

SINGLE DOSE PHARMACOKINETICS OF LAMIVUDINE IN HEALTHY VOLUNTEERS: COMPARISON OF BLOOD AND URINE KINETICS

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Aims: To study single dose pharmacokinetics of lamivudine (3TC) in healthy subjects.

Methods: Twelve healthy subjects were administered 3TC (150 mg) followed by timed blood and urine collections up to 24 hours. Pharmacokinetic variables and percent dose of 3TC in urine were calculated.

Results: Plasma exposure and percent dose of 3TC in urine were highly correlated ($p < 0.001$; $r = 0.96$). 3TC concentration at 24 hours was undetectable in all study subjects.

Conclusions: Timed urine measurements could be used to study bioavailability of 3TC. Plasma 3TC measurements could be used to monitor adherence among HIV-infected patients on antiretroviral treatment.

Key words: lamivudine; plasma; urine; compliance to treatment

Introduction

Lamivudine (3TC) forms an important component of highly active antiretroviral therapy (HAART) that is used to treat HIV-infected individuals in India. It is well tolerated and can be administered as either 150mg bi-daily or 300 mg once-daily along with other antiretroviral drugs. Lamivudine is present in all fixed dose combination (FDC) pills, has a short elimination half-life, and hence estimation of the drug in spot urine could be useful in monitoring patient

adherence to antiretroviral treatment (1). Earlier studies have shown that 3TC exhibits similar pharmacokinetic profiles in healthy volunteers, asymptomatic HIV-infected individuals and patients with AIDS (2, 3). The primary pharmacokinetic parameters of 3TC in Indian subjects have been shown to be comparable to those previously reported in other populations (4). We undertook a single dose pharmacokinetic study of 150 mg 3TC in healthy subjects with the aim of correlating plasma exposure of 3TC with that of percent dose of 3TC excreted in urine over a particular period of time, and also to assess the feasibility of monitoring patient adherence to antiretroviral treatment using a trough plasma concentration of 3TC.

Methods

Subjects: Healthy adult males meeting the following inclusion criteria were recruited to the study. (i) aged 20 to 60 years (ii) body weight > 45 kg (iii) not suffering from any illness [blood chemistry (random blood glucose, creatinine, transaminases) and hematology (hemoglobin,

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total & differential counts) parameters within normal limits] (iv) not taking concurrent medications at the time of the study and (v) willing to give informed written consent. Smokers and chronic alcoholics were not included into the study.

Conduct of study: The study was carried out at the Pharmacology Ward in Madras Medical College, Chennai, India, and commenced after obtaining clearance from the Institutional Ethics Committees of Tuberculosis Research Centre, Chennai and Madras Medical College, Chennai. Eligible study participants were admitted to the ward a day prior to the study. Informed written consent was obtained from all the volunteers before start of the study.

On the day of the study, they were instructed to empty their bladder. A sample of blood (3ml) was collected in a heparinised vacutainer (0 hour), after a 12-hour fast. They were administered 3TC (150mg) under supervision with 200ml water. Blood samples were collected at 1, 2, 4, 6, 8, 12 and 24 hours after drug administration. They were instructed to make complete urine collections excreted up to 24 hours after drug administration. Breakfast, lunch and dinner were provided uniformly to all the study participants.

The blood samples were centrifuged immediately and plasma stored at -20°C until estimation of 3TC was undertaken. The total volume of urine was measured and aliquots stored at -20° C until analysis of 3TC.

Estimation of plasma and urine lamivudine: Lamivudine concentrations in plasma and urine were estimated by HPLC (Shimadzu Corporation, Kyoto, Japan) according to validated methods described earlier (5, 1).

Pharmacokinetic analysis: Certain pharmacokinetic variables such as peak concentration, time to attain peak concentration,

exposure (0 to 24 hours & 0 to infinity), clearance and half-life were calculated employing a non - compartmental model following first-order kinetics using WinNonlin software (Version 5.1) (Pharsight Corporation, Mountain View, CA, USA).

The percent dose of 3TC excreted in urine collected between 0 to 24 hours was calculated

Statistical Evaluation: Analysis of data was performed using SPSS (version 13) package. Pearson's correlation test was used to evaluate correlation between plasma exposure of 3TC with that of percent dose of 3TC excreted in urine over a 24-hour period.

Results

The pharmacokinetic study of 3TC was conducted in 12 healthy adult Indian men whose age, body weight and height ranged from 19-25 years, 54-71 kg and 162-175.5 cm respectively. The peak concentration of 3TC was achieved at about one hour, suggesting rapid and almost complete absorption. Lamivudine was undetectable in plasma at 24 hours in all the 12 study subjects. The major pharmacokinetic variables and percent dose of 3TC in urine are given in Table 1. The correlation between plasma exposure (0 to infinity) and percent dose of 3TC excreted in urine between 0 to 24 hours was highly significant ($p < 0.001$; $r = 0.96$).

Table 1 Plasma & urine estimates of lamivudine in 12 healthy subjects

Parameters	Mean \pm SD
Peak concentration ($\mu\text{g/ml}$)	1.56 \pm 0.51
Time to attain peak concentration (h)	1.25 \pm 0.45
Exposure (0-24h) ($\mu\text{g/ml.h}$)	6.56 \pm 2.52
Exposure (0-infinity) ($\mu\text{g/ml.h}$)	6.98 \pm 2.63
Clearance (L/h)	25.48 \pm 12.66
Half-life (h)	2.38 \pm 0.69
% dose in urine (0-24 h)	77.05 \pm 14.22

Discussion

A high degree of correlation usually exists between plasma and urine estimates of those drugs whose primary route of elimination is through the kidneys. Although the route of elimination of 3TC is mainly renal, knowledge about urinary excretion of 3TC and its correlation with plasma concentrations is not available in the literature. This single dose pharmacokinetic study in healthy volunteers has demonstrated that urine 3TC excreted over a period of 24 hours was highly correlated with plasma exposure, which suggests that urine 3TC estimations can be used to infer bioavailability of the drug. This finding is particularly important and could be useful in situations where bioequivalence studies of 3TC are performed. Thus invasive blood collections can be replaced by simple, non-invasive urine collections. The study has also demonstrated the usefulness of plasma 3TC in predicting antiretroviral treatment adherence. At a dose of 150mg, 3TC was measurable in blood collected at 12 hours, but could not be detected at 24 hours. This suggests that if 3TC is not measured in blood collected at a particular time point, the patient has not taken the drug in the last 12 hours or longer. Thus, information on one or more missed doses can be obtained. Since 3TC is present in all FDC pills manufactured in India and other countries, trough plasma 3TC estimation can be used as a marker for predicting antiretroviral treatment adherence of patients. A similar approach has been reported by Liechty et al (6), who reported that abnormally low, untimed antiretroviral drug levels in blood could identify individuals with very low adherence at high risk of HIV disease progression and death. Measurement of 3TC in urine and indinavir in saliva has been reported to be useful in monitoring patient compliance to treatment (1, 7). Plasma 3TC estimation could serve as yet another means to monitor antiretroviral treatment adherence.

The pharmacokinetic profile of 3TC obtained in healthy Indian subjects is similar to that reported

by Narang et al. (4). However, the elimination half-life was lower than that reported in White and Hispanic subjects (2, 3). Since plasma 3TC concentrations are of limited value in evaluating efficacy or toxicity, it may be of interest to establish the pharmacokinetic profile of the parent drug and its intracellular metabolite in different populations.

A notable limitation of this study was that it was a single dose pharmacokinetic study done in healthy subjects. It is important to study the pharmacokinetics of 3TC in HIV-infected persons who have been receiving the drug for a long period of time. In summary, the study has shown a good correlation between plasma and urine concentrations of 3TC, suggesting that timed urine measurements could be used to study the bioavailability of 3TC. Plasma 3TC measurements could serve as a useful tool to predict adherence to antiretroviral treatment.

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