

Do We Need PK/PD in the Treatment of Urogenital Infections?

Florian M.E. Wagenlehner*

Department of Urology, Pediatric Urology and Andrology of the Justus-Liebig-University, Giessen, Germany

Urogenital infections are very frequent infections, in the outpatient setting as well as in the health care associated setting and account for a large number of antibiotic administrations in the society. Increasing antimicrobial resistance rates are nowadays observed in uncomplicated and complicated Urinary Tract Infections (UTI), as well as in bacterial prostatitis. An important strategy to cope with this development is the development of an antibiotic stewardship policy with regards to decreasing antibiotic consumption, selecting antibiotic substances with little or no potency for collateral damage and decrease antibiotic selection pressure [1]. Pharmacokinetic/Pharmacodynamic (PK/PD) aspects in the treatment of urogenital infection are therefore becoming more and more interesting, important to optimize antibiotic treatment and to evaluate novel or unique antibiotic substances for therapy in these infectious entities.

PK/PD assessment in the treatment of infectious diseases is usually addressed by correlating the active serum concentration of an antibiotic (PK) with the pharmacodynamic (PD) *in vitro* antibacterial activity against a certain pathogen. This way of looking at the problem does however not necessarily reflect the antibacterial activity of a certain antibiotic substance at the site of the infection and its distinct immunological circumstances. Urogenital infections comprise a broad spectrum of infectious entities ranging from life threatening systemic diseases such as urosepsis or pyelonephritis, to local infections such as cystitis, to recurrent cystitis, and to prostatitis and epididymo-orchitis, exhibiting specific pharmacological and immunological properties.

In complicated cystitis the thresholds of AUC/MIC and C_{max}/MIC for predicting a microbiological cure are much lower than those in other kinds of infections. In particular, the C_{max}/MIC thresholds for Gram-positive cocci assessed in a clinical study were below 1 mg/liter [2]. This finding can be interpreted to mean that, in addition to its plasma concentration, the antibacterial activity in the urine plays a significant role in eradicating bacteria [2]. Comparable investigations for pyelonephritis are missing. Urine concentrations however need to be interpreted with caution, as there exists a significant adverse effect of urine on the antibacterial activity of an antimicrobial substance [3]. Furthermore the influence of the fluctuating pH on the antibiotic molecules in the urinary tract is also important [3]. In this respect Urinary Bactericidal Titers (UBT) and the area under the UBT time curve have been shown to correlate well with treatment results in complicated UTI [4].

The impact of the immune system in the different urogenital infections is another fairly unknown factor. The target PK/PD parameters for the treatment of complicated UTI therefore not necessarily need to meet target parameters for the treatment of uncomplicated cystitis.

It can be argued that the antibacterial activity of most antibiotics in the urine is generally high enough to ensure a high probability of cure, which would render specific PK/PD assessment for urogenital infections superfluous. This is however not true as the pharmacokinetic distribution of antibiotics is significantly different in the various urogenital organs. The prostate for example is characterized by low antibiotic concentrations compared to plasma with most antibiotic

substances [5]. PK/PD aspects are therefore even more important. PK/PD parameters in the treatment of chronic bacterial prostatitis have however been considered only in very few studies. It has been shown that in the treatment of chronic bacterial prostatitis with levofloxacin a satisfactory probability of cure can only be met, if the Minimal Inhibitory Concentrations (MIC) of the pathogens are below 1 mg/liter [6]. Therefore an MIC increase of causative pathogens even still below the defined threshold of resistance is clinically important in the treatment of chronic bacterial prostatitis, as it might result in treatment failure [6].

Additionally many forms of UTI exhibit complicating bacterial growth qualities, such as biofilm growth in complicated UTI or chronic bacterial prostatitis, and it is also discussed in certain forms of uncomplicated recurrent cystitis. The PK/PD targets to eradicate bacteria growing in biofilm are much different from those needed to treat planctonic growing organism and eradication is seriously deteriorated [7].

Specific evaluation of PK/PD in the different entities of urogenital infections would therefore allow for adequate dosing strategies in these distinct infectious entities. It will also allow selecting unique antibiotic substances only for specific infections such as uncomplicated cystitis, which is responsible for a large part of antibiotic administration in the society.

The evaluation of PK/PD parameter specific for urogenital infections therefore resemble an important aspect in the treatment of urogenital infections, which should be included in clinical studies in order to optimize dosing strategies and evaluate novel antibiotics for this indication.

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*Corresponding author: Florian M.E. Wagenlehner, Department of Urology, Pediatric Urology and Andrology, Justus-Liebig-University, Giessen, Rudolf-Buchheim-Str. 7, 35385 Giessen, Germany, Tel: +49-641/ 98544516; Fax: +49-641/ 98544509; E-mail: Wagenlehner@aol.com

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