Parameterization of a physiologically-based pharmacokinetic (PBPK) model for the simulation of ibuprofen pharmacokinetics under exercise and heat stress with evaluation using clinical data

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INTRODUCTION

- Personnel working in areas such as the Middle East are subjected to heat and exercise stress. The need for altered dosing of medications in this sub-population may be required to maintain therapeutic plasma concentrations.
- Physiologically-based pharmacokinetic (PBPK) models are able to incorporate physiological changes associated with altered states in order to make predictions regarding their effects on drug pharmacokinetics.
- **Objective:** To parameterize a physiologically-based pharmacokinetic (PBPK) model using ibuprofen as a proof-of-concept allowing for changes in physiological parameters associated with operational stressors, heat + exercise (simulated patrol), with further model evaluation using preliminary clinical data

METHODS

Clinical protocol

- A prospective pharmacokinetic cross-over study was designed & conducted at DRDC Toronto. Participants (age 19 – 34 years) were randomly assigned to each session and, prior to each session, administered Advil® Gel-caps (400 mg racemic ibuprofen):

☼ **Rest** (*n*=8) ☼ **Exercise*** (*n*=6) ☼ **Heat** (42ºC, 9% humidity) (*n*=3) ☼ **Exercise* + Heat** (*n*=5)

(* = 15 min. walk/5 min. rest for 2.5 hrs. followed by 2.5 hr rest)

- Blood samples taken 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 h post-administration and analyzed by UPLC/MS/MS.

PBPK model development

- A coupled PBPK model was developed for R-and S-ibuprofen taking into account the chiral inversion of R- to S-ibuprofen *in vivo* (~ 60% of R- is inverted to S-ibuprofen) (**Fig. 1**)
- A literature search and quantitative analysis of the physiological changes associated with heat and exercise stress was completed taking into account cardiac output, hematocrit, organ-specific blood flows, albumin concentrations and gastrointestinal tract changes.

PBPK model evaluation

- Model evaluation and hypothesis testing were completed using the clinical data.

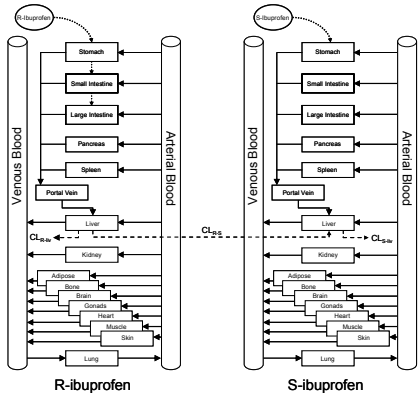

Fig 1. Schematic of the PBPK structure using nested models for R- and S-ibuprofen where both R-ibuprofen and S-ibuprofen are the administered form (racemic mixture).

PRELIMINARY RESULTS

Clinical experiment

- **Table 1** presents preliminary PK parameters for each clinical trial arm (one-compartment, first order absorption and elimination with lag time)
- Absorption rate increased during exercise and was reduced during heat stress
- Increased AUC during exercise compared to rest and heat only arms
- V/F and CL/F similar across treatments (statistical analysis pending)

Table 1. Pharmacokinetic parameters using the geometric mean of the data from the available study participants.

Compound	Parameter	Rest (*n*=8)	Heat (*n*=6)	Exercise (*n*=3)	Heat + Exercise (*n*=5)
R	V/F (L)	16.7	10.7	21.8	14.6
	T_{lag} (h)	0.39	0.29	0.20	0.23
	k_a (h^{-1})	2.94	0.74	6.96	7.01
	$t_{1/2}$ (h)	1.80	1.0	2.55	2.15
	$AUC_{0\text{-}last}$ (mg*h/L)	30.9	26.3	33.7	42.3
	CL/F (L/h)	6.43	7.61	5.92	4.71
	T_{max} (h)	1.18	1.67	0.68	0.69
	C_{max} (mg/L)	8.82	6.98	8.02	11.8
S	V/F (L)	10.0	11.6	12.8	9.93
	T_{lag} (h)	0.40	0.35	0.21	0.23
	k_a (h^{-1})	2.34	1.22	4.44	4.47
	$t_{1/2}$ (h)	1.84	2.01	2.52	2.10
	$AUC_{0\text{-}last}$ (mg*h/L)	52.9	50.1	57.0	60.9
	CL/F (L/h)	3.77	3.98	3.50	3.28
	T_{max} (h)	1.33	1.81	0.87	0.86
	C_{max} (mg/L)	14.0	10.5	13.0	16.3

PBPK model development

- Heart rate was used as a means of scaling organ blood flows with their sum being equal to heart rate-dependent cardiac output (**Table 2**)
- Hematocrit and albumin concentration (unbound fraction) were altered in exercise
- Based on literature data, simulated gastrointestinal parameters (gastric emptying time, transit time, permeability) were not altered from the resting state

Table 2. Change in organ blood flows as a percentage of cardiac output during heat and exercise stress at heart rates of 70 (a), 120 (b) and 180 (c) beats/min.

Organ	% of Cardiac Output				
	Rest [a]	Heat [b]	Exercise [b]	Heat [c]	Exercise [c]
Bone	5.3	3.1	3.1	2.1	2.1
Brain	12.7	7.4	7.4	5.0	5.0
Fat	5.3	3.1	3.1	2.0	2.0
Gonads	0.053	0.031	0.03	0.021	0.021
Heart	4.3	5.7	5.7	6.4	6.4
Kidney	21.7	9.6	9.6	4.1	4.1
Large intestine	4.3	1.6	2.0	0.59	0.79
Liver	6.9	2.6	3.3	0.97	1.3
Muscle	18.1	8.2	50.0	5.5	66.5
Pancreas	1.1	0.40	0.51	0.15	0.20
Skin	5.3	52.6	8.2	71.1	8.8
Small intestine	10.6	4.0	5.1	1.5	2.0
Spleen	3.2	1.2	1.5	0.44	0.59
Stomach	1.1	0.40	0.50	0.15	0.20

PBPK model evaluation

- Optimized gastric emptying explained changes in T_{max}
- Simulated $t_{1/2}$ similar to observed $t_{1/2}$ (**Fig. 2**)
- PK changes due to operational stress likely not clinically relevant (**Fig. 3**)

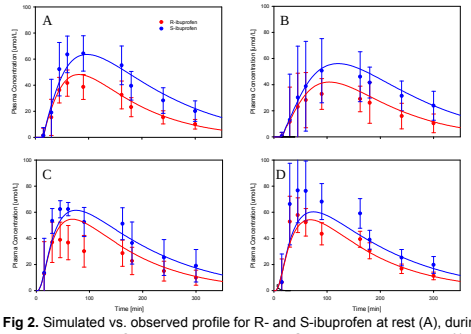

Fig 2. Simulated vs. observed profile for R- and S-ibuprofen at rest (A), during heat (B), exercise (C) and heat + exercise (D). Gastric emptying time (63%) was 30 min at rest, and optimized to 65 min (heat) and 10 min (exercise).

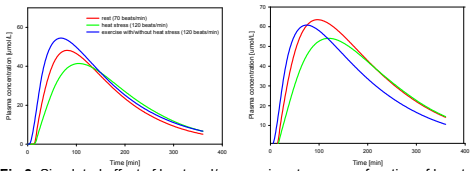

Fig 3. Simulated effect of heat and/or exercise stress, as a function of heart rate, on the pharmacokinetic profile of R-and S-ibuprofen following a 400 mg oral administration of the racemic mixture (Advil gelcaps).

PRELIMINARY CONCLUSIONS

- **Preliminary data suggested that dose adjustment under operational stressors unlikely to be required.**
- **While the PBPK model adequately predicted little change in the distribution and elimination of ibuprofen under stress, the model was used to test the hypothesis that gastric emptying time is indeed responsible for heat and exercise-dependent absorption.**
- **The heat and exercise stress parameterized PBPK models will be used to focus resources, with respect to future clinical trials, to rank those commonly used drugs in the field that have the greatest chance of requiring dose adjustment**.