Nonlinear absorption pharmacokinetics of amoxicillin

F. de Velde, B.C.M. de Winter, B.C.P. Koch, T. van Gelder, J.W. Mouton
Erasmus University Medical Center, Rotterdam, The Netherlands
On behalf of COMBACTE consortium

f.develde@erasmusmc.nl
Tel. +31-10-7033202

ICAAC ICC2015 San Diego, California | September 17–21

A-985

INTRODUCTION

Amoxicillin is an aminopenicillin that has been in clinical use for decades. Despite its abundant use, amoxicillin pharmacokinetics (PK) has been described in a few studies only. Some have shown nonlinearity in absorption[1-5]. A population PK model of oral amoxicillin tablets is not yet available. The aim of this study was to describe the population PK of oral amoxicillin with a focus on absorption and consequences for exposure.

METHODS

Re-used data of trial 25000/360 (Smith-Kline Beecham, 1994):

- 28 healthy male volunteers
- amoxicillin/clavulanic acid tablets on 2 days (randomized order) at the start of a meal with 200ml water:
  1. twice-daily (b.i.d.) 875/125mg or 500/125mg
  2. three-times daily (t.i.d.) 500/125mg or 250/125mg
- blood samples: 0,0.5,1,1.5,2,2.5,3,4,6,8,10,12 h (t.i.d. ≤8h)
- 140 concentration-time profiles with 1428 samples.

Non-compartmental PK analysis with PKSolver.

Population PK analysis with nonlinear mixed effect modelling: NONMEM 7.2 (FOCE+I). Model selection criteria: decrease in objective function value, diagnostic plots and visual predictive checks (VPC's). Comparison of:

- first-order / zero-order / Michaelis-Menten absorption
- lag-time / transit compartments
- with / without absorption storage compartment
- one / two distribution compartments.

A non-parametric bootstrap method was performed to obtain the 95%CI of each parameter.

Monte-Carlo simulations (n=5000) with several amoxicillin dosing regimens.

Table 1. Population PK parameters

Parameter	Estimate	95%CI	BSV (%)	95%CI
BIO (-)	0.7 (fixed)	–	35.1	29.2 – 71.6
MTT (h)	0.524	0.455 – 0.591	46.8	38.1 – 55.9
N (-)	4.41	3.29 – 8.20	112.7	73.5 – 130.1
Vm (mg/h)	1220	960 – 2036	31.9	21.5 – 120.0
Km (mg)	287	191 – 572	98.7	78.5 – 164.1
Vc (L)	27.7	25.0 – 29.6	34.4	26.4 – 70.9
CL (L/h)	21.3	20.1 – 22.2	25.8	17.0 – 66.7
Q (L/h)	1.70	1.07 – 3.03		
Vp (L)	3.02	2.48 – 3.89		
Add. error	0.0524	0.0406 – 0.700		
Prop. error	0.0824	0.0680 – 0.0931		

BIO: bioavailability
MTT: mean transit time to depot
N: number of transit compartments
Ktr: transit rate constant
Vm: maximal absorption rate
Km: amount corresponding to 50% Vm
Vc: central volume of distribution
CL: clearance
Q: intercompartmental clearance
Vp: peripheral volume of distribution

RESULTS

Non-compartmental PK analysis: Figure 1 shows a non-proportional increase in $AUC_{0\text{-}24h}$ to the dose. A dose-dependent saturation was also shown for C_{max}. T_{max} increased with rising doses. $t_{1/2}$ was comparable for the 4 doses.

Population PK analysis: Amoxicillin PK was best described by a transit compartment model[6] followed by Michaelis-Menten absorption, 2 distribution compartments and first-order elimination (figure 2). The PK parameters estimates and between-subject variability (BSV) are described in table 1. None of the (limited available) covariates were retained in the final model. A combined error model was used. The diagnostic plots and VPC's (figure 3+4) indicate a good predictive performance.

Monte Carlo simulations: Results shown in figure 5.

Adverse events: Diarrhoea was most frequently reported. The frequency declined with total daily doses (5, 4, 2, 2 events with 1750/250, 1500/375, 1000/250, 750/375 mg/day).

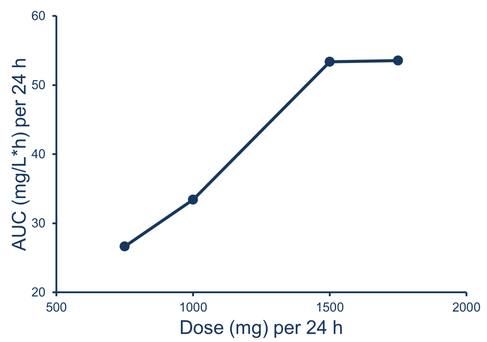

Figure 1. $AUC_{0\text{-}24h}$ vs. $dose_{0\text{-}24h}$

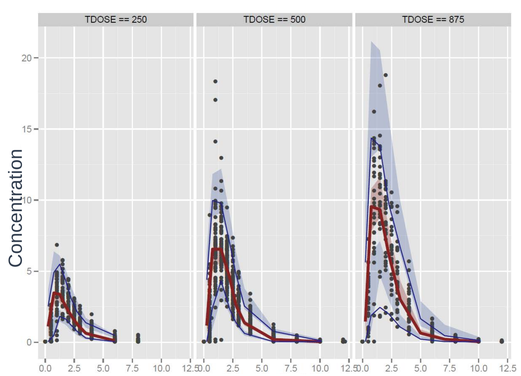

Figure 4. VPC's (per time dose)
red+blue lines: 50th, 5th,95th percentile of observations; *red+blue areas*: 95%CI of corresponding percentiles of predictions.

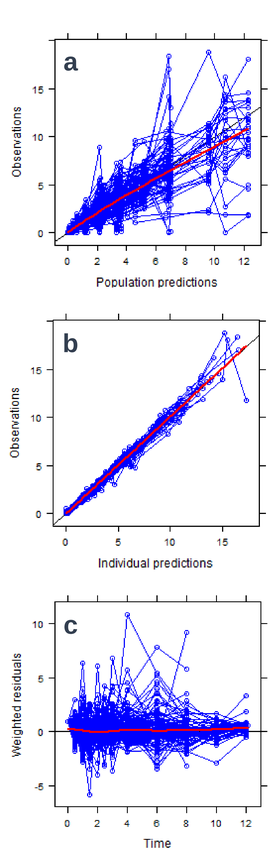

Figure 3a-c. Diagnostic plots

CONCLUSIONS

Amoxicillin absorption is dose-dependent and best described by a Michaelis-Menten absorption model. A saturable absorption may be wasteful in case of high doses and can lead to an increased risk of adverse events and disturbances in intestinal microflora[7].
Twice daily amoxicillin dosing is unfavourable to three- or four-times daily dosing. These results can be used for dose optimization and breakpoint setting.

REFERENCES

1. Bulitta J (2006). Thesis, Würzburg: 355-375.
2. Chulavatnatol S (1994). Br J Clin Pharmacol 38(3): 274-277.
3. Piotrovskij VK (1994). Pharm Res 11(9): 1346-1351.
4. Sjövall J (1985). Clin Pharmacol Ther 38(3): 241-250.
5. Spyker DA (1977) Antimicrob Agents Chemother 11(1): 132-141.
6. Savic RM (2007). J Pharmacokinet Pharmacodyn 34(5): 711-726.
7. Nord CE (1990). J Chemother 2(4): 218-237.

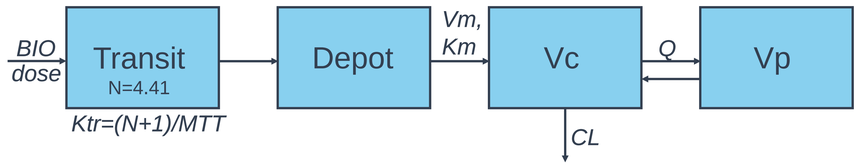

Figure 2. Schematic representation of the final model

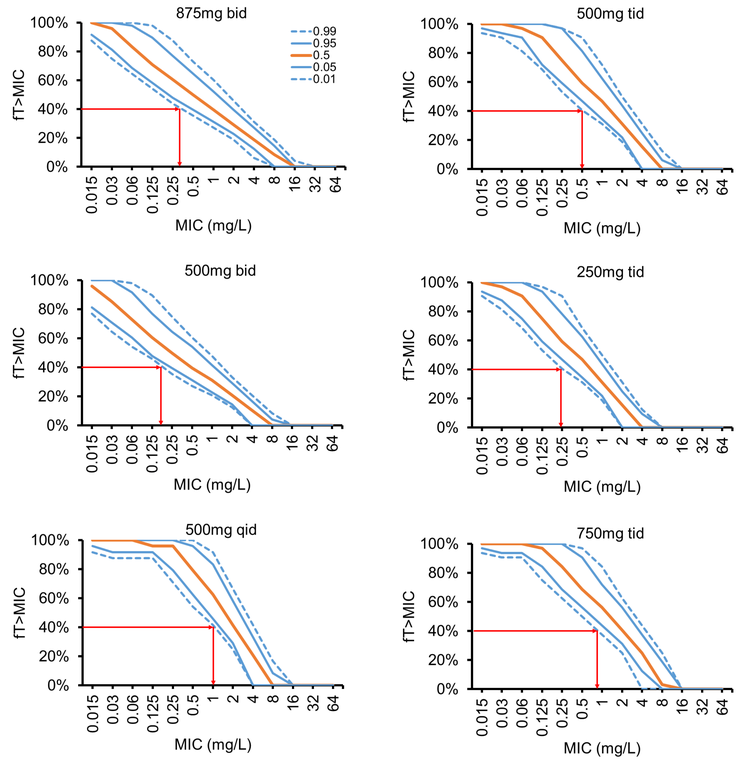

Figure 5. %fT>MIC vs. MIC for several dosing regimens

COMBACTE / STAT-Net is supported by IMI/EU and EFPIA