The impact of modified-release formulations on bridging of pharmacokinetic data from adults to children

Georgios Vlasakakis (1), Massimo Cella (1,2), Oscar Della Pasqua (1,2)

1 Clinical Pharmacology Modelling & Simulation, Tech & Dev, GlaxoSmithKline, Stockley Park, UK
2 Division of Pharmacology, LACDR, Leiden University, Leiden, The Netherlands

Leiden / Amsterdam Center for Drug Research
Leiden University / Vrije Universiteit Amsterdam

GlaxoSmithKline

Introduction

Besides the known effects of developmental growth and maturation on drug disposition, formulation-specific differences create additional complexities in the extrapolation of data from adults to children. Of particular interest is the role of transit time and gastric emptying on lag time, rate and extent of the absorption processes. Nevertheless, the limited availability of data around the absorption phase make the characterisation of such processes mathematically intractable by conventional estimation procedures.

Objective

The aim of this investigation was to assess the feasibility of applying Bayesian methods to deal with data sparseness and problematic absorption profiles when using small data sets. Diclofenac was selected as a paradigm compound.

Methods

Pharmacokinetic data from enteric-coated diclofenac tablets (30 adults) derived from a previously analysed large population (141 adults and children) was used in this evaluation. The original dataset consisted of different formulations, but the enteric coated data was discarded due to the long lag time observed in the trial [1]. The high variability in lag time is illustrated in Figure 1.

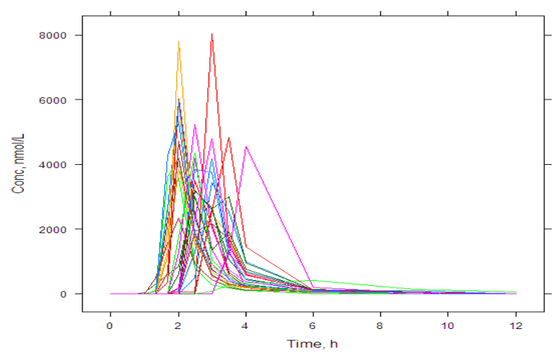

Fig 1. Concentration time course profiles after oral administration of 50 mg enteric-coated diclofenac tablets to adult healthy subjects (n=30).

Data fitting in NONMEM using FOCEI was not feasible. WinBUGS was therefore used to describe the lag time (Tlag) under the assumption of a one-compartment model with 1st-order absorption. IMP and SAEM methods were subsequently used in NONMEM v.7.1 to estimate the absorption rate constants, volume of distribution and clearance according to a one-compartment model with dual absorption taking into account the parameter estimates obtained from WinBUGS.

Analytical (TLAG) Model in WinBUGS

```
model{ for( i in 1:n){
conc[i]<-  step(t[i]-tlag)*((dose*ka)/( (ka-k)*V)
)* (exp(-k*(t[i]-tlag))-exp(-ka*(t[i]tlag)))
fit[i]~dnorm(conc[i],0.01)}
ka~dlnorm(-0.3,0.01)
k~dlnorm(3,0.01)
V~dlnorm(1.5,0.01)
tlag~dnorm(1,0.01)
CL<-k*V }
```

Results

WinBUGS 1.4

Figure 2 shows the individual model fit for all 30 adults. The fitting was successful even in severely ill-posed datasets, e.g., #16 and #20.

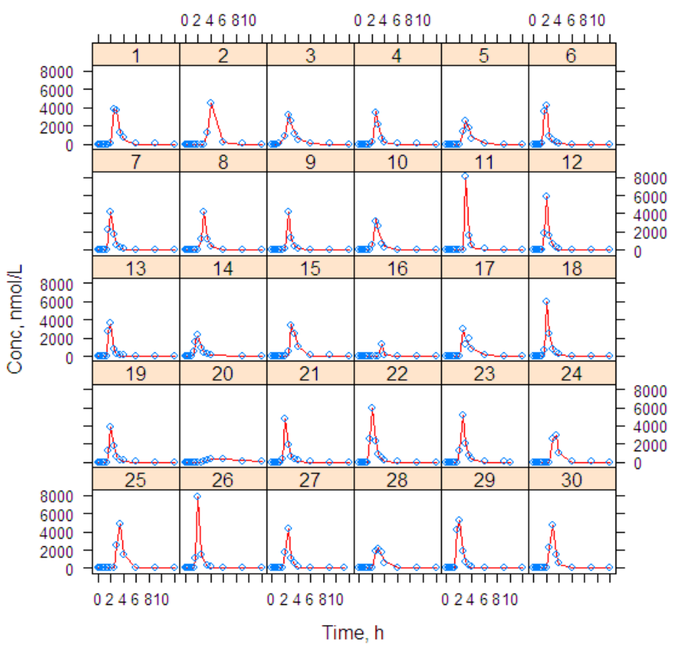

Fig 2. Individual model fits for concentration time course of diclofenac as assessed by the LAG model in WinBUGS.

Population mean lag time (BSV) was found to be 2.05 h (23%). Parameter estimates were then used as input for PK modelling in NONMEM.

NONMEM v.7.1

A diagram of the pharmacokinetic model used to fit diclofenac data is shown below:

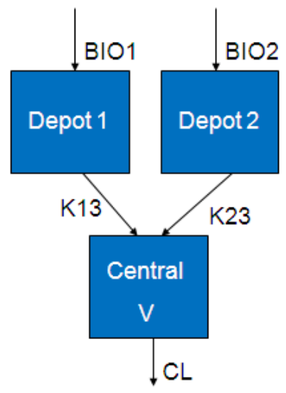

Fig 3. A one-compartment model with dual absorption rate was required to describe the concentration time course of diclofenac after administration of enteric-coated tablets.

PK parameter estimates and diagnostic plots obtained from the analysis are shown below.

The goodness-of-fit plots are depicted in Figure 4. Parameter estimates are summarised in Table 1.

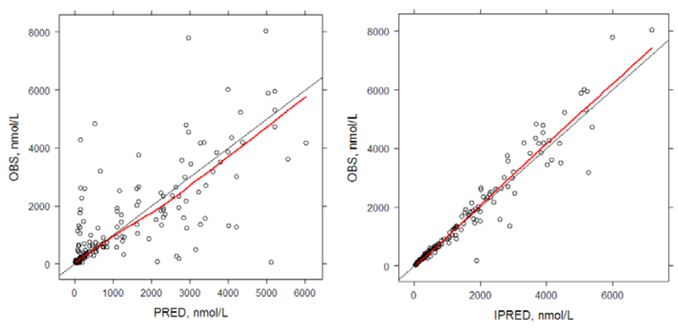

Fig 4 . (left panel) Observed vs. population predicted concentrations. (right panel) Observed vs. individual predicted concentrations. Black and red lines indicate unity and smoothing line respectively.

	Mean (BSV)	(SE)
CL (L/h)	35.51 (23%)	0.049
V (L)	8.49 (85%)	0.162
K13 (h)	1.09 (47%)	0.147
K23 (h)	3.45 (30%)	0.096
BIO1 (%)	24%	0.083
BIO2 (%)	76%	-
WT^EXP on CL	0.175	0.337

Table 1. Diclofenac PK parameter estimates.

Diagnostic plots (CWRES, NPDE) for the final model are shown below.

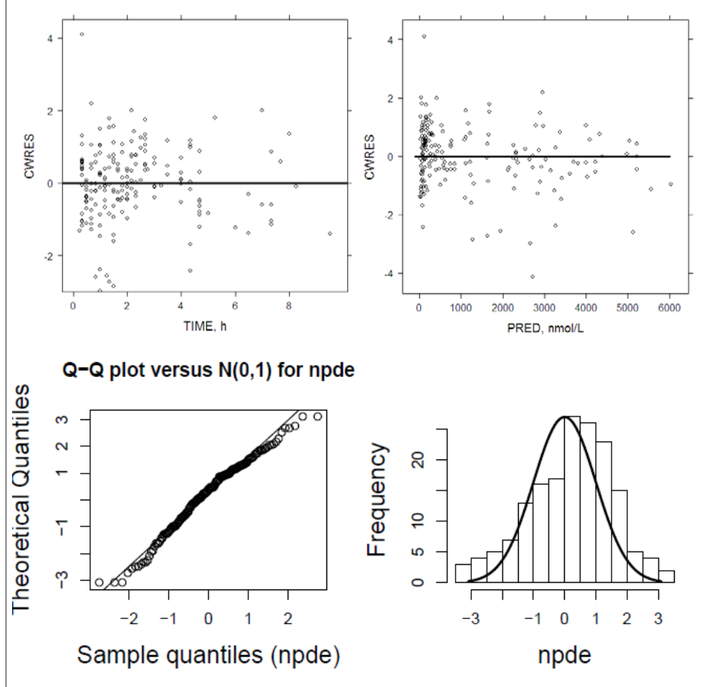

Fig 5. (upper left panel) CWRES vs. Time and CWRES vs. PRED. (lower left panel) NPDE results: QQ plot and histogram of residuals.

Figure 6 illustrates the distribution of the adult data and the prediction intervals on a VPC graph. Despite comparable dosing regimen, model predictions do not reflect children data limiting the capability for further extrapolation.

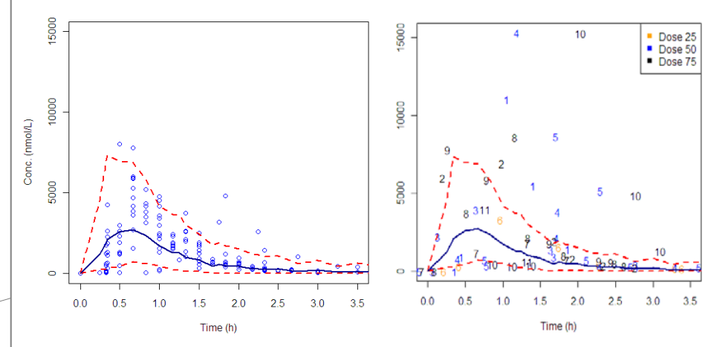

Fig 6. (left panel) Visual predictive check based on adult data. (right panel) Observed concentration in children vs. model prediction intervals.

Conclusions

The use of PK bridging is highly desirable in paediatric drug development. However, whilst scaling has been the focus of the debate, pharmaceutical factors have been neglected. Their effects on drug disposition must be accounted for when extrapolating data across populations. A Bayesian approach may be required to overcome the limitations of methods based on the maximum likelihood.

AKCNOWLEDGMENTS

We thank Hugo Maas and Anne Chain for their valuable contribution.

REFERENCES

[1]Standing, J.F., Tibboel, D.,Korpela, R.,Olkkola, K.T. Diclofenac pharmacokinetic meta-analysis and dose recommendations for surgical pain in children aged 1-12 years. *Paediatr Anaesth.* **21**, 316-324 (2011).