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Use of population pharmacokinetics to assess adherence to amodiaquine used for seasonal malaria chemoprevention

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Introduction

Seasonal malaria chemoprevention (SMC) has been widely implemented by MSF in the African Sahel. It consists of monthly courses of antimalarial drugs during the high-risk season. A single dose of sulfadoxine-pyrimethamine (SP) and a dose of amodiaquine (AQ) are administered by a health worker, and doses of AQ are administered by caregivers at home on the following two days. Poor adherence to AQ might reduce the protective effectiveness of SMC. In an area of Niger where MSF was concerned about the effectiveness of SMC, we performed a study to describe the population pharmacokinetic (PK) properties of AQ when administered as part of SMC. These data were used to develop models describing adherence to SMC among children participating in a case-control study performed in the same area.

Methods

A convenience sample of 165 children aged 3-59 months was enrolled in Magaria, Niger, in November 2016. All three doses of SMC were administered at home by nurses, and then blood samples were drawn in six predefined sampling windows over the following six weeks. Drug concentrations were determined using a liquid chromatography tandem mass spectrometry-based assay. Concentration-time data were evaluated simultaneously using nonlinear mixed-effects modelling in the software NONMEM (Icon, Hanover, USA). In the case-control study, one-half (n=297) of cases and their 859 healthy village- and age-matched controls were randomly selected to be analysed for drug concentrations and adherence.

Ethics

This study was approved by the MSF Ethical Review Board and the Comité Consultatif National d'Éthique of Niger.

Results

We used two-compartment and three-compartment disposition models respectively to describe AQ and desethylamodiaquine (DEAQ) concentration-time profiles. This method for evaluation of adherence showed a sensitivity of 65-71%, when the first dose of SMC was directly observed by a health worker.

Among case-control study participants, modelled adherence simulations and measured DEAQ concentrations showed poor adherence. Using the optimal model, only 7% of cases and 8% of controls had complete adherence to AQ. Even when using the most conservative cut-offs in the model (5^{th} percentile of DEAQ concentration), only 10% of cases and 17% of controls had complete adherence.

Conclusion
To our knowledge, this is the first description of the population pharmacokinetics of AQ when used in the setting of SMC; the model was robust and showed good predictive performance. Despite community engagement efforts, adherence to SMC was very poor in this setting. Efforts to improve adherence are urgently needed, both to protect children against malaria and to prevent emergence of resistance to SP and AQ.

Conflicts of Interest
None declared.

Word count: 418 final

OK depending on the two minor responses above. Thanks – Matt Coldiron 25 February 2020