Predicting the PK/PD of Ibuprofen in Children

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Background

Many studies have investigated the pharmacodynamics of ibuprofen (IBU) in children [1-3]. It is expected that age dependent physiological changes during childhood affect exposure and hence response in children. While physiologically Based Pharmacokinetic (PBPK) models have previously been used to predict drug exposure in children [4], to the best of our knowledge they have not been applied in the modelling of developmental changes in concentration–response relationships of IBU.

Objectives

The aims of this study are:

- To simulate the exposure and antipyretic effect of racemic IBU after a single oral dose of 10mg/kg in a virtual healthy paediatric population.
- To predict the exposure and response following 10mg/kg IBU administration in Poor metabolizers (PM) and extensive metabolizers (EM) with respect to the CYP2C9 phenotype of paediatric populations.

Methods

Prior *in vitro* information on the metabolism and kinetics of IBU and developmental physiology of paediatric populations were incorporated into the Simcyp Paediatric V12 Release 1 Simulator. Simulations of IBU PK/PD were performed to replicate reported clinical studies in children aged 4-16 years [1, 2], where the reduction of body temperature was used as a PD marker of antipyretic effect [1, 2]. The PK/PD relationship was represented by an indirect turnover model for body temperature, as reported by Trocóniz *et al*., 2000 [1].

Specifications of the Simcyp model were as follows:

- An absorption phase was predicted using the Advanced Dissolution, Absorption and Metabolism model.
- The drug distribution was modeled using the a PBPK model, where the drug distributes to different tissues.
- The elimination phase was predicted based on *in vitro* enzyme kinetics for CYP2C9 and CYP2C8.
- The PD relationship was represented by an indirect turnover model for body temperature. Model parameters were taken from Trocóniz *et al*., 2000 [1].
- Trial design: 10 trials in each 10 individuals (total 100 subjects)

Results

Simulation results were in good agreement with observed data. The simulated PD response is compared with the data from Troconiz *et al.* (see Figure 1).

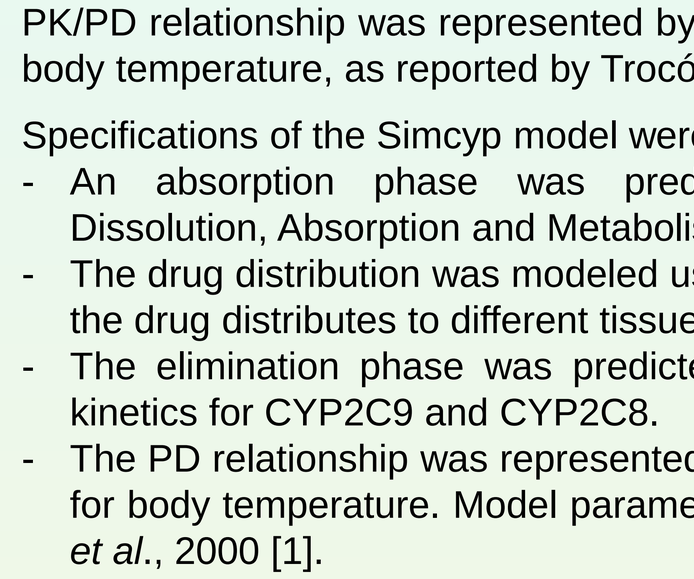

Figure 1. Simulated response-time profile for IBU with 95% predictive intervals (blue). Observations from Troconiz *et al.* (2000) are shown by black circles.

The maximum response (R_{max}), time of Rmax (t_{Rmax}) and the area for the time response curve after 4h ($AURC_{4h}$) are compared in Table 1.

	Observed	Simulated	Ratio
Rmax (°C)	36.85	37.24	1.01
t_{Rmax} (h)	3	2.4	0.8
$AURC_{4h}$ (°C·h)	5.5	6.1	1.11

Table 1. Observed *vs* predicted (Troconiz *et al.* (2000)) reduction in body temperature

The simulated PD response is compared with the data from Walson *et al.* (Fig 2). The ratio of Simulated to Observed PK values for C_{max}, t_{max}, and AUC_{8hr}, were 0.93, 0.67, and 1.20, respectively. Likewise, the corresponding ratios for PD values R_{max}, t_{Rmax} and AURC were 0.98, 0.78 and 1.76, respectively (Table 2).

Variable	Observed*	Simulated	Ratio
Pharmacokinetics			
C_{max} (mg/ml)	39.7	37	0.93
T_{max} (h)	1.5	1.0	0.67
AUC_{8hr} (mg/ml/h)	133	159	1.20
Pharmacodynamics			
R_{max} (°C)	37.9	37.2	0.98
$t_{(Rmax)}$ (h)	4	3.12	0.78
$AURC_{8hr}$ (°C· h)	7.2	12.7	1.76

Table 2. PK/PD Parameters for simulated *vs* predicted IBU after administration of 10mg/kg as single oral dose.
*Walson *et al.* (1989)

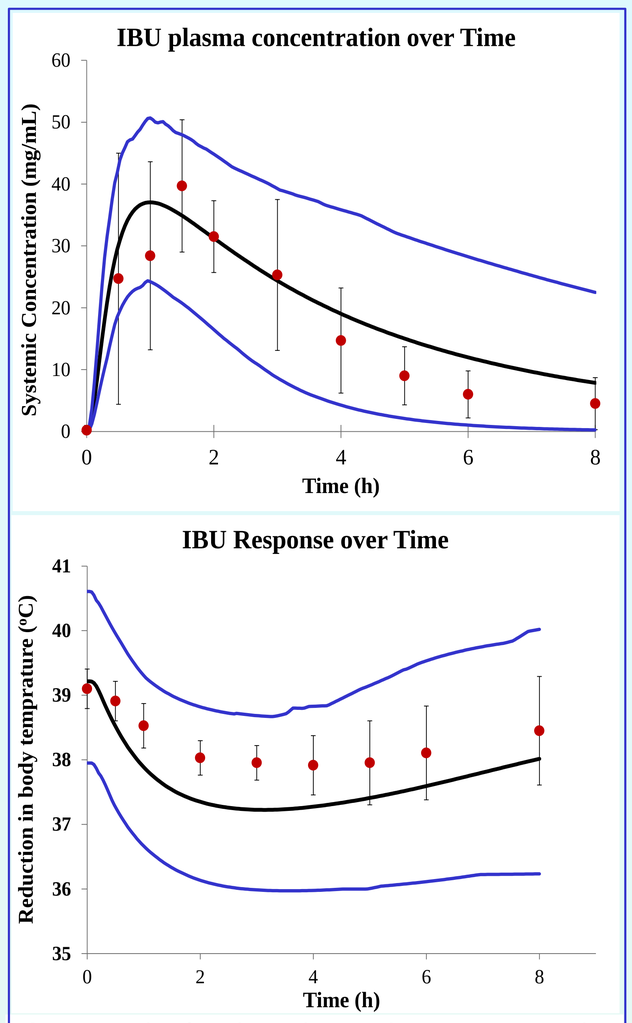

Figure 2. Simulated *vs* Observed* IBU concentration (left) and response (right) time profiles for paediatric populations.
*mean±SD data from Walson *et al*. (1989) given as red circles.

Finally, the predicted IBU plasma concentrations for different sub-population with respect to their CYP2C9 phenotype status showed a higher C_{max} and AUC_{24h} in PM compared to the EM group. The higher exposure is propagated to greater effect in PM compared to EM (see Figure 3 and Table 3).

Variable	PM	EM	Ratio
Pharmacokinetics			
C_{max} (mg/ml)	37.45	29.81	1.30
T_{max} (h)	2.16	1.68	1.30
AUC_{8hr}(mg/ml/h)	403.21	193.64	2.1
Pharmacodynamics			
R_{max} (°C)	37.14	37.22	1.0
$t_{(Rmax)}$ (h)	4.44	3.48	1.3
$AURC_{8hr}$ (°C· h)	34.86	19.32	1.8

Figure 3. PK/PD parameters for **s**imulated mean PK/PD time profiles for children with different CYP2C9 phenotypes.

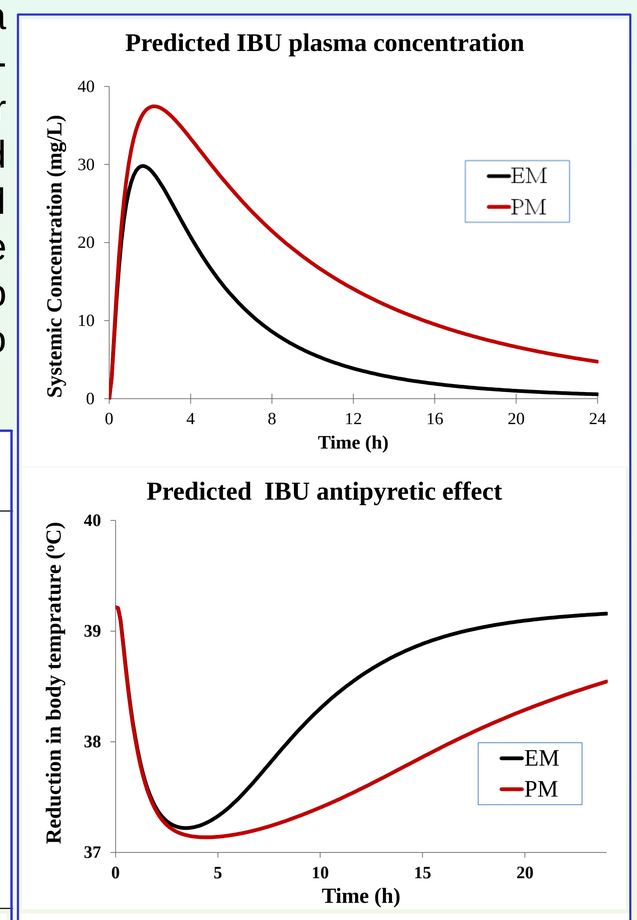

Figure 3. Simulated mean PK (top) response (bottom) time profiles of IBU in 4-11 years old children having different CYP2C9 phenotypes.

Conclusions

Incorporation of developmental changes and prior *in vitro* information in physiologically based PK/PD models produced a successful simulation of the antipyretic effect of IBU observed in clinical studies. The short-duration response observed in EM may imply it would be necessary to increase the drug dose in this population and/or administer a longer acting formulation. Clinical trial simulations similar to the one shown in this study can be used to investigate the design and power of POPPK/PD studies performed across a variety of different age ranges.

References

1.Trocóniz *et al.*, Clin Pharmacokinet 2000 Jun; 38 (6): 505-518
2. Walson *et al.*, Clin Pharmacol Ther. 1989 Jul;46(1):9-17.
3. Brown RD *et al.*, J Pharmacokinet Biopharm. 1998 Oct;26(5):559-79.
4. Johnson & Rostami-Hodjegan.Paediatr Anaesth. 2011 Mar;21(3):291-301