RCCT in paediatric development: dealing with heterogeneity in treatment response in children.

Massimo Cella(1), Meindert Danhof(1), Oscar Della Pasqua(1,2)*

1 Division of Pharmacology, LACDR, Leiden University, Leiden, The Netherlands
2 Clinical Pharmacology & Discovery Medicine, GlaxoSmithKline, Greenford, United Kingdom

Introduction

The efficacy of a pharmacological treatment is usually described by a function that relates the effect with the dose. However, drug concentration or exposure (e.g., AUC) are known to be better descriptors of the pharmacological effect. Yet, fixed dose protocols are considered best practice in the assessment of efficacy in clinical trials, which often results in (an unnecessarily) large variability in response. This issue is particularly important in paediatric pharmacology, where differences in response may exist due to development changes and no clear relationship between dose and exposure is available to support appropriate dose selection.

Objective

To assess whether an adaptive design in early clinical trials based on controlled exposure can provide better dosing recommendation as compared to a fixed dose approach when weight is used as covariate for dose adjustment. The concept is illustrated for the antiviral drug abacavir.

Methods

Based on a one-compartment model with oral absorption previously used[1] to describe the pharmacokinetics of abacavir in children, we simulated a new paediatric population with a broad range of weight and ages. Age distribution included children from 2 to 17 year. Weight distribution was calculated according to growth charts available from the National Center for Health Statistics[2].
Body Weight (BW) was included in the model as covariate on clearance and volume using a power model:

$$\theta = \theta_{TV} * (BW/70)^{EXP}$$

Parameters estimates from the original analysis are shown in Table1.

Parameters	*Mean (%CV)*	*BS mean (%CV)*	*% IIV (%CV)*	*BS % IIV (%CV)*
Fixed effects				
CL (L/h)	37.7 (19)	38.5 (6.3)	27 (27)	27 (10)
V (L)	67.6 (11)	66.2 (4.8)	11 (34)	11 (4.4)
KA (h^{-1})	3.43 (34)	3.94 (47)	93 (32)	94 (13)
F (%)	0.83 fix	0.83 fix	55 (73)	52 (70)
Exponent on CL	0.693 (22)	0.705 (11)		
Exponent on V	0.802 (13)	0.804 (10)		
Residual error %				
ε	3.5 (16)	3.7 (32)		

Table 1. Summary of PK parameter estimates for the original model. BS = Bootstrap validation of the model, based on 1000 replications.

For the purposes of our evaluation, simulated datasets were created with 128 children and three different dosing regimens:

1. according to current dosing recommendations (single dose of 8 mg/Kg, with a maximum of 300 mg) → ***FIXDOSE***

2. with a single dose aiming at reach an AUC of 7 mg*h/L (above median AUC of 6.02) → ***FIXAUC***

3. according to a b.i.d. dosing regimen, with an initial starting fixed dose followed by FIXAUC → ***TITRATION***

The simulated data were re-fitted with the same model used for the original data, with the prior subroutine based on the PK parameters in adults. Then bootstrap was performed with 500 replicates to estimate 95%CI and assess the stability of the model.
To mimic a paediatric trial in early clinical development, in which few patients are usually enrolled, another set of bootstraps was performed, sampling only 30 subject out of the original population, stratified by age, with at least 10 children 2- 4 years old. Final parameters estimates and exposures were compared.

Results: parameter estimates

The diagnostics of the fitting of the ***FIXDOSE*** dataset are shown in Figure 1.

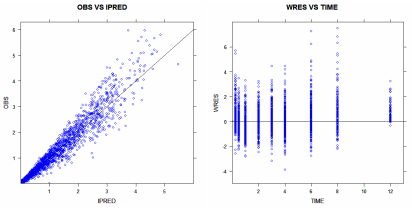

Fig 1. Diagnostic plots of the FIXDOSE regimen: OBS vs. IPRED and WRES vs. TIME.

Parameter estimate are shown in Table 2.

	Original	*Bootstrap*	*Original*	*Bootstrap*	
n. of subjects	128	128	30	128	128	30
Parameters				Inter-individual variability		
CL (L/h)	46.1	45.7	37.8	26.4%	25.7%	56.0%
V (L)	67.7	67.5	65.7	11.1%	10.9%	11.4%
Ka (1/h)	3.3	3.3	2.8	83.4%	83.2%	88.6%
Exponent on CL	0.788	0.765	0.605			
Exponent on V	0.728	0.712	0.712			
residual error %	3.7	3.6	3.7			
number of runs	1	500	500			
successful runs		98.8%	79.2%			

Table 2. Summary of PK parameter estimates of ***FIXDOSE*** regimen.

Pharmacokinetic analysis of the controlled-exposure dataset did not show significant differences in the parameters estimates obtained for the fixed dose protocol (Table 3). The results of the b.i.d. dosing regimen are summarised in Table 4.

	Original	*Bootstrap*	*Original*	*Bootstrap*	
n. of subjects	128	128	30	128	128	30
Parameters				Inter-individual variability		
CL (L/h)	46.0	38.0	37.8	26.5%	39.4%	55.2%
V (L)	67.8	66.6	66.1	10.7%	10.6%	11.4%
Ka (1/h)	3.3	3.1	2.9	82.3%	83.1%	87.2%
Exponent on CL	0.783	0.596	0.590			
Exponent on V	0.726	0.693	0.693			
residual error %	3.3	2.7	2.7			
number of runs	1	500	500			
successfull runs		93.0%	54.0%			

Table 3. Summary of PK parameter estimates of ***FIXAUC*** regimen.

	Original	*Bootstrap*	*Original*	*Bootstrap*	
n. of subjects	128	128	30	128	128	30
Parameters				Inter-individual variability		
CL (L/h)	46.3	38.0	37.8	26.3%	39.2%	55.8%
V (L)	67.6	66.0	66.0	11.5%	11.1%	11.5%
Ka (1/h)	3.3	3.2	2.9	81.8%	83.9%	87.8%
Exponent on CL	0.793	0.612	0.612			
Exponent on V	0.717	0.708	0.714			
residual error %	3.3	3.3	3.2			
number of runs	1	500	500			
successfull runs		97.0%	87.8%			

Table 4. Summary of PK parameter estimates of ***TITRATION*** regimen.

Results: AUC distribution

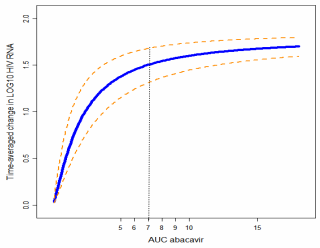

Fig 2. PKPD relationship of abacavir on HIV-1 RNA suppression[3]

Figure 3 shows the distribution of the exposure according to the different dosing regimens.

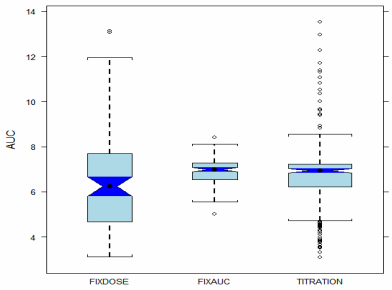

Fig 3. Box-plots of the exposure obtained with the three dosing protocols. Note that ***TITRATION*** protocol includes data from the first dosing, prior to the ***FIXAUC*** adaptation.

	Original data (n=14)	***FIXDOSE*** (n=128)	***FIXAUC*** (n=128)
Subjects underdosed (AUC< 6.02)	7	57	7
Subjects overdosed (AUC> 10.00)	1	10	0
Total subjects with inappropriate exposure	***8 (57.1%)***	***67 (52.3%)***	***7 (5.5%)***

Table 5. Consequences of fixed dosing regimen vs. exposure controlled protocol

Conclusions

Results of this analysis show that adaptive titration can be used to optimise dose finding in paediatric development, instead of relying solely on body weight as covariate for dose adjustment.
This approach increases statistical power and hence the probability of demonstrating efficacy. Furthermore, it contributes to further understanding of the role of dose on the total heterogeneity in clinical response.

[1]Cella et al., PAGE 16 (2007) Abstr 1203
[2] www.cdc.gov/GROWTHCHARTS
[3]Weller et al. 44 (8): 2052. (2000)