



Paracetamol and diclofenac additive effects after tonsillectomy

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Background

PKPD of paracetamol studied for analgesia in children

- TCI 10.0mg/l effect site (Anderson et al)

PK of diclofenac studied in children

- doses recommended from predicted AUC = to effective adult AUC
- concentration - analgesia relationship not studied

Aim: describe PKPD relationship for diclofenac/paracetamol combination therapy

Data

Study – unpublished, randomised, placebo controlled study of children after tonsillectomy

n=151

- paracetamol 40mg/kg oral + 20mg/kg rectal with: placebo, diclofenac 0.1 mg/kg, diclofenac 0.5 mg/kg or diclofenac 2.0 mg/kg

n=93

- diclofenac 0.1- 2.0 mg/kg only
- Postop pain scores (0-10)

Data

Pooled with

PKPD paracetamol study (Anderson et al., 2001)

- 152 children
- preop dose of 40mg/kg oral, 100mg/kg oral or 40mg/kg rectal
- pain scores, plasma concentrations

PK diclofenac study (Standing et al., 2011)

- 70 children + 30 adults (bioequivalence study)
- 1mg/kg oral suspension diclofenac
- plasma concentrations

Methods

- n=496
- 1552 pain scores
- 829 paracetamol & 911 diclofenac plasma concs
- One compartment, first order absorption & elimination model
- Pain score related to plasma concentration with effect site compartment & model of combined drug effect
- Model of placebo effects
- Model of study dropout

PD model

Combined effect model: modified sigmoidal dose response curve

Where $U_P = \text{CONC}_P / \text{EC}_{50,P}$
 $U_D = \text{CONC}_D / \text{EC}_{50,D}$

Shared slope parameter

$$R = E_0 - E_{MAX} \cdot \frac{\left(\frac{(U_P + U_D)}{U_{50}(\theta)} \right)^{\text{hill}}}{\left(1 + \left(\frac{(U_P + U_D)}{U_{50}(\theta)} \right) \right)^{\text{hill}}}$$

Modifies combination dependent on ratio of drug 1 : 2 (θ)

- Interaction parameter (β) in quadratic function and applied to Hill equation parameters as required
- $U_{50}(\theta) = 1 - \beta \theta + \beta \theta^2$

PK estimates

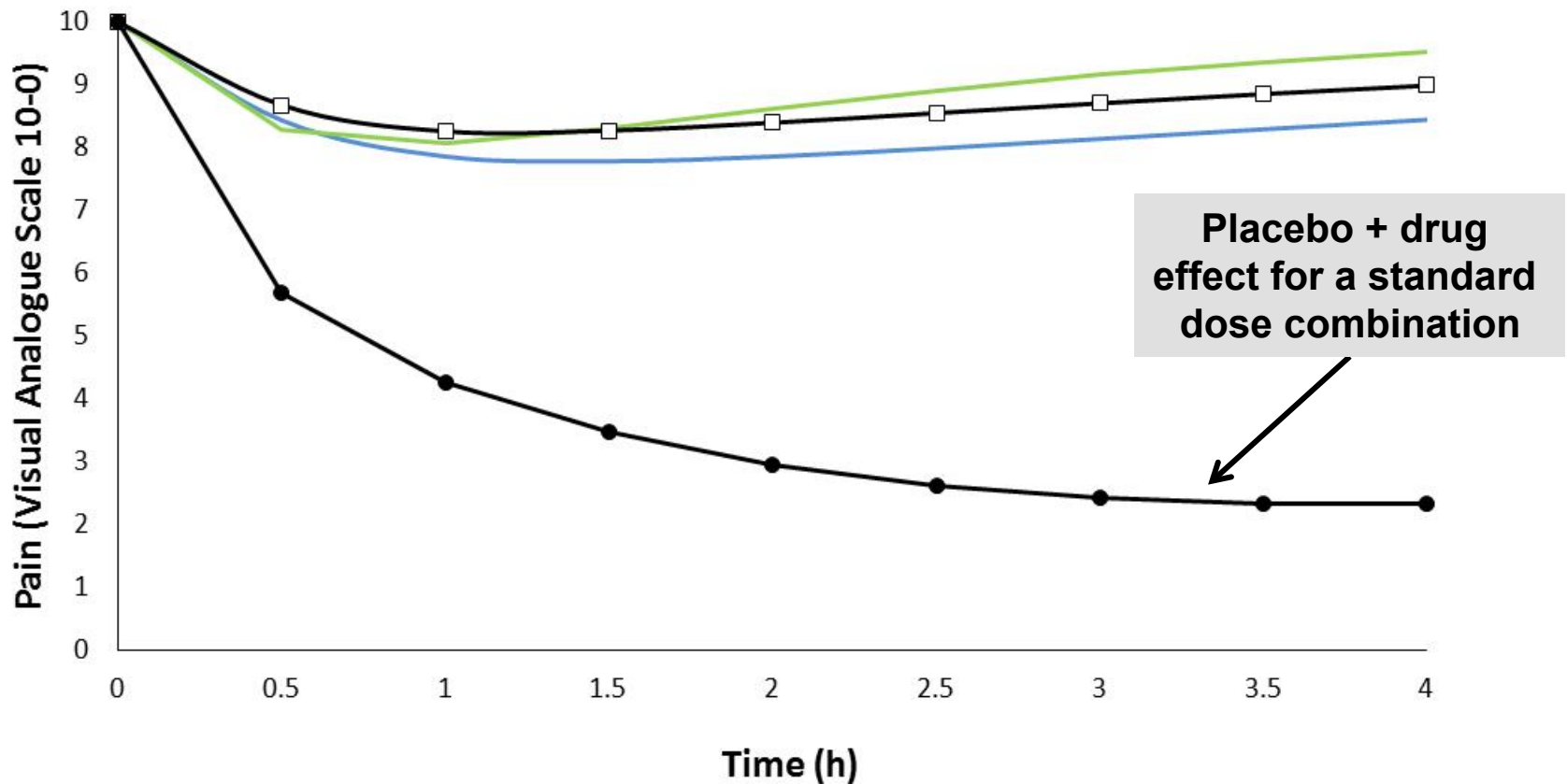
Parameter	Estimate	Literature estimates
V_{PARA} (l/70/kg)	56.0	60.0
CL_{PARA} (l/h/70kg)	11.7	13.5
V_{DICL} (l/70kg)	16.0	15.0 - 22.0
CL_{DICL} (l/h/70kg)	53.2	24.5 - 44.8

Pharmacodynamics

Parameter	Estimate	Literature estimates
$C_{50, \text{PARA}}$ (mg/l)	13.3	10.0
$C_{50, \text{DICL}}$ (mg/l)	1.2	?
$T_{1/2 \text{eqPARA}}$ (min)	30.0	53.0
$T_{1/2 \text{eqDICL}}$ (min)	12.0	?
E_{MAX} (Units)	5.0	
β	0 FIXED	
Hill	1.0	

E_0 assumed as equal to 10, interval censored dropout model used

Simulation of predicted pain scores for single oral doses of paracetamol and diclofenac (in a 5y, 20kg child)



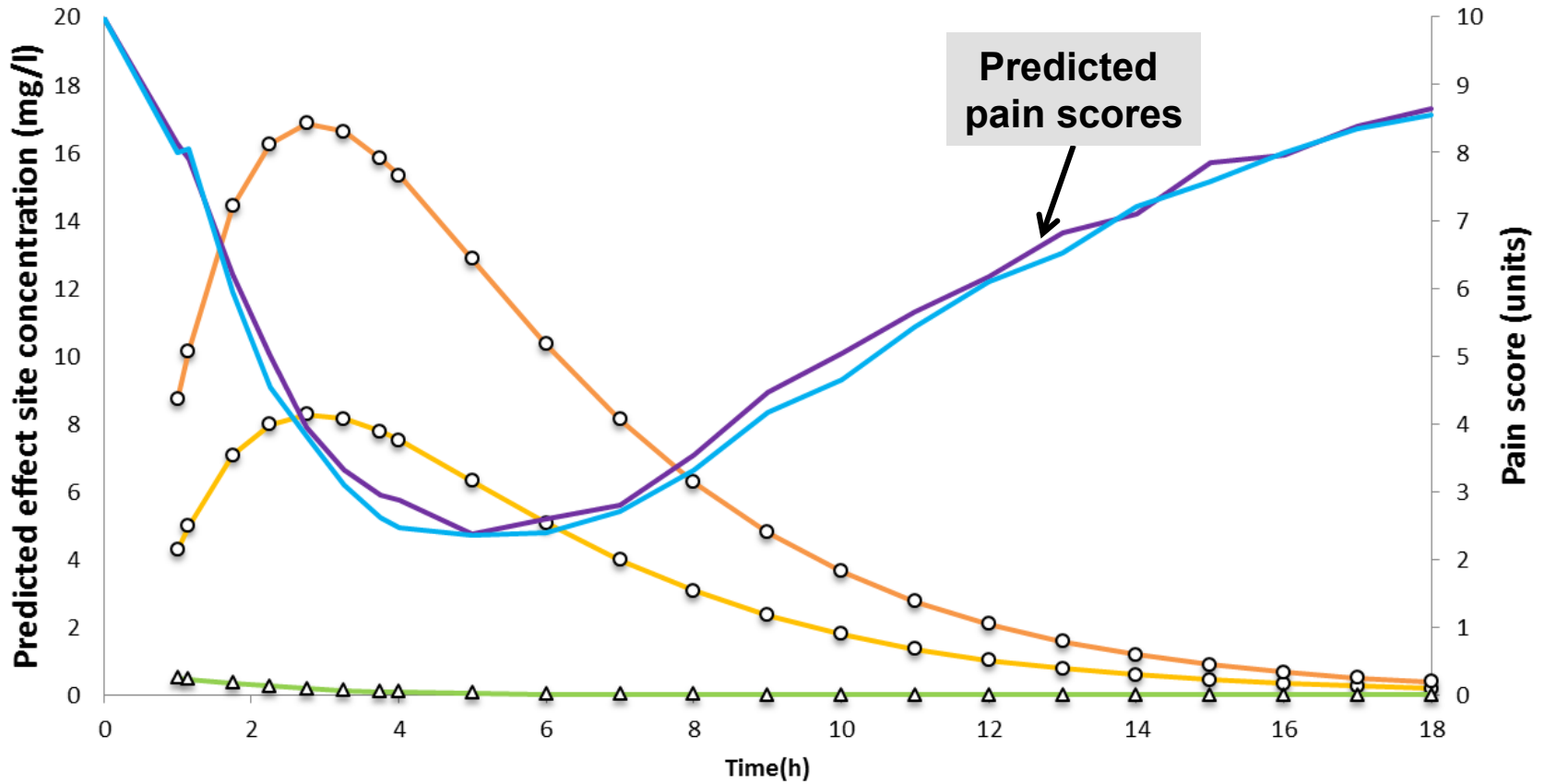
— 12.5 mg/kg paracetamol

— 2 mg/kg diclofenac

—□— 0.5 mg/kg diclofenac with 6.25 mg/kg paracetamol

—●— Placebo effect plus drug effect for 30mg/kg paracetamol with 1 mg/kg diclofenac

Predicted effect site concentrations and pain scores following 520 mg paracetamol alone, and 255 mg paracetamol with 25 mg diclofenac (in a 5y, 20 kg child)



- Target 5.0mg/l paracetamol
- Target 10.0mg/l paracetamol
- Pain score: paracetamol only

- △ Target 0.5mg/l diclofenac
- Pain score: combination



Conclusions:

- Likely additive effects for analgesia
- 1.25 mg/kg of diclofenac allows TCI of paracetamol 10mg/l to be halved
- Work in progress...



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