THE PHARMACOKINETICS OF LAMIVUDINE IN HEALTHY RABBIT TREATED WITH CIMETIDINE

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ABSTRACT

The effects of cimetidine on the plasma concentration of Lamivudine (3TC) were examined in rabbits. Three subjects were given 14 mg/kg BW lamivudine alone. On day 8, the three subjects were given 78 mg/kg BW cimetidine one hour before a dose of lamivudine. There were statistically significant differences in the pharmacokinetic parameter produced by administration with cimetidine. There were C max and AUC 0-120 but t max was no difference. The different had apparent effect on the plasma concentrations of lamivudine and was determined with HPLC.

Keywords: lamivudine, cimetidine, HPLC

INTRODUCTION

Lamivudine (Fig.1) is a synthetic nucleoside analog, reverse transcriptase inhibitor that shown in vitro and in vivo activity against human immunodeficiency virus (HIV) and hepatitis B virus. Nucleoside analogues enter cells and undergo phosphorylation, mediated by cellular kinase, to active 5”-triphosphate anabolite, which in turn inhibit HIV reverse transcriptase and proviral DNA chain extension. Lamivudine is being developed as a potential antiviral agent for use in man.

In a separate study, the effect of food on lamivudine absorption was examined. In the absence of food, lamivudine was rapidly absorbed, with a time to reach maximum concentration (t max) of 0.88 ± 0.25 hours. In the presence of a standard meal (breakfast of 55% fat, 32% carbohydrates, and 13% protein), the rate of absorption remains in adequately defined (Moore 1999).

A measure such as t max, does not adequately describe situations in which double peaking may occur or in which prolonged absorption are observed. Cimetidine is an H₂ receptor antagonist that is widely used for a variety of indications (duodenal ulcer disease, Zollinger-Ellison syndrome, gastric ulcers, upper GI tract hemorrhage) (American 2002; Fact and
Comparation 2001). The probability that lamivudine will be given to patients receiving long-term therapy with cimetidine is high. Since cimetidine affects the oral absorption and/or disposition of a variety of agents, the effect of administration of cimetidine on the absorption of lamivudine was studied (Moore 1999). Therefore studies were performed to determine the effect of cimetidine administration on the oral absorption of lamivudine in healthy rabbits.

**MATERIALS AND METHODS**

Lamivudine was a kind gift of Glaxo. Methanol (HPLC gradient) was purchased from JT Baker. Dipotassium hydrogenphosphate and Phosphoric acid 85% were purchased from Merck (Darmstadt, Germany), Aqua Bidestilata Steril was obtained from PT. Ikapharmindo Putramas (Indonesia).

The Instrument of HPLC system consisted of a Model LS-6A solvent delivery pump (Shimadzu, Japan), a Model Rheodyne injector (USA), a Model UV-VIS SPD – 6AV wave-length detector (Shimadzu, Japan), a Model Chromatopac C – R 3A integrator (Shimadzu, Japan), a Model System Controller 8CI-6A and Column Oven CTO – 6A (all from Shimadzu-Japan). The analytical columns used was shim-pack CLC- Phenyl column (150x 6.0 mm I.D; Shimadzu, Japan); SPE Octyl (C8) disposable columns (JT Beker, USA).

For method animal we used Australian Rabbit from Batu Malang, weight 2.5 kg. Treatment 14 mg/ kg BW of rabbit and 70 mg/ml oral solution form (Paget 1964). The three rabbits were fasted overnight before drug administration and 2 hours after the dose was administered. Water was allowed ad libitum 10 ml. Blood sample (2ml) were collected with spuit injection 2.5 cc containing anticoagulant via ear of marginal venous. Samples were collected in a vacuum test tube. Blood samples were obtained in a vacuum test tube. Blood samples were obtained immediately before and 5, 10, 20, 30, 45, 60, 75, 90, 120 minutes after ingestion of the orally administered formulation. Plasma was harvested and samples were stored at -20°C until assayed. Plasma concentration of lamivudine was determined by high-performance liquid chromatography (HPLC). The assay was linear over the calibration range 100 to 5000 ng/ml (Hoetelmans, 1998).

The three rabbits were the same treatment as lamivudine above, but cimetidine was administered 1 hour before lamivudine. The pharmacokinetic analysis of plasma concentration of lamivudine was determined using high-performance liquid chromatography (HPLC) involving solid-phase extraction and U.V. detection. The assay had a dynamic range of 100 to 5000 ng/ml (Hoetelmans 1998). The maximum plasma concentration of lamivudine (Cmax) and earliest time at which Cmax occurred (tmax) were estimated directly from the experimental data. The area under the plasma concentration-time curve from time zero to the last time (t) plasma lamivudine was measurable (AUC0-120) was estimated by the linear trapezoidal approximation (Shargel 1999). Student’s t tests with 95% confidence limits were used to examine pair-wise differences between the groups. Value of p<0.05 were considered to be statistically significant (Daniel 2005).

**RESULTS**

The mean plasma lamivudine concentration-time curves for the two treatment groups were difference, but tmax was similar (75 minutes) (Figure 3 and 4). The mean AUC0-120, Cmax value in the lamivudine-cimetidine were significantly different from those in the lamivudine alone group. The tmax of lamivudine in the lamivudine-cimetidine was identical to that in the group receiving lamivudine alone (Table 1).

**DISCUSSION**

Finding from this study indicated that concomitant administration of cimetidine produces increase in systemic exposure to lamivudine as measured by AUC0-120, Cmax although tmax was similar (Table 1). Cimetidine is a cationic drug known to inhibit renal tubular secretion of co-administered organic cations and basic drugs (Takubo 2000) (Figure 2). Lamivudine is cationic drug ionized by protonization of an amino group in the cytocine portion, and it is reasonable to expect that the renal tubular secretion of lamivudine would be inhibited by a coadministered cationic drug (Figure 1). The lack of clinically significant effects of cimetidine on the pharmacokinetics of lamivudine was observed despite the fact that secretion of lamivudine at the renal proximal tubule may be inhibited by cimetidine (Takubo 2000).
Table 1. Summary of pharmacokinetic parameter of lamivudine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Plasma concentration of lamivudine</th>
<th>Plasma concentration of lamivudine + cimetidine</th>
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<tbody>
<tr>
<td>$t_{\text{max}}$</td>
<td>75 minutes</td>
<td>75 minutes</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>$1298.529 \pm 384.0281$ ng/ml</td>
<td>$5106.028 \pm 1655.705$ ng/ml</td>
</tr>
<tr>
<td>AUC$_{0-120}$</td>
<td>$89757.17 \pm 21570.91$ ng min/ml</td>
<td>$332968.2833 \pm 94897.64$ ng min/ml/</td>
</tr>
</tbody>
</table>

Figure 3. Mean plasma Lamivudine concentration by treatment group (Lamivudine (L); Lamivudine-Cimetidine (L-C))

Figure 4. Chromatogram serum sample from rabbit containing 14mg Lamivudine and 78 mg Cimetidine, $t_{\text{max}}$ 75 minute ($t_R = 8,216$ min)
CONCLUSION

The concomitant use of cimetidine and lamivudine will increase plasma lamivudine level due to the inhibition of lamivudine clearance.

REFERENCES