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 racemiac ibuprofen):
- Rest (n=8)
- Exercise* (n=6)
- Heat (42°C, 9% humidity) (n=3)
- Exercise* + Heat (n=5)

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.

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.

<table>
<thead>
<tr>
<th>Component</th>
<th>Rest</th>
<th>Exercise*</th>
<th>Heat</th>
<th>Exercise* + Heat</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/F (L)</td>
<td>10.0</td>
<td>11.6</td>
<td>9.93</td>
<td>9.93</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>3.77</td>
<td>3.98</td>
<td>3.50</td>
<td>3.28</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.33</td>
<td>1.81</td>
<td>0.87</td>
<td>0.86</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>8.82</td>
<td>6.98</td>
<td>8.02</td>
<td>11.8</td>
</tr>
</tbody>
</table>

PK changes due to operational stress likely not clinically relevant (Fig. 3)

Table 2. Change in organ blood flows as a percentage of cardiac output.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rest</th>
<th>Exercise*</th>
<th>Heat</th>
<th>Exercise* + Heat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>4.3</td>
<td>5.7</td>
<td>5.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Liver</td>
<td>6.9</td>
<td>2.6</td>
<td>3.3</td>
<td>0.97</td>
</tr>
<tr>
<td>Small intestine</td>
<td>10.6</td>
<td>4.0</td>
<td>5.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Large intestine</td>
<td>4.3</td>
<td>1.6</td>
<td>2.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Brain</td>
<td>5.3</td>
<td>3.1</td>
<td>3.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Muscle</td>
<td>18.1</td>
<td>8.2</td>
<td>50.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Skin</td>
<td>11.8</td>
<td>4.0</td>
<td>3.3</td>
<td>0.97</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.1</td>
<td>0.40</td>
<td>0.50</td>
<td>0.15</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.36</td>
<td>0.17</td>
<td>0.40</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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.

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 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).

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).