Selection of dosing regimens for fixed-dose combinations in children.

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Background: The rationale for dose and dosing regimen in children remains a challenge in drug development. Many assumptions are commonly made by researchers in this field, often relying on empirical approaches. One of these assumptions is that when two drugs are given in combination to children, the ratio between the compounds must remain the same as assessed in adults.

Methods: Using nonlinear mixed effects modelling, the pharmacokinetics of atovaquone (ATV) and proguanil (PGN) was characterised. These drugs are currently used in combination with a fixed-ratio of 2.5 : 1 to threat malaria in both adult and paediatric patients. Using data from 12 different clinical trials, we evaluated the differences in parameter distributions and their implications for systemic exposure to ATV and PGN. Simulations were subsequently performed to define the appropriate dosing regimen and ratios in children, assessed as the dose that warrants comparable target exposure in adults and children.

Results: Body weight and ethnicity were found to be significant covariates determining the exposure to both drugs. Therefore, in order to achieve the target exposure, doses should be adjusted according to the differences in weight and ethnicity. Such an dosing regimen results in different ratios between ATV and PGN across the population.

Conclusions: A model-based approach enables characterisation of systemic exposure to drug combinations in a strictly quantitative manner. The adjustment of the dose ratio according to the distribution of covariates affecting the pharmacokinetics is critical to achieve effective and safe exposures across a wide weight/age range. These factors may represent further challenges to dosing recommendation and to the choice solid dosage forms.