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Impact of urine and urinary pH levels on pharmacodynamics of nitrofurantoin

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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 in urine have hardly been studied and are poorly understood. We determined the PD properties of nitrofurantoin at four different pH levels in urine against Enterobacteriaceae using time-kill assays and compared these with earlier results in Mueller Hinton (MH).

Material/methods: In total 36 time-kill curves were performed in urine at 4 pH levels (5.5,6.5,7.5 and 8.5) at two-fold increasing concentrations from 0.125 up to 32xMIC. Seven ESBL strains (4 *E. coli*, 2 *K. pneumoniae*,1 *E. cloacae*) and two ESBL negative strains (*E. coli* and *E. cloacae,*) (MICs 8-32 mg/L) were used. The Δ $\log_{10}$ cfu/mL(change in $\log_{10}$ cfu/mL from initial inocula) at 6 and 24h were plotted against each $\log_{10}$ transformed concentration and analysed with nonlinear regression analysis using the sigmoidal *Emax* model with variable slope. Geometric mean(gmean) corrected for the MIC of the 50% effective concentration (EC50), stasis (no cfu reduction compared to initial inoculum) ,1- and 3 $\log_{10}$cfu/mL kill at 6 and 24 hours were calculated.

Results: The growth rates in the drug-free control as determined over the first 6h varied significantly between and within isolates for the different urine pH levels. The gmean growth rates in urine over the first 6h were low, 0.34, 0.36 and 0.30 $\log_{10}$CFU/ml/h for pH 5.5;6.5 and 7.5 respectively. A significantly lower rate was observed at pH 8.5 (0.082)(range -0.10-0.25)$\log_{10}$CFU/ml/h and three strains did not grew at all; they were (almost) dead at 24h. The growth rates in MH were rather similar

(0.54-0.65)$\log_{10}$CFU/ml/h and all strains grew well. In urine for *E. coli* strains that did grow, a significantly lower concentration was needed at pH levels (5.5 and/or 6.5) compared to 8.5 to reach either 50% effect, stasis or 1 log kill at 6 hours. In MH for almost all species and tested Emax output parameters, at 6h and 24h a strong decrease in concentration (trend) was observed with lower pH levels. Compared to all observations in MH independent of species, a less pronounced effect of pH was observed in urine.

Conclusions:

Higher urine pH had an negative effect on the max growth(rate),with significant isolate-dependent differences, while this was not the case for MH broth. In urine nitrofurantoin activity increased significantly only for *E. coli* at lower pH levels. However in MH this was also observed for the other species at 6- and 24h. Antibacterial effects in urine were significantly different from that in MH and are in general less pH dependent. Efficacy of nitrofurantoin in patients may be better than predicted from MIC testing in MH.