

Pharmacokinetics of Nevirapine when Co-administered with Rifampin in HIV-Infected Thai Children with Tuberculosis

Wasana Prasitsuebsai¹, Tim R. Cressey^{2,3}, Edmund Capparelli⁴, Nirun Vanprapar¹, Keswadee Lapphra¹, Pimpanada Chearskul¹, and Kulkanya Chokephaibulkit¹

¹Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, ²Harvard School Public Health, Boston, MA, USA,
³PHPT-IRD, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand, ⁴University of California, San Diego, CA, USA

ABSTRACT

Background: Approximately a quarter of HIV-infected Thai children are co-infected with Tuberculosis (TB). In Thailand the current first line antiretroviral treatment is a nevirapine based HAART regimen, primarily administered using adult fixed drug combinations (FDC). Rifampin is a key component of TB treatment but is a potent inducer of the hepatic cytochrome P450 enzymes responsible for the metabolism of nevirapine. Concomitant NVP-rifampin treatment can lead to subtherapeutic NVP plasma levels. We report the pharmacokinetics (PK) of NVP in HIV/TB coinfecting children receiving NVP-based HAART FDC formulation and rifampin.

Methods: This is a cross-sectional, open-label, single arm PK study. Thai children with HIV/TB infection receiving NVP either as FDC of AZT/3TC/NVP (GPO-VIR@Z250) or d4T/3TC/NVP (GPO-VIR@ S30) for at least 4 weeks and rifampin-based anti-TB therapy for at least 2 weeks were enrolled. NVP-FDC dosing was based upon the NVP dose of 150-220 mg/m², twice daily. Adherence to ARV and anti-TB drugs was assessed 3 days prior to PK blood sampling. Blood samples were taken at pre-dose and 1, 2, 4, and 6 hours after NVP drug administration. Plasma concentrations of NVP were measured by HPLC and PK data were analyzed using a one-compartment model with empiric Bayesian individual subject parameter estimates generated by the program NONMEM.

Results: Eight children have completed the PK sampling. Five children were using GPOvir-S30, 3 children using GPOvir-Z250. At the time of PK sampling, median age (range) was 9.7 (4.4-11.8) years, weight was 18.9 (14.5-28.6) kg, CD4% was 19.6 (7.8-37.7), and 5 of 8 children had an HIV RNA viral load < 40 copies/mL. Average NVP and rifampin dosages were 171.3 (150.7-262.7) mg/m²/dose, and 9.8 (8.3-11.8) mg/kg/dose respectively. Median (range) NVP clearance was 0.08 (0.06-0.16) L/hr/kg. Median NVP AUC and predose levels were 86.80 (40.56-171.73) mcg*hr/mL, and 6.48 (3.03-13.66) mcg/mL, respectively. All children achieved a pre-dose NVP concentration above the recommended therapeutic target of 3.0 mcg/mL. No drug adverse events occurred during the study.

Conclusions: These results show that co-administration of rifampin with NVP, using generic FDC at the higher end of the NVP dose range, resulted in appropriate NVP exposure in Thai children.

BACKGROUND

Tuberculosis in Thailand: In 2007, there were 31,817 cases of TB reported in Thailand and 2.8% of these were children. Of these, 24,434 (76.8%) had pulmonary TB.^[1] 27% of children with TB were coinfecting with HIV-infection.^[2]

HIV Infection in Thailand: As of 2006, there were 20,000 children living with HIV in Thailand.^[3] 7.6% of HIV infected patients had TB coinfection.^[4] The current first line regimen in children is nevirapine based HAART regimen, primarily administered using adult fixed drug combinations (FDC) of GPO-VIR@S30 (d4T/3TC/NVP) or GPO-VIR@Z250 (AZT/3TC/NVP) that will often require breaking the tablet to attain the required dose.

Concurrent treatment of HIV and TB: Rifampin is a key component of TB treatment but is a potent inducer of the hepatic cytochrome P450 enzymes, particularly CYP3A4, responsible for the metabolism of nevirapine.^[5] Concomitant NVP-rifampin treatment can lead to subtherapeutic NVP plasma levels in adults raising concerns regarding treatment outcome.^[6] This study determined the effect of rifampin on nevirapine plasma levels in children with HIV and TB coinfection.

OBJECTIVES

Primary Objective:
o To determine nevirapine AUC, C_{min}, and C_{max} levels in Thai children with HIV infection and tuberculosis receiving concomitant GPO-VIR@S30 or GPO-VIR@Z250 and rifampin treatment.

Secondary Objective:
o To assess immunological and virological responses in relation to nevirapine drug levels in patients who have taken at least 8 weeks of concomitant GPO-VIR@S30 or GPO-VIR@Z250 and rifampin treatment.

METHODS

STUDY POPULATION

o HIV-infected children with tuberculosis, age 1-13 years old who are receiving concomitant rifampin with a maintenance dose of GPO-VIR@S30 (d4T/3TC/NVP 30/150/200 mg/tab) or GPO-VIR@Z250 (AZT/3TC/NVP 250/150/200 mg/tab) for at least 2 weeks

DRUG REGIMENS

- o The dosage of nevirapine with GPO-VIR@S30 and GPO-VIR@Z250 was equivalent to 120-200 mg/m²/dose given every 12 hours (tablet divided if necessary).
- o The dosage of rifampin was 10-20 mg/kg/day given once daily in the evening.

PK STUDY

- o Drug adherence of the 3 days period prior to the PK blood sampling was assessed by self report. Blood samples were taken following the morning dose of either GPO-VIR@S30 or GPO-VIR@Z250 at pre-dose, and 1, 2, 4, and 6 hours post-dose.
- o Plasma concentrations of NVP were measured by a validated HPLC assay and PK data were analyzed using a one-compartment model with empiric Bayesian individual subject parameter estimates generated by the program NONMEM.

RESULTS

Demographic Data

Eight children were enrolled between September 2007 and October 2008 at Siriraj Hospital, Bangkok. Four (50%) of children were male. All children had been diagnosed with pulmonary TB. Five children were receiving GPO-VIR@S30 and 3 children were receiving GPO-VIR@Z250.

Table 1: Patient characteristics and history of ARV treatment (N=8)

Demographic Data	Median	Min-Max
Age (yrs)	9.7	4.4-11.8
Weight (kg)	18.9	14.5-28.6
Duration of taking GPO-VIR@S30 or GPO-VIR @Z250 (months)	6.5	1.8-25.6
Duration of taking rifampin (months)	4.8	1.2-11.8
HIV RNA viral load (copies/mL)	<40	<40-18,100
CD4 cell count (cells/mm ³)	504.5	229.0-1458.0
%CD4 cells	19.6	7.8-37.7
Hemoglobin (g/dL)	12.0	10.6-12.4
SGPT (U/L)	41.5	13.0-59.0

Table 2: Pharmacokinetic parameters of nevirapine (both GPO-VIR@S30 or GPO-VIR@Z250)

Parameters	Median	Min-Max	Recommended /Target
Nevirapine Dosage (mg/m ² /dose)	171.3	150.7-262.7	>150 [7]
Rifampin Dosage (mg/kg/day)	9.8	8.3-11.8	10-20
Predose levels (mcg/ml)	6.48	3.03-13.66	>3.00 [8]
Nevirapine AUC (mcg*hr/ml)	85.16	40.56-171.73	78.4 [9]
Nevirapine Clearance (L/hr/kg)	0.08	0.06-0.16	0.08 [9]



Figure 2: Individual nevirapine concentrations and predicted concentrations

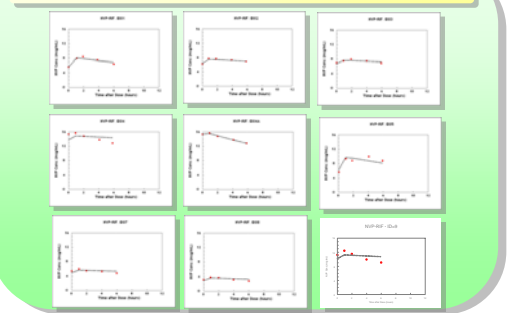
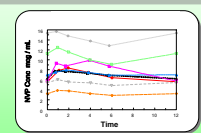


Figure 3: Individual NVP Concentration versus time curves



Concentrations at 12 hr were assumed to be equal to predose concentration.

DISCUSSION

- o A previous study of the concomitant use of nevirapine and rifampin based regimen in Thai adults reported significant reductions in nevirapine trough levels but only 14% of patients reported subtherapeutic nevirapine plasma levels.^[9]
- o Despite 29.7% of patients having subtherapeutic nevirapine plasma levels, virological and immunological outcomes at 24 weeks were not different between patients in HIV infected patients receiving nevirapine with and without rifampin.^[9]
- o This study found that all 8 children receiving standard NVP dosage concomitant with rifampin had adequate trough level (>3.0 mcg/mL) and adequate NVP AUC with median of 85.16 mcg*hr/mL.

CONCLUSION

These results show that co-administration of rifampin with NVP using FDC at the higher end of the NVP dose range, resulted in appropriate NVP exposure in Thai children.

REFERENCE

- National Notifiable Disease Surveillance (Report 506): Center of Epidemiology Information, Bureau of Epidemiology, DDC, MOPH, Thailand: 2008.
- Lotehka R, et al., Childhood TB epidemiology and treatment outcomes in Thailand: a TB active surveillance network, 2004 to 2006. BMC Infect Dis 2008; 8:94.
- World Health Organization: Epidemiological fact sheets on HIV/AIDS and sexually transmitted infections: Thailand 2006 update. Geneva: World Health Organization; 2006.
- World Health Organization: Tuberculosis in South-East Asia region: The regional report; 2008.
- Autar RS, et al., Nevirapine plasma concentrations and concomitant use of rifampin in patients coinfecting with HIV-1 and tuberculosis. Antivir Ther 2005; 10(8):937-43.
- Manosuthi W, et al., Plasma Nevirapine Levels and 24-week efficacy in HIV-infected patients receiving nevirapine-based Highly Active Antiretroviral Therapy with or without rifampin. Clin Infect Dis 2006; 43:253-5.
- Boehringer Ingelheim Pharmaceuticals. Package insert for nevirapine; 2008.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139.
- Chokephaibulkit K, et al., Pharmacokinetics of nevirapine in HIV-infected children receiving an adult fixed-dose combination of stavudine, lamivudine, and nevirapine. AIDS 2005; 19:1495-9

ACKNOWLEDGEMENTS

o The authors would like to thank all the patients who participated in this trial and all study staff.
o This study was supported by The Thai Commission on Higher Education.