P-1392

Pharmacodynamics of nitrofurantoin against pathogens involved in urinary tract infections

Fiona Fransen,[1] Ria Melchers,[1] Joseph Meletiadis [2,3] Johan W.Mouton[1, 3]

[1]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Clinical Microbiology Laboratory, Attikon Hospital, University of Athens, Athens, Greece; [3]Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, The Netherlands

Introduction

Urinary tract infections are one of the most common human infections. Due to the progressive increase of ESBL producing bacteria and the unavailability of new antibiotics, re-evaluation of "old" antibiotics is needed to establish PK/PD relationships, optimization of dose and duration of nitrofurantoin therapy

Aim of the study

To determine the basic PD properties of nitrofurantoin against *E. coli*, *K. pneumoniae* and *E. cloacae* by in vitro time-kill assays

Methods

Strains

- Nine ESBL producing strains (6 *E. coli*, 2 *K. pneumoniae*, 1 *E. cloacae*) and one ESBL negative *E. cloacae* strain with nitrofurantoin MICs 8-32 mg/L.

Antibiotic and susceptibility testing

- Nitrofurantoin (CAS 67-20-9), solvent N'N-dimethylformamide, MIC determined by broth microdilution (ISO).

Time-Kill assay and Analysis

- Exposure to two- or four-fold concentrations ranging from 0.125 to 16 times the MIC, incubation in dark at 37 °C for 24h.
- The kill rate (log_{10} CFU/ML x h^{-1}) was determined by log-linear regression analysis for the time interval of 1 until 6 hours.
- A sigmoidal *Emax* model with variable slope was fitted the kill rate-drug concentration data and the PD parameters (max kill rate, Hill slope, concentration corresponding to 50% of maximal killing- EC50) were determined for each strain.

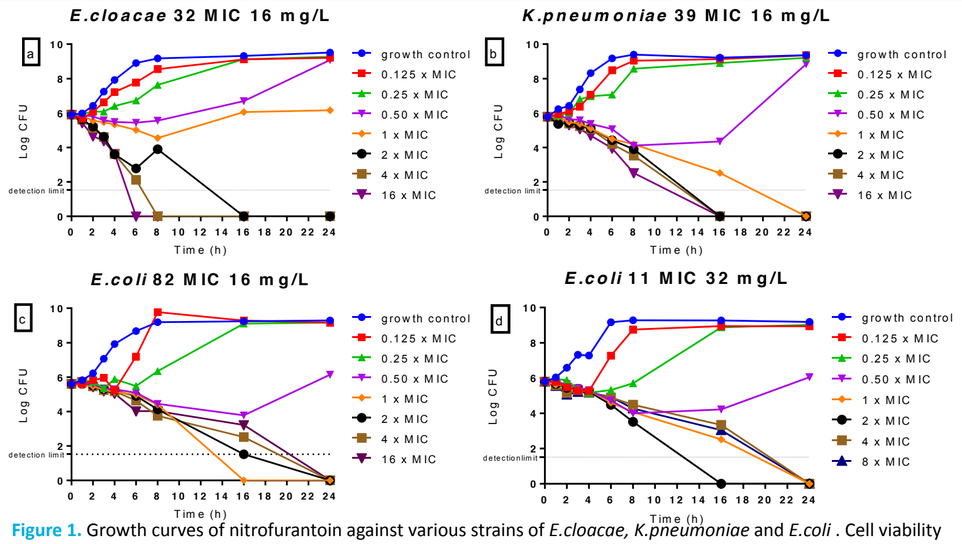

Figure 1. Growth curves of nitrofurantoin against various strains of *E.cloacae, K.pneumoniae* and *E.coli* . Cell viability (Log CFU) plotted for cultures grown at different concentrations of nitrofurantoin relative to strain-specific MICs. CFU: colony forming units.

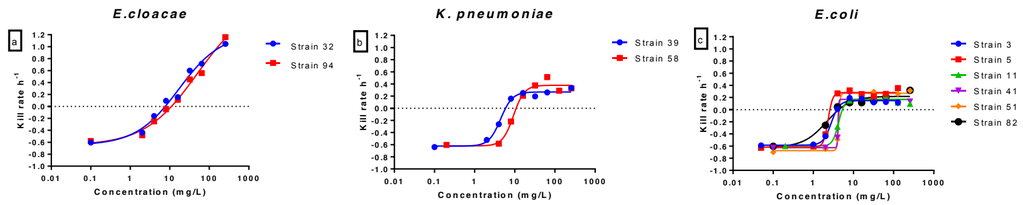

Figure 2. Best fitted sigmoid curves obtained from sigmoid maximum effect (*Emax*) model for *E.cloacea*, *K.pneumoniae* and *E.coli* exposed to nitrofurantoin between 1-6 hours.

Table 1: Parameter estimates, *Emax*, 50 % effective concentration (EC50), Hill's slope and R^2 derived from sigmoidal maximum effect model.

Species	*E. cloacae*		*K. pneumoniae*		*E. coli*					
Strains	Strain 94	Strain 32	Strain 58	Strain 39	Strain 82	Strain 51	Strain 41	Strain 11	Strain 5	Strain 3
MIC (mg/L)	16	16	32	16	16	16	16	32	8	8
Max killrate (h^{-1})	1.76	1.23	0.38	0.27	0.22	0.27	0.17	0.17	0.28	0.15
Species max killrate mean ± SD	**1.49 ± 0.27**		**0.32 ± 0.05**		**0.21 ± 0.05**					
Hill slope	0.65	0.81	3.19	2.97	1.49	21.32	45.67	5.80	7.72	4.26
Species Hill slope mean ± SD	**0.73 ± 0.076**		**3.08 ± 0.11**		**14.38 ± 15.35**					
EC50 (mg/l)	50.21	16.84	9.27	4.43	2.15	4.28	4.12	4.25	2.33	2.79
Species EC50 mean ± SD	**33.53 ± 16.69**		**6.85 ± 2.42**		**3.32 ± 0.92**					
R^2	0.989	0.986	0.977	0.990	0.962	0.995	0.979	0.976	0.991	0.993

Results

- Complete killing was observed after 16h for 2-16 x MIC for *E. cloacae* and *K. pneumoniae* but not for *E. coli.* Regrowth occurred after initial killing in all experiments for 0.50 x MIC (Fig. 1).
- Different killing patterns among the different species
  - In *E. coli* a maximal kill observed at relative low concentrations in a concentration independent manner (time dependent → b-lactam like) (Fig. 1C and D).
  - In *E. cloacae* concentration dependent killing was found (Fig. 1A).
- The highest killing rate was observed against *E. cloacae* followed by *K. pneumoniae* and *E.coli* (Fig. 2 and Table 1).
- The antibiotic concentration corresponding to 50% of maximal effect was lower in *E. coli* and *K. pneumoniae* and higher in *E. cloacae* (Table 1).

Conclusion

- **Nitrofurantoin was bactericidal against all species.**
- **High killing rates were observed against *E. cloacae* strains. The lowest killing rates were observed for *E. coli* strains.**
- **Kill patterns differed among species.**
  -Time-dependent vs. concentration-dependent killing
- **The species-dependent pharmacodynamic differences may have consequences on dosing frequencies against different pathogens.**

Acknowledgments

The AIDA project: preserving old antibiotics for the future, a 7th Framework Program (FP7) is funded by the European Union project number: 278348

Contact: jwmouton@gmail.com
Radboudumc, Nijmegen, The Netherlands

Erasmus MC University Medical Center Rotterdam

AIDA COOPERATION

Institute for Health Sciences
Radboudumc