The role of fluoroquinolones in the management of urinary tract infections in areas with high rates of fluoroquinolone-resistant uropathogens

Y.-H. Chen · W.-C. Ko · P.-R. Hsueh

Received: 20 September 2011/Accepted: 11 October 2011/Published online: 4 November 2011
© Springer-Verlag 2011

Abstract Fluoroquinolones have been recommended as the drugs of choice for the empirical treatment of uncomplicated and complicated urinary tract infections (UTIs) caused by trimethoprim-sulfamethoxazole-resistant uropathogens. However, because of the increased use of both oral and parenteral fluoroquinolones for other kinds of infections, increasing rates of resistance to fluoroquinolones among the most common uropathogens have challenged this recommendation, particularly in the Asia-Pacific region. The current interpretative criteria for the in vitro susceptibility of uropathogens to some fluoroquinolones, such as levofloxacin and ciprofloxacin, are set according to their therapeutic efficacy for bloodstream infections, and are not specific to UTIs. Fluoroquinolones exhibit concentration-dependent antibacterial activity, high renal excretion, and relatively early and prolonged urinary bactericidal titers. Whether or not current interpretative criteria for the in vitro susceptibility of uropathogens to fluoroquinolones predict clinical failure in treating UTIs is still controversial. The Clinical and Laboratory Standards Institute (CLSI) has established UTI-specific breakpoints for resistance to a few fluoroquinolones. However, the application of high-dose fluoroquinolone therapy for the treatment of mild to moderate UTIs caused by isolates with higher minimum inhibitory concentrations (MICs) of several fluoroquinolones needs to be re-validated based on more relevant clinical studies, prudent pharmacokinetic/pharmacodynamic (PK/PD) considerations, and thorough study of the mutant prevention concentration of fluoroquinolones in the treatment of UTI.

Introduction

Community-acquired and healthcare-associated urinary tract infections (UTIs) are associated with high rates of morbidity and mortality, and pose a significant economic burden to healthcare systems worldwide [1–4]. Escherichia coli, other members of the Enterobacteriaceae family, and Enterococcus species (such as Enterococcus faecalis) are the primary causative agents of UTIs [5, 6]. Clinical guidelines based on surveillance data and clinical response have been developed in many countries in order to improve the quality of care of patients with these infections [7–10]. Enterobacteriaceae isolates remain the major pathogens, but their susceptibility profiles have changed. The rate of resistance to trimethoprim–sulfamethoxazole (TMP–SMX), one of the drugs recommended for uncomplicated UTIs in these guidelines [6–8], is high (>20%) in many regions of
the world, particularly among E. coli isolates [5, 6, 11, 12]. This change in resistance profile makes TMP-SMX unsuitable for the empirical treatment of UTIs, at least in parts of Europe, Asia, and the United States [6-8]. Fluoroquinolones, such as levofloxacin or ciprofloxacin, are now recommended as empirical treatment for UTIs, especially catheter-associated UTIs [8]. However, the increased use of fluoroquinolones has resulted in the rapid emergence of fluoroquinolone-resistant E. coli and other uropathogens, raising concerns about whether fluoroquinolones should remain the drugs of choice for UTIs [13, 14]. In a current consensus review from the Asia-Pacific region, fluoroquinolones (ciprofloxacin and levofloxacin) are not recommended as the drugs of choice of the treatment of UTIs if the rates of resistance for urinary E. coli isolates to fluoroquinolones were >20% [14]. Furthermore, fluoroquinolone-resistant E. coli isolates from urine are frequently resistant to multiple drugs, including ampicillin (79.8%) and TMP-SMX (66.5%), thereby, posing serious challenges to clinicians who are faced with treating patients, especially outpatients, with UTIs [15].

The purpose of this review is intended to understand the role of fluoroquinolones in the treatment of UTIs in areas with high rates of fluoroquinolone-resistant uropathogens.

Fluoroquinolone resistance among uropathogens

Increasing resistance of uropathogens to fluoroquinolones is of clinical concern. Although the Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC) study conducted in nine countries in Europe and in Brazil from 2003 to 2006 showed an overall high rate of ciprofloxacin susceptibility (91.7%) among E. coli isolates, lower susceptibility rates were found in several countries, such as Russia (86.4%), Italy (87.5%), and Spain (89.3%) [5]. Furthermore, in Spain, E. coli isolates from the genitourinary system isolated during the period 2007 to 2009 showed increasing resistance to ciprofloxacin, especially among men [16]. In the USA, high rates of quinolone resistance among uropathogens were found in several states, with some hospitals reporting that more than 25% of E. coli isolates were resistant to fluoroquinolones [17, 18]. An outpatient study in the USA showed that the rate of levofloxacin resistance among E. coli isolates increased from 1% to 9% during the period 1998 to 2005 as a result of the increased consumption of levofloxacin (from 3.1 to 12.7 prescriptions per 1,000 visits) during the study period [19]. Furthermore, another study conducted in the USA during the period 2008 to 2009 revealed that the overall rate of resistance of uropathogens to levofloxacin in emergency departments was 17% [20]. In Asia, the Study for Monitoring Antimicrobial Resistance Trends (SMART) in 2009 revealed that the rates of susceptibility to levofloxacin among clinical urinary isolates of E. coli from hospitals in various countries in the Asia-Pacific region ranged from 83% in New Zealand to as low as 15% in India (average, 51%) (Fig. 1) [6].

The risk factors for UTIs caused by fluoroquinolone-resistant uropathogens include recent hospitalization, urinary indwelling catheters, long-term medical conditions, healthcare-associated UTIs, and prior quinolone use [19-22]. These risk factors may have a great influence on the choices of empirical therapy for UTIs.

In vitro fluoroquinolone resistance and clinical efficacy

According to the updated international guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women recommended by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID) in 2010, fluoroquinolones should not be administered as empirical
therapy in locations where the resistance rate of community uropathogens exceeds 10% [7]. However, whether the results of the in vitro susceptibility testing of bacterial isolates to fluoroquinolones can predict the clinical outcome of patients with UTIs, especially complicated UTIs, is controversial, particularly when patients are treated with higher than regular doses of levofloxacin (e.g., 750 mg q24h) [23].

According to the recommendations of the Clinical and Laboratory Standards Institute (CLSI), the current minimum inhibitory concentration (MIC) breakpoints for trimethoprim and TMP-SMX are for urinary isolates of Enterobacteriaceae and staphylococci [13]. Studies have shown that the clinical outcomes of patients with UTIs due to TMP-SMX-resistant pathogens are worse than those of patients with UTIs due to susceptible isolates [24, 25]. It was reported that 29% of cultures from uncomplicated UTIs grew TMP-SMX-resistant pathogens and that the clinical cure rate of TMP-SMX for the women infected with TMP-SMX-resistant pathogens was 54% [25]. The resistance prevalence threshold of TMP-SMX has been estimated to be 20% [7]. However, few studies have focused on the clinical outcomes of patients with UTIs due to fluoroquinolone-resistant isolates based on current CLSI recommended, non-urine-specific susceptibility breakpoints.

According to the most recent performance standards update provided by the CLSI in January 2011, only UTI-specific breakpoints for lomefloxacin, norfloxacin, and ciprofloxacin are listed [13]. Therefore, clinicians need to follow the breakpoints set for bloodstream infections in order to determine the susceptibilities of urinary isolates of Enterobacteriaceae to other agents in the fluoroquinolone class, such as levofloxacin and ciprofloxacin. The correlation of such susceptibility data to the therapeutic outcomes of UTIs warrants additional study.

Pharmacokinetics and pharmacodynamics of fluoroquinolones

The bactericidal activity of fluoroquinolones has been shown to be concentration-dependent. Peak concentrations in urine might be the key factor in the therapeutic outcome of patients with UTIs [26, 27]. An area under the curve (AUC)/MIC greater than 100 or a maximum concentration (Cmax)/MIC greater than 10 against Gram-negative bacteria would indicate a good clinical response [28]. Among the fluoroquinolones indicated for UTIs, both levofloxacin (87%) and ciprofloxacin (30–50%) have significant renal excretion [26]. Furthermore, the post-antibiotic effect of fluoroquinolones contributes to their therapeutic efficacy [29]. Therefore, fluoroquinolones have the potential to provide high urinary levels and prolonged bactericidal activity in urine [30]. But, intensive acidified urine (pH around 5–6) was found to impair the antimicrobial effects of fluoroquinolones in a recent in vitro study [31]. However, the impact of urine acidification for prophylaxis and the treatment of urinary tract infection is very controversial [31, 32].

Previously, lower doses of fluoroquinolones (such as levofloxacin 250 mg q24h) were recommended, which showed low urinary bactericidal titers, ranging between 0 and 128 [33]. However, higher daily doses of fluoroquinolones (such as levofloxacin 750 mg q24h) have been currently recommended, which increase significantly the urinary bactericidal titers. Stein et al. showed that the mean urinary Cmax following a single dose of levofloxacin was 347 μg/mL for a 500-mg dose and 620 μg/mL for a 750-mg dose [34]. Based on the pharmacokinetic/pharmacodynamic (PK/PD) parameters of fluoroquinolones, clinical failure can be predicted when the levofloxacin MIC of the causative uropathogen is higher than 32 μg/mL when measured in urine 8–12 h after the administration or 64 μg/mL when measured in urine sampled 12–24 h after drug intake (Fig. 2). Those values are markedly higher than the current CLSI recommended breakpoints. Furthermore, they reported that the in vitro urinary bactericidal assay showed that levofloxacin exhibited early and extended bactericidal activity in urine specimens against 90% of isolates with MIC values ≤32 μg/mL, especially in the presence of high-dose levofloxacin (750 mg) [33]. Furthermore, high-dose levofloxacin (750 mg) exhibited early and prolonged (8–12 h) urinary bactericidal activity in virtually all subjects against levofloxacin-resistant isolates of E. coli (MIC range, 4–32 μg/mL) [34]. Based on those findings, at least 90% of E. coli (MIC90 of 16 μg/mL) strains that cause complicated UTIs in Japan [35] and 90% of E. coli isolates recovered in intensive care units (MIC90 of 16 μg/mL) in Taiwan [36] might have the potential for being susceptible, according to these PK/PD data. But, urinary bactericidal titers do not necessarily translate to the cure of the patients. We need more clinical studies in order to prove their correlations.

The urinary Cmax of ciprofloxacin at the recommended dose of 250 mg every 12 h ranges from 160 to 255 μg/mL [37], and the Cmax/MIC would be much higher than 10 for a uropathogen with a ciprofloxacin MIC of 4 μg/mL. In addition, ciprofloxacin at standard doses or ciprofloxacin XR (1,000 mg) once daily has also been shown to have prolonged bactericidal activity in urine [38]. However, for E. coli isolates, the MIC90 of ciprofloxacin (64 μg/mL) has been shown to be higher than that of levofloxacin (16 μg/mL), indicating a higher rate of resistance to ciprofloxacin [36]. Besides, levofloxacin was the most capable of limiting the occurrence of resistance in E. coli and Klebsiella species.
The frequencies of mutation among _E. coli_ and _Klebsiella_ species were less than $10^{-11}$ under levofloxacin 750 mg and ciprofloxacin 500 mg [39]. This difference might be related to the various mechanisms underlying the resistance of _Enterobacteriaceae_ species to fluoroquinolone-class drugs, such as the greater effect of the AcrAB, MFS, and NorE efflux pumps on ciprofloxacin than on levofloxacin in _E. coli_ [40, 41].

Although the pharmacokinetics and pharmacodynamics of fluoroquinolones favor their use as therapeutic options for UTIs caused by fluoroquinolone-resistant isolates, few clinical studies support the widespread use of that class of antimicrobial agents. Among the studies which have shown that fluoroquinolones are effective, Miller et al. showed that the clinical symptoms of a young female with uncomplicated cystitis due to ciprofloxacin-resistant _E. coli_ (MIC $>4$ mg/L) resolved within 7 days of oral ciprofloxacin therapy (500 mg twice daily) [42]. In addition, the results of a clinical trial on the use of ciprofloxacin and levofloxacin for the treatment of acute pyelonephritis revealed that ciprofloxacin (500 mg twice daily for 10 days) and levofloxacin (750 mg daily for 5 days) were effective at eradicating two isolates (MICs of ciprofloxacin: 8 mg/L and $>32$ mg/L) and one isolate (MIC of levofloxacin: 32 mg/L), respectively [43]. Therefore, a 5-day course of levofloxacin or a 10-day course of ciprofloxacin is recommended for patients with complicated UTI or acute pyelonephritis, if the causative uropathogen is susceptible [23, 43]. Based on these findings, in areas with a resistance rate among uropathogens of more than 20%, high-dose levofloxacin (750 mg) would be considered as an option for mild to moderate complicated UTIs or complicated UTIs caused by _E. coli_ isolates with a levofloxacin MIC $\leq 32$ mg/L. For severe cases of complicated UTI or urosepsis with concurrent bacteremia, additional clinical trials are warranted to justify that type of empirical therapy.

The proposed UTI-specific MIC breakpoint ($\leq 32$ mg/L) for _E. coli_ to levofoxacin could be challenged when considering the effect of mutation prevention concentration (MPC) and the mutation selection window (MSW). A Cmax of fluoroquinolones greater than MPC, which were usually 8-fold to 16-fold (MSW) higher than MIC90 values, would predict the low potential of resistance selection [28]. For levofloxacin, the mean urinary Cmax of 640 mg/L is higher than 16-fold of the levofloxacin MIC90 (256 mg/L) [34, 36], suggesting a lower resistance emergence when a high dose of levofloxacin is used for the treatment of mild-to-moderate UTI. For ciprofloxacin, the higher mean urinary Cmax and higher MIC90 than those of levofloxacin [28, 34, 36] suggest the probably higher potential of resistance selection when a standard dose of ciprofloxacin (500 mg twice daily) is used for the treatment of mild-to-moderate UTI.

However, adverse effects of long-term high doses of fluoroquinolones might also be considered, which are applied to chronic bacterial prostatitis. Paglia et al. showed that the rates of treatment-emergent adverse events by levofloxacin resulting in therapy discontinuation were 3.8% (3/80), 11.1% (9/81), and 16% (13/81) in the 500-mg (2-week), 750-mg (3-week), and 750-mg (4-week) treatments, respectively [44]. However, no patients died in this study, although there were two patients with serious adverse events (syncope and coronary artery disorder) in the 750-mg (2-week) and one patient with adverse events (depression, hallucination, and suicidal ideation) in the 750-mg (3-week) treatments. Also, none of the serious adverse events were considered to be related to levofloxacin in these investigations.

The setting of urine-specific susceptibility breakpoints for levofloxacin and ciprofloxacin needs to be re-validated clinically, especially in several regions with a high prevalence of UTIs caused by multidrug-resistant (espe-
cially by combined TMP-SMX- and fluoroquinolone-resistant) uropathogens. The application of high-dose fluoroquinolone therapy for the treatment of mild to moderate UTIs caused by isolates with higher MICs of several fluoroquinolones needs to be re-validated based on more relevant clinical studies, prudent PK/PD considerations, and thorough study of the mutant prevention concentration of fluoroquinolones in the treatment of UTI. Furthermore, several main concerns with this approach (increased collateral damage and selection of fluoroquinolone resistance in the society) should also be meticulously investigated.

Conflicts of interest None of the authors have anything to declare.

References