Modeling the permeability of fosfomycin into abscess fluid

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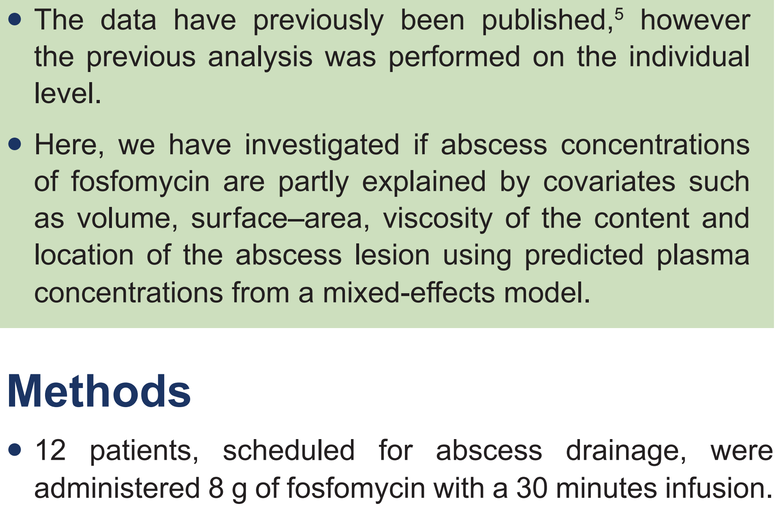
Background

- Explaining the observed effects of a drug as a function of plasma concentrations is a generally accepted approach in pharmacokinetic-pharmacodynamic modeling.
- As most drugs do not exert their effect in plasma, the actual concentration in the target tissue is assumed to be approximately the same as in plasma. How well this assumption holds true depends on the distribution of drug to the target tissue, which is among other things dependent on the location of the target tissue.
- For drug treatment of infectious diseases where lesions are formed (*e.g.* tuberculosis and abscesses), the penetration of the drug into the lesions is crucial for the success of the treatment.
- If the concentrations in the lesions are sub-therapeutic, there is a risk of development of resistance to bacteria, besides the obvious risk of treatment failure.
- In tuberculosis, it has been suggested that lesion size, location, structure, and cellular/acellular content may contribute to the reported low penetration of drugs into lesions.[1–4]
- Abscess lesions are similar to tuberculosis lesions in structure and content with an outer fibrotic wall, an inner layer of leukocytes and a necrotic core.
- The objective of this analysis was to describe the plasma and abscess concentrations of fosfomycin in single dosed patients.
- The data have previously been published,[5] however the previous analysis was performed on the individual level.
- Here, we have investigated if abscess concentrations of fosfomycin are partly explained by covariates such as volume, surface–area, viscosity of the content and location of the abscess lesion using predicted plasma concentrations from a mixed-effects model.

Methods

- 12 patients, scheduled for abscess drainage, were administered 8 g of fosfomycin with a 30 minutes infusion. This infusion was initiated at different time points before their surgery, ranging from 17 min to almost 4 h pre-surgery.
- Repeated plasma concentration measurements were made. One concentration measurement was also available in the drained pus.
- The pharmacokinetics of fosfomycin 8 g has previously been reported described using a two-compartment model. To predict the abscess concentrations, an additional effect compartment was added to the two-compartment model. The model is schematically depicted in **Figure 1**.

Figure 1. *A two-compartment model was used to describe the pharmacokinetics of plasma for fosfomycin, while an effect compartment was used to mimic any diffusion hindrance resulting in delayed absorption of fosfomycin into abscess*



R0, the infusion rate; Q, the inter-compartmental clearance; CL, the elimination clearance

- The effect compartment was used to mimic diffusion hindrance as may be observed with drug penetration into abscess lesions. The resulting three compartment model is described in Eq. 1, in which C_{plasma}, $C_{peripheral}$ and $C_{abscess}$ are the concentrations measured in central, peripheral and abscess compartments, respectively, with C_{plasma} and $C_{peripheral}$ calculated as A_{plasma} divided by V_{plasma}, and $A_{peripheral}$ divided by $V_{peripheral}$, respectively. R_0 is the infusion rate, Q, the inter-compartmental clearance, CL, the elimination clearance, and k_{lesion}, the equilibration rate constant.

$$dA_{plasma}/dt = R_0 \cdot Dose - Q \cdot C_{plasma} + Q \cdot C_{peripheral} - CL \cdot C_{plasma}$$

$$dA_{peripheral}/dt = Q \cdot C_{plasma} - Q \cdot C_{peripheral} \quad \text{..... Eq. 1}$$

$$dC_{abscess}/dt = k_{lesion} \cdot [C_{plasma} - C_{abscess}]$$

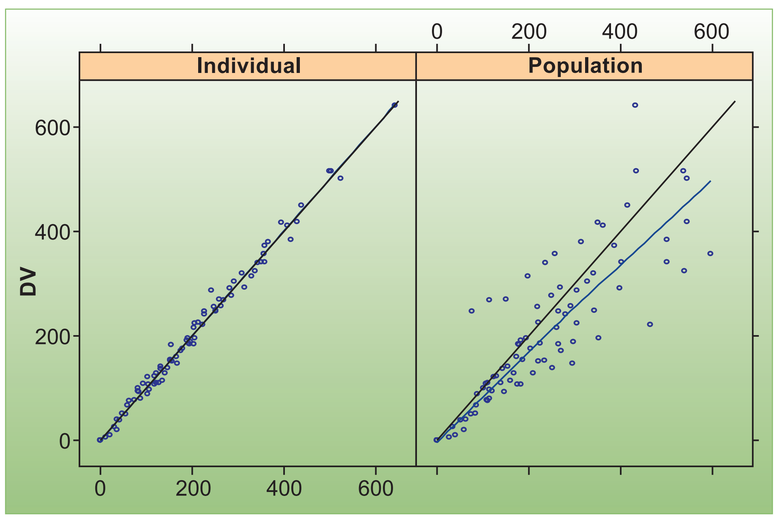
- All analyses were conducted using the FOCE-INTER method in NONMEM[6] version VI (Globomax Corp., Hanover, MD, USA) and model fit was assessed using the likelihood ratio test (LRT), goodness of fit-graphs available in Xpose4[7] and bootstrap confidence intervals (CI) based on 2000 bootstrap samples.
- In the previous analysis of this data, abscess lesion concentrations were modeled using the diffusion equation presented by Barza and Cuchural,[8] described in Eq. 2 with C_{plasma} being the individual predicted concentrations based on the individual fit, P, the estimated permeability of drug into the lesion, and V and A, the measured volume and surface–area of the abscess, respectively. This approach was also applied for comparisons.

$$dC_{abscess}/dt = P \cdot \frac{A}{V} \cdot [C_{plasma} - C_{abscess}] \quad \text{..... Eq. 2}$$

Results

- Plasma concentrations of fosfomycin 8 g were well described using a two-compartment model including log-normally distributed IIV on clearance/central volume and the peripheral volume **(Figure 2).**

Figure 2. *Goodness of fit-graphics for the final model showing the observed plasma concentrations vs. the individual and population predictions of plasma concentrations*



- The IIV for clearance and volume of the central compartment were modeled with a full correlation, estimating only the scaling of the volume IIV relative to the clearance IIV.
- The previously reported high IIV[5] was quantified with the use of the population analysis approach. A median-centered linear relationship between creatinine clearance and elimination clearance was also included in the model.
- Originally, the model included both an additive and a proportional residual error term, but as the proportional error term was estimated to a negligeable low value, this parameter was removed. Parameter estimates with CIs based on 2000 bootstrap samples are given in **Table 1**.
- With only one observation of lesion concentration per individual, no IIV on k_{lesion} can be estimated. Thus, the whole IIV of permeability depends on the IIV of plasma. A separate residual error term for the abscess lesions was investigated, however it was not supported by the data.

Table 1. *Parameter estimates of the final model*

Parameter	Estimate	Estimate 90% CI*
Plasma PK		
CL (L/h)	0.0968	0.0632:0.130
*V*1 (L)	10.1	5.36:14.8
Q (L/h)	0.256	0.152:0.360
*V*2 (L)	9.80	5.70:13.9
CLCR-CL	0.0141	0.00769:0.0205
Ω^2-CL	0.238	0.00647:0.470
Ω^2-V2	0.197	-0.0658:0.460
Scaling of Ω-V1	1.64	1.06:2.22
Abscess PK		
k_{lesion} (h^{-1})	0.000221	-0.0000887:0.00053
Residual error		
Additive (mg/L)	15.2	5.69:24.7

* based on 2000 bootstrap samples.

- According to the LRT volume and surface-area were significant covariate relationships at a 5% level **(Table 2).**
- However, CI from the bootstrap included zero for all covariate relationships. Also, no visual improvement was observed (results not shown). Also supporting the exclusion of these covariates was the small difference in parameter values for the individuals with the highest and the lowest volume and surface area, respectively.
- However, with only 12 individuals the discrepancy between the LRT and the bootstrap CI is not surprising as we are expecting a selection bias.[9]

Table 2. *Change in objective function value (OFV) with inclusion of covariates on k_{lesion}*

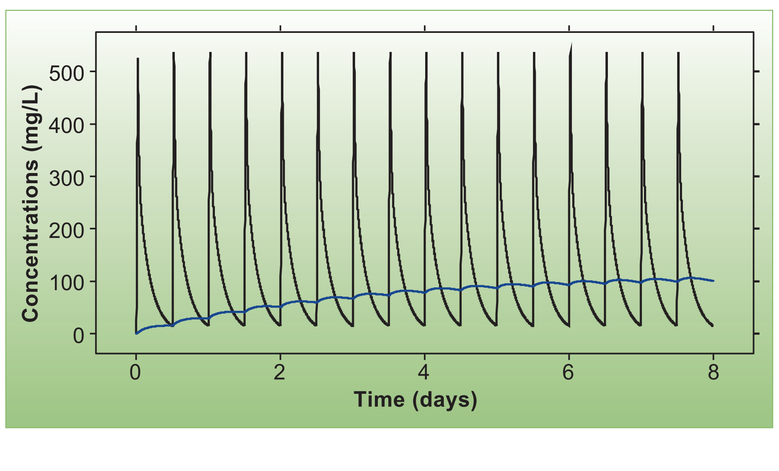
Covariate	ΔOFV*	90% CI**
Volume *(V)*	-25	-5.2:7.0
Surface area *(A)*	-5.3	$-4.0 \cdot 10^{-5}$:$4.4 \cdot 10^{-5}$
A/V	-2.3	$-1.4 \cdot 10^{-3}$:$1.1 \cdot 10^{-3}$
location (well- *vs.* poorly-perfused)	-0.22	-0.33:5.0
content (viscous *vs.* liquid)	-0.029	-9.2:12

*difference between objective function value of the basic model without the covariate and the full model including a linear relationship with the covariate median centered.

**based on 2000 bootstrap samples.

- When comparing the effect compartment model (Eq. 1) and the diffusion model (Eq. 2), the effect compartment model gave much lower OFV and in general a more stable model.
- The equilibrium between plasma and lesion is slow, and it will take almost seven days to reach equilibrium, also shown in the predictions of repeated dosing (**Figure 3**).

Figure 3. *Predicted concentrations in central compartment (black line) and in lesions (blue line) after repeated administration of fosfomycin*



Conclusions

- Plasma concentrations of fosfomycin 8 g were well described using a population analysis approach.
- No covariates were concluded to be significant for inclusion into the model of abscess concentrations on basis of goodness of fit and bootstrap distribution.
- The IIV was quantified for the plasma pharmacokinetics but no IIV could be included for the permeability into lesions, *i.e.* on k_{lesion}
- This population analysis approach may be well suited for analysis of other lesions, such as tuberculosis lesions.

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References

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