Pharmacokinetic-pharmacodynamic analyses of oral antibiotics for pyelonephritis

JWS Cattrall[1*], IF Trocóniz[3], E Asín-Prieto[3], J Freeman[2], A Kirby[2]
Univ. of Leeds, UK [1]
Microbiology, Leeds Teaching Hospitals & Univ. of Leeds, UK [2]
Univ. de Navarra, ES [3]

Background

- Acute pyelonephritis often requires hospital admission incurring costs to both patients and health services.
- Increasing resistance within populations of the main aetiological organism, *E.coli*, complicates treatment.[1 2]
- International guidelines (IDSA, ESCMID) recommend management of pyelonephritis by oral ciprofloxacin empirically or with oral trimethoprim-sulfamethoxazole if susceptibility is known.[3] If no susceptibility data is available when using trimethoprim-sulfamethoxazole, or if local resistance to ciprofloxacin is over 10%, alternative intravenous (IV) antibiotics are recommended.
- A wide range of alternative oral antibiotics are known to have activity against *E.coli*, yet within international recommendations no comment is made on empirical treatment using many of these antibiotics as alternatives in pyelonephritis.[3]

Objectives

- To determine if there was a pharmacological basis on which non-IDSA/ESCMID guideline antibiotics could be considered for the treatment of acute pyelonephritis.

Methods

Selection of models

- A systematic literature search identified studies containing pharmacokinetic models for selected antibiotics (amoxicillin, amoxicillin clavulanate, cephalexin, ciprofloxacin, fosfomycin, nitrofurantoin, norfloxacin, trimethoprim, trimethoprim-sulfamethoxazole).
- Identified models were evaluated for robust development methodology using quantitative and qualitative methods:
  1) a numerical score: confidence-in-quality check based on key components (goodness-of-fit, software precision estimate, bootstrap analysis and simulation-based model diagnostics)
  2) reviewer assessment of quality (raw data fit and potential for extrapolation to relevant populations).
- Highest quality models were selected.
- Simulations were possible for n=5/10 antibiotics based on model quality (amoxicillin, amoxicillin clavulanate, cephalexin, ciprofloxacin, fosfomycin).

Methods

Bacterial isolates and MICs

- MICs were generated for antibiotics using ≈100 *E.coli* isolates from bacteraemic patients with pyelonephritis using an agar incorporation method (CLSI) and used in simulations with reference to published in vitro or clinical pharmacodynamic (PD) targets.

Outcome measures

- Probability of target attainment (PTA): The probability that the PD target is achieved at a given MIC.[4]
- Cumulative fraction of response (CFR): The expected population PTA for a specific drug dose and a specific population of bacteria.[4]

PK/PD simulations

- PK/PD simulations (R packages mlxR) used the Monte Carlo method and calculated areas under curves (AUC) and time above MIC (T>MIC) from concentration/time graphs.
- PTA was calculated for highest standard doses (BNF) and lowest dose to achieve PTA>90%. A CFR was also calculated for each antibiotic using both EUCAST sensitivity values and local MIC data collected in Leeds, 2016.
- Table 2 was generated by increasing doses by 10mg in each simulation until the target of 90% PTA was reached. Simulations were stopped at 10g.

Antibiotic	Highest standard dose (BNF)	Admin.	PTA (%) with MIC_{50}	PTA (%) with MIC_{90}	CFR MIC_{50} (local)	CFR MIC_{90} (local)	CFR whole pop. (local)	CFR for a EUCAST sensitive isolate
Amoxicillin	1000 mg	every 8 hours	0.3	0.3	0.207	0.207	0.207	0.479
Amoxicillin Clavulanate	500/125mg	every 8 hours	21.2	0.2	0.863	0.623	0.559	0.863
Cephalexin	1500 mg	every 6 hours	73	39.5	0.835	0.761	0.636	0.761
Ciprofloxacin	750 mg	every 12 hours	100 [a]	0 [a]	1.00	0.903	0.835	1.00
Fosfomycin	3000 mg	once only	100 [a b]	98.9 [a b]	1.00	0.994	0.938	0.947

Table1. PTA & CFR- highest standard doses (UTIs): [a] *CL_{CR} = 112.5 mL/min*, [b] *Body weight = 75 kg*

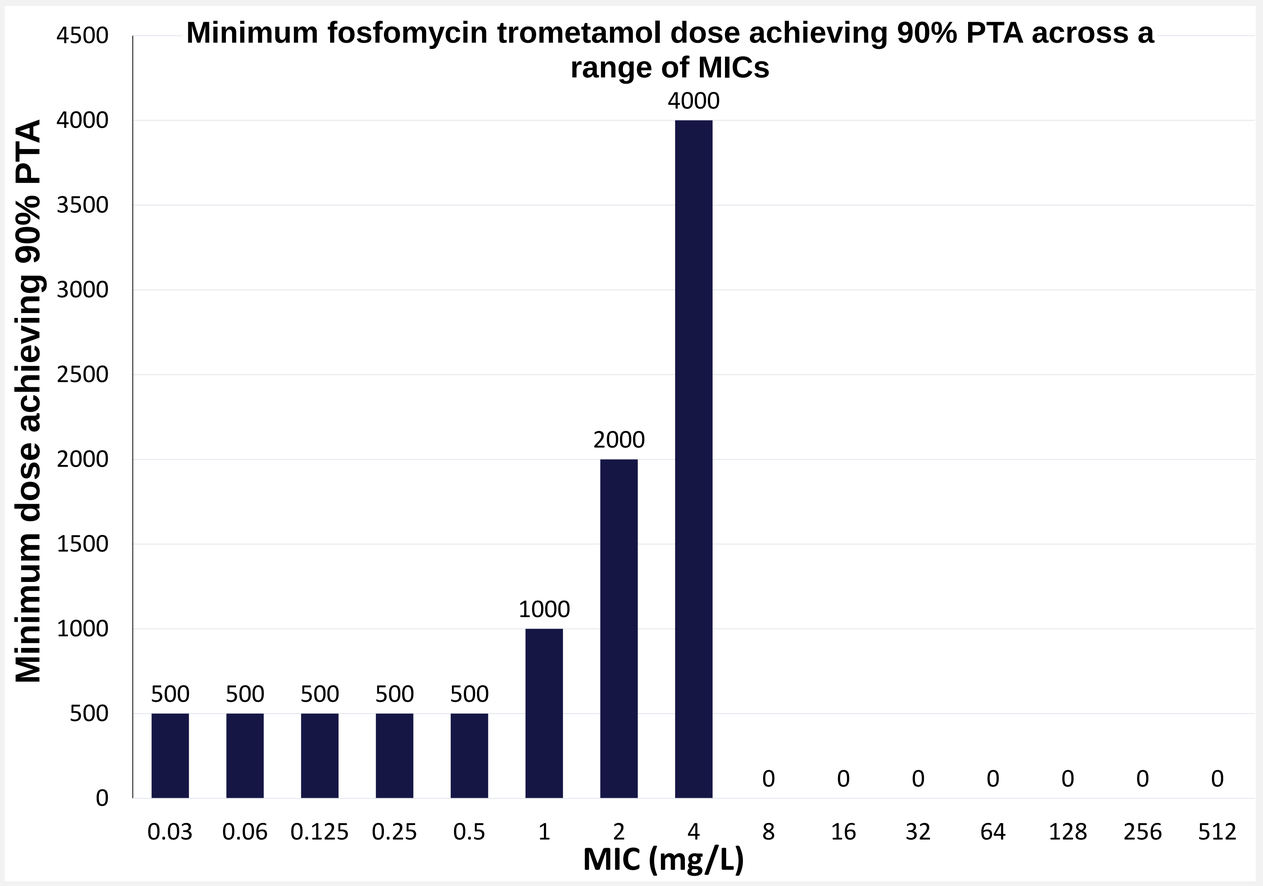

Figure 1. Describes simulation results for Fosfomycin trometamol using Leeds MIC data. It shows the minimum dose of Fosfomycin trometamol (once only) needed to achieve 90% PTA at each MIC.

Antibiotics	Admin.	Dose	PTA (%) MIC_{50}	Dose	PTA (%) MIC_{90}
Amoxicillin	every 8 hours	>10g	NA	>10g	NA
Amoxicillin Clavulanate	every 8 hours	2690mg	90.2	>10g	NA
Cephalexin	every 6 hours	2240mg	90.5	4420mg	90.6
Ciprofloxacin	every 12 hours	50mg	92.7 [a]	>10g	NA [a]
Fosfomycin	once only	490mg	92.4 [a b]	1930mg	90.3 [a b]

Table 2. Lowest doses achieving 90% PTA: [a] *CL_{CR} = 112.5 mL/min*, [b] *Body weight = 75 kg*

Results

Fosfomycin trometamol's simulated outcomes were promising. A 490mg fosfomycin dose achieved PTA=92.4% and a 1930mg dose achieved 90.3% using the MIC_{50} and MIC_{90} values respectively. A standard 3g dose also therefore produced high PTAs. The CFR values were also high using local MIC data and reached a CFR of 0.947 when including all isolates defined as sensitive by EUCAST. Amoxicillin, amoxicillin-clavulanic acid and cephalexin required higher than current standard doses to reach 90% PTA. Ciprofloxacin however had a high success rate (PTA=92.7%) at doses as low as 50mg twice daily when the MIC_{50} of the population studied was used; one tenth of the standard 500mg twice daily dose prescribed currently. The CFR results for ciprofloxacin were also high, including results for all isolates identified by EUCAST as sensitive (CFR=1.00). Table 1 shows the varying success rates for highest standard doses for these antibiotics. Table 2 shows the potential of each antibiotic varies with both the sensitivity of the isolate targeted, and the dose given, but all antibiotics excluding amoxicillin reached a PTA of 90% when doses were increased and when using the MIC_{50} in simulations.

Conclusions

- Fosfomycin model quality was high and PTA results promising. They suggest that once-only administration of fosfomycin may be an oral treatment for pyelonephritis with a high likelihood of clinical efficacy.
- There is potential for ciprofloxacin use at lower doses than currently administered.
- Additional pharmacokinetic analyses are required to produce high quality models in order to expand simulations to antibiotics for which simulations were not possible.

References

1. Prabhu A, Taylor P, Konecny P, Brown MA. Pyelonephritis: what are the present day causative organisms and antibiotic susceptibilities? Nephrology. 2013;18(6):463-7.
2. Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. Am J Infect Control. 2006;34(5 SUPPL.):20–8.
3. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical Infectious Diseases. 2011;52(5):103-20.
4. Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: An update. J Antimicrob Chemother. 2005;55(5):601–7.

***Corresponding author: um13jwsc@leeds.ac.uk**