfomycin are old antibiotics. They share some important properties including high concentrations in the urinary tract, a minimal impact on gastrointestinal flora and a low propensity for resistance (Table).

Nitrofurantoin

Nitrofurantoin has been available since 1953, and in Australia since the 1970s. Its exact mechanism of action is not well understood and presumably multifactorial. Nitrofurantoin requires reduction by bacterial enzymes producing 'highly reactive electrophilic' metabolites. These then inhibit protein synthesis by interfering with bacterial ribosomal proteins.[11]

Nitrofurantoin has 80% oral bioavailability, and approximately 25% is excreted unchanged in the urine, with only a small portion reaching the colon.[12] Like fosfomycin, therapeutic concentrations are only reached in the urinary tract,[13] so the clinical use of nitrofurantoin is limited to the treatment of uncomplicated urinary tract infection in women. Administration with food results in higher urinary concentrations and fewer gastrointestinal adverse effects.

Antimicrobial activity

Nitrofurantoin is active against common causes of urinary tract infection including *E. coli*, *Citrobacter* and *Enterococcus*. *Klebsiella* and *Enterobacter* are less reliably susceptible. *Serratia*, *Acinetobacter*, *Morganella*, *Proteus* and *Pseudomonas* are usually resistant.[14] Overall, resistance to nitrofurantoin is uncommon and many multidrug resistant organisms retain susceptibility.[15-17] Australian data are limited, but studies suggest resistance rates in *E. coli* of 1–2%.[4,6]

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Table **Features of nitrofurantoin and fosfomycin**

Characteristic	Nitrofurantoin	Fosfomycin
Year of discovery	1953	1969
Formulations	Nitrofurantoin macrocrystal 50 mg, 100 mg capsules Slow-release formulation not available in Australia Older microcrystal formulation less available now (more adverse effects)	Fosfomycin trometamol 3 g sachet containing granules to be dissolved in water Intravenous formulation available but for specialised use only
Pharmacokinetics	High urinary concentrations Serum concentrations negligible	Long half-life with high urinary concentrations Serum concentrations inadequate for treatment of systemic infection
Mechanism of action	Not well understood, multifactorial, inhibits ribosomal protein synthesis	Inhibits pyruvyl transferase and therefore cell wall synthesis
Spectrum of activity	Mostly susceptible: *E. coli*, *Enterococcus* Variably susceptible: *Klebsiella*, *Enterobacter*, *Citrobacter* and *Providencia* Typically resistant: *Proteus*, *Serratia*, *Acinetobacter*, *Morganella* and *Pseudomonas*	Mostly susceptible: *E. coli* Variably susceptible: *Klebsiella*, *Proteus*, *Citrobacter*, *Enterobacter*, *Pseudomonas* and *Enterococcus* Typically resistant: *Morganella* and *Acinetobacter*
Resistance	Uncommon	Uncommon
Indications	Uncomplicated urinary tract infection in women	Uncomplicated urinary tract infection in women
Dosing	50–100 mg 4 times a day for 5 days	Single 3 g oral dose
Adverse events	Infrequent, mainly gastrointestinal Rare reports of pulmonary or liver toxicity, peripheral neuropathy	Infrequent, mainly gastrointestinal (9% diarrhoea, 4% nausea)
Pregnancy and breastfeeding	Category A, although not recommended beyond 38 weeks gestation due to risk of haemolytic anaemia in neonates. For this reason it is also best to avoid during the first month of breastfeeding	Category B2, small amounts excreted in breast milk so not recommended in breastfeeding
Children	Avoid <1 month of age	Avoid <12 years of age
Interactions	Few significant drug interactions	Co-administration with metoclopramide can lower serum and urine concentrations
Renal impairment	Contraindicated if CrCl <30 mL/min Cautious use between CrCl 30–60 mL/min if benefits outweigh risks	Dose reduction required if CrCl <50 mL/min

CrCl creatinine clearance

Efficacy and safety

A meta-analysis of 27 older controlled trials (4807 patients) found clinical cure rates of 79–92%, similar to comparator antibiotics. Only mild toxicities (most commonly gastrointestinal) and no cases of pulmonary fibrosis or hepatotoxicity were reported.[18] Dosing recommendations for the standard formulation are 50–100 mg four times daily. There is a long-acting formulation available overseas, but not in Australia, which can be dosed twice daily. This slow-release formulation (100 mg three times daily) was used in a recent open-label comparison with fosfomycin. The cure rate was 70% in the nitrofurantoin group.[19]

Historically nitrofurantoin was thought to be contraindicated if the creatinine clearance was less than 60 mL/minute due to an increased risk of toxicity. However, recommendations have been changing to allow cautious, short-term use in patients with mild renal impairment (30–60 mL/min) if there are no alternative antibiotics.[20,21] Nitrofurantoin can be used to treat cystitis in pregnancy (although not beyond 38 weeks gestation due to the risk of haemolytic anaemia in the neonate).

Nitrofurantoin became a preferred drug in the international consensus guidelines for urinary tract infection in 2010.[22] These emphasised the lower rates of 'collateral damage' on gastrointestinal flora.[23-24]

It remains to be seen if resistance rates increase as a consequence of this recommendation and the subsequent rise in nitrofurantoin prescribing. The true incidence of major hepatic and pulmonary toxicity is unclear, but this appears to be more common with long-term use in the elderly.[14] For the short-term treatment of uncomplicated urinary tract infection in otherwise healthy young women, nitrofurantoin is a safe and effective choice, and overall efficacy and rates of adverse events appear similar to comparator antibiotics. In patients with infections due to multidrug resistant organisms and therefore few alternative treatment options, we recommend using 100 mg four times daily for five days, administered with food to optimise absorption and efficacy.

Fosfomycin

Fosfomycin was first isolated in Spain in 1969, and was introduced in Europe throughout the 1970s.[25] It is a small molecule from a unique drug class that acts by inhibiting pyruvyl transferase. This enzyme is responsible for synthesising the precursors of peptidoglycan, the key component of the bacterial cell wall. Uptake in the USA was initially limited due to problems with susceptibility testing, but this was standardised in 1983.

Fosfomycin trometamol, an oral formulation that can be taken as a single 3 g dose, was introduced in 1995. In many countries it is now a first-line treatment option for uncomplicated urinary tract infection in women.[22] This single-dose regimen is attractive due to better adherence and is generally well tolerated. While transient gastrointestinal disturbance can occur, serious adverse events are rare.[26]

In Australia, fosfomycin was only previously available via the Special Access Scheme. The Therapeutic Goods Administration has now approved it for acute uncomplicated lower urinary tract infection, in females more than 12 years of age, caused by susceptible organisms (Enterobacteriaceae including *E. coli*, and *Enterococcus faecalis*).

Antimicrobial activity

Susceptibility testing for fosfomycin is available, but can be complicated and is not necessarily routine in Australian microbiology laboratories. Fosfomycin is most active against *E. coli*, and minimum inhibitory concentrations are typically low.[27-29] Other urinary pathogens such as *Klebsiella*, *Proteus*, *Citrobacter*, *Enterobacter*, *Pseudomonas* and *Enterococcus* have variable susceptibility.[30-32] *Morganella morganii* and *Acinetobacter* are typically resistant.[28] Urinary concentrations following a single 3 g dose are generally sufficient to treat patients infected with susceptible organisms, although some recent data suggest more variability in urinary concentrations than previously thought.[33,34]

As fosfomycin has a unique structure there is minimal cross-resistance with other antibiotics. At present, many multidrug resistant isolates remain susceptible to fosfomycin, even in geographic regions where there has been widespread use of the drug.[35,36] No comprehensive studies examining fosfomycin susceptibility have been conducted in Australia.

While resistant subpopulations of bacteria may develop with fosfomycin exposure, resistant strains do not seem to easily survive in vivo.[32,37-40] However, there are multiple resistance mechanisms and there are reports of increasing resistance correlating with higher fosfomycin usage in Spain.[32,41-43] Plasmid-mediated resistance, which could disseminate more readily, has been described in Japan,[44] and among livestock[45] and pets[46] in China.

Efficacy and safety

Historically, the clinical efficacy of fosfomycin was thought to be similar to antibiotics such as trimethoprim, trimethoprim/sulfamethoxazole, fluoroquinolones, beta-lactams and nitrofurantoin, with reported cure rates of 75–90%.[47-51] However, methodological flaws in the older studies may have resulted in clinical efficacy being overestimated. A recent large randomised trial found a lower clinical cure rate with fosfomycin compared with nitrofurantoin (58% vs 70%, p=0.004).[19] While some recent observational studies have demonstrated fosfomycin efficacy in uncomplicated urinary tract infection caused by resistant organisms,[52-56] including non-inferiority to carbapenems,[57,58] there are reports of treatment failures particularly with *Klebsiella*.[59]

As low serum concentrations lead to treatment failures, fosfomycin is not appropriate for patients with bacteraemia or upper urinary tract infections such as pyelonephritis. Occasionally, longer courses have been used to treat complicated urinary tract infection, for example as completion therapy when there are no oral alternatives to intravenous antibiotics.[57] There is also an emerging role in prostatitis and perioperative prophylaxis for urological procedures in men.[60-62] Specialist infectious diseases input should be sought for these complex cases if off-label use or prolonged courses of therapy are being considered.

Fosfomycin is generally well tolerated, with adverse events rare and usually transient. Gastrointestinal events (9% diarrhoea, 4% nausea) have been most commonly reported with rare reports of other more serious problems.[26] Co-administration with metoclopramide can lower serum and urinary concentrations and should be avoided, but there are few other problematic drug

interactions. Fosfomycin is classified in pregnancy category B2. It is not recommended in breastfeeding as small amounts are excreted in breast milk. Given there are minimal data on use in children under 12 years of age, it is not advised for this group.

In Australia, we currently recommend reserving fosfomycin for the treatment of uncomplicated urinary tract infection in patients when the standard first-line drugs are not an option. Part of the rationale behind this is to minimise the emergence of resistance and prolong the usefulness of fosfomycin for patients without alternative options.[35] As resistance to other drugs inevitably rises and local experience increases, fosfomycin may become a first-line option in the future.

Antibiotic resistance

While re-exploring older 'forgotten' drugs like nitrofurantoin and fosfomycin is a useful strategy, it represents only part of the multifaceted response required to tackle the complex problem of antimicrobial resistance and 'preserve the miracle' of antimicrobials over the coming decades.[63] As we have seen historically with virtually all other antibiotics, resistance is likely to emerge as usage increases. It remains to be seen how long this will take, to what extent it will occur and whether it will be via dissemination of existing resistance mechanisms or evolution of new ones. The increasing failure of standard empirical therapy for urinary tract infection is foreseeable, and it is likely that more patients will require microbiological testing before starting antibiotics, not only for individualised patient management but also for broader epidemiological surveillance to inform guideline recommendations.

Consultation with an infectious diseases specialist can assist with the management of patients with multidrug resistant infections and leads to better outcomes.[64] Other important strategies include the development of new antimicrobial drugs, preserving those currently available by judicious use, implementation of comprehensive antimicrobial stewardship programs and stringent infection control practices worldwide to reduce the spread of resistant organisms.

Conclusion

Nitrofurantoin is suitable for uncomplicated lower urinary tract infections. Bacterial resistance is uncommon.

Fosfomycin is a safe and effective antibacterial drug for urinary tract infections, but its use should be limited to delay the development of resistance. It will prove to be a useful treatment option for community-based treatment of patients with resistant organisms. ◁

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