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Antimicrobial Original Research Paper

Pharmacological properties of oral antibiotics for the treatment of uncomplicated urinary tract infections

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The therapeutic management of uncomplicated bacterial urinary tract infections (UTIs) is based on short-term courses of oral antibiotics. The preferred drugs are nitrofurantoin trimethoprim-sulfamethoxazole, fosfomycin trometamol, fluoroquinolones and β-lactam agents. The choice of agent for treating uncomplicated UTIs should be based on the pharmacokinetic characteristics of the molecule so that clinical benefit is optimized and the risk of antibacterial resistance is minimized. This article discusses the general pharmacokinetic-pharmacodynamic (PK/PD) aspects of antimicrobial chemotherapy, the PK/PD characteristics of oral antimicrobial agents for the treatment of uncomplicated UTIs and the pharmacological and therapeutic strategies for limiting or preventing bacterial resistance.

Keywords: Uropathogens, Urinary tract infections, Pharmacokinetics, Fosfomycin trometamol, Quinolones, Nitrofurantoin, Beta-lactams, Co-trimoxazole

Introduction

The therapeutic management of uncomplicated bacterial urinary tract infections (UTIs) is based on antibiotic therapy. Major international and national guidelines recommend the short-term use of oral antibiotics for uncomplicated UTIs; these are summarised in Table 1.[1–3] The preferred drugs are nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin trometamol, fluoroquinolones and β-lactam agents.

The choice of the most suitable agent to treat uncomplicated UTIs should be based not only on the spectrum of antimicrobial activity, but also on the pharmacokinetic (PK) characteristics of the molecule so that optimal clinical benefit can be achieved while avoiding antibacterial resistance. Other aspects to consider include patient characteristics (allergy, comorbidities, concomitant therapy and compliance), local practice patterns, local community resistance prevalence, product availability and costs.[4] Table 2 shows the characteristics of an ideal drug for treatment of uncomplicated UTIs.[4]

General pharmacokinetic-pharmacodynamic (PK/PD) aspects of antimicrobial chemotherapy

There has been much critical evaluation of the rules for selecting antibiotics and their ideal dosage regimen for the control of infections, with the goals of increasing treatment efficacy and reducing the risk of selecting multi-resistant pathogens.[5–9] PK and pharmacodynamic (PD) properties are fundamental to the choice of drug dose and regimen. PK parameters relate to drug absorption, tissue distribution, metabolism and elimination, while the antimicrobial activity is covered under PD parameters, the most important of which are the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), post-antibiotic effect (PAE) and killing rate. On the basis of their different patterns of bactericidal activity (killing curves), antibiotics can be divided into two groups, having either time-dependent or concentration-dependent antimicrobial activity. Beta-lactams, nitrofurantoin, erythromycin, tigecycline and oxazolidinones are time-dependent drugs, whereas the aminoglycosides, quinolones, fosfomycin and semisynthetic macrolides tend to have concentration-dependent activity.[5–9]

Some important PK-PD parameters have shown good correlation between *in vitro* and *in vivo* animal infection models and therapeutic efficacy of antibiotics.[9–11] The first of these is time between doses with antibiotic concentration exceeding the MIC (T > MIC), the second is the ratio between peak concentration (C_{max}) and MIC (C_{max}/MIC) and the third is the ratio between the area under the plasma concentration curve (AUC) and the MIC (AUC/MIC) (Fig. 1).

The T > MIC parameter is recognized as being a predictor of clinical and microbiological success or failure for time-dependent antibiotics. C_{max}/MIC and AUC/MIC are

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Table 1 National and international guideline recommendation for the treatment of uncomplicated urinary tract infections

Infectious diseases society of America 2011[1]	European association of urology guidelines 2017[2]
• Nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for 5 days (A–I) • Trimethoprim-sulfamethoxazole 160/800 mg bid for 3 days* (A–I) • Fosfomycin trometamol 3 g single dose (A–I) • Pivmecillinam(400 mg bid for 5 days (A–I) • Fluoroquinolones in 3-day regimens* (A–I) but should be considered alternative antimicrobials for acute cystitis (A–III). • Beta-lactam agents in 3- to 7-day regimens when other recommended agents cannot be used (B–I)	*First choice agents* • Fosfomycin trometamol 3 g single dose • Pivmecillinam 400 mg tid for 3–5 days • Nitrofurantoin macrocrystal 100 mg bid for 5 days *Alternative agents* • *Cephalosporins (e.g. cefadroxil) 500 mg bid for 3 days

Notes: bid, twice daily; tid, three times daily.
*Only if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible.

Table 2 Characteristics of an ideal drug for treatment of uncomplicated urinary tract infections[4]

• Maximum *in vitro* activity against prevalent uropathogens
• Minimum percentage of resistance
• Possibility of overcoming resistance to other molecules
• Optimum pharmacokinetic-pharmacodynamic profile
• Good tolerability and documented clinical efficacy

the PK-PD parameters that predict efficacy for concentration-dependent drugs, although there are some important clinical data demonstrating that the AUC/MIC ratio might also be useful for assessing the effectiveness of certain time-dependent antimicrobial agents.

PK-PD properties are useful for optimizing drug dosages and outcomes and for limiting or preventing bacterial resistance. However, it could be argued that PK-PD parameters are less useful for determining treatment for uncomplicated UTIs because most of the potential antibiotic agent choices are able to reach and maintain relatively high urinary concentrations, much higher than the MICs of the causative pathogens, thus theoretically reducing the need for a critical PK-PD analysis to ensure treatment success. Nevertheless, in our opinion, theoretical urinary PK-PD thresholds should be considered even in uncomplicated UTIs because the patient's condition (i.e. urinary pH, different risk factors such as pre-existing diseases, reduced oral absorption and faster elimination) and bacterial strain characteristics (lower susceptibility, virulence factors etc.) may play an important role. Finally, because dose–effect relationships have now been quite well established for the majority of antibiotic classes, PK-PD data should be used to reappraise current clinical break points, giving the clinician more information on resistance and, therefore, on treatment choices.[9]

PK/PD characteristics of oral antimicrobials in uncomplicated UTIs

Quinolones/fluoroquinolones

There are three generations of quinolone antibiotics. The first is represented by nalidixic acid and derivatives. In terms of second-generation quinolones, those still used for UTIs are broad-spectrum agents such as ciprofloxacin, ofloxacin, lomefloxacin, norfloxacin and prulifloxacin. Third-generation quinolones include newer agents that are especially active against Gram-positive bacterial species and anaerobes and are therefore not clearly indicated for UTIs,[10] with the exception of levofloxacin. Differences between the different generations are due to modifications in the structural formula, resulting in different activity.[11] The mechanism of action of these antibiotics is inhibition of DNA gyrase and partly of bacterial topoisomerase IV, resulting in cell death due to complex binary or tertiary formations among DNA, the enzyme and the antibiotic.[10–12] Quinolones have bactericidal activity, and the mechanisms of bacterial resistance are primarily linked to modifications at the binding site or active drug extrusion from the bacteria through efflux pumps.[10,11]

Second- and third-generation molecules have favourable kinetic characteristics with high oral bioavailability (approximately 100% for levofloxacin), good tissue penetration and primarily renal elimination (Table 3).[10,12–19] Among the fluoroquinolones indicated for the treatment of uncomplicated UTIs, both levofloxacin (85%) and ciprofloxacin (30–50%) are predominantly excreted via the renal route, reaching very high concentrations in urine (521–771 and 200 mg/L, respectively). The long half-life of some compounds, namely levofloxacin and prulifloxacin, allows for once-daily administration, which makes compliance with treatment easier. The combination of these PK characteristics together and bactericidal activity mean that second- and third-generation quinolones are indicated for the short-term treatment (3 days) of uncomplicated UTIs.

The post-antibiotic effect of fluoroquinolones contributes to their therapeutic efficacy.[20,21] Acidified urine (pH = 5–6) was found to impair the antimicrobial effects of fluoroquinolones in some *in vitro* studies. However, the impact of urine acidification on the prophylaxis and treatment of UTIs is controversial.[22–24]

As mentioned, fluoroquinolones are concentration-dependent antibiotics, and a peak/MIC ratio of 10–12 and an AUC/MIC ratio of about 100–125 (at least against Gram-negative bacteria) must be obtained to avoid the increase of resistance and to guarantee potential efficacy. These values have been documented not only in animal models but also in serious infections in hospitalized patients.[25,26]

Fluoroquinolones are generally well tolerated. Although the level of evidence for adverse events varies, these include gastrointestinal problems (e.g. nausea and vomiting), neurological disturbances (due to GABA inhibition) and cardiovascular effects (e.g. prolonged QT

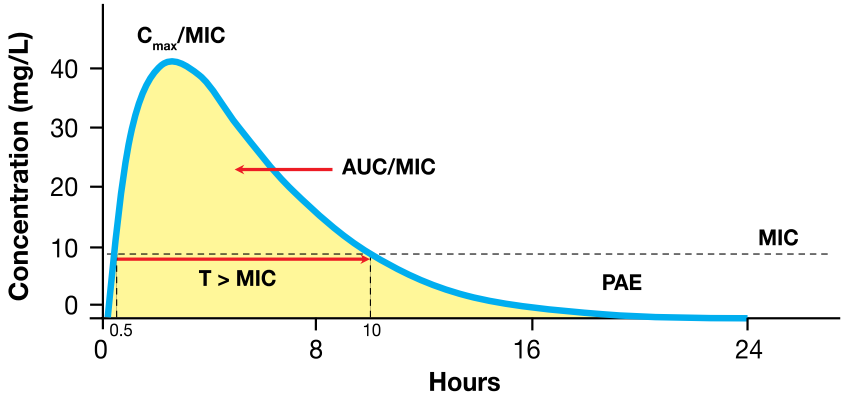

Figure 1 **Pharmacokinetic-pharmacodynamic parameters for antimicrobial activity of antibiotics.**

Table 3 **Pharmacokinetic parameters of quinolones indicated for the treatment of uncomplicated UTIs**[10,12–19]

Quinolones	Dose (mg)	C_{max} (mg/L)	$t_{½β}$ (h)	Bioavailability (%)	Protein binding (%)	Metabolism (%)	Fu (%)	Peak urine concentration (mg/L)
First generation								
Nalidixic acid	1000	20–35	1.5	95	90	70	90	150–400
Pipemidic acid	400	3–4	3.5	70	15	<5	50–70	600–900
Second generation								
Norfloxacin	400	1–2	3.5–5	40	15	20	30	30
Ofloxacin	300	5–7	6–8	90	25	<10	80	85–95
Ciprofloxacin	250	0.8–1.9	–	–	–	–	–	–
	500	2–3	5–6	70–80	30	35	40–50	200
Prulifloxacin	600	~2	10	–	50	<20	20	110
Third generation								
Levofloxacin	500*	5–7	7–8	99	24–38	–	85	521–771

Notes: C_{max}, peak plasma concentration; Fu, urinary recovery; $t_{1/2β}$, elimination half-life.
*250 mg dose is recommended for urinary tract infections.

interval).[27] The risk of fluoroquinolone-induced tendinopathy and tendon rupture is well established and is higher in men than in women (2:1 ratio). The Achilles tendon is most commonly affected, and risk factors include age (>60 years), corticosteroid therapy, renal failure, diabetes mellitus and history of tendon rupture.[28]

Administration of fluoroquinolones in combination with, or within a few hours of, antacids containing zinc (Zn^{++}), aluminium (Al^{+++}) or magnesium (Mg^{++}) significantly reduces oral drug absorption and constitutes an important pharmacological interaction.[27] In patients with renal failure (creatinine clearance <50 mL/min), the dose or frequency of fluoroquinolones should be reduced.

Although fluoroquinolones are generally very active, their microbiological, pharmacological and toxicological properties mean that they should be used only for the most serious conditions and in special populations. Moreover, due to the fact that antimicrobial resistance in common urinary pathogens is increasing globally at an alarming rate due to the overuse and misuse of antibiotics, fluoroquinolones should no longer be used as first-line empiric therapy for uncomplicated UTIs.[29]

Co-trimoxazole

Co-trimoxazole is a synergistic combination of trimethoprim and sulfamethoxazole (TMP/SMX) that has been used as first-line therapy for UTIs for over 30 years. After oral administration of SMX 800 mg and TMP 160 mg, the mean peak serum concentration is approximately 40/60 mg/L for SMX and 1–2 mg/L for TMP, with an elimination half-life of 10–12 h; in the first 24 h post-dose, 60–70% of SMX has been eliminated (20% as parent drug) and 50–60% of TMP has been eliminated (80% as parent drug), with peak urinary concentrations of 190 and 75 mg/L, respectively.[18,30,31]

Table 4 shows PK parameters after a single oral 800/160 mg dose of TMP/SMX. The main statistically significant difference in kinetic parameters between the two components is the volume of distribution, which is higher for TMP. However, the widespread use of TMP/SMX has resulted in a progressive emergence of resistance, and resistant strain rates of over 20% have been reported in several European countries and in the USA, as well as in developing countries, limiting the clinical usefulness of this therapy in the modern management

Table 4 Pharmacokinetic parameters after a single oral 800/160 mg dose of co-trimoxazole[30,31]

Parameter	Sulfamethoxazole	Trimethoprim
Bioavailability (%)	85–90	85–90
C_{max} (mg/L)	35–65	1.2–1.9
Vd (L)	13	100
Protein binding (%)	65	45
K_{el} (h^{-1})	0.060	0.060
$t_{1/2\beta}$ (h)	10–12	10–12
pKa	5.8	7.3

Notes: C_{max}, peak plasma concentration; K_{el}, elimination rate constant; $t_{1/2\beta}$, elimination half-life; pKa, acid dissociation constant; Vd, volume of distribution.

of UTIs, as recognized in clinical guidelines. Several studies have shown that clinical outcomes in patients with UTIs due to TMP-SMX-resistant pathogens are worse than those in patients with UTIs due to susceptible isolates.[32]

Common side effects associated with TMP/SMX, primarily occurring in elderly patients, are blood dyscrasias, drug fever, hyperkalemia and rash. In a nested case-control study, TMP/SMX-induced hyperkalemia was investigated in elderly patients receiving spironolactone. Compared with amoxicillin, TMP-SMX was associated with a more than 12-fold increase in the risk of hospital admission for hyperkalemia. It has been suggested that approximately 60% of all cases of hyperkalemia could be avoided if TMP/SMX was not prescribed.[33] It has also been suggested that acute kidney injury might be associated with TMP/SMX.[34] In patients with renal failure (creatinine clearance <80 mL/min), dosing frequency should be reduced (to every 18 h for those with creatinine clearance of 50–80 mg/mL and to every 24 h in those with creatinine clearance of 10–50 mg/mL); the administration of TMP/SMX should be avoided in patients with a creatinine clearance <10 mL/min. As a result of increasing resistance and these tolerability issues, TMP/SMX use is decreasing.[35]

Beta-lactams

The beta-lactams, characterized by a mechanism of action targeting the bacterial cell wall, are generally active against both Gram-positive and Gram-negative bacteria. These antimicrobial agents have a time-dependent killing activity at therapeutically achievable concentrations. They have minimal to moderate persistent antibiotic effects, and their efficacy is optimized by maximising the duration of exposure. Therefore, time above a threshold amount of drug (e.g. MIC) is the dominant PD index.[36] Resistance in *Enterobacteria* is mainly due to inactivation by hydrolytic enzyme production (beta-lactamases). Therefore, there is a tendency to use aminopenicillins in combination with suicide inhibitors (e.g. amoxicillin-clavulanic acid) or oral cephalosporins, mainly third-generation agents, because of their higher potency against Gram-negative rods, even if they are not active against *Enterococcus sp.*

Table 5 shows the main PK parameters of oral beta-lactams.[37–44] Many cephalosporins do not have high oral bioavailability and require administration as prodrugs (different esters). Beta-lactams generally have a relatively short elimination half-life, which means they should not be administered once-daily for the treatment of uncomplicated UTIs. Possible exceptions are cefixime and ceftibuten, although a twice-daily schedule would guarantee the maintenance of adequate antimicrobial levels for a longer time. Urinary recovery of oral beta-lactams ranges from 20 to 75%, amoxicillin/clavulanic acid and ceftibuten have the highest rates (75 and 70%, respectively). After an oral dose of ceftibuten 200 mg, the maximum urinary concentration is about 800 mg/L, while peak levels after a single oral dose of cefuroxime axetil 500 mg and amoxicillin/clavulanic acid 875 mg are about 400 mg/L and 200 mg/L, respectively. However, urinary levels fall rapidly within 2 to 4 h post-dose.[37–39]

Pivmecillinam, a prodrug of mecillinam, has been widely used for the treatment of acute lower UTI, mainly in Northern Europe. Mecillinam is an amidine derivative of the penicillin group. This molecule has high activity against Gram-negative organisms such as *Escherichia coli*, with a low level of resistance (<2%). Pivmecillinam is well absorbed after oral administration, with a bioavailability of 60–75%, although the moderate reduction in Gram-negative *Enterobacteriaceae* in the intestinal flora may occur.[45] About half (45%) of the drug is excreted in the urine, and mean peak urinary concentrations might be as high as 300 mg/L, usually within the first 3-h period; these fell to almost 50 mg/L at 6 h after administration and were ≤5 mg/L after 12 h.[44,46]

Beta-lactams are generally well tolerated by both paediatric and adult patients, and they can be used during pregnancy (with the partial exclusion of clavulanic acid). However, the rising prevalence of antimicrobial resistance in uropathogens, even in strains causing community-acquired uncomplicated infections, mainly for extended spectrum beta-lactamase (ESBL) production, and the increasing prevalence of invasive pan-resistant *E. coli* strains (resistant to aminoglycosides, fluoroquinolones and third-generation cephalosporins) suggest that a conservative approach to the use of these agents in community infections is warranted.[47,48]

Nitrofurantoin

Nitrofurantoin, a synthetic nitrofuran derivative, has been available for the treatment of UTIs since 1952. It still has relatively high activity against *E. coli* and *E. faecalis* uropathogens. However, nitrofurantoin is less effective against Gram-negative pathogens other than *E. coli*, such as *Klebsiella* spp. (69.2%) or *Enterobacter* spp. (63%) and is almost inactive against *Proteus mirabilis*.[49] The nitro group coupled in the heterocyclic furan ring represents the specific active site of the drug and once activated by

Table 5 Pharmacokinetic parameters of oral beta-lactams[37–44]

Beta-lactam	Dose (mg)	C_{max} (mg/L)	t_{max}(h)	$t_{½β}$(h)	Bioavailability (%)	Dosing interval (h)	Fu(%)
Amoxicillin/clavulanic acid	875/125	10.4–3.5	1	1.2/1	90/75	12	75/60
Cefuroxime axetil*	500	4.4–9.9	2.3–3.4	1.3–1.8	36–52	12	32
Cefixime**	400	4	4	3.8	40–48	24	18
Ceftibuten**	400	15	2	2.5	80–85	24	70
Cefpodoxime proxetil	200	2.6	2.8	2.7	50	12	46
Pivmecillinam	200	1.7±1.2	1.5	10.0	65–70	24	40

Notes: C_{max}, peak plasma concentration; Fu, urinary recovery; $t_{1/2\beta}$, elimination half-life; t_{max}, time to peak plasma concentration.
*Prodrug.
**Intrinsic bioavailability.

Table 6 Pharmacokinetic parameters of nitrofurantoin in healthy subjects*[,52]

Parameter	Value
C_{max} (mg/L)	0.875–0.963
$t_{1/2\beta}$ (h)	0.72–0.78
$AUC_{0-\infty}$ (mg·h/L)	2.21–2.42
CL_R (L/h)	16.7–19.4
Fu (%)	38.8–44.3

Notes: AUC, area under the concentration-time curve; CL_R, renal clearance; C_{max}, peak plasma concentration; Fu, urinary recovery; $t_{1/2\beta}$, elimination half-life.
*36 subjects with different expression of the ABCG2 421 genotype.

Table 7 Pharmacokinetic parameters of fosfomycin trometamol[57,59]

Parameter	Value
C_{max} (mg/L)	25–30
t_{max} (min)	45–120
C_{min} (mg/L)	~3 mg/l
$t_{1/2\beta}$ (h)	5–7
Vd (L/kg)	0.3–0.4
CL_R (L/h)	~7.8

Notes: CL_R, renal clearance; C_{max}, peak plasma concentration; C_{min}, trough concentration; $t_{1/2\beta}$, elimination half-life; t_{max}, time to peak plasma concentration; Vd, volume of distribution.

microbial nitro-reductases is able to interfere with protein and DNA synthesis, thus impairing energy metabolism, cell wall and carbohydrate synthesis.[50]

From a PK point of view, the bioavailability of nitrofurantoin is about 90% but plasma concentrations are very low (<1 mg/L after an oral dose of 100 mg). The elimination half-life is short (around 1 h), and 27–50% of the drug is excreted unchanged in the urine. Even though peak urinary levels might be >100 mg/L (range 50–200 mg/L), these are maintained for a relatively short time.[18,51] Adkinson et al. confirmed the PK profile of nitrofurantoin in 3 groups of healthy subjects with different expression of the ATP-binding cassette transporter subfamily ABCG2 421 genotype, showing that the ABCG2 C421A polymorphism had no effect on nitrofurantoin plasma and urine pharmacokinetic parameters (Table 6).[52]

Nitrofurantoin has a bactericidal effect against susceptible organisms. However, this antibiotic primarily has time-dependent activity, with $T >$ MIC being the PK-PD parameter that best correlates with efficacy; maintenance of plasma concentrations higher than the MIC for a relatively long-time post-dose is required. Therefore, there might be a risk of treatment failure for pathogens with a higher MIC value, while the sensitivity threshold of 64 mg/L for urinary pathogens still seems too high.[53] Nitrofurantoin has been associated with neurotoxicity (including peripheral neuropathy, dizziness, vertigo, diplopia, and cerebellar dysfunction) and benign intracranial hypertension. These side effects are most prevalent in women and elderly patients, and their pathogenesis is hypothesized to be due to axon loss.[54] Other possible side effects, generally after long-term therapy, include sub-acute and chronic pulmonary reactions and chronic hepatitis. Over recent years, new insights into the immune capability of nitrofurantoin have emerged. Although nitrofurantoin rarely causes autoimmune hepatitis, prescribers should be aware of this adverse event and caution is warranted in the geriatric population because this agent is increasingly being used both for long-term prophylaxis and the treatment of acute and chronic UTIs.[55,56] Finally, nitrofurantoin should be avoided in patients with moderate-severe renal failure (creatinine clearance <50 mL/min).

Fosfomycin trometamol

Fosfomycin is a phosphonic acid derivative, isolated for the first time in Spain in 1969 from a *Streptomyces fradiae* strain, and has a broad spectrum of antibacterial activity against both Gram-positive and Gram -negative bacteria, including ESBL-producer strains. This antibiotic has good *in vitro* activity against more common multidrug-resistant uropathogens. In addition, in a recent microbiological study performed in Italy, fosfomycin inhibited all ESBL-positive *E. coli*, *P. mirabilis* and methicillin-resistant *S. saprophyticus* strains isolated from urine, as well as 82% of KPC-producing *K. pneumoniae* isolates.[57]

The bactericidal activity of fosfomycin is a result of the epoxy ring, which inhibits a cytoplasmic enzyme (phosphoenolpyruvate synthetase) active during the first step of bacterial cell wall (peptidoglycan) synthesis.[58,59] Fosfomycin acts as a phosphoenolpyruvate analogue, irreversibly inhibiting enolpyruvil transferase (UDP-N-acetylglucosamine-3-O-enolpyruvil transferase), a cytoplasmic enzyme which catalyzes the first step of the biosynthesis of the heteropolymer peptidoglycan through the incorporation of phosphoenolpyruvate to uridine-diphosphate-N-acetyl-glucosamine forming

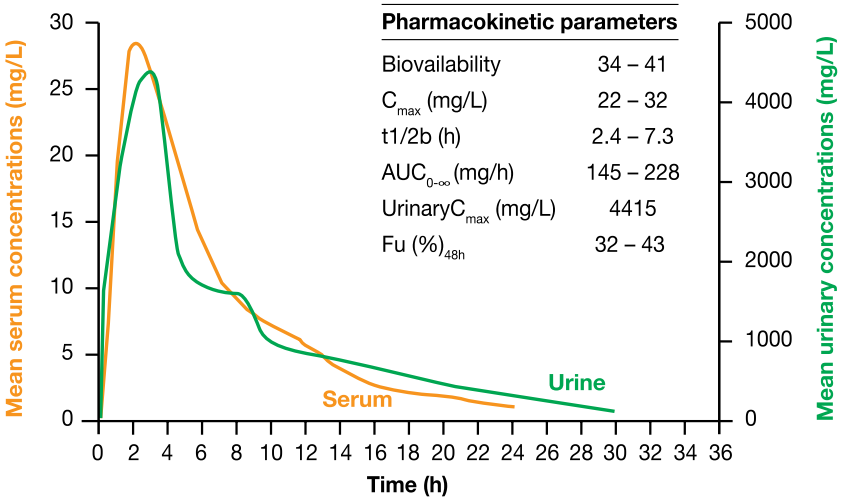

Figure 2 Mean serum and urinary drug concentrations after a single oral 3 g dose of fosfomycin trometamol.[57]

uridine-diphosphate-N-acetylmuramic acid.[60] It has a relatively broad spectrum of activity and, notwithstanding the possible mechanisms of bacterial resistance, has maintained good activity against the main bacterial species responsible for UTIs.[60–63] Many different factors may play a role in this preserved activity. These include the use of a single dose for the treatment of uncomplicated UTIs and two consecutive doses for prophylaxis of urological procedures, the rapid concentration-dependent killing activity with reduced effect on selecting resistant mutants (and when present, these strains have reduced fitness due to the high biological cost of the genetic modification) and the limited use in veterinary medicine.[64] Fosfomycin has concentration-dependent activity against both Gram-positive and Gram-negative strains and has a long post-antibiotic effect (PAE) *in vitro,* even at sub-inhibitory concentrations and over periods of 3.2–4.7 h.[65–67]

Fosfomycin trometamol is a monobasic anionic salt, with a molecular weight of 259.2 g/mol, metabolized from fosfomycin after absorption. Fosfomycin trometamol is more soluble and stable in the gastric acidic environment. After oral administration, it is rapidly absorbed and converted to the free acid, fosfomycin, with a good bioavailability (37–44%).[59] Co-administration of fosfomycin trometamol with food may reduce drug absorption (37% fasting versus 30% with food). After administration of a single 3 g oral dose of fosfomycin trometamol, peak plasma concentrations (C_{max}) is 25–32 mg/L, occurring within 2–2.5 h (t_{max}), and trough concentrations at 24 h are about 3 mg/L. The corresponding AUC is approximately 145–228 mg·h/L. There is a linear relationship between the main PK parameters, such as C_{max} and $AUC_{0-\infty}$, and fosfomycin trometamol dosage.[58,65,67] The elimination half-life is 5–7 h, and the volume of distribution (after IV dosing) is 0.3–0.4 L/kg, with good distribution into the extravascular compartment (Table 7).[58,60] Fosfomycin is widely distributed into tissues, achieving clinically relevant concentrations in serum, kidneys, bladder wall, prostate, lungs, inflamed tissues, bone, cerebrospinal fluid, abscess fluid and heart valves.[62] For example, at 3 and 12 h after an oral 3 g dose, prostatic fosfomycin concentrations are 25 and 7 mg/L, respectively.[68,69]

Fosfomycin is excreted unchanged in the urine via glomerular filtration. Urinary recovery is almost 40%, and high urinary concentrations (1000–5000 mg/L) are achieved and maintained for long periods after oral administration, with a mean urinary level of 1000 mg/L at 12 h and 500 mg/L at 24 h. Urinary concentrations remain >100 mg/L for at least 30–40 h post-dose. This means that drug levels capable of eliminating the majority of common uropathogens are maintained, providing good clinical efficacy in the treatment of uncomplicated UTIs even after a single dose (Fig. 2).[58,60,65] Based on these data, both the urinary peak/MIC and AUC/MIC ratios are very high given that uropathogens have MIC values within the sensitivity threshold of 32 mg/L. In patients with chronic severe renal failure, the half-life of fosfomycin is increased significantly (up to 50 h), and fosfomycin recovery in urine is lower.[60] However, it is not necessary to reduce the dose if creatinine clearance is >10 mL/min.

Fosfomycin trometamol is generally well tolerated, with a very low incidence of side effects. The most commonly reported events are gastrointestinal (e.g. diarrhoea and nausea), although these are usually mild in severity and occur at a low incidence (2–3%), lower than that observed with beta-lactams.[70] A single dose of fosfomycin trometamol has been used successfully to treat lower UTIs in pregnant women.[70,71]

Overall, fosfomycin trometamol is an appealing oral outpatient alternative, even in older women and for resistant isolates.[48]

Conclusions

An adequate therapeutic approach to bacterial infection must take into account drug safety, including the presence and incidence of side effects and the possibility of

antimicrobial resistance (i.e. the selection of resistant organisms and colonization or infection with multidrug-resistant pathogens). Some pharmacological and therapeutic strategies for limiting or preventing bacterial resistance can be adopted in clinical practice. The treatment of uncomplicated UTIs is mostly empiric, based on the common aetiology of these infections (where *E. coli* represents 75–90% of causative pathogens), local epidemiology of resistance and local antimicrobial susceptibility patterns. It is well known that there is a considerable geographic variability in the susceptibility of uropathogens and therefore each physician should know their own local epidemiological pattern of resistance in uropathogens in order to avoid empiric treatment of uncomplicated UTIs with an ineffective antibiotic. Treatment guidelines recommend that a class of antibiotics should not be used when local resistance in *E. coli* exceeds 20% of strains. For example, in most countries in Southern Europe, the resistance of *E. coli* strains to quinolones and co-trimoxazole is >20%, automatically excluding these drugs from empiric use to treat uncomplicated UTIs. Given the trend for increasing resistance to most antimicrobials, ongoing monitoring is required to continually optimize empiric UTI therapy. One strategy for preventing or limiting bacterial resistance is to use antibiotics with adequate urinary kinetics (i.e. achievement of high urinary drug concentrations exceeding the MIC of uropathogens for a sustained period) at optimal dosage and for an appropriate duration. Based on this pharmacological and therapeutic strategy, fosfomycin trometamol appears to be a useful agent given its wide spectrum of activity (including ESBL-positive strains), a favourable PK profile (high urinary concentrations maintained over 3 days post-dose), proven clinical efficacy and safety in the management of uncomplicated UTIs and good compliance with the single-dose treatment regimen.

Conflict of interest

The authors state that they have no conflict of interest to declare.

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