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Poster presentation

Didanosine population pharmacokinetics in West African HIV-infected children administered once daily tablets in relation to efficacy after one year of treatment (ANRS 12103)

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Background

Didanosine is a potent nucleoside reverse transcriptase inhibitor used for HIV infection treatment. A once daily administration of chewable/dispersible didanosine tablets (Videx®) was available for children in Burkina Faso but few pharmacokinetic data were reported with these galenic form and administration scheme. This study is part of a phase II trial on once-a-day pediatric HAART. The objectives were to describe didanosine pharmacokinetics and to establish relationships between doses, plasma concentrations and treatment efficacy in children.

Methods

Didanosine concentrations were measured in 40 children after 2 weeks and in 9 children after 2 to 5 months of didanosine lamivudine efavirenz combination. A total of 166 didanosine plasma samples were measured using an HPLC assay with detection by UV absorbance. A population pharmacokinetic model was developed with NONMEM. The link between maximal concentration (C_{max}), area under the curve (AUC) and the decrease in HIV-1 RNA levels after 12 months of treatment was evaluated. The threshold AUC and C_{max} improving efficacy were determined and an optimized dosing schedule was simulated.

Results

Didanosine pharmacokinetics was best described by a one-compartment model with first order absorption and elimination. Mean population pharmacokinetic estimates with the corresponding inter-subject variabilities (%) were: apparent elimination clearance CL/F = 146 L/h (90%) and apparent volume of distribution V/F = 356 L (122%). CL/F and V/F were increased, probably due to a lower bioavailability with tablets than with pediatric powder. Clearance increased with body surface area. The decrease in viral load after 12 months of treatment was significantly correlated with didanosine AUC and C_{max} ($p \leq 0.02$) during the first weeks of treatment. An AUC > 0.85 mg/l.h was significantly linked to better viral load decrease (3 *vs.* 2.4 $\log_{10}$ copies/ml, $p < 0.03$) and higher percentage of children with undetectable viral load after one year of treatment (95% *vs.* 68%, $p = 0.056$). Four children developed viral resistances to didanosine before one year of treatment, all of them had an AUC < 0.85 mg/L.h. A C_{max} > 0.4 mg/L was also correlated to a better viral load

decrease and to the absence of viral resistance to didanosine.

Conclusion

A 360 mg/m^2 ddI dose administered as tablets should be a more appropriate dose to improve efficacy than 240 mg/m^2 in these children. However data on adverse events with this dosage are missing.