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Pharmacokinetic Comparison of Generic and Trade Formulations of Lamivudine, Stavudine and Nevirapine in HIV-Infected Malawian Subjects

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Abstract

Objective: Several generic antiretroviral formulations have been removed from the WHO medication list for inadequate bioequivalence. Malawi has introduced an antiretroviral program using generic Triomune (containing d4T,3TC,NVP). This study determined the pharmacokinetic properties of generic and trade formulations of d4T, 3TC, and NVP in HIV-infected Malawians.

Design and Methods: Randomized, Cross-Over Pharmacokinetic Study
Patients currently receiving Triomune-40 were randomized to receive generic or trade formulations of d4T (40mg), 3TC and NVP for 1 month. Subjects then crossed-over to the alternate formulation for 1 month. Blood samples were collected at 0, 0.5, 2, 4, 6, and 8 hours post-observed dose. Geometric mean ratios and 90% confidence intervals (CI) for Cmax and AUC were calculated to determine bioequivalence (Cmax and AUC 90% CI=0.8-1.25).

Results: 12 patients enrolled (6M, 6F). Age, weight, and height were 38.4±7.7yr, 71.2±7.0kg, and 164.8±6.3 cm, respectively. Geometric mean ratios for Cmax were: 3TC, 1.1 [0.8-1.6], d4T, 1.4 [1.2-1.7], NVP 0.9 [0.7-1.2]. For AUC0-8h, Geometric mean ratios were 3TC, 1.0 [0.7-1.3], d4T 1.1 [1.0 1.2], NVP 0.9 [0.7-1.1]. d4T Cmax was significantly higher with the Triomune than trade (0.9±0.3 vs 0.6±0.2). Malawians had significantly higher NVP exposures with both formulations compared to historical reports for mixed populations of Western HIV-infected patients. 3/9 (33%) patients with grade 1 neuropathy reported less symptoms on the trade formulation.

Conclusions: In this pilot study, although exposures were generally similar between the formulations, Triomune did not meet the strict definition of bioequivalence. d4T peak concentrations were significantly higher with Triomune, which may be related to neuropathic toxicity. Since genetic and environmental factors may influence the PK of antiretrovirals, evaluation of drug exposure should be performed as these medications are introduced to new populations.

Introduction

Many developing countries have introduced antiretroviral programs.

Many of these programs are relying on less costly generic medications to achieve treatment goals consistent with the World Health Organization (WHO) 3x 5 initiative [1].

Malawi introduced their antiretroviral program in 2001 using generic Triomune made by Cipla.

Current Malawi guidelines advocate the use of WHO approved fixed dose combination therapy of d4T, 3TC, and NVP [2].

Initially, several of these generic formulations were endorsed by the WHO [3] but recently, several generic medications have been removed from the WHO list for inadequate bioequivalence [4].

Cipla Ltd. has demonstrated that Triomune 40™ is bioequivalent to trade formulations after a single dose in healthy volunteers [3].

Little pharmacokinetic (PK) data exists among HIV positive Africans, and no data exists among Malawians.

This open-label, randomized, crossover study compares the PK properties of generic, fixed dose Triomune 40 (d4T, 3TC, NVP) and trade formulations of the same drugs in HIV infected Malawians.

Methods

Study Setting: UNC project is a research and care centre located at Kamuzu Central Hospital (KCH), a government tertiary care hospital, in Lilongwe Malawi.

Study Design
Patients currently receiving Triomune-40 were randomized to receive generic or trade formulations of d4T (40mg), 3TC and NVP for 1 month. Subjects crossed-over to the alternate formulation for 1 month. Subjects took each formulation for at least 21 days prior to pharmacokinetic sampling.

Study Population
HIV infected subjects that were enrolled in a prospective observational study of generic antiretroviral therapy at the Lighthouse clinic were evaluated for possible enrollment in this component of the study. All subjects were required to be taking Triomune 40 (d4T 40mg, 3TC 150 mg, Nevirapine 200 mg) twice daily for greater than 2 weeks at the time of enrollment. Subjects were excluded if hemoglobin was less than 10mg/dl, weight was less than 60kg, attendance to clinic was irregular or adherence to therapy was poor.

***Medications*:**
The patient was randomized to either first month Triomune 40 (Cipla, India) or first month trade formulations (Epivir®, GlaxoSmithKline, Zerit®, Bristol Myers Squibb, and Viramune®, Boehringer Ingelheim). The dosages of the trade medication were Stavudine 40 mg twice daily, Lamivudine 150mg twice daily; and Nevirapine 200mg twice daily. Equivalent doses were contained in Triomune 40 which was taken 1 tablet twice daily.

Study Visits:
Subjects took their medication between 7:30 pm and 8:00 pm the evening prior to the study visit. The subject reported to the study site by 7:30 am (fasting) on the study day prior to taking their morning dose of antiretroviral therapy. An intravenous catheter was placed in the arm of the subject for blood sampling. A 5mL blood sample was obtained in an EDTA tube, and the time of sampling recorded. After observed doses of medications, 10 mL blood samples were obtained at 0.5h, 2h, 4h, 6h and 8h. Subjects received a standardized breakfast after the 0.5h sample and lunch after the 4h sample.

Patients answered a brief questionnaire that included the time of the previous three doses of medication, assessment of adherence over the preceding day, 3 days and 30 days, reasons for missed doses, adherence techniques and perceived differences in trade or generic medications. Clinical and laboratory data from the main observational study was available for each participant.

Sample Processing and Analysis
Blood samples were immediately centrifuged at 2600rpm at 4°C x 10 minutes. Plasma was removed and placed in 2ml cryovials and stored at -70°C. Specimens were shipped on dry ice to the CLIA certified UNC CFAR Clinical Pharmacology/Analytical Chemistry Laboratory for University of North Carolina in Chapel Hill for measurement of drug concentrations using published methods.

Statistical Analysis:
Descriptive statistics were performed using Stata 8.2 (College Station, TX). Area under the concentration-time curve over 8 hours (AUC_{0-8h}) was calculated using non-compartmental methods (WinNonLin 4.0.1). C_{12h} and AUC_{0-12h} were derived using λz extrapolations. Geometric mean ratios (R) and 90% confidence intervals (CI) were calculated to determine bioequivalence (Cmax and AUC 90% CI=0.8-1.25). Results were compared to historical data.

Results

Demographics: 6 males and 6 females enrolled in the study. Mean±standard deviation patient age was 38.4±7.7 years; weight was 71.2±7.0 kilograms; height was 164.8±6.25 centimeters; and body mass index was 26.2 ±3.6 kg/m^2. There were no significant differences in these parameters according to randomization arm. Subjects were on Triomune for a 10.8 ± 1.4 months prior to study entry.

Table 1. Pharmacokinetic Parameters [Mean ± SD] And Geometric Mean Ratios [R] for Generic vs Trade Formulations of Lamivudine, Stavudine, and Nevirapine

Drug	Cmax (mg/L)			T_{max} (hr)			AUC_{0-8hr} (hr*mg/L)			C_{12hr} (mg/L)		
	Trade	Generic	R [90% CI]	Trade	Generic	R [90% CI]	Trade	Generic	R [90% CI]	Trade	Generic	R [90% CI]
Lamivudine	1.2 ± 0.5	1.4 ± 1.1	1.1 [0.8-1.6]	2.3 ± 1.2	1.4 ± 0.6	0.5 [0.3-0.7]	6.5 ± 3.6	6.3 ± 2.8	1.0 [0.7-1.3]	0.33 ± 0.3	0.24 ± 0.23	0.6 [0.3-1.1]
Stavudine	0.6 ± 0.2	0.9 ± 0.3	1.4 [1.2-1.7]	1.3 ± 1.1	0.8 ± 0.6	0.7 [0.4-1.1]	1.8 ± 0.5	2.1 ± 0.6	1.1 [1.0-1.2]	0.032 ± .02	0.024 ±.027	2.2 [0.7-7.1]
Nevirapine	9.3 ± 4.0	8.3 ± 2.8	0.9 [0.7-1.2]	3.3 ± 2.2	2.5 ± 2.1	0.7 [0.5-1.0]	66.1 ± 28.7	57.5 ± 19.3	0.9 [0.7-1.1]	7.65 ± 3.3	6.0 ± 1.9	0.9 [0.7-1.2]

Figure 1. Lamivudine, Stavudine, and Nevirapine Concentrations vs Time for Generic and Trade Formulations [Mean ± SD], and Historical Western Cohorts [Mean]

Figure 1A. Lamivudine

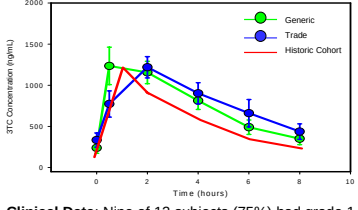


Figure 1B. Stavudine

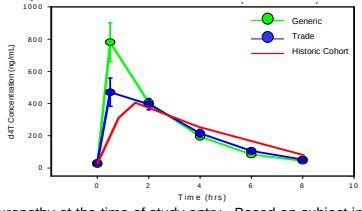
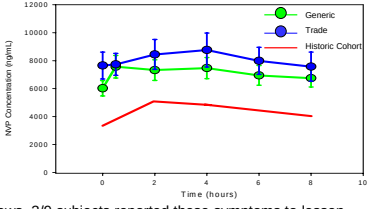


Figure 1C. Nevirapine



Clinical Data: Nine of 12 subjects (75%) had grade 1 neuropathy at the time of study entry. Based on subject interviews, 3/9 subjects reported these symptoms to lessen when taking the trade version of medications. Adherence did not differ among the patients according to generic or trade formulation and was =100% for 10/12 on both visits and >95% for the other 2 subjects. Two subjects reported that three tablets were more difficult to swallow than the single Triomune tablet, but it did not affect their adherence.

Conclusions and Discussion

In this pilot study, although exposures were generally similar between the formulations, Triomune did not meet the strict definition of bioequivalence. d4T peak concentrations were significantly higher with Triomune, which may be related to neuropathic toxicity. Notably, nevirapine levels in Malawians were markedly higher than western cohorts of similar body weight suggesting a possible genetic metabolic etiology for the difference in drug exposure. Since genetic and environmental factors may influence the PK of antiretrovirals, evaluation of drug exposure should be performed as these medications are introduced to new populations.

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