High-Dose Amoxicillin Pharmacokinetics (PK) and Pharmacodynamics (PD) in Children

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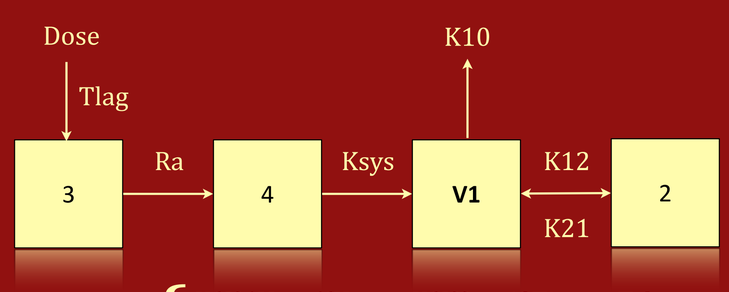
Objectives

- We are unaware of any published PK data addressing oral amoxicillin (amox) doses >25 mg/kg in children.
- Since amox absorption is saturable,[1,2] we wished to estimate the percentage of the dosing interval that the plasma amox concentration would exceed *S. pneumoniae* (pneumococcal) breakpoint minimum inhibitory concentrations (T>MIC), and the percent of children with the target T>MIC of at least half the dosing interval after various amox doses, up to the commonly used daily dose of 90 mg/kg.

Methods

- We adapted a published adult four-compartment model (**Figure 1**) with saturable, delayed, time-limited amox absorption through an absorptive compartment into a central compartment with linear elimination and transfer to/from a peripheral compartment.[1,2] The original model was derived from 6 adult patients first given a single dose of amox 500 mg IV, with intensive 10-hour post-dose PK sampling. A two-compartment model was fitted to the data. Each subject was then given single oral amox doses of 500 mg and 3000 mg with the same sampling after each dose as for the IV dose. The order of oral doses was random and separated by a week minimum. For the oral model, volume and inter-compartmental rate transfer constants were fixed for each participant according to their estimates from the IV model.
- We log-transformed and allometrically scaled the reported model parameters as the initial ranges prior to fitting the data. No parameter in our model was fixed, including volume.
- Individual data after oral dosing from the original study were used to fit the model using non-parametric methods implemented in MM-USCPACK (available from www.lapk.org), with standard visual/numerical checks.
- Upon comparison of model-simulated profiles with published Cmax and AUC ranges for doses of 15 and 25 mg/kg in children,[3] volume and elimination terms were multiplied by population-constant age functions to accurately simulate the adult and pediatric data.
- Finally, single-dose T>MIC were simulated in 1000 representative 15 month, 12 kg children for varying amox doses and dose intervals.



$$Ra = \begin{cases} X(3)*Vma/(Kma + X(3)) & \text{if Time} < Tabs \\ 0 & \text{if Time} \geq Tabs \end{cases}$$

$$AgeMult1 = \begin{cases} 3.5 & \text{if} \leq 2 \text{ years} \\ 3.5 - 1.25*Age & \text{if} > 2 \text{ to} \leq 20 \text{ years} \\ 1 & \text{if} > 20 \text{ years} \end{cases}$$

$$K10 = K10s / (AgeMult1*kg^{0.25})$$

$$dX(1)/dt = Ksys*X(4) - (K12 + K10)*X(1) + K21*X(2)$$
$$dX(2)/dt = K12*X(1) - K21*X(2)$$
$$dX(3)/dt = -Ra$$
$$dX(4)/dt = Ra - Ksys*X(4)$$

OUTPUT

$$AgeMult2 = \begin{cases} 4.5 & \text{if} \leq 2 \text{ years} \\ 4.5 - 0.175*Age & \text{if} > 2 \text{ to} \leq 20 \text{ years} \\ 1 & \text{if} > 20 \text{ years} \end{cases}$$

$$Y(1) = X(1) / (AgeMult2*V1s*kg)$$

Figure 1 - Structural model and defining equations.

Results

Parameter	Fitted	Published[1]
Tlag (h)	0.04 (0.01 - 0.11)	0.09
Tabs (h)	2.59 (1.91 - 3.36)	1.72
Tabs - Tlag (h)	2.51 (1.80 - 3.32)	1.60
Ksys (h^{-1})	1.10 (0.82 - 2.97)	1.31
Kma (mg)	864.39 (341.16 - 2286.17)	1077
Vma (mg/h)	1056.70 (841.00 - 1862.80)	1407
Vma/Kma (h^{-1})	0.98 (0.69 - 3.52)	1.78
V1s (L/kg)	0.11 (0.10 - 0.12)	0.15*
K10s ($kg^{*}h^{-1}$)	5.86 (5.59 - 7.03)	4.48*
K12 (h^{-1})	0.81 (0.51 - 1.04)	1.11
K21 (h^{-1})	0.92 (0.87 - 1.08)	1.31

Table 1 - Median (interquartile) parameter estimates for the population model compared with those in the published reference study of 6 adults. *Assuming weight of 70 kg and age ≥20 years, which were not reported.

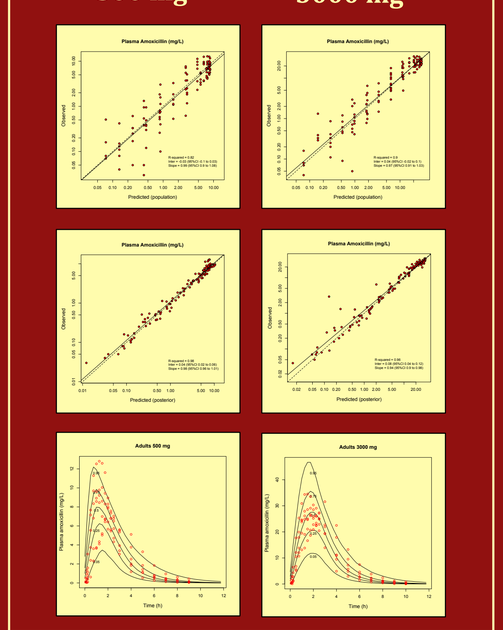
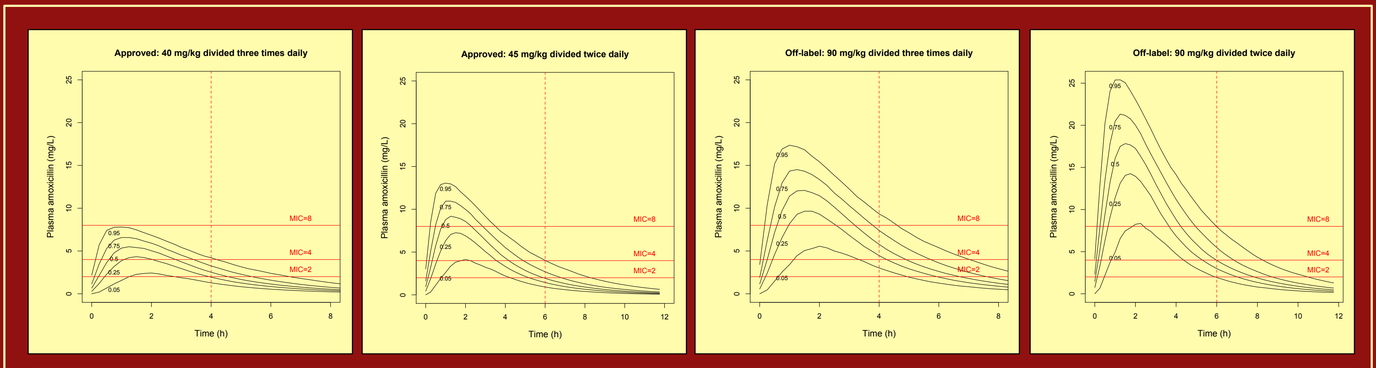


Figure 2 - Observed vs. population (top) or Bayesian posterior (middle) predicted plots. Visual predictive check (bottom).

Group	Cmax (mg/L)		AUC_{0-12} (mg*h/L)	
Adult, 3000 mg [1,2]	Sim: 29.5 (11.0) Obs: 26.8 (3.9), n=6	P=0.55	Sim: 96.2 (28.8) Obs: 91.0 (17.0), n=6	P=0.44
Adult, 500 mg [1,2]	Sim: 8.4 (2.6) Obs: 8.8 (1.8), n=6	P=0.71	Sim: 24.4 (6.1) Obs: 25.0 (3.0), n=6	P=0.24
Child, 15 mg/kg [3]	Sim: 6.6 (1.8) Obs: 6.9 (3.0), n=27	P=0.40	Sim: 25.7 (6.5) Obs: 24.9 (9.6), n=26	P=0.53
Child, 25 mg/kg [3]	Sim: 10.7 (3.0) Obs: 10.6 (5.1), n=23	P=0.87	Sim: 42.6 (10.8) Obs: 44.1 (24.6), n=22	P=0.50

Table 2 - Numerical predictive check comparing simulated (Sim) vs. observed (Obs) maximum amox concentration (Cmax) and area under the time-concentration curve (AUC) for varying doses with a dose interval of 12 hours in adults and children. Observations are taken from referenced studies, with the number (n) of participants in each group indicated. Simulations for children were done using a weight of 12 kg and an age of 15 months.



MIC	T>MIC	T>MIC≥50%	T>MIC	T>MIC≥50%	T>MIC	T>MIC≥50%	T>MIC	T>MIC≥50%
2	53 (15) %	64%	47 (11) %	39%	79 (14) %	99%	63 (12) %	91%
4	28 (14) %	4%	32 (10) %	3%	58 (15) %	75%	48 (11) %	41%
8	1 (3) %	0%	14 (9) %	0%	33 (15%)	10%	32 (10) %	3%

PRIMARY OUTCOME - The first two graphs show the model-simulated distribution of amox concentrations for FDA-approved dosing, followed by two distributions for off-label dosing at 90 mg/kg/day. Reference lines are drawn at non-meningitis MIC breakpoints for IV penicillin (≤2 susceptible; 4 intermediate; ≥8 resistant) and 50% of the dosing interval. The resistance breakpoint for oral penicillin is ≥2. The table indicates the mean (SD) percentage T>MIC and percent of 1000 simulated profiles with T>MIC for at least half of the dosing interval.

Conclusions

- We extended a published adult model of saturable oral amox absorption to children.
- Simulation from the model suggests that amox plasma exposure in children is dose proportional at least to a dose of 45 mg/kg. At a median dose of 864 mg (Kma), bioavailability is expected to be 50% of maximal.
- A resistance breakpoint of ≥2 mg/L for oral amox is appropriate at approved doses (40-45 mg/kg/day).
- With a higher daily dose of 90 mg/kg, by percentage target attainment of a T>MIC for at least half the dosing interval, more resistant organisms could likely be treated, especially with dosing three times daily.
- Confirmation of this simulation study is desirable.

References

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Acknowledgements/Declarations

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