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Why fosfomycin trometamol as first line therapy for uncomplicated UTI?

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Abstract

Uncomplicated urinary tract infection (UTI) is one of the most common conditions requiring diagnostic and therapeutic intervention. The aetiology and the treatment of these infectious diseases have changed little during last years of the 'antibiotic era'. *Escherichia coli* is the most prevalent uropathogen (85– >90%) and treatment is aimed at eradicating the infection using shorter regimes that typically may employ a 3-day course with once-a-day dosing of a selected drug or a single dose of a particular efficacious antibiotic. Antibiotic resistance to commonly used agents, such as trimethoprim and ampicillin, often now exceeds 30–50%, while fosfomycin trometamol, despite many years of usage, continues to be characterized by an extremely low incidence of *E. coli* resistant strains (about 1%) worldwide. Many factors may have contributed to preserve fosfomycin trometamol antibacterial activity including single dose usage limited to urinary infections, very high and sustained urinary concentrations that rapidly kill bacteria reducing the opportunity for mutant selection. In addition there is no animal feed that contains the drug, resistance is most commonly acquired by chromosomal mutations that do not spread easily and the biological cost of these genetic modifications is high. To these parameters fosfomycin trometamol adds excellent tolerability and safety. Although nowadays, microbial resistance limits available resources and some drugs can no longer be recommended as reliable agents, fosfomycin trometamol, because of its properties, remains a drug of choice for the eradication of uncomplicated UTI.

Keywords: Fosfomycin trometamol; Uncomplicated UTI; Therapy; Resistance

1. Introduction

Over 150 million urinary tract infections (UTI), including both uncomplicated and complicated cases, occur yearly in the world [1]. Uncomplicated UTI are the most frequent bacterial infections in women while complicated UTI may involve up to 10% of all hospitalized patients and are the most common type of nosocomial infections. Uncomplicated UTI are chiefly found in otherwise healthy females but may also affect male infants. They have been described occasionally in adolescent and adult males. Numerous studies have also reported an association between UTI during pregnancy and adverse maternal, as well as foetal, outcome. Anaemia, pyelonephritis, renal failure and hypertension are among the conditions that may be observed in the mother, while pre-term delivery, growth restriction, low birth weight and rare deaths have been reported for the infant. Recent observations by McDermott et al. [2] have pointed out that there is a statistically significant association between mental retardation or development delay in infants born to mothers that, while suffering of UTIs during pregnancy, were left untreated.

2. Treatment

In uncomplicated UTI treatment is aimed at eradicating the infection and at reducing the associated morbidity due to relapses and re-infections. In this connection, approaches to therapy have moved towards eradicating each episode of infection using shorter regimens that typically may employ a 3-day course with once-a-day dosing of the selected drug, to a single dose of a particularly efficacious antibiotic [3,4]. Single-dose therapy of uncomplicated UTI offers several advantages over longer courses. These include better compliance, fewer untoward side effects and lower costs [5]. Single-

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Table 1
Uropathogens isolated (441)

Species	Number	%
E. coli	387	87.75
P. mirabilis	24	5.4
K. pneumoniae	15	3.4
E. cloacae	5	1.1
S. marcescens	4	0.9
C. freundii	3	0.7
M. morganii	3	0.7

dose treatments of uncomplicated UTI are generally not based on the availability of diagnostic microbiology reports. For this reason in the ensuing empirical therapy, a high prevalence of antibiotic resistance in common uropathogens drastically limits the usefulness of any type of single dose approach [3]. This behavior stems from the fact that with cotrimoxazole-resistant *Escherichia coli* the eradication rate with the drug found inactive in vitro is not satisfactory, ($<50\%$) when compared with the results ($>90\%$) obtained when the pathogen is susceptible. For this reason, recent international guidelines recommend that a drug having a 10–20% resistance rate in the community should not be used at all empirically. This tenet holds true not only for cotrimoxazole but can be applied to any type of antibiotic, especially the β-lactams to some of which there is a high level of resistance worldwide [3].

Since 1988 fosfomycin trometamol has been extensively used in several European countries for single-dose therapy of uncomplicated UTI. It is thus mandatory to monitor the trends of resistance to fosfomycin trometamol in the primary pathogens of uncomplicated UTI if the drug is to be employed safely and effectively today. In order to do so, a survey was carried out in Genoa in September–November 2000 [6]. All Gram-negative uropathogens isolated from outpatients were included (Table 1).

Table 2
Prevalence of antibiotic susceptibility in 387 *E. coli* isolated from uncomplicated UTIs

Drug	MIC range (mg/l)	MIC 50 (mg/l)	MIC 90 (mg/l)	S (%)
Fosfomycin trometamol	0.5–256	32	64	99
Nitrofurantoin	8–>64	16	32	97
Co-amoxiclav	1–16	4	16	89
Ciprofloxacin	<0.06–>64	<0.06	8	88
Norfloxacin	<0.06–>64	0.25	32	85
Cotrimoxazole	0.12–>64	0.5	4	76

Table 3
Trends in the prevalence of drug resistance (%) in urinary *E. coli* isolated in Genoa

	Year (number)	Year (number)	Fold increase
Drug	1990 (576) [8]	2000 (387)	
Fosfomycin trometamol	1	1	0
Nitrofurantoin	1.7	3	2
Norfloxacin	0.3	15	45
Cotrimoxazole	11.3	24	2.2

3. Survey results

As expected from previous reports in the international literature, *E. coli* was the prevalent uropathogen obtained (Table 1). Only this organism was, therefore, tested with regard to its antibiotic susceptibility; NCCLS methodologies and breakpoints were used [7]. For fosfomycin trometamol sensitivity testing, cation-adjusted Mueller Hinton agar plates were supplemented with 25 mg/l glucose 6-phosphate. Besides fosfomycin trometamol, co-amoxyclavulanate, norfloxacin, ciprofloxacin, cotrimoxazole and nitrofurantoin were assessed (Table 2).

The two antibiotics that expressed an activity against *E. coli* >90% were fosfomycin trometamol and nitrofurantoin; the latter, however, is devoid of any useful action on the second most frequently isolated uropathogen, *P. mirabilis*. All other drugs showed effective activity against 80–90% but 24% strains were resistant to cotrimoxazole. The trend in the prevalence of drug resistance for urinary *E. coli* in Genoa could be compared over a 10-year period and is shown in Table 3.

The only drug that did not suffer from an increase in the incidence of resistance, which is particularly low in any case, was fosfomycin trometamol with all other antimicrobials showing increased resistance levels. Of special note was the 45-fold increase shown by the

Table 4
Comparative features of cotrimoxazole (fluoroquinolones) and fosfomycin trometamol with respect to usage and other properties

Cotrimoxazole (fluoroquinolones)	Fosfomycin trometamol
Usage	
Widespread: (URTI, UTI, prophylaxis)	Uncomplicated UTIs only
Multiple-dose	Single-dose
Long treatment	Very short
Animal feeds	No
Genetics	
Conjugative plasmids	Rare (<2%)
Co-selection by β-lactams, tetracyclines	No co-selection
Faecal flora	
Resistant strains: Yes	No

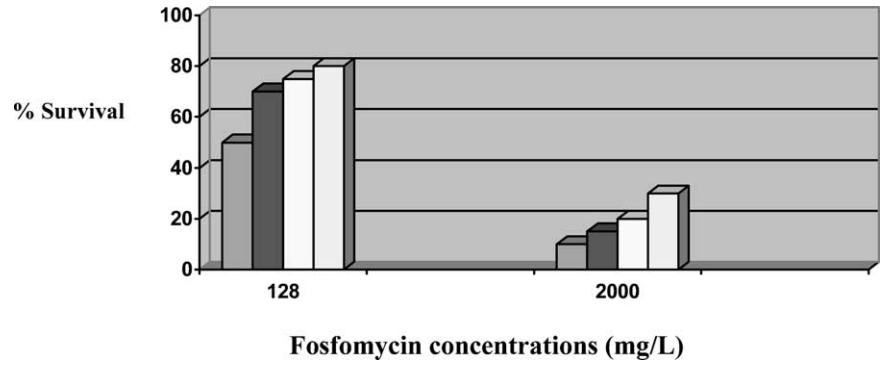

Fig. 1. Survival of *E. coli* (four strains) in mature (48 h) biofilms after exposure (24 h) to fosfomycin trometamol.

fluoroquinolone tested, a factor also reflected in ciprofloxacin and cotrimoxazole resistance in most areas of the world investigated [9–15]. This finding is corroborated by numerous other investigators that have confirmed the powerful and enduring activity of fosfomycin trometamol against urinary pathogens in Europe [10] and the USA [16] with resistance rates very rarely in excess of 1%.

It seems, therefore, mandatory to understand why resistance to fosfomycin trometamol in uropathogens remains so rare despite ample usage in several countries and why, by the same token, resistance to other antibiotics is increasing rapidly in the same species. A rationale for explaining these different behaviors is given in Table 4.

4. General properties of fosfomycin trometamol

In general practice, usage of fosfomycin trometamol is limited to the eradication of bacterial pathogens from uncomplicated UTI and administration lasts only 1 day. There is no animal feed that contains the drug, resistance is most frequently acquired by chromosomal mutations that do not spread to other organisms easily [17]. Selection operated by drugs with different mechanisms of action is not a problem and the faecal flora of humans does not host resistant strains after the very short time course of treatment. Other features that certainly contribute to hinder the selection and diffusion of fosfomycin trometamol-resistant clones, especially in *E. coli*, depend on the very high and sustained urinary concentrations achieved that rapidly kill uropathogens, reducing the opportunity for mutant selection. This tenet can now be extended to a new property recently highlighted and concerning the ability of fosfomycin trometamol to inhibit the formation, and even to promote disruption, of *E. coli* biofilms present in the bladder in acute cystitis [18,19], thus helping to prevent recurrence and chronic infection developing. Emergence of mutants is due to alterations in the alpha-glycerophosphate transport system [20]. It has clearly been established that the physiological fitness of these rare mutants is drastically impaired. Li Pira et al. have clearly shown that these strains manifest a decreased growth rate in common media [21] and recently this defect has also been noted in fosfomycin trometamol-resistant *E. coli* multiplying in urine [6]. Reduced adherence to uroepithelial cells (up to 60%) and to urinary catheters, diminished cell surface hydrophobicity (up to 50%), higher sensitivity to polymorphonuclear cell and serum complement killing (up to 70%) has also been noticed under appropriate experimental conditions. All these important modifications lead to a profound reduction of physiological fitness in resistant *E. coli* accompanied by modifications in their pathogenicity traits finally resulting in loss of virulence. These organisms are, therefore, totally incapable of spreading in the environment and of giving rise to relapses or reinfections. Acquisition of fosfomycin trometamol resistance by uropathogens demands prohibitive biological costs. This unique situation will contribute to maintain in time the potent antibacterial activity of the drug and its efficacy in the treatment of uncomplicated UTI.

5. Fosfomcin trometamol and biofilms

One other major point in favor of fosfomycin trometamol has emerged recently with the publication of important new data concerning the evidence that, even in uncomplicated UTIs, including cystitis, the offending pathogen generally involved, *E. coli*, may be organized in the form of biofilms with sessile elements embedded in a vast slime layer. This situation provides the infecting microorganisms with a sort of phenotypic resistance to antibiotics even in the absence of genes normally dictating loss of susceptibility. These biofilms also maintain symptomatic cystitis by shedding, at random intervals, waves of planktonic cells that replicate in the urine [18]. We have now demonstrated, using a demanding in vitro model represented by four *E. coli* uropathogenic strains colonizing polystyrene as plastic support and employing the methodology developed by

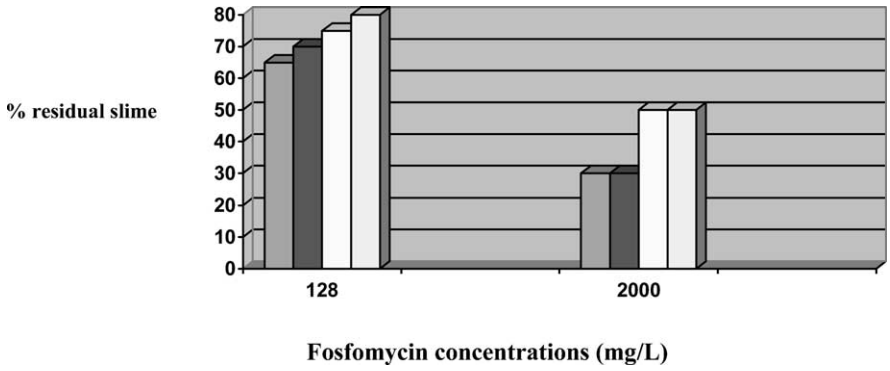

Fig. 2. Disruption of *E. coli* (four strains) in mature (48 h) biofilms after exposure (24 h) to fosfomycin trometamol.

Crampton et al. [22], that fosfomycin trometamol not only kills sessile cells but also displays the ability to disrupt *E. coli* preformed biofilms [19]. Fig. 1 summarizes the findings concerning the survival of the pathogen in mature (48 h of development) biofilms after exposure for 24 h to two different concentrations of fosfomycin trometamol. At a concentration of 128 mg/l, in a strain-dependent fashion, killing of sessile cells by the drug ranged from 50 to 20%. When the concentration of fosfomycin trometamol was maintained at 2000 mg/l, a value easily reached during normal treatment, the effect is more pronounced, with counts of viable organisms suggesting killing of around 70–90% of the bacterial load depending on the isolate involved. Disruption of preformed mature *E. coli* biofilms also takes place in the presence of fosfomycin trometamol, as shown in Fig. 2. While some effect is apparent at 128 mg/l, the maximum efficacy is reached at 2000 mg/l with the breakdown of 50–70% of the slime structures. Complete disruption, however is never achieved, at least under the conditions tested here. It can be anticipated that fosfomycin trometamol activity on *E. coli* biofilms may be more efficacious in vivo, due to the fact that in the patient bladder the drug may interact positively with normal host defences represented by polymorphonuclear cells and other unspecific immunomodulatory elements. The contribution of the antibiotic may, therefore, speed up cure times and avoid recurrent infections.

6. Use of fosfomycin trometamol in uncomplicated UTI

There are several microbiological considerations that reaffirm the primary role of fosfomycin trometamol as a first line drug in the eradication of uncomplicated UTIs. These include the appropriate antimicrobial spectrum, the minimal resistance found worldwide in primary pathogens of the urinary tract, the fact that the very few resistant clones are genetically and physiologically crippled, the ability to overcome resistance to unrelated drugs, often widely diffused, the prevention of biofilm formation and the ability to partially disrupt slime in mature biofilm structures. To these parameters may be added pharmacokinetic and pharmacodynamic advantages including high urinary levels maintained for extended periods of time. Its in vivo activity and clinical efficacy in uncomplicated UTIs has been proven in numerous well-designed and performed peer-review-published studies [23]. Tolerability and safety are also excellent [23]. Usage during pregnancy has demonstrated consistent success without the risk of untoward effects. In the same studies fosfomycin trometamol has demonstrated minimal rates of recurrences when compared with other well established drugs.

Finally, in an era of limited resources, it is important to underline that the cost of the short course of therapy with fosfomycin trometamol is comparable with that of less effective and safe drugs.

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