How delayed or missed doses influence efficacy of amoxicillin in outpatients with community-acquired pneumonia: A pharmacokinetic/pharmacodynamic simulation analysis

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BACKGROUND

For outpatients with community-acquired pneumonia by *S. pneumoniae*, empirical therapy with amoxicillin (AMOX) in high doses is recommended [1]. Treatment needs to be effective against this microorganism and should take the local prevalence of resistance into account. Due to its short half-life, AMOX requires to be administered thrice daily, and that complicates treatment adherence. Poor compliance can result in failure to achieve optimum drug concentrations and this has been linked with reductions in clinical success rates and with the development of antibiotic resistance [2].

AMOX pharmacokinetic (PK) and pharmacodynamic (PD) characteristics condition the potential that delayed or missing doses will have consequences in its expected efficacy [3]. AMOX is a drug with dose-dependent absorption and is eliminated fundamentally by the kidney, with a clear correlation with creatinine clearance [4].

Because it is unethical to investigate the consequences of non-compliance in designed trials, simulation PK/PD outcomes is used instead [5] and presented here for AMOX.

PURPOSE

To evaluate the impact on efficacy of non adherence (irregular timing dose and missed dose) to treatment by AMOX 1000 mg thrice daily in outpatients with community-acquired pneumonia, based on simulation PK/PD analysis of AMOX.

METHODS

Plasma AMOX concentrations reported by Sjöval et al [6] after doses of AMOX were used as the data source for developing a dose saturable PK model for AMOX. The study was performed in a group of 12 non-obese healthy subjects (>18 years old). In this group, AMOX was given in single oral doses of 375, 750, 1500 and 3000 mg. Blood samples for AMOX were drawn just before dosing and 30, 45, 60 and 90 minutes and 2, 2.5, 3, 4, 6, 8 and 10 hours thereafter. The PK model was estimated using a mixed 1st and 0th order absorption monocompartment model. The PK model was parameterized in terms of PK parameters using NONMEM, ver 6 (Icon Development solutions, Elliot City, MD, USA). Clearance of AMOX is creatinine clearance-dependent, so this parameter was reparametrized as CL= THETA.Cl_{Cr}/102 [4,7,8].

Virtual outpatients (weight 70 kg) were simulated in subgroups according to age (young: 18-25 years; adults: 25-65 years; and elderly: 65-80 years) and interindividual variability in creatinine clearance (CLcr calculated according the Cockcroft-Gault formula), based on demographic characteristics and serum creatinine (Crs) (0.7-1.3 mg/dl).

Treatment control and non-compliance scenarios were applied in these virtual patients for a missed or delayed dose (1, 2, 3, 4, 6, 8 h delays), and the impact on drug exposure (target $fT_{>MIC}$) calculated for patient proportions (Monte Carlo simulations) as probability of target attainment (% PTA). MIC was obtained for *Streptoccoccus pneumoniae* from EUCAST [9]. Date of antimicrobial resistance surveillance in Europe (2014) were obtained [10].

The % PTA (50% $fT_{>MIC}$ as PK/PD predictor of antimicrobial efficacy), was calculated in each scenario, with a 90% clinical efficacy threshold [11] .

RESULTS

The estimated PK parameter values (CV%) were: absorption rate constant (Ka) (0.635 (15.7)), Delay to start of 0th order absorption (ALAG 2) (0.19 (38.7)), 0th order dose duration, D2 (1.44 (18.3)), and dose scaling on the 0th order dose fraction as F2*1-Dose/(KD+Dose), KD (1300 (58.2)), apparent volume of distribution (Vd/F) (22.8 (15.7)) and apparent clearance (CL/F) (15.5 (20)). Global pharmacokinetic parameters calculated for the model were in the range of those described for AMOX in the scarce literature [4,7,12,13].

Table 1. Population PK parameters estimated for AMOX age subgroups at 5 levels of serum creatinine*. Mean ± standard deviations.

Young Group

	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Cl_{Cr} (ml/min)	161 ± 5	141±5	125±4	113±4	86±4
CL/F (L/h)	24.6±4.5	21.6±4.0	19.2±3.5	17.2±3.2	13.2±2.5
V/F (L)	23.3±3.9	23.3±3.9	23.3±3.9	23.3±3.9	23.3±3.9
$t_{1/2}$ (h)	0.7 ±0.1	0.8 ±0.2	0.9 ±0.2	1 ±0.2	1.2 ±0.3

Adult Group

	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Cl_{Cr} (ml/min)	131 ±10	115±9	102±8)	92±7	70±6
CL/F (L/h)	20.1±4.0	17.6±4.0	15.6±3.1	14.1±2.8	10.8±2.1
V/F (L)	23.3±3.9	23.3±3.9	23.3±3.9	23.3±3.9	23.3±3.9
$t_{1/2}$ (h)	0.8 ±0.2	0.9 ±0.2	1 ±0.2	1.2 ±0.3	1.5 ±0.3

Elderly Group

	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Cl_{Cr} (ml/min)	87±5	76±4	68±4	61±3	47±1
CL/F (L/h)	13.4±2.5	11.7±2.2	10.4±2.0	9.4±1.7	7.2±1.4
V/F (L)	23.3±3.9	23.3±3.9	23.3±3.9	23.3±3.9	23.3±3.9
$t_{1/2}$ (h)	1.2 ±0.3	1.4 ±0.3	1.6 ±0.4	1.8 ±0.4	2.3 ±0.5

* Cl_{Cr} was calculated according the Cockcroft-Gault formula.

Table 2: Probability of attainment of target ratios of $fT_{>MIC}$ (% PTA) for AMOX administered 1000 mg thrice daily in control and delayed (1, 2, 3, 4 or 8h) dose regimen scenarios (MIC≤0.064 mg/ml)[1].

Group*					
	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Scenario	% PTA				
Control	100	100	100	100	100
Delayed 1-2-4-6-8h	100	100	100	100	100

*Results for Young, Adult or Elderly Group

[1]Countries with low *S. pneumoniae* resistance [10].

Table 3: Probability of attainment of target ratios of $fT_{>MIC}$ (% PTA) for AMOX administered 1000 mg thrice daily in control and delayed (1, 2, 3, 4, 6 or 8h) dose regimen scenarios (MIC≤1 mg/ml)[1].

Young Group

	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Scenario	% PTA				
Control	50	77	91	97	100
Delayed 1h	19	46	69	86	99
Delayed 2h	6	17	38	85	94
Delayed 3h	2	9	20	85	87
Delayed 4h	0.5	2	8	62	68

Adult Group

	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Scenario	% PTA				
Control	86	96	99	100	100
Delayed 1h	59	82	93	98	100
Delayed 2h	30	56	76	89	100
Delayed 4h	7	17	36	57	93
Delayed 6h	0.8	4	9	18	65
Delayed 8h	0.4	2	6	11	53

Elderly Group

	Serum Creatinine (mg/dl)				
	0.7	0.8	0.9	1	1.3
Scenario	% PTA				
Control	100	100	100	100	100
Delayed 1h	99	100	100	100	100
Delayed 2h	94	99	100	100	100
Delayed 4h	86	96	99	100	100
Delayed 6h	66	77	95	98	100
Delayed 8h	14	37	59	79	100

[1]Countries with *S.pneumoniae* resistance [10].

CONCLUSION

In non-adherent dosing scenarios for virtual outpatients of different age and physiological interindividual variability on serum creatinine, amoxicillin dose 1000 mg thrice daily achieved the PK/PD index guaranteeing clinical efficacy in community-acquired pneumonia for Countries with low *S. pneumoniae* resistance.

However, in countries with resistance problems, this dose regimen would be not always able to reach this target especially in young patients with a serum creatinine lower to 0.9 mg/dl.

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