Population pharmacokinetics of cotrimoxazole West African HIV-infected children

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BACKGROUND

This project is part of the MONOD-ANRS 12206 trial designed to evaluate a simplified once-daily antiretroviral therapy in children infected with HIV in Ivory Coast and Burkina Faso. In addition to antiretroviral treatment, all children received **cotrimoxazole prophylaxis**. The drug, used to prevent opportunistic infections, is a combination of two active molecules: **trimethoprim (TMP) and sulfamethoxazole (SMX)**. Some pharmacokinetics (PK) data in neonates and children are available but the age group 6 months - 3 years is very poorly described. However, these limited available data suggest that current doses should evolve as the maturation of the child to prevent from over or under dosages of medication. Our aim was to investigate the **PK of cotrimoxazole in a therapeutic cohort of children** initiated < 2 years of age on a combination antiretroviral therapy (cART).

METHODS

- All HIV-infected children from MONOD trial, diagnosed before 2 years old, and confirmed by DNA-PCR were enrolled in an initial therapeutic cohort offering a cART with cotrimoxazole prophylaxis (TMP/SMX: 40 mg/200 mg/day once daily) in Ouagadougou, Burkina Faso, and Abidjan, Ivory Coast according to the 2010 WHO recommendations (5 ml from 6.0 to 13.9 kg weight band/day).
- Quantification of TMP and SMX in human plasma collected 6 months after cART initiation was performed using a validated **liquid chromatography method with UV detector.**
- Plasma concentrations of HIV-infected children aged from 6 months to 2.5 years were analysed using a **nonlinear modelling with mixed effects**, with NONMEM software. Estimated individual PK parameters were used to calculate individual exposures to TMP and SMX. **Individual areas under curves (AUC) in children** were compared with AUC in adults known to be effective.
- PK data were associated with the risk of severe adverse event leading to death or hospitalisation, classified into 3 categories: bacterial infections, acute gastro enteritis, malaria infection.

RESULTS

114 children with a median age of 1.6 years (IQR = 0.9), a median weight of 9 kg (IQR = 2.5), and sex ratio (M/F) of 0.88 were analysed.

PK analysis

TMP's PK and SMX's PK were described by **a one-compartment model with absorption and first-order elimination**. No effects of covariates (weight, age and sex) were found on these two parameters in our population.

The models were validated by Visual Predictive Check and Bootstraps (Figure 1).

Estimated individual PK parameters were used to calculate individual exposures to TMP and SMX. **Individual areas under curves (AUC) in children** were compared with AUC in adults known to be effective (*Amini H, Ahmadiani A. Rapid and simultaneous determination of sulfamethoxazole and trimethoprim in human plasma by high-performance liquid chromatography. J Pharmac and Biomedical Analysis. 2006 Oct; 43: 1146-1150).*

This comparison (Figure 2) showed **that children are less exposed to both cotrimoxazole components than adults**. This underexposure is more important for TMP than SMX.

Figure 1: Visual Predictive Check

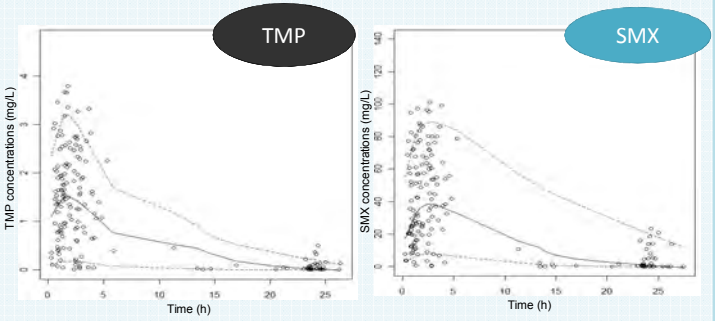
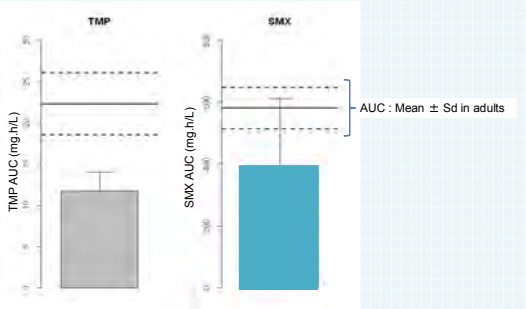
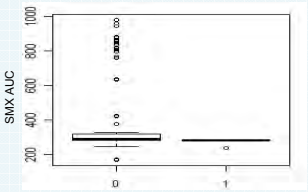


Figure 2: Comparison with AUC data in adults



PK-PD analysis

PK data were associated with the overall risk of severe adverse event leading to death or hospitalisation



No relationship was found between the concentrations of cotrimoxazole and bacterial infections or acute gastro enteritis. **A trend was observed only between lower cotrimoxazole exposure and infection with malaria (p=0.08).**

CONCLUSION & PERSPECTIVES

- PK of TMP and SMX have been properly described. No effects of covariates were found, but the study of genetic polymorphism is underway.
- **Children are under exposed in cotrimoxazole** (TMP and SMX) compared to adults, raising the issue of revising the dosing of cotrimoxazole prophylaxis in children.

The ANRS 12206 MONOD Collaboration Study Group (as of April 1st, 2014)

Participating sites

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