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Effect of Trimethoprim on the Renal Clearance of Lamivudine in Rats

TAKATOSHI TAKUBO, TOSHIHIRO KATO, JUNJI KINAMI, KAZUHIKO HANADA* AND HIROYASU OGATA*

Bioanalysis & Drug Metabolism Research Laboratories, Safety Evaluation Department, Glaxo Wellcome K.K., Tsukuba Research Laboratories, 43, Wadai, Tsukuba-shi, Ibaraki, 300-4247 and **Department of Biopharmaceutics, Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose, Tokyo, 204-8588, Japan*

Abstract

Lamivudine undergoes minimal metabolism and renal clearance of the unchanged drug is the predominant mechanism of clearance. The effect of trimethoprim on the renal clearance of lamivudine was investigated in rats in-vivo.

Total renal clearance of lamivudine was about three times higher than the glomerular filtration rate in rats receiving an infusion of tritium-labelled lamivudine. Concomitant infusion of trimethoprim reduced the renal clearance of lamivudine to about half, but did not affect the level of radioactivity in the renal cortex. When rats received an infusion of lamivudine with probenecid, cimetidine or quinidine, the renal clearance of lamivudine was only significantly reduced by co-administration of cimetidine.

These findings suggest that secretion in the renal proximal tubule takes an active part in the total renal clearance of lamivudine, and that cationic drugs such as trimethoprim and cimetidine may inhibit the secretion of lamivudine without greatly affecting the concentration of lamivudine in the renal cortex.

Lamivudine ((−)-2′-deoxy-3′-thiacytidine, 3TC, Figure 1) is a new nucleoside derivative developed by Glaxo Wellcome Research and Development, UK, and is reported to be a very effective agent against human immunodeficiency virus (HIV) and human hepatitis B virus (HBV) (Doong et al 1991; Chang et al 1992; Coates et al 1992; Hart et al 1992). Previous studies on the metabolic fate of lamivudine in humans and rats have indicated that lamivudine is well absorbed after oral administration, undergoes minimal metabolism and that renal clearance of the unchanged drug is the predominant mechanism of clearance (Takubo et al 1997a; Tsuno-o et al 1997). Investigation using the isolated perfused rat kidney technique showed that tubular secretion in addition to glomerular filtration would contribute significantly to the renal clearance of lamivudine (Sweeney et al 1995).

It is well known that renal tubular secretion of drugs involves transport systems such as organic cation/anion transport and p-glycoprotein (Bendayan 1996; Bonate et al 1998). Also, certain adverse events, such as reduced renal clearance of a drug caused by competition in the secretion processes, can increase the concentration of the drug in the blood and also potentiate its pharmacological or toxicological effect, and are observed in drug–drug interactions related to renal clearance (Bendayan 1996; Bonate et al 1998).

As mentioned above, previous investigation using the isolated perfused rat kidney technique indicated that lamivudine would be excreted actively by tubular secretion, and also that renal clearance of lamivudine would be greatly inhibited in the presence of trimethoprim, an antifungal agent (Sweeney et al 1995). This effect of trimethoprim was also studied in clinical use, and co-administration of lamivudine with trimethoprim resulted in an increased area under the concentration–time curve (AUC) of approximately 40% and a decreased renal clearance of lamivudine (Moore et al 1996).

To further examine the renal clearance of lamivudine, especially its renal tubular secretion, and to consider drug–drug interactions related to the renal clearance of lamivudine, we confirmed the effect of

Correspondence: T. Takubo, Bioanalysis & Drug Metabolism Research Laboratories, Safety Evaluation Department, Glaxo Wellcome K.K., Tsukuba Research Laboratories, 43, Wadai, Tsukuba-shi, Ibaraki, 300-4247 Japan.

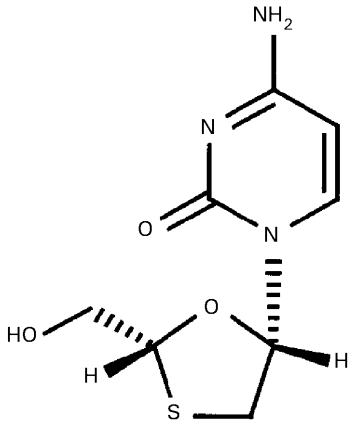

Figure 1. Structure of lamivudine.

trimethoprim on the renal clearance of lamivudine in rats in-vivo and on the change in concentration of lamivudine in rat renal cortex. We also investigated the effect of probenecid, cimetidine and quinidine, which are known to be inhibitors of transport systems related to renal tubular secretion, on the renal clearance of lamivudine.

Materials and Methods

Materials

Tritium-labelled and unlabelled lamivudine was supplied by Glaxo Wellcome Research and Development, UK; trimethoprim, probenecid, cimetidine and quinidine were purchased from Sigma Chemical Co., and inulin from Kanto Chemical Co., Inc. All other reagents and solvents used were guaranteed reagent grade.

Animal study

Male, 9-week-old Wistar rats (299–349 g) were anaesthetized by intraperitoneal injection of 25% (w/v) urethane solution (5 mL kg^{-1}). After the rats had been fixed on their backs, the right femoral vein and left jugular vein were catheterized for infusion and the right femoral artery for blood collection. Then, 6% (w/v) mannitol in Ringer's solution was infused (0·1 mL min^{-1}) into the femoral vein to stabilize the urinary flow rate, and the right and left ureters were catheterized via a mid-abdominal incision for urine collection.

Trimethoprim was administered first as a bolus dose (12 mg kg^{-1}), followed by a 0·08 mg $kg^{-1}min^{-1}$ infusion, with 12% (w/v) mannitol in Ringer's solution in the test group (n = 4), and mannitol solution alone in the control group (n = 4). After infusion for 10 min, tritium-labelled lamivudine ([^{3}H]lamivudine, 74 KBq mg^{-1}) and inulin were administered (1 mg kg^{-1} for [^{3}H]lamivudine, 50 mg kg^{-1} for inulin) into the jugular vein and infused with Ringer's solution (0·02 mg kg^{-1} min^{-1} for [^{3}H]lamivudine, 0·6 mg kg^{-1} min^{-1} for inulin). After infusion for a further 30 min, urine was collected from the ureters every 10 min. About 0·4 mL of blood was obtained from the femoral artery at the midpoint of the urine collection period and the plasma was separated by centrifugation. After collection of urine for 30 min, the right and left kidneys were removed and the renal cortex was sectioned.

Probenecid, cimetidine or quinidine were also administered as a bolus dose and then infused with 12% (w/v) mannitol in Ringer's solution in the test group (n = 4 for each concomitant drug), with only the mannitol solution infused in the control group (n = 2 for each concomitant drug). The dosage was 10 mg kg^{-1} bolus dose and 0·65 mg kg^{-1} min^{-1} infused dose for probenecid, 2 mg kg^{-1} bolus dose and 0·08 mg kg^{-1} min^{-1} infused dose for cimetidine and 0·1 mg kg^{-1} min^{-1} infused dose only for quinidine. After infusion for 10 min, non-labelled lamivudine and inulin were administered as a bolus, then infused, and plasma and urine samples were collected as described above.

Sample analysis

The concentrations of lamivudine in plasma and urine were determined by high-performance liquid chromatography (HPLC) after solid-phase extraction (Takubo et al 1997a). A portion (100 μL) of plasma or urine was loaded into an solid-phase extraction cartridge (Lichrolut SCX, Merck) with 0·5 mL of 1% (v/v) perchloric acid solution and the cartridge was washed with 2 mL of distilled water and methanol. Finally, 2 mL of 1% ammonia in methanol was added and the eluate introduced onto a reversed-phase column (L-Column, Chemicals Inspection and Testing Institute). The mobile phase consisted of 10% (v/v) methanol in 50 mM phosphate–citrate buffer (pH 7·5) and the flow rate was 1·0 mL min^{-1}. Lamivudine was detected by UV measurement at 270 nm.

The level of radioactivity in the renal cortex was determined by combustion and liquid scintillation counting (Wallac 1410, Pharmacia). Samples of the renal cortex were combusted using an automatic sample oxidizer (Tricarb 307, Canberra-Packard) to measure radioactivity. Concentrations of inulin in plasma and urine were determined by a modification of the method described by Dische & Borenfreund (1951). Concentrations of trimethoprim,

probenecid, cimetidine and quinidine in plasma were also determined by a modification of HPLC, as described in previous reports (Vree et al 1978; Veenendaal & Meffin 1981; Nagai et al 1995; Nielsen et al 1994).

Data analysis

Total body clearance of lamivudine (CLt) was calculated as the infusion rate, which was corrected for the body weight of each rat, divided by the plasma concentration at steady state (Cpss). Renal clearance of lamivudine (CLr) was estimated as the urinary excretion rate, which was obtained as the urinary concentration of lamivudine multiplied by the urinary flow rate, divided by the Cpss. Glomerular filtration rate (GFR) was determined as the renal clearance of inulin. The excretion ratio (ER) of lamivudine was calculated as the CLr divided by the GFR. The level of radioactivity in the renal cortex was represented as μg equivalents of lamivudine per gram of wet tissue and the ratio of the radioactivity level in the renal cortex to the Cpss was estimated.

Statistical analysis

Data are expressed as means $\pm$ s.d. of separate experiments. The differences between data were analysed using two-tailed Student's *t*-test or a one-way analysis of variance followed by a multiple range test (Dunnett test). Statistical significance was assumed when the corresponding *P* value was lower than 0·05.

Results

The concentration of lamivudine in plasma (Cp), CLr and GFR during infusion of [^{3}H]lamivudine with or without trimethoprim are presented in Figure 2. The Cp was kept constant and remained almost at a steady state and neither the GFR nor CLr fluctuated significantly during the experimental period.

The effect of trimethoprim on the renal clearance of lamivudine is summarized in Table 1. The Cpss, CLt, CLr and ER in controls were $1{\cdot}70 \pm 0{\cdot}27\ \mu g\ mL^{-1}$, $3{\cdot}74 \pm 0{\cdot}64\ mL\ min^{-1}$, $3{\cdot}31 \pm 0{\cdot}93\ mL\ min^{-1}$ and $2{\cdot}97 \pm 0{\cdot}35$, respectively. Concomitant infusion of trimethoprim raised the Cpss and reduced the CLt, CLr and ER significantly, but the GFR was not affected.

The effect of trimethoprim on the level of radioactivity in the renal cortex is presented in Table 2. In controls, the level of radioactivity in the renal cortex was $8{\cdot}44 \pm 2{\cdot}67\ \mu gEq\ g^{-1}$ and the ratio of the radioactivity level to the Cpss was $5{\cdot}04 \pm 1{\cdot}59$. With concomitant infusion of trimethoprim, the level of radioactivity increased to $9{\cdot}77 \pm 0{\cdot}61\ \mu gEq\ g^{-1}$ and the ratio of radioactivity to Cpss concentration decreased to $4{\cdot}20 \pm 0{\cdot}24$, although the difference was not significant.

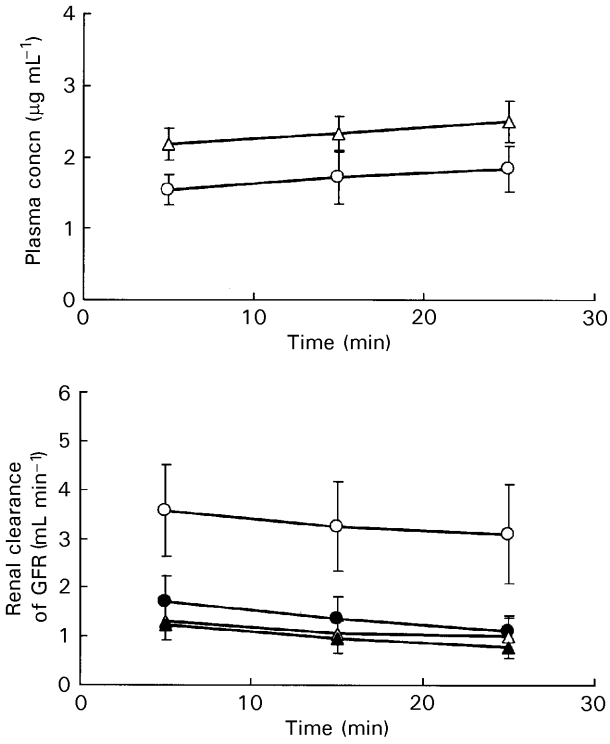

Figure 2. A: plasma concentration of lamivudine in rats with (○) or without (△) concomitant administration of trimethoprim. B: renal clearance of lamivudine (●) and glomerular filtration rate (GFR: ▲) during the experimental period; open symbols indicate controls, closed symbols indicate concomitant administration of trimethoprim. Data are expressed as the mean $\pm$ s.d., n = 4.

The effect of probenecid, cimetidine or quinidine on renal clearance of lamivudine is summarized in Table 3. The CLt, CLr and ER were significantly reduced by concomitant infusion of cimetidine. However, none of these parameters were affected by concomitant infusion of probenecid or quinidine.

Discussion

Our previous studies indicated that lamivudine undergoes minimal metabolism and that renal clearance of unchanged drug is the predominant mechanism of clearance (Takubo et al 1997a). Therefore, the effect of co-administered drugs on the renal clearance of lamivudine can be estimated accurately in the rat in-vivo. Since the plasma protein binding of lamivudine was below 5% in rats

Table 1. Effect of co-administration of trimethoprim on the urinary excretion of [^{3}H]lamivudine in rats.

	Cpss (μg mL^{-1})	CLt (mL min^{-1})	CLr (mL min^{-1})	GFR (mL min^{-1})	ER (CLr/GFR)	Cp (TMP) (μg min^{-1})
Control	1·70 ± 0·27	3·74 ± 0·64	3·31 ± 0·93	1·13 ± 0·32	2·97 ± 0·35	–
+ Trimethoprim	2·34 ± 0·26*	2·69 ± 0·29*	1·39 ± 0·42*	0·98 ± 0·26	1·42 ± 0·16*	3·04 ± 0·38

Each value represents the mean ± s.d. (n = 4). Cp (TMP): concentration of trimethoprim in plasma. *$P < 0·05$ compared with the control value.

Table 2. Effect of co-administration of trimethoprim on the concentration of lamivudine in plasma and radioactivity in the renal cortex of rats.

	Plasma concn of lamivudine (μg mL^{-1})	Radioactivity in renal cortex (μgEq g^{-1})	Concn ratio (renal cortex/plasma)
Control	1·71 ± 0·27	8·44 ± 2·67	5·04 ± 1·59
+ Trimethoprim	2·36 ± 0·26*	9·77 ± 0·61	4·20 ± 0·24

Each value represents the mean ± s.d. (n = 4). *$P < 0·05$ compared with the control value.

Table 3. Effect of co-administration of probenecid, cimetidine and quinidine on the urinary excretion of lamivudine in rats.

	Cpss (μg mL^{-1})	CLt (mL min^{-1})	CLr (mL min^{-1})	GFR (mL min^{-1})	ER (CLr/GFR)	Cp (con) (μg mL^{-1})
Control	1·64 ± 0·19	3·96 ± 0·30	3·10 ± 0·52	0·99 ± 0·28	3·29 ± 0·49	–
+ Probenecid	1·48 ± 0·18	4·34 ± 0·56	3·53 ± 0·90	1·20 ± 0·18	2·93 ± 0·45	107 ± 5.1
+ Cimetidine	2·18 ± 0·44	2·93 ± 0·50*	1·98 ± 0·32*	0·85 ± 0·10	2·35 ± 0·31*	3·51 ± 0·57
+ Quinidine	1·61 ± 0·17	4·05 ± 0·45	3·24 ± 0·57	1·12 ± 0·28	2·94 ± 0·28	0·851 ± 0·034

Each value represents the mean ± s.d. (n = 6 for control and n = 4 for other groups). Cp (con): concentration of each concomitant drug in plasma. *$P < 0·05$ compared with the control value.

in-vitro (Takubo et al 1997b), the pharmacokinetic parameters of lamivudine would be almost insensitive to plasma protein binding.

The clinical dosage of lamivudine is 100 mg once a day, which produced a maximum concentration of lamivudine in plasma (Cmax) of 1·2 μg mL^{-1} in healthy volunteers (Tsuno-o et al 1997). In our study, we found Cpss to be about 1·7 μg mL^{-1} (7·4 μM) in the control group, which is very close to the Cmax in clinical use. We also determined the plasma concentrations of concomitant drugs in this study to compare their effects on the renal clearance of lamivudine. The plasma concentration of the concomitant drug was 3·04 μg mL^{-1} (10·5 μM) for trimethoprim, 107 μg mL^{-1} (375 μM) for probenecid, 3·51 μg mL^{-1} (13·9 μM) for cimetidine and 0·851 μg mL^{-1} (2·6 μM) for quinidine.

As mentioned above, the renal clearance of lamivudine (CLr) during infusion of [^{3}H]lamivudine in rats accounted for about 90% of its total clearance (CLt) and was about three times higher than the GFR. The CLr significantly declined by about half after co-administration of trimethoprim, suggesting that lamivudine is excreted mainly by renal clearance, especially tubular secretion, and that the secretion is strongly inhibited by trimethoprim. Similar findings were also obtained in a previous investigation using the isolated perfused rat kidney technique (Sweeney et al 1995) and the propriety of the technique in-vitro is proved beyond doubt by this study in-vivo.

In this study, the level of radioactivity in the renal cortex of rats receiving infusion of [^{3}H]lamivudine was 8·44 μgEq g^{-1}. Lamivudine undergoes minimal metabolism in the rat (Takubo et al 1997a) and therefore it is possible to regard the level of radioactivity as representing unaltered drug, estimated as about 40 μM lamivudine. It was reported that the nephrotoxicity of aminoglycosides and cephalosporins would be related to their concentration in renal tubular cells, and the concentration of some aminoglycosides in the renal cortex reached 100–1000 times their concentration in serum (Walker et al 1990; Dekant & Vamvakas 1996). However, in this study the concentration of lamivudine in the renal cortex was about five times

its concentration in plasma and was not greatly affected even if the renal clearance of lamivudine was reduced by co-administration of trimethoprim.

The Cpss, CLr and ER during infusion of lamivudine in rats were scarcely affected by concomitant infusion of probenecid, although the molarity of probenecid in plasma was about 50 times that of lamivudine. As probenecid has been reported to be a potent inhibitor of the renal organic anion transport system (Bendayan 1996; Nakamura et al 1996), renal clearance of lamivudine would clearly not involve the anion transport system of the renal proximal tubule.

The CLr and ER were significantly reduced by concomitant infusion of cimetidine, while the Cpss remained largely unchanged. Cimetidine is a cationic drug known to inhibit renal tubular secretion of co-administered organic cations and basic drugs (Somogyi & Muirhead 1987; Dutt et al 1994; Bendayan 1996; Nakamura et al 1996). Trimethoprim is also a cationic drug and was also observed to reduce the renal clearance of other organic cations (Cacini 1987). These findings suggest that secretion of lamivudine at the renal proximal tubule may be inhibited by cationic drugs such as trimethoprim and cimetidine.

No significant effect of quinidine on the CLr was observed, although quinidine is a cationic drug reported to inhibit the renal organic cation transport system (Somogyi & Muirhead 1987; Bendayan 1996; Nakamura et al 1996). The molarity of quinidine in plasma was about one-fourth the concentration of trimethoprim or cimetidine and may have been insufficient to inhibit the CLr. The lower concentration of quinidine in this study was unavoidable because of its circulatory effect in rats. Quinidine was also shown to be a potent inhibitor of p-glycoprotein, which is expressed in the brush-border membrane of proximal tubular cells (Lieberman et al 1989; Dutt et al 1994; Wacher et al 1995). This suggests that the renal clearance of lamivudine may not be mediated by p-glycoprotein.

Lamivudine is a cationic drug ionized by protonization of an amino group in the cytosine portion, and it is reasonable to expect that the renal tubular secretion of lamivudine would be inhibited by a co-administered cationic drug. However, a previous study using the isolated perfused rat kidney technique indicated that the renal clearance of lamivudine was significantly reduced by co-administration of trimethoprim but not cimetidine (Sweeney et al 1995). It seems that the effect of trimethoprim on the CLr is greater than that of cimetidine at almost the same molarity in plasma; nevertheless, both their metabolites would be related to the effect on CLr. These findings indicate that secretion of lamivudine at the renal proximal tubule might be mediated by a transport system inhibited specifically by trimethoprim. It was reported that trimethoprim reduced Na^+/K^+-ATPase activity in the renal proximal tubule and caused hyperkalaemia by decreasing urinary potassium excretion (Eiam-ong et al 1996). It is possible that a transport system related to urinary potassium excretion may contribute to the renal clearance of lamivudine.

Findings related to renal secretion or reabsorption of nucleosides in urinary excretion have been reported previously. Nelson et al (1988) reported that adenosine and 5-fluorouracil underwent net renal reabsorption that was not prevented by inhibitors of the nucleoside transporter, dipyridamole and nitrobenzylthioinosine, whereas deoxyadenosine and 5′-deoxy-5-fluorouridine were excreted by renal secretion that was reduced by the inhibitors. Renal tubular secretion of 3′-azido-3′-deoxythymidine (AZT), which is used clinically with lamivudine for treatment of acquired immunodeficiency syndrome (AIDS), was also observed by Chatton et al (1990) and Patel et al (1989). Griffith & Jarvis (1996) summarized the nucleoside transport systems of mammalian cells, which they broadly classified as being either equilibrative nucleoside transport systems (facilitated diffusion) or sodium-dependent concentrative nucleoside transport systems. They also stated that at least four active carriers of the latter would be identified by selectivity of their substrates. However, transport of nucleosides in renal epithelial cells of the proximal tubule, especially renal secretion, has not yet been definitely elucidated. Further investigation is necessary to clarify the mechanism of renal excretion of lamivudine and to identify transport systems mediating the renal secretion of nucleosides.

In summary, investigating the urinary excretion of lamivudine in rats suggested that secretion at the renal proximal tubule plays an active part in the renal clearance of lamivudine, and that this secretion may be inhibited by co-administration of cationic drugs. This in-vivo model would be useful to predict the effect of co-administered drugs on the renal clearance of lamivudine in clinical use.

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