Comparison of elimination and absorption pharmacokinetics of linezolid in cystic fibrosis patients

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Introduction

In the population of cystic fibrosis (CF) patients, morbidity and mortality is most often due to pulmonary infections by *P. aeruginosa, H. influenzae* and *S. aureus* [1]. Linezolid (LZD), the first agent of oxazolidinone antibiotics, shows *in vitro* activity against these pathogens and excellent penetration into pulmonary fluid, rendering it to a widely used therapeutic option in CF patients [2]. Because of altered pharmacokinetic (PK) behaviour of several antibiotics in this population, especially in absorption and elimination processes [3] and a postulated LZD clearance (CL) decreasing over time [4], development of a reliable and plausible PK model is desirable. The objective of this analysis was to compare six developed or published PK models for LZD [4-7] in terms of adequately reflecting measured concentration-time profiles in CF patients and their predictive performance.

Materials and Methods

Study characteristics

In a prospective, single-center, randomised, cross-over study 8 (1 female) cystic fibrosis patients (median (range): age 25 yr (23–47 yr), height 170 cm (152–183 cm), weight 63.4 kg (52.3–93.6 kg)) were enrolled for PK analysis. Data were collected after 600 mg twice daily p.o. and i.v., single and multiple dose administration [8]. Data were analysed using validated HPLC method [9].

Population PK modelling

For PK analyses 315 plasma samples were available (range: 0.32–45.4 µg/mL). Model comparison was performed using the nonlinear mixed-effect modelling approach implemented in NONMEM™ (Version VI; FOCE Interaction). Statistical and graphical data analyses were performed using R 2.11.1 and MS Excel 2010. Model comparison was guided by the Akaike information criterion (AIC) [10] for non-nested models, goodness of fit (GOF) plots, comparison of precision and plausibility of parameter estimates as well as visual predictive checks (VPC).

Results

Elimination and absorption process modelling strategy

Based on a 2-compartment disposition PK model, four key models with various elimination processes were compared (Fig.1). After selection of the final elimination model the absorption process after p.o. dosing was investigated introducing a transit compartment model (TA) [7] or a lag-time model (ALAG). Central and peripheral volumes of distribution (V2, V3), intercompartmental clearance (Q), absorption rate constant (k_a) and bioavailability (F1) for p.o. data were estimated in all compared models.

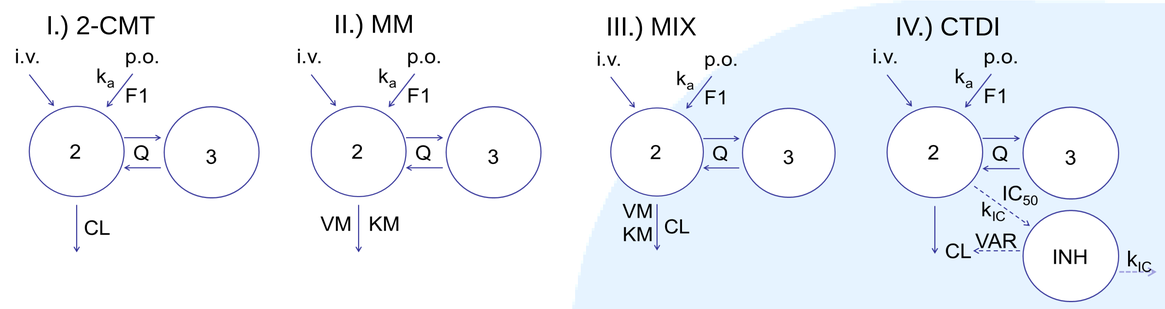

Figure 1: Schematic structur of I) classical, linear elimination 2-compartment (2-CMT) model, II) nonlinear Michaelis-Menten-type elimination (MM) model, III) parallel linear and nonlinear elimination (MIX) model and IV) elimination dependening on a concentration-time profile in a theoretical inhibition compartment (CTDI) model. VM: Maximum elimination rate, KM: Michaelis-Menten constant, k_{IC}: Rate constant for transfer to the inhibition CMT, IC_{50}: Concentration of LZD in inhibition CMT inhibiting 50% max. CL, VAR: Maximum fraction of CL that cannot be inhibited

Goodness of fit

GOF plots (Fig.2) indicated that MM and MIX models overpredicted data observed in high concentration ranges in contrast to 2-CMT and CTDI models which depicted a more random distribution and closer scattering of predictions vs. observations around the line of unity. In direct comparison to 2-CMT model, CTDI model was overall able to better predict observed concentrations especially for the female patient. Thus, TA and ALAG models were introduced in the CTDI model. In contrast to the CTDI ALAG model the CTDI TA model overpredicted the measured concentrations around C_{max} after p.o. dosing, indicating that the ALAG model better described the absorption process.

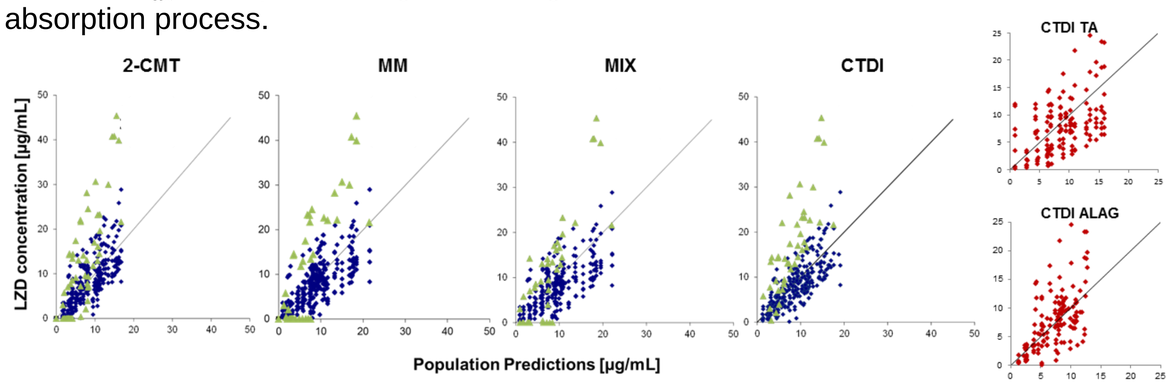

Figure 2: GOF plots of the final models; green: female; blue: male, red: p.o. dose only

Akaike information criteria, precision and plausibility of parameter estimates

The final model estimates are summarised in Tab.1. Comparison of AIC values for examined models revealed the lowest AIC value (779) for CTDI model compared to other elimination models (819-1080). In addition, the ALAG model statistically significantly improved the AIC of the CTDI model (OFV>13.82, df=2, p=0.001). The estimated value of CL in the MIX model, of VAR (including IIV on VAR) in the CTDI TA model and of Q, V2 and V3 in the 2-CMT model deviated from the reference values reported in the literature [11]. The proportional errors of MM and MIX models were higher than those in the others. Precision of parameter estimates were in comparable and acceptable ranges across the 2-CMT, MM, CTDI and CTDI ALAG models except the IIV on ALAG. In contrast the MIX and CTDI TA model imprecisely estimated some parameters. In total, the CTDI ALAG model described the data best regarding the AIC and the plausibility of the parameter estimates.

Table 1: Parameter estimates (RSE%) and AIC of all investigated structural models

Model	Units	2-CMT	MM	MIX	CTDI	CTDI ALAG	CTDI TA
Parameter		841	1067	915	816	779	-188*
Fixed effects							
CL	[L/h]	5.52 (18)	--	0.39 (52)	8.92 (18)	8.83 (16)	6.99 (9)
V2	[L]	45.0 (11)	25.3 (4)	31.1 (24)	26.7 (7)	23.7 (6)	28.9 (19)
V3	[L]	79.0 (26)	29.5 (34)	25.9 (25)	17.5 (38)	22.2 (14)	18.1 (39)
Q	[L/h]	2.35 (9)	99.1 (35)	60.1 (124)	104 (18)	96.0 (24)	50.4 (117)
k_a	[1/h]	2.04 (30)	2.57 (18)	1.63 (43)	1.89 (11)	2.36 (37)	2.22 (21)
F,%		78.0 (11)	88.0 (12)	87.1 (3)	85.7 (10)	81.2 (10)	-
k_{IC}	[1/h]	-	-	-	0.0005 (FIX)	0.0005 (FIX)	0.0005 (FIX)
IC_{50}	[mg/L]	-	-	-	0.36 (30)	0.43 (29)	0.37 (19)
VAR,%		-	-	-	33.8 (34)	27.2 (26)	7.80 (98)
VM	[µg/h]	-	51.8 (5)	44.0 (FIX)	-	-	-
KM	[µg/mL]	-	1.16 (37)	0.65 (41)	-	-	-
MTT	[h]	-	-	-	-	-	0.48 (7)
NN	-	-	-	-	-	-	47.4 (44)
ALAG	[h]	-	-	-	-	0.32 (43)	-
Between-patient variability	[%CV][a]						
ωCL		54.4 (40)	92.5 (100)	-	45.8 (40)	44.8 (48)	79.5 (43)
ωV3		59.5 (42)	-	103 (104)	85.2 (67)	61.8 (61)	61.2 (99)
ωVAR		-	-	-	91.1 (77)	94.0 (50)	440 (195)
ωF		27.7 (68)	12.4 (43)	12.2 (47)	23.0 (50)	25.0 (47)	-
ωV2		28.8 (43)	-	-	-	-	-
ωk_a		73.8 (65)	-	70.1 (127)	-	-	-
ωMTT		-	-	-	-	-	25.8 (31)
ωALAG		-	-	-	-	42.9 (242)	-
Residual variability							
$\sigma_{proportional}$	[%CV][a]	24.1 (18)	35.6 (15)	36.9 (14)	22.4 (19)	21.7 (13)	29.8 (17)
$\sigma_{additiv}$	[µg/mL]	-	-	-	-	0.0001 (FIX)	0.0001 (FIX)

[a] $\sqrt{\omega^2 \cdot 100}$, *non comparable due to log transformed data for model stability, MTT= mean transit time, NN= number of transit-compartments

Visual predictive check

VPC were generated for the i.v. and p.o. multiple dosing (MD) by simulation of 1000 profiles. Fig. 3 shows that the median concentration-time course was overpredicted by MM and MIX compared to the observed median suggesting that the central tendency (CT) was not adequately described. The 2-CMT model were comparable to the CTDI model for i.v. dosing, but inferior for p.o. dosing. The VPC of the ALAG model better reflected CT and variability than the TA model. In summary, VPC suggested that the predictive performance of the CTDI ALAG model was best.

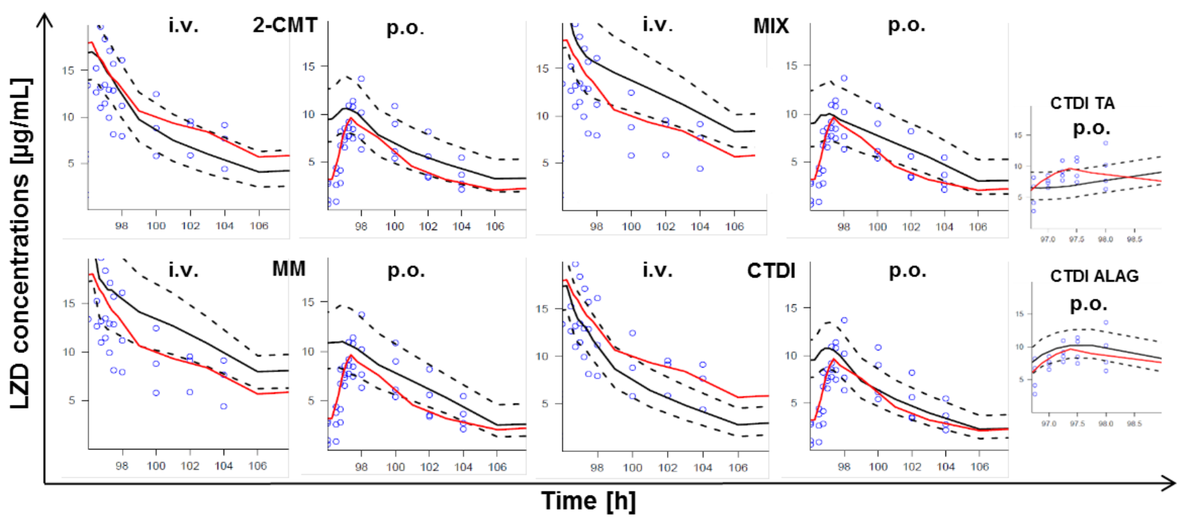

Figure 3: VPCs of the models after MD. Solid black line and dashed lines present the median, 30th and 70th percentile of simulation. Red line represent median of observations (blue dots).

References
[1] Tuberculosis (2008) [2] Santos, RP et al. (2009) [3] Touw, DJ et al. (1998) [4] Plock, N et al. (2007) [5] Swoboda, S et al. (2010) [6] Meagher, A et al. (2003) [7] Savic, RM et al. (2006) [8] Keel, RA et al. (2011) [9] Buerger, C et al. (2003) [10] Bonate, P (2005) [11] Bosso, J et al. (2004)

Conclusions

Six PK models with various elimination and absorption pathways for **linezolid in cystic fibrosis patients** were applied to determine the model with best predictive performance. Inspection of the chosen criteria suggested that the MM and MIX model did not adequately describe and predict the concentration-time profiles of LZD. Although the 2-CMT model was comparable to the CTDI model for single dosing, it was inferior for multiple dosing. In contrast to the TA model the absorption process was best described by the ALAG model. In summary, the **CTDI ALAG model** as the **most mechanistically and physiologically-motivated PK model** was the model with the **best descriptive and predictive performance** compared to all other investigated models and is therefore preferable for assessing various dosing strategies [8] for the population of CF patients.

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