Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints

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Objectives: To describe the population pharmacokinetics of oral amoxicillin and to compare the PTA of current dosing regimens.

Methods: Two groups, each with 14 healthy male volunteers, received oral amoxicillin/clavulanic acid tablets on two separate days 1 week apart. One group received 875/125 mg twice daily and 500/125 mg three times daily and the other group 500/125 mg twice daily and 250/125 mg three times daily. A total of 1428 amoxicillin blood samples were collected before and after administration. We analysed the concentration–time profiles using a non-compartmental pharmacokinetic method (PKSolver) and a population pharmacokinetic method (NONMEM). The PTA was computed using Monte Carlo simulations for several dosing regimens.

Results: AUC_{0-24} and C_{max} increased non-linearly with dose. The final model included the following components: Savic's transit compartment model, Michaelis–Menten absorption, two distribution compartments and first-order elimination. The mean central volume of distribution was 27.7 L and mean clearance was 21.3 L/h. We included variability for the central volume of distribution (34.4%), clearance (25.8%), transit compartment model parameters and Michaelis–Menten absorption parameters. For 40% $fT_{>MIC}$ and >97.5% PTA, the breakpoints were 0.125 mg/L (500 mg twice daily), 0.25 mg/L (250 mg three times daily and 875 mg twice daily), 0.5 mg/L (500 mg three times daily) and 1 mg/L (750, 875 or 1000 mg three times daily and 500 mg four times daily).

Conclusions: The amoxicillin absorption rate appears to be saturable. The PTAs of high-dose as well as twice-daily regimens are less favourable than regimens with lower doses and higher frequency.

Introduction

Amoxicillin is an aminopenicillin that has been used to treat bacterial infections since the 1970s. It is frequently combined with the β-lactamase inhibitor clavulanic acid to target β-lactamase-producing strains. Either alone or in combination with clavulanic acid, amoxicillin was the most consumed antibacterial agent in primary care in two-thirds of the EU/EEA countries in 2012.[1]

In an era of increasing antimicrobial resistance and with few new drugs making it to the market, antibiotic use must be optimized in order to improve clinical outcomes of infections.[2] These clinical outcomes are dependent on the relationship between MIC, efficacy and exposure.[2] For β-lactams, the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with efficacy is the duration that the unbound concentration exceeds the MIC, expressed as a percentage of the dosing interval (%$fT_{>MIC}$).[3] The minimal PK/PD index value that ensures a high probability of successful treatment is the PD target.[4] The PD target

appears to be different for each β-lactam group (penicillins, cephalosporins and carbapenems).[5] For penicillins, the PD target is >30%–50% $fT_{>MIC}$, dependent on the microbial species and the choice of the antibacterial endpoint (i.e. the necessary %$fT_{>MIC}$ is larger for a 1 or 2 log bacterial kill than for a static effect).[3,5–8] While a high %$fT_{>MIC}$ is related to increased bacterial efficacy, an inadequate %$fT_{>MIC}$ is associated with emergence of resistance and selection of resistant strains.[5,8] To attain a specific PD target, the exposure of the microorganism to the antibacterial agent needs to be adequate. This exposure is dependent on the dose and PK properties of the drug.

Despite the abundant use of oral amoxicillin, the drug's PK has been described in only a few studies. While small-scale PK studies have shown amoxicillin to have a non-linear absorption profile,[9–14] it remains unclear how such non-linear absorption might influence the exposure of the various dosing regimens. At present, standard dosing regimens of oral amoxicillin in adults and children ≥40 kg vary between 750 and 3000 mg/day, divided into two to four

doses (e.g. 250, 500 or 1000 mg three times daily, 500 mg twice daily and 500 mg four times daily). For oral amoxicillin/clavulanic acid, standard dosing regimens are 500/125 mg three times daily or 875/125 mg twice or three times daily.

A population PK model can be used to estimate the exposure of various dosing regimens and variability of the antibiotic in the population. However, such a model is currently not available for oral amoxicillin in the literature. Monte Carlo simulations based on a population PK model can support recommendations for more-appropriate dosing regimens with a reduced likelihood of ineffectiveness and resistance (with too low doses) and adverse events (with too high doses).

Information about the PD target, PK, exposure, variability and dosing regimens is needed to set clinical breakpoints. Clinical breakpoints are MICs that define microorganisms as susceptible, intermediate or resistant to specific antibiotics.[4]

The purposes of this study were to estimate the exposure of various oral amoxicillin dosing regimens and the variability in the population, to compare the probability of PD target attainment of these dosing regimens and to suggest which clinical breakpoints would be justified for oral dosing. We therefore developed a population PK model using NONMEM and performed Monte Carlo simulations.

Methods

Study design and population

The study was designed as an open-label, randomized, two part, crossover investigation to study the PK of oral amoxicillin/clavulanic acid. Male volunteers were enrolled into the study if they were aged between 18 and 50 years and in good general health. Exclusion criteria were: >20% deviation from ideal weight for height; use of prescribed medication in the 2 weeks prior to the study (or 4 weeks for antibiotics); use of any medication during the study without consent; alcohol intake >3 U/day; participation in a trial within 2 months prior to the start of this study; prior hypersensitivity to the trial drug or to drugs with a similar chemical structure; diseases known to interfere with the drug PK; or blood donation of >1500 mL within the previous year.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Freiburg Ethics Committee (Freiburg, Germany). All volunteers gave written informed consent prior to the study. The study (reference number 25000/360)[15] was conducted in 1993 at FOCUS Clinical Drug Development GmbH (Neuss, Germany) under commission of SmithKline Beecham Pharmaceuticals (Harlow, UK).

Study procedures

The study consisted of two parts, each with two dosing regimens given for 1 day. The order of the dosing regimens was randomized and treatment days were separated by 6 or 7 days. In part 1, 16 subjects were allocated to amoxicillin/clavulanic acid at 875/125 mg twice daily and 500/125 mg three times daily. In part 2, 16 other subjects were assigned to 500/125 mg twice daily and 250/125 mg three times daily. Each dose was provided as a single amoxicillin/clavulanic acid tablet (Augmentin®, SmithKline Beecham Pharmaceuticals, Bristol, TN, USA). Doses were administered with 200 mL of water at the start of a standard meal. The first dose of each day was administered at 0800 h after having fasted from food and fluids from 2200 h the night before.

Blood samples were collected just before administration and after 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h (three times daily regimens until 8 h). Samples were frozen at −70°C within 1 h of sampling and were assayed within 6 weeks of collection. Amoxicillin plasma concentrations were determined by Hazleton Laboratories (UK) using the ASTED (Automated Sequential Trace Enrichment of Dialysates) system coupled to HPLC with ultraviolet absorbance detection. The lower limit of quantification was 0.1 mg/L.

PK analysis

Non-compartmental PK analysis of the plasma concentration–time data was performed using PKSolver[16] (version 2.0, China Pharmaceutical University, Nanjing, China). Population PK analysis was performed using non-linear mixed-effects modelling (NONMEM version 7.2, ICON Development Solutions, Ellicott City, MD, USA). The Intel Visual Fortran Compiler XE 14.0 (Santa Clara, CA, USA) was used. The first-order conditional estimation method with interaction was used throughout the model-building process. Tools used to evaluate and visualize the model were RStudio (version 0.98.1028), R (version 3.1.1), XPose (version 4.5.0) and PsN (version 4.2.0), all with the graphical interface Pirana[17] (version 2.9.0). Different absorption models (first-order, zero-order and Michaelis–Menten) with and without lag time or Savic's transit compartment model[18] were evaluated in combination with one- and two-compartment distribution models and an absorption storage compartment. Model selection criteria were a decrease in the NONMEM objective function value (OFV), goodness-of-fit plots and visual predictive checks (VPC). A decrease in the OFV of 3.84 U was considered statistically significant ($P < 0.05$) in a nested model.[19] For each VPC, a set of 200 simulated datasets was created to compare the observed concentrations with the distribution of the simulated concentrations (using the final model and parameter estimates). Between-subject variability was tested using an exponential variance model. Residual variability was evaluated with a combined (additive and proportional) error model.

From the available subject characteristics (age, height and weight), weight was selected to evaluate as a covariate. Dose was also evaluated as covariate. One covariate at a time was included using the likelihood ratio test. The covariate effect was considered significant at $P < 0.05$ (decrease in the OFV of 3.84 U).

The 95% CI of each parameter in the final model was determined from a non-parametric bootstrap analysis, in which the dataset was resampled 500 times.

Monte Carlo simulations

Monte Carlo simulations were performed using the final model in NONMEM. Eight amoxicillin dosing regimens were evaluated: 250 mg three times daily, 500 mg twice daily, 500 mg three times daily, 500 mg four times daily, 750 mg three times daily, 875 mg twice daily, 875 mg three times daily and 1000 mg three times daily. Five thousand subjects were simulated for each dosing regimen. For each simulated concentration–time profile, the %$fT_{>MIC}$ was calculated for MICs of 0.015–64 mg/L. The unbound amoxicillin concentration was calculated from the total concentration using a fixed value for protein binding of 20%.[20–22] The PTA was assessed for MICs of 0.015–64 mg/L.

Table 1. Characteristics of study population

Characteristic	Total ($n = 28$)	Part 1 ($n = 14$)	Part 2 ($n = 14$)
Age (years)	33 ± 7	35 ± 8	31 ± 6
Height (cm)	179 ± 6	179 ± 6	179 ± 7
Weight (kg)	77 ± 8	78 ± 5	77 ± 10
BMI (kg/m^2)	24 ± 2	24 ± 2	24 ± 2

Values are expressed as mean $\pm$ SD.

Table 2. Results of the non-compartmental pharmacokinetic analysis of amoxicillin

Dosing regimen amoxicillin/clavulanic acid	C_{max} (mg/L)	Dose normalized C_{max} (mg/L)/g	T_{max} (h)	AUC_{0-24} (mg·h/L)	Dose normalized AUC_{0-24} (mg·h/L)/g	$t_{1/2}$ (h)
250/125 mg three times daily	3.93 ± 1.13	15.74 ± 4.53	1.31 ± 0.33	27.29 ± 4.72	36.39 ± 6.29	1.13 ± 0.38
500/125 mg twice daily	7.17 ± 1.63	14.34 ± 3.26	1.40 ± 0.44	34.33 ± 7.12	34.33 ± 7.12	1.23 ± 0.33
500/125 mg three times daily	8.12 ± 2.71	16.25 ± 5.43	1.33 ± 0.38	54.67 ± 8.98	36.44 ± 5.99	1.11 ± 0.22
875/125 mg twice daily	11.21 ± 3.42	12.81 ± 3.91	1.52 ± 0.40	55.04 ± 12.68	31.45 ± 7.24	1.14 ± 0.21

Values are expressed as mean $\pm$ SD.

Results

Study population

Thirty-two healthy male volunteers (16 per part) entered the study. After two withdrawals (one because of diarrhoea and one due to personal reasons), amoxicillin plasma concentrations were determined in 30 volunteers (15 per part) completing both dosing regimens. PK could not be evaluated in one subject in part 1 due to very low plasma concentrations and in one subject in part 2 because of analytical interference. The characteristics of the 28 pharmacokinetically evaluable subjects are shown in Table 1.

Adverse events

Mild-to-moderate diarrhoea was the most frequently reported drug-related adverse event. The number of these events increased with total daily doses (1750/250 mg/day: five events; 1500/375 mg/day: four events; and 1000/250 and 750/375 mg/day: two each). In addition, mild abdominal pain and mild nausea were both reported once.

PK analysis

One hundred and forty amoxicillin concentration–time profiles (five profiles per subject) with a total of 1428 samples were analysed. The results of the non-compartmental PK analysis are shown in Table 2.

The increase in mean C_{max} and AUC_{0-24} was proportional to the daily dose for 750, 1000 and 1500 mg/day amoxicillin, but the mean AUC_{0-24} of 1500 mg/day was equal to 1750 mg/day and the mean C_{max} of 875 mg was lower than expected. T_{max} increased with rising doses. The $t_{1/2}$ was comparable for all four doses.

Population PK analysis showed that amoxicillin PK was best described by Savic's transit compartment model[18] followed by Michaelis–Menten absorption, two distribution compartments and first-order elimination (NONMEM subroutine ADVAN6 and TOL=5). A literature-based[20] fixed value of 70% for bioavailability was used because no PK data with intravenous administration were collected in this study. With each concentration–time profile analysed separately, variability was included for central volume of distribution, clearance, the parameters belonging to the transit compartment model and the Michaelis–Menten absorption parameters. Weight and dose didn't improve the model as a covariate and, therefore, were not included in the final model. A schematic representation of the final model is shown in Figure 1.

As shown in Table 3, the model-based parameter estimates were similar to the values computed from the bootstrap analysis, indicating the stability of the model.
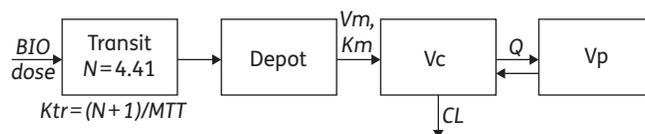
Figure 1. Schematic representation of the final model. BIO, bioavailability; MTT, mean transit time to depot; N, number of transit compartments; Ktr, transit rate constant; Vm, maximal absorption rate; Km, amount corresponding to 50% Vm; Vc, central volume of distribution; CL, clearance; Q, intercompartmental clearance; Vp, peripheral volume of distribution.

Table 3. Model-based population pharmacokinetic parameter estimates and values obtained after bootstrap analysis

Parameter	Final model estimate	Bootstrap median	Bootstrap 95% CI
Fixed effects			
BIO	0.7 (fixed)	0.7 (fixed)	—
MTT (h)	0.524	0.521	0.455–0.591
N	4.41	4.43	3.29–8.20
Vm (mg/h)	1220	1222	960–2036
Km (mg)	287	289	191–572
Vc (L)	27.7	27.2	25.0–29.6
CL (L/h)	21.3	21.2	20.1–22.2
Q (L/h)	1.70	1.75	1.07–3.03
Vp (L)	3.02	3.12	2.48–3.89
Between-subject variability (% CV)			
BIO	35.1	39.0	29.2–71.6
MTT	46.8	46.2	38.1–55.9
N	113	107	73.5–130
Vm	31.9	44.9	21.5–120
Km	98.7	110	78.5–164
Vc	34.4	36.5	26.4–70.9
CL	25.8	29.4	17.0–66.7
Residual variability			
additive	0.0524	0.0525	0.0406–0.700
proportional	0.0824	0.0809	0.0680–0.0931

BIO, bioavailability; MTT, mean transit time to depot; N, number of transit compartments; 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.

The goodness-of-fit plots in Figure 2 show that the model adequately described the observed concentrations. The VPC plots, presented in Figure 3, indicate a good predictive performance for each of the used doses of 250, 500 and 875 mg of amoxicillin.

Monte Carlo simulations

The results of the simulations, presented in Figure 4, showed that 100% of the population reached the PD target 40% $fT_{>MIC}$ for MICs up to 0.125 mg/L with all dosing regimens. For >95% PTA, the breakpoints were 0.125 mg/L (500 mg twice daily), 0.25 mg/L (250 mg three times daily and 875 mg twice daily), 0.5 mg/L

(500 mg three times daily) and 1 mg/L (750 mg, 875 mg or 1000 mg three times daily and 500 mg four times daily). Figure 5 shows the %$fT_{>MIC}$ as a function of the MIC for several dosing regimens. The breakpoints that correspond to the 95% CI (97.5% PTA) are the same as the aforementioned breakpoints for >95% PTA.

Discussion

Our population PK model includes a saturable absorption rate for amoxicillin, which corresponds to the non-linear and delayed absorption found in the non-compartmental analysis.
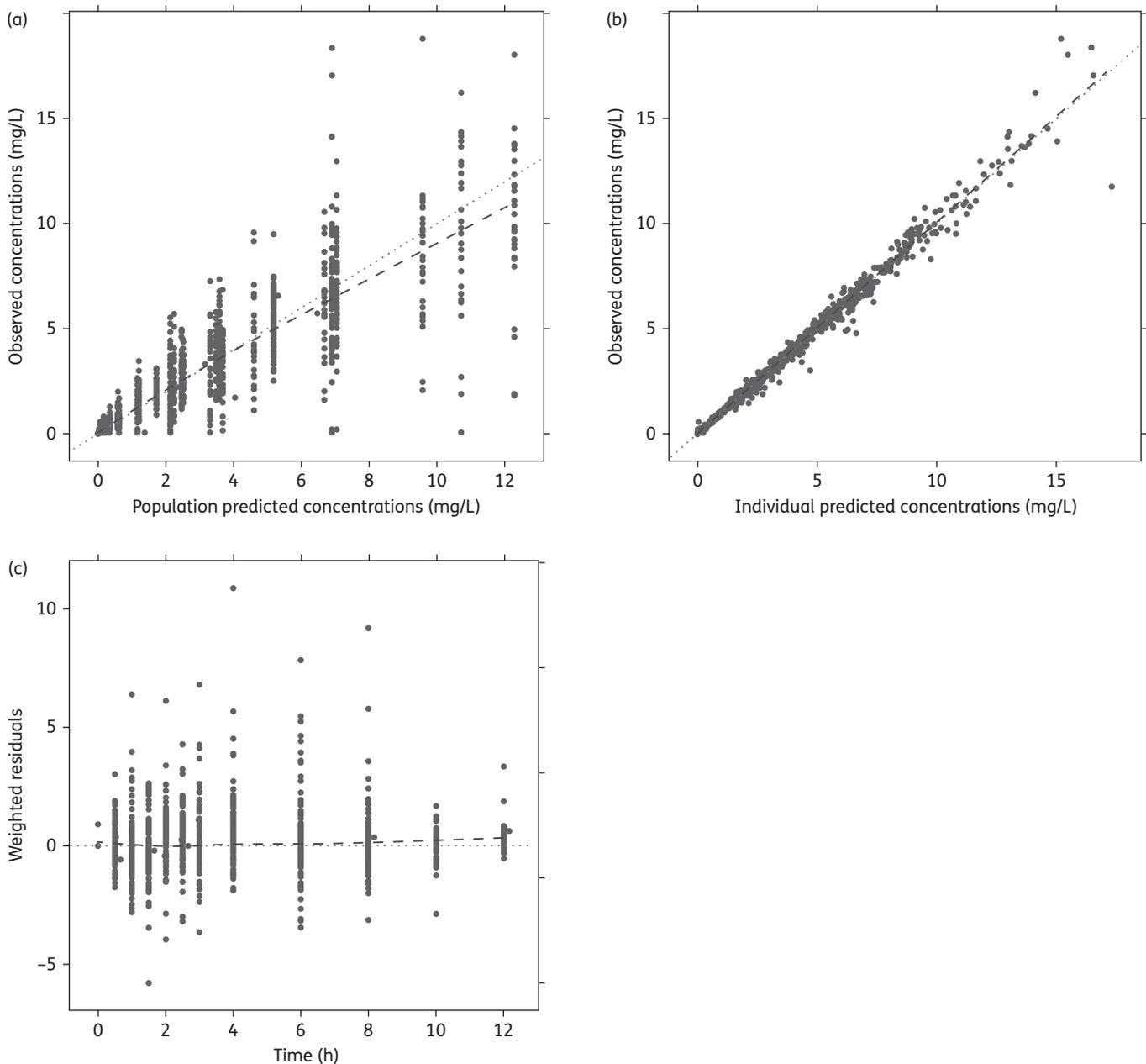
Figure 2. Goodness-of-fit plots for the final model. (a) Observed versus population predicted amoxicillin concentrations. (b) Observed versus individual predicted amoxicillin concentrations. (c) Weighted residuals versus time.
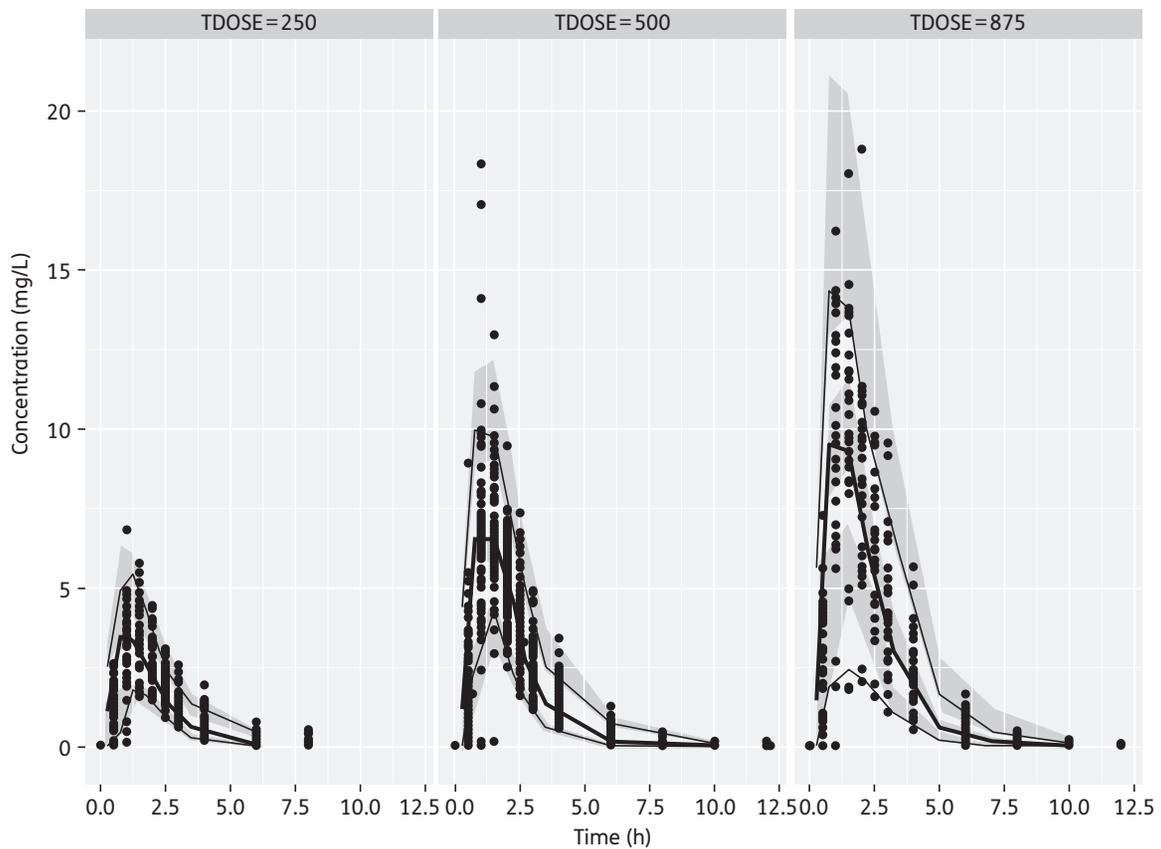
Figure 3. Visual predictive check stratified on dose (TDOSE). The solid circles are observed concentrations. The upper, middle and lower lines indicate the 95th, 50th and 5th percentile of observations, respectively. The shaded areas represent the 95% CI of the corresponding percentiles of predictions.
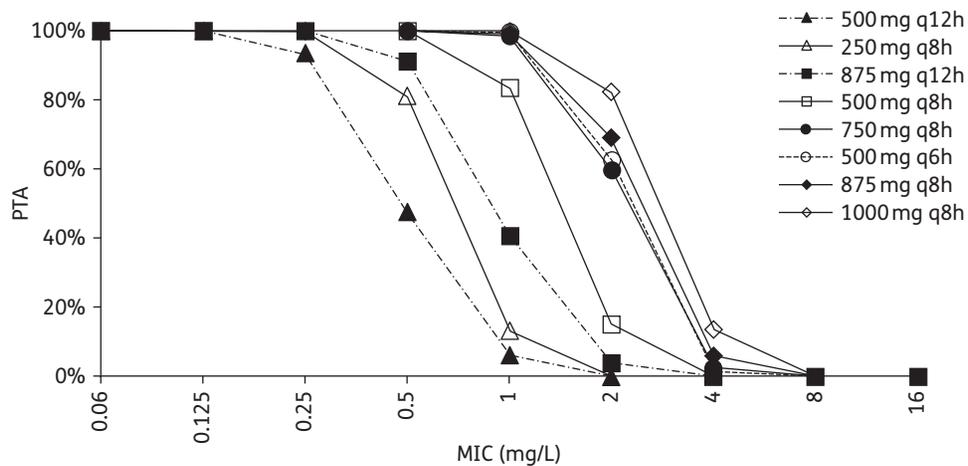
Figure 4. PTA for various amoxicillin dosing regimens to reach the pharmacodynamic target 40% $fT_{>MIC}$ for a range of MICs.

The findings of our non-compartmental and population PK analyses with rich data are similar to the smaller studies that previously reported the absorption PK of amoxicillin to be non-linear,[9–14] mostly based on non-compartmental analysis and standard two-stage methods.[9–13] Evidence for non-linear PK was provided by the fact that C_{max} and AUC were relatively low and T_{max} was later for increasing single doses up to 3000 mg.[9,10,12] Spyker et al.[9] showed a reduction in absorption rate for increasing single doses up to 1000 mg. In two studies with single doses up to 3100 mg, Michaelis–Menten parameters were used to describe the non-linear relationship between dose and the amount absorbed.[11,12] Two analyses that studied oral
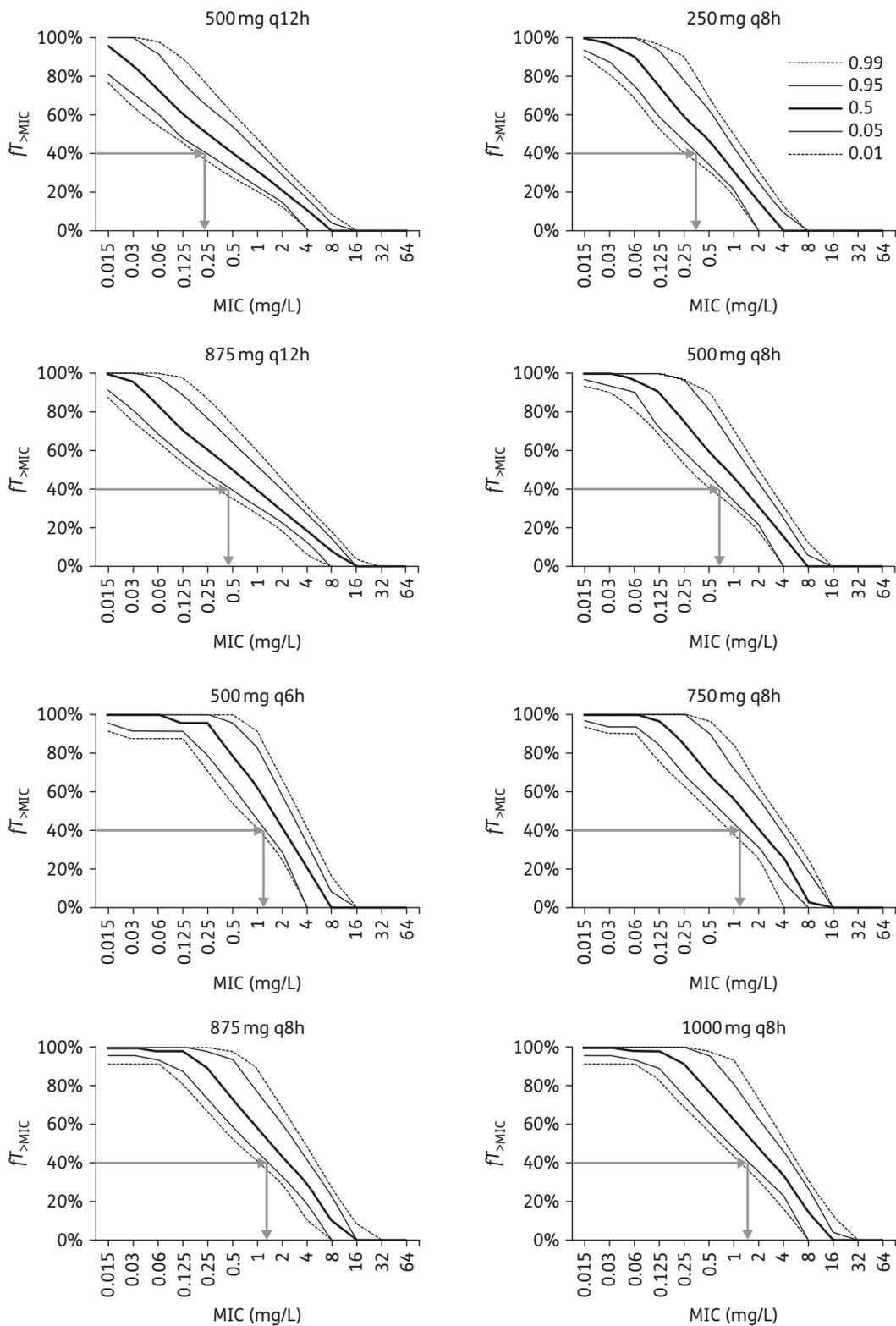
Figure 5. %$fT_{>MIC}$ displayed as a function of the MIC for several dosing regimens.

suspension data resulted in a time-constrained Michaelis–Menten absorption model with lag time followed by a storage compartment and two disposition compartments.[13,14] In our population

PK analysis, models with Michaelis–Menten absorption described the data better than models with first- or zero-order absorption, as expected given previous studies.[11–14] Similar to the two oral

suspension studies,[13,14] our model became better when we added a storage compartment. The absorption phase of our model further improved when we replaced the lag time with Savic's transit compartment model, which describes the absorption delay as a multiple step process represented by a chain of pre-systemic compartments.[18] Because the model with a combination of Savic's transit compartment model and a storage compartment was similar to the model with the transit compartment model alone, the final model only included the transit compartment model.

The non-linearity in C_{max} and AUC that was found in our study and those of others may potentially be explained by several factors other than absorption, such as disposition or clearance. However, a proportional increase in the AUC for increasing intravenous doses of 250–1000 mg[9,23] excludes the probability of non-linear disposition. Dose-dependent renal drug clearance is unlikely, because of the finding in our study that $t_{1/2}$ was stable throughout the dose range of our study as well as in another study with oral doses of 375–3000 mg.[12]

Regarding the influence of fasting/non-fasting on amoxicillin C_{max} and AUC, previous studies have shown results that contradict our results. SmithKline Beecham performed a study similar to ours in which oral amoxicillin/clavulanic acid was administered to fasting subjects[24] and which also demonstrated a non-linear increase in C_{max} and AUC_{0-24}. In this study with fasting subjects,[24] the amoxicillin C_{max} and AUC_{0-24} were lower than those in the here-presented SmithKline Beecham study in which the subjects were non-fasting. Indeed, the current instructions for use recommend that amoxicillin/clavulanic acid be taken at the start of a meal.[20] In contrast, Welling et al.[25] revealed that fasting subjects had higher amoxicillin serum levels than non-fasting subjects. These contrary results may be explained by the differences in the amounts of water with which the drug was administered, which could affect the dissolution of amoxicillin. The here-presented SmithKline Beecham study with non-fasting subjects used 200 mL of water for 250–875 mg of amoxicillin, compared with 120 mL for 250–875 mg in the other SmithKline Beecham study with fasting subjects[24] and 25–250 mL for 500 mg in the study of Welling et al.[25] This is evidenced by the fact that fasting subjects given a 500 mg dose had significantly lower amoxicillin serum levels when the water volume was reduced from 250 to 25 mL.[25] An in vitro study showed that the solubility curve of amoxicillin is U-shaped with a minimum of 5.5 mg/L at pH 5 and 37°C.[26] Since in our study the highest concentration was <5.5 mg/L (875 mg of amoxicillin administered with 200 mL of water results in a concentration of 4.4 mg/L), we do not expect that the amoxicillin solubility influenced drug absorption.

Non-linear absorption in human subjects has also been demonstrated for other aminopenicillins, such as ampicillin and bacampicillin.[12,27] Penicillins can be regarded as a dipeptide derived from cysteine and valine[12] and a rat model suggests that aminopenicillins are absorbed via intestinal dipeptide carrier-mediated transport.[28] The amoxicillin absorption percentage from rat small intestine decreased with increasing concentrations, which indicates a saturable rate-limiting step in the absorption process.[29]

Our final population PK model includes a Michaelis–Menten equation for absorption, which indicates that the absorption rate is saturable. This finding corresponds to the non-linear and delayed absorption shown in the non-compartmental analysis. Despite the non-proportional increase in C_{max}, the dosing simulations demonstrate that increasing the dose results in a larger $\%fT_{>MIC}$, which is explained by the delayed absorption. However, high doses may increase the risk of adverse events and of disturbances in the intestinal microflora.[30] In our study, the frequency of diarrhoea tended to increase at higher daily doses of amoxicillin, which may be explained by the higher amount of unabsorbed antibiotic.[30] Sjövall et al.[12] described an increased number of adverse events at higher single doses of amoxicillin. In another study,[31] high doses of clavulanic acid were related to upper digestive adverse events, but the amounts used (750 mg/day) were much higher than those currently used (maximal 500 mg/day). The daily clavulanic dose in our study seems to be so low (250–375 mg/day) that it is not likely to be the cause of the diarrhoea. We did not found any correlation between diarrhoea and daily clavulanic acid amounts.

The $\%fT_{>MIC}$ also becomes larger when the frequency of dosing increases. On the other hand, less-frequent dosing can lead to a too low $\%fT_{>MIC}$, which reduces the probability of antimicrobial efficacy and may contribute to the development of resistance. The balance between dose and frequency should be optimal to maximize antimicrobial efficacy and to minimize the risk of adverse events. For example, the breakpoint of 250 mg three times daily is similar (0.25 mg/L) to that of 875 mg twice daily, based on 95% CI and 40% $fT_{>MIC}$. The first regimen with a lower dose and a higher frequency is preferred to the second regimen with a higher dose and a lower frequency, because both the daily dose and the dose taken at one time of the first regimen are lower, which appears to reduce the risk of adverse events. In the case of regimens with a high dose and low frequency that have the same breakpoint as regimens with a lower dose and higher frequency, high doses are wasteful. It is not possible to recommend a maximal dose using the current data of 1750 mg/day and 875 mg/dose, because the non-proportional increase in C_{max} did not reach a plateau.

The view that amoxicillin/clavulanic acid at 500/125 mg three times daily is interchangeable with 875/125 mg twice daily should be reconsidered, because the target attainment and therefore the breakpoint of the twice-daily regimen is lower than the three times daily regimen (0.25 mg/L versus 0.5 mg/L based on 95% CI and 40% $fT_{>MIC}$).

The current EUCAST PK/PD non-species-related breakpoints for amoxicillin are based on an $fT_{>MIC}$ target of 30%–40% and a PTA >90%, which resulted in susceptible ≤2 mg/L (500 mg three times daily) and resistant >8 mg/L (1000 mg three times daily).[6] These amoxicillin breakpoints are based on intravenous administration. The acceptance level of PTA is still under debate and PTA values of 99%, 95% and 90% have all been used. In the majority of the present rationale documents for EUCAST breakpoints, the $\%fT_{>MIC}$ as a function of the MIC is displayed with CIs. CIs of 99%, 95%, 90% and 80% correspond to PTAs of 99.5%, 97.5%, 95% and 90%, respectively.[4] Most current EUCAST PK/PD breakpoints for β-lactams (e.g. piperacillin/tazobactam, ceftazidime and meropenem) are based on the 95% CI (i.e. 97.5% PTA). In this paper, we used a 40% $fT_{>MIC}$ target and a 95% CI to simplify the comparison of dosing regimens. Obviously, the PK/PD breakpoint for oral amoxicillin is lower than that for intravenous administration due to a bioavailability of ~70%.[20] A 95% CI of 500 mg three times daily results in a breakpoint of 0.5 mg/L for 40% $fT_{>MIC}$.

While our study describes the population PK of amoxicillin administered with clavulanic acid, we expect that the results of amoxicillin alone are similar, as others have shown.[32]

This study has a number of limitations. First, only a few covariates were available and creatinine data were lacking. However, the participants were healthy volunteers with normal renal function. Since oral amoxicillin or amoxicillin/clavulanic acid is mostly prescribed to patients with only relatively mild infections and normal renal function, the results of our study can be extrapolated to such patients. A second limitation is that the current model is only suitable for single doses, because we analysed each concentration–time profile separately. Incorporation of between-occasion variability was not successful. If a multiple dose model were to be developed, an output from the depot compartment should be considered to prevent possible accumulation of non-absorbed amoxicillin. Our population PK model is based on single doses up to 875 mg for which concentrations are measured 12 h after administration. Because the maximum simulated dose of 1000 mg is just slightly higher than 875 mg and the interval between doses never exceeds 12 h, we assume that the extrapolation is justified.

In conclusion, the amoxicillin absorption rate appears to be saturable, which results in a non-linear increase in C_{max} and a later T_{max} for higher doses. Increasing the dose results in a larger $\%fT_{>MIC}$ due to this delayed absorption, despite the non-proportional increase in C_{max}. However, a higher dose increases the risk of adverse events. A smaller interval between doses leads to a larger $fT_{>MIC}$ as well. The balance between dose and frequency should be optimal to maximize antimicrobial efficacy ($fT_{>MIC}$) and to minimize the risk of adverse events. Clinicians should take care when prescribing oral amoxicillin regimens with high doses as well as those involving twice-daily doses.

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