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Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring

Impact of different pH levels on the pharmacodynamics of nitrofurantoin for pathogens involved in urinary tract infections

Fiona Fransen*[1], Claudia Lagarde[1], Maria Melchers[1], Joseph Meletiadis[2], Johan Willem Mouton[3]

[1]*Radboud University Medical Center Nijmegen, Department of Medical Microbiology, Nijmegen, Netherlands*

[2]*Erasmus MC, Department of Medical Microbiology and Infectious Diseases, Rotterdam, Netherlands*

[3]*Erasmus MC, Mmiz, Rotterdam, Netherlands*

Background:

Nitrofurantoin has been used for treatment of urinary tract infection for over 50 years. However, as an old drug, the pharmacodynamics (PD) of nitrofurantoin under physiological conditions have hardly been studied and are poorly understood. Several factors may influence antimicrobial activity in urinary tract infections like urine pH, we therefore determined the PD properties of nitrofurantoin at four different pH levels in urine against *E. cloacae, E. coli* and *K. pneumoniae* using time-kill assays

Material/methods:

Seven ESBL strains (4 *E. coli*, 2 *K. pneumoniae*,1 *E. cloacae*) and two ESBL negative strains (1 *E. cloacae,* 1 *K. pneumoniae*) with nitrofurantoin MICs 8-32 mg/L were used. Time-kill assays were performed at 4 pH levels (5.5,6.5,7.5 and 8.5) at 37°C during 24h at two-fold increasing concentrations from 0.125 up to 32xMIC. The kill rate (log_{10}CFU/mL x h^{-1}) was determined by linear regression analysis of the log_{10}CFU/ml data for the time interval of 1-6h. A sigmoidal *Emax* model with variable slope was used to fit the 6h kill rate-drug concentration data and the maximal kill-rate (*Emax*) as well as the concentration corresponding to 50% of *Emax* (EC50) was determined for each strain and pH.

Results:

The growth rates in the drug-free control as determined over the first 6h varied significantly between and within isolates for the different pH levels. For 6 strains a reduced growth rate between the -0.11 and 0.15 log_{10}CFU/ml x h^{-1} was observed at the highest pH level. Three strains (2 *K. pneumoniae* and 1 *E. coli*) were not able to grow at pH 8.5 and were (almost) dead at t24

For *E. coli* and *E. cloacae* strains were the pH did not affect growth, a >3log_{10}CFU/ml reduction was observed at 24h for concentrations 0.5-2xMIC at pH 5.5 whereas at higher pH slightly higher concentrations (1-4xMIC) were needed. In addition also a delay in killing was observed for some *E. coli/ E. cloacae* strains at higher pH levels compared to pH 5.5. No clear trend was observed in *K. pneumoniae.*

In the *Emax* model no apparent differences in mean maximum kill-rates were observed between the pH 5.5/6.5 or 7.5 (0.52 vs. 0.47 vs. 0.54)h^{-1}. However a higher nitrofurantoin concentration was needed to reach a 50% effect in pH level 8.5 as compared to pH levels 5.5/6.5. The mean EC50s were respectively for pH8.5 vs. 5.5/6.5 (116.44 vs. 13.98 mg/L) indicating an increased susceptibility to nitrofurantoin at lower pH levels.

Conclusions:

Urine pH had an effect in the growth of ESBL(+) bacteria with significant species- and isolate-dependent differences. Nitrofurantoin activity increased at lower pH levels. The efficacy of nitrofurantoin against urinary tract infections may be dependent on urine pH level and the pH susceptibility of the causative pathogen.