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Background and objective: Nevirapine (NVP) is part of first line antiretroviral regimens (HAART) of most resource limited countries. Rifampicin (RFM), an essential component of tuberculosis (TB) therapy, significantly reduces NVP plasma levels. We have determined the full pharmacokinetic curves of NVP and RFM in HIV-TB patients on combined therapy in Burkina Faso.

Methods: We have enrolled 16 patients with documented HIV-1 infection, CD4+ T lymphocyte < 100 cells /cm³, no previous history of HAART and TB disease (TB diagnosis was based on national TB guidelines). Standard anti-TB therapy (2 RHZE/4 RH) and standard HAART (fixed dose combination of stavudine, lamivudine and nevirapine) were used in all cases. HAART was started within 30 days from anti-TB therapy; NVP was given as 200 mg OD for 2 weeks, then 200 mg BID. Three NVP pharmacokinetic curves were done: 1°) after 4 weeks of RFM+NVP (T1); 2°) after 10 weeks of RFM+NVP (T2); 3°) 4 weeks after termination of antituberculosis therapy (T3). RFM pharmacokinetic curves were: 1°) at steady state before NVP (T0); 2°) after 4 weeks of RFM+NVP (T1); 3°) after 10 weeks of RFM+NVP (T2). NVP and RFM parameters were measured by HPLC in plasma samples at 0, 1, 2, 4, 6, 8, 12 hours after drug intake.

Conclusions: RFM determined a reduction of the AUC of NVP in TB/HIV co-infected patients that was rapidly reversible and virtually disappeared after 10 weeks of combined therapy. The AUC of RFM was lower then previously described in TB/HIV co-infected patients but increased significantly during combined treatment. These data warrant the implementation of larger clinical trials on the association of NVP and RFM with tolerability and efficacy end-points.

Results

NVP pharmacokinetic curves

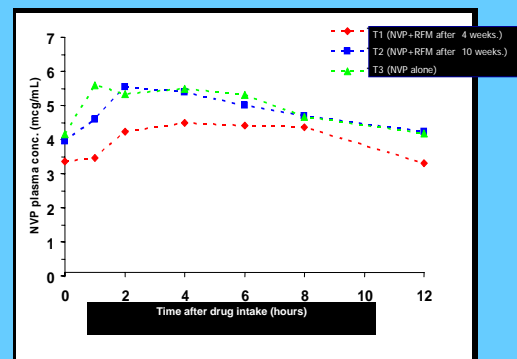
The main pharmacokinetic parameters of nevirapine are presented in table 1. We observed a reduction of median value of the area under the curve (AUC) of NVP of 27.7% at T1 compared to NVP alone (T3) (44.1 mcg/ml/h vs. 61.0 mcg/ml/h; p=0.02). The reduction virtually disappeared at T2 (3.7%, AUC of 58.8 mcg/ml/h)(Figure 1). Values of C_{trough} < 3 mcg/ml were observed in 33.3%, 30.8% and 12.5% of cases at T1, T2, and T3 (NVP alone) respectively.

Table 1. Pharmacokinetic parameters of nevirapine [median values (range)] during combined therapy with rifampicin (T1 and T2) and after TB therapy (T3).

Pharmacokinetic parameters	P*	T1 (NVP+RFM 4 w)	P**	T2 (NVP+RFM 10 w)	P***	T3 (NVP)
AUC [0-12] (mcg.h/mL)	0.07	44.1 (19.6 – 134.2)	0.02	58.8 (19.9 – 125)	0.05	61.0 (25.0 – 97.8)
C _{trough} (mcg/mL)	0.53	3.35 (0.6-10.5)	0.02	3.9 (0.9 – 10.6)	0.07	4.2 (1.5 – 8.3)
C _{min} (mcg/mL)	0.35	3.3 (0.6-10.5)	0.02	3.96 (0.9 – 9.8)	0.12	3.97 (1.15 – 6.6)
C _{max} (mcg/mL)	0.27	5.1 (2.7-12.4)	0.03	5.9 (2.5 – 12.7)	0.01	6.6 (3.3 – 10.8)
T _{max} (h)	0.03	4.0 (1.0 – 4.0)	0.17	2.0 (2.0 – 6.0)	0.04	1.5 (1.0 – 6.0)
t _{1/2} (h)	0.51	12.3 (4.8 – 54.9)	0.24	14.7 (6.4 – 21.3)	0.67	13.6 (6.0 – 24.3)

* Wilcoxon signed-rank test ; *p value T1 vs. T2; ** p value T1 vs. T3; *** p value T2 vs. T3

Figure 1. Nevirapine pharmacokinetic curves



RFM pharmacokinetic curves

The median AUC values of RFM were low at T0 (11.9 mcg/ml/h), but increased of 57.3% at T1 (18.6 mcg/ml/h; p=0.01) and of 74.1 % at T2 (20.6 mcg/ml/h; p=0.001). Efficacy of TB and HIV treatment were not hampered by combined therapy.

Table 2. Pharmacokinetic parameters of rifampicin [median values (range)] before (T0) and during combined therapy with nevirapine (T1 and T2).

Pharmacokinetic parameters	P*	T0 (RFM)	P**	T1 (NVP+RFM 4 w)	P***	T2 (NVP+RFM 10 w)
AUC [0-24] (mcg.h/mL)	0.01	11.9 (2.2 – 34.6)	0.001	18.6 (4.5 – 53.3)	0.03	20.6 (7.4 – 41.5)
C _{trough} (mcg/mL)	0.03	0 (0-0)	0.07	0 (0 – 0.78)	0.25	0 (0 – 0.33)
C _{min} (mcg/mL)	0.04	0 (0-0)	0.07	0 (0 – 0.6)	0.5	0 (0 – 0.1)
C _{max} (mcg/mL)	0.01	2.51 (0.6-6.8)	0.003	3.1 (1.1 – 9.6)	0.27	2.83 (1.0 – 6.7)
T _{max} (h)	0.73	2.0 (1.0 – 6.0)	0.44	2.0 (1.0 – 4.0)	0.23	2.0 (1.0 – 8.0)
t _{1/2} (h)	0.30	2.65 (1.5 – 5.0)	0.12	2.9 (1.4 – 5.9)	1	2.6 (1.9 – 8.8)

* Wilcoxon signed-rank test ; *p value T0 vs. T1; ** p value T0 vs. T2; *** p value T1 vs. T2

Figure 2. Rifampicin pharmacokinetic curves

