Acute Organophosphorus Poisoning in Humans: A PK Model for Chlorpyrifos

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Background

• OP poisoning from self harm is a concerning problem in Sri Lanka. 853 deaths in 2007.

• One OP, chlorpyrifos (CPF), is commonly used for self harm, exerting its effect via chlorpyrifos oxon (CPO). 1/3 of all OP admissions.

• The toxicokinetics/dynamics in humans have not been studied in poisoning

• Margin of safety for CPF is unclear

• AIM: To develop a Population pharmacokinetic/pharmacodynamic (PK/PD) model of acute poisoning of CPF in humans.
Modelling?
Organophosphate metabolism

Diethyl-OP-thion \( \xrightarrow{CYP450} \) Diethyl-OP

**OP Hydrolase** (A-esterase) \( \xrightarrow{OP metabolites DAP’s} \)

+ AChE

**Phosphorylation**

Phosphorylated oxime

**OP Hydrolase**

Reversibly inhibited AChE

+ oxime (praladoxime)

OP metabolites
methods

- 72 patients
- Ingested CPF (40% agricultural preparation in xylene)
- 7 Female, age range 15-65 years.
- Reported volumes ingested ranged from 10 to 350 ml however many inaccurate.
- 45 patients received pralidoxime which was accounted for as a confounder of clearance.
- 7 patients died.
- The (PK/PD) analysis was performed using NONMEM 7.
Toxicokinetic model

**PK**

- **DOSE**
- **Ka**
- **Q**

**Central Comp.** → **Periph. Comp.**

**e**

**Active metabolite**

**PD**

**AChE inhibition**

- **Death T(hrs)**
- **Survival outcome**
Results

• A 2 compartment for the parent compound with first order absorption kinetics described the data best.

• Apsorption (Ka) was fixed to a literature value

• V/F and CL/F are seemingly low.

• CL/F is predicted to be ~22ml/min

• T1/2 = 45Hrs
Parameter estimates for fixed effects

<table>
<thead>
<tr>
<th>Estimate</th>
<th>RSE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ka (Hr)</td>
<td>0.48 *</td>
</tr>
<tr>
<td>V2/F (L)</td>
<td>1.647</td>
</tr>
<tr>
<td>CL/F (L/Hr)</td>
<td>0.857</td>
</tr>
<tr>
<td>Q (L/Hr)</td>
<td>1.903</td>
</tr>
<tr>
<td>V3 (L)</td>
<td>37.348</td>
</tr>
<tr>
<td>Res. Error</td>
<td>0.363</td>
</tr>
</tbody>
</table>

* Fixed from Literature Tamchalk 2002 and Nolan 1984
## Parameter variance estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>RSE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIV(V2)</td>
<td>2.550</td>
<td>32</td>
</tr>
<tr>
<td>IIV(CL)</td>
<td>0.111</td>
<td>65</td>
</tr>
<tr>
<td>IIV(F1)</td>
<td>0.708</td>
<td>17</td>
</tr>
<tr>
<td>IIV(Q)</td>
<td>0.388</td>
<td>40</td>
</tr>
<tr>
<td>Corr(CL-V)</td>
<td>0.520</td>
<td>12</td>
</tr>
</tbody>
</table>
16 of 72 individual plots for CHL. Patients have extremely variable kinetics.
The model fits the data well in most cases.
In some patients data appears random and the model is not good at describing the data.
80% prediction interval for chlorpyrifos in plasma. The dotted lines show the 10th and 90th percentiles of simulated (black) and observed (red) values. The solid lines show the 50% percentile with confidence interval (shaded green).
Dose estimations for CPF
Discussions/Conclusions

• In general, the PK model was able to fit the wide range of observed concentrations (0.1 to 18.32 nM) and the dose function was successfully applied.

• similar to other models in the low concentration range.

• Patients with recorded doses were generally overestimated. Patients assigned the median dose were generally underestimated.

• This preliminary PK model will be used to form the basis of a more complete PK/PD acute poisoning model.
The importance of CPO data

Eyer F 2009. Extreme variability in the formation of chlorpyrifos oxon (CPO) in patients poisoned by chlorpyrifos (CPF). *Biochemical pharmacology* 78 531-537
Future direction

- More patients? YES
- Will be able to validate the CPF/CPO model. Preliminary work suggests CPO conversion is via a first order process

- A survival model? YES
- Survival is not significantly associated with CPF, or BChE concentrations. There is a trend with AChE
- However, CPO model required
Future direction cont.

• Treatment options for patients? MAYBE

• A chronic exposure model? HOPEFULLY
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References


2. Timchalk C et.al. 2002 A physiologically based PBPK/PD model for the organophosphorus insecticide chlorpyrifos in rats and humans.

Company promotion
Normal nerve function
OP effect

AChE

ACh

OP