Pharmacometric modelling of antimalarial drugs in development


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PK/PD of antimalarial drug combinations

Symptomatic infection

Limit of detection

Therapeutic success

MIC: Minimum Inhibitory Concentration

Release of merozoites from the liver

10 × multiplication / 48 hrs

Artemisinin

Partner drug

Total parasite count

Drug concentration (ng/mL)

1.E+10
1.E+09
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00

0 1 2 3 4 5 6

Time (weeks)

MIC

Post-prophylactic effect
Dose-optimisation of antimalarial drugs

Uncomplicated *falciparum* malaria

Piperaquine exposure

- **Standard oral dose**
  - Lower exposures in small children

Piperaquine exposure

- **Optimised oral dose**
  - Equivalent exposures in all weight groups

Dihydroartemisinin exposure

- **Standard parenteral dose**
  - Lower exposures in small children

Dihydroartemisinin exposure

- **Optimised parenteral dose**
  - Equivalent exposures in all weight groups

Severe *falciparum* malaria

Many of the antimalarial drugs were introduced at the wrong dose, especially for children
Novel methodologies for dose-selection

- Low non-curative single dose to non-immune volunteers/patients
- Frequent parasite measurements
- Frequent drug measurements
- Rescue treatment before symptomatic malaria
- Ideal data for PK/PD modelling
  - MPC determination
  - MIC determination
  - Evidence-based dose selection
  - Drug combination selection

White, AAC, 2013
A novel study to estimate the MIC in patients

- An adaptive design and PK/PD modelling approach was used to determine the MIC of cipargamin (KAE609) in patients
- Vietnamese adults with uncomplicated *P. falciparum* malaria (n=25)
- 30 mg, 20 mg, 15 mg or 10 mg single dose of cipargamin
- Extensive blood sampling was carried out for PK, microscopy and qPCR measurements
- Artemisinin-based combination therapy was administered as rescue treatment (i.e. rising parasite levels but before symptoms)
- NONMEM
Pharmacokinetic properties

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimate (RSE)</th>
<th>IIV CV% (RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>1.72 (5.69)</td>
<td>18.5 (12.4)</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>40.6 (4.71)</td>
<td>-</td>
</tr>
<tr>
<td>No tran comp</td>
<td>3 fix</td>
<td>-</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>1.65 (25.2)</td>
<td>176 (30.4)</td>
</tr>
<tr>
<td>MTT (h)</td>
<td>0.867 (12.6)</td>
<td>65.2 (13.5)</td>
</tr>
<tr>
<td>F (%)</td>
<td>100 fix</td>
<td>26.2 (25.3)</td>
</tr>
<tr>
<td>σ (%)</td>
<td>17.5 (10.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

- Body weight allometrically on CL/F and V/F
- Dose-proportional PK

![Graph showing pharmacokinetic properties](image)
Pharmacodynamic data considerations

- qPCR is 100-1,000 times more sensitive than microscopy
- Low density persistent parasitaemia
  - Microscopy: observational bias
  - qPCR: asexual and sexual parasite measurements (DNA-based)
- Censoring of data
- Pool microscopy and qPCR data
Final model describing PK and PD

- Fixed growth rate (10-fold per cycle)
- Dormant parasite population (1%)
- Increased $E_{\text{MAX}}$ with increasing dose

$$dP_{NS}\frac{dt}{dt} = -P_{NS} \times K_{ACT}$$

$$dP_S\frac{dt}{dt} = P_S \times K_{GROW} - P_S \times K_{KILL} + P_{NS} \times K_{ACT}$$
Dose-selection based on the final PK/PD model

23 out of 25 patients characterised accurately as cured or recrudescent

Dose-optimisation in silico

Mono therapy

50 mg KAE609 + partner drug (100-fold kill/48h)

Combination therapy
Concluding remarks

- Many of the currently used antimalarial drugs were introduced at the wrong doses, especially in young children
- Pharmacometric approaches can be used to identify patient groups at particular risk of therapeutic failures and emergence of parasite resistance
- Pharmacometric approaches can be used to optimise the dosing in these sub-populations of patients
- The presented novel study design, analysed with a pharmacometric approach, can provide an evidence-based tool for:
  - Dose selection
  - Dose strategy selection
  - Drug combination selection
Acknowledgements

- All patients that participated in this study

Co-investigators:

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Thank you for your attention
Pharmacodynamic data censoring

All data

Censored data

Cured patient

Recrudescent patient

ID1

ID2

Time (days)

Micro

qPCR

Gamet

Ring

Total parasite biomass

Time (days)

0 10 20 30 40

1.E+04

1.E+05

1.E+06

1.E+07

1.E+08

1.E+09

1.E+10

1.E+11

1.E+12

0 10 20 30 40

1.E+04

1.E+05

1.E+06

1.E+07

1.E+08

1.E+09

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1.E+09

1.E+10

1.E+11

1.E+12

MIC

Recrudescent patient

ID2

Cured patient

ID1