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Effect of Lamivudine on Uptake of Organic Cations by Rat Renal Brush-Border and Basolateral Membrane Vesicles

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

*Bioanalysis and 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

The effect of lamivudine on uptake of a representative organic cation, tetraethylammonium (TEA), by rat renal brush-border membrane vesicles (BBMV) and basolateral membrane vesicles (BLMV) has been investigated.

The pH-driven uptake of TEA by BBMV ($pH_{in} = 6{\cdot}0$, $pH_{out} = 7{\cdot}5$) was inhibited by lamivudine. The IC50 value (concentration resulting in 50% inhibition) for the concentration-dependent effect of lamivudine on TEA uptake by BBMV after 30 s was 2668 μM whereas IC50 values for cimetidine and trimethoprim were $< 2{\cdot}5$ μM and < 25 μM, respectively. The early uptake of TEA by BLMV was also reduced significantly by lamivudine. The IC50 value for the concentration-dependent effect of lamivudine on uptake of TEA by BLMV at 30 s was > 25 mM, whereas the IC50 values for cimetidine and trimethoprim were 2116 μM and 445 μM, respectively.

These findings suggest that compared with other cationic drugs, such as trimethoprim and cimetidine, lamivudine is a weak inhibitor of organic cation transport into the tubules by the brush-border and basolateral membranes of renal epithelial cells. It is unlikely lamivudine will have any significant effect on the excretion of co-administered cationic drugs by the renal tubules.

Lamivudine ((−)-2′-deoxy-3′-thiacytidine, 3TC; Figure 1) is a cytosine dideoxynucleoside analogue reported to inhibit DNA replication in human immunodeficiency virus (HIV) and human hepatitis B virus (Doong et al 1991; Chang et al 1992; Coates et al 1992; Hart et al 1992). It is available for treatment of acquired immunodeficiency syndrome (AIDS) and chronic hepatitis B (Glaxo Wellcome Research and Development, UK).

Previous studies found lamivudine was well absorbed after oral administration and was excreted mainly in the urine, in an unchanged form, in rats and man (Takubo et al 1997; Tsuno-o et al 1997). Urinary excretion of lamivudine was investigated further and renal tubule excretion and glomerular filtration were both found to contribute to renal clearance (Sweeney et al 1995).

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

Information on drug-drug interactions is important in the development of a new drug. An understanding of drug–drug interactions with compounds such as lamivudine, which are excreted predominantly in the urine, is particularly important, because it has been recognized that renal clearance might be affected by concomitant use of other drugs, resulting in the increased toxicity or reduced efficacy of the drug in question (Bendayan 1996; Bonate et al 1998). The effect of co-administered drugs on the renal clearance of lamivudine has already been investigated by use of the rat isolated perfused kidney technique; it was observed that excretion of lamivudine by the renal tubules could be reduced by co-administration of the antibacterial agent trimethoprim (Sweeney et al 1995). The effect of lamivudine on the renal clearance of co-administered drugs has not been elucidated.

Lamivudine is an organic cation ionized by protonation of an amino group in the cytosine portion of the molecule. Renal tubular excretion would consist of two processes, influx at the basolateral

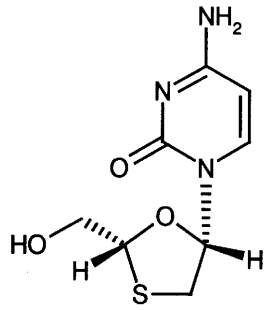

Figure 1. The structure of lamivudine.

membrane and efflux at the brush-border membrane of the renal tubule epithelium. Influx and efflux of organic cations mainly involve electrogenic-facilitated diffusion and H^+–organic cation exchange, respectively (Wright 1996; Pritchard & Miller 1997). It has also been suggested that competitive inhibition of these processes, by the concomitant use of other cationic drugs, would reduce their renal clearance (Bendayan 1996; Bonate et al 1998). Investigation of the effect of lamivudine on the renal clearance of co-administered drugs might aid prediction of drug–drug interactions with lamivudine, with particular reference to other cationic drugs excreted by the renal tubules.

Cellular membrane vesicles have been widely used to investigate the transport of organic cations by the renal tubular epithelium, and the methods of transport of representative substrates such as tetraethylammonium (TEA) and *N*-methylnicotinamide have already been characterized (Takano et al 1984, 1985; Wright 1985; Bendayan 1996). The effect of drugs on the uptake of TEA or *N*-methylnicotinamide by cell membrane vesicles has also been examined to estimate the effect of these compounds on the transport of organic cations by the renal tubule epithelium (Griffiths et al 1991, 1992; Somogyi et al 1994). In this study the effect of lamivudine on the uptake of TEA by rat renal brush-border membrane vesicles (BBMV) and basolateral membrane vesicles (BLMV) was investigated to evaluate the effect of lamivudine on renal tubular excretion of co-administered cationic drugs.

Materials and Methods

Materials

^{14}C-labelled TEA ([^{14}C]TEA) was purchased from Daiichi Pure Chemicals. Lamivudine was supplied by Glaxo Wellcome Research and Development, UK. Trimethoprim, cimetidine, probenecid and percoll were purchased from Sigma, and Tris-hydroxymethylaminomethane (Tris), *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulphonic acid (HEPES) and 2-*N*-morpholinoethanesulphonic acid (MES) were purchased from Wako Pure Chemical Industries. Other reagents and solvents were guaranteed reagent-grade.

Preparation of vesicles

BBMV were prepared by a modification of the calcium precipitation method described elsewhere (Evers et al 1978; Takano et al 1984; Griffiths et al 1992). Briefly, renal cortex was sliced from kidneys of seven, 8-week-old, male Wistar rats and homogenized for 1 min in buffer A (2 mM Tris, 2 mM HEPES, 10 mM mannitol; pH 7·1; 81 mL). $CaCl_2$ solution (4·5 M; 200 μL) was added, and the homogenate was left to stand for 15 min and then added to buffer B (buffer A containing 10 mM $CaCl_2$; 90 mL) and centrifuged at 500 *g* for 10 min. The supernatant was then centrifuged again at 15 000 *g* for 10 min.

The resulting pellet was homogenized in buffer A (22·5 mL) and left to stand for 15 min after addition of $CaCl_2$ solution (4·5 M; 55 μL). The homogenate was added to buffer B (22·5 mL) and centrifuged at 750 *g* for 10 min. The supernatant was centrifuged again at 30 000 *g* for 10 min and the resulting pellet was homogenized in buffer C (20 mM Tris, 20 mM HEPES, 100 mM mannitol; pH 7·5; 45 mL) and centrifuged at 48 000 *g* for 20 min. The resulting pellet was resuspended in buffer D (20 mM MES, 100 mM mannitol, 100 mM KCl; pH 6·0; 4·5 mL) or buffer E (20 mM Tris, 20 mM HEPES, 100 mM mannitol, 100 mM KCl; pH 7·5; 4·5 mL) and left to stand for 60 min. After centrifugation at 2000 *g* for 5 min, the supernatant was re-centrifuged at 48 000 *g* for 20 min. The resulting pellet (BBMV) was resuspended in buffer D or E (2·0 mL).

BLMV were prepared by a modification of the percoll density-gradient-centrifugation method described elsewhere (Takano et al 1984; Murer & Gmaj 1986; Griffiths et al 1991). Briefly, renal cortex was sliced from the kidneys of ten, 8-week-old, male Wistar rats and homogenized in buffer F (250 mM sucrose, 1 mM EDTA, 10 mM Tris; pH 7·5; 60 mL). The homogenate was centrifuged at 2400 *g* for 20 min and the supernatant and fluffy layer were then centrifuged at 20 500 *g* for 20 min. The supernatant was discarded and the fluffy layer was collected with a small amount of buffer F and finally diluted to 45 mL with the same buffer. The solution was homogenized and percoll solution (250 mM sucrose, 10 mM Tris (pH 7·5) : percoll, 1 : 9; 5 mL) was added and the sample was mixed.

The solution was divided equally into two tubes and centrifuged at 48 000 *g* for 30 min. Fractions (1 mL) were removed from the top of the centrifuged solution and the activity of alkaline phosphatase, an index enzyme of the brush-border membrane fraction, and that of Na^+-K^+ ATPase, an index enzyme of the basolateral membrane fraction, were measured in selected fractions. Fractions containing the basolateral membrane were pooled and buffer G (150 mM mannitol, 20 mM HEPES, 20 mM Tris; pH 7·5; 17 mL) was added and the sample was mixed. After centrifugation at 100 000 *g* for 60 min the resulting pellet was homogenized in buffer H (100 mM KCl in Buffer G; 20 mL) and the homogenate was centrifuged at 100 000 *g* for 60 min. The resulting pellet (BLMV) was resuspended in buffer H (1·0 mL).

The activity of alkaline phosphatase in BBMV and that of Na^+-K^+ ATPase in BLMV were, respectively, 8·0–11·1-fold and 8·7–14·2-fold those in the initial homogenate of renal cortex. This indicates that each membrane fraction had been separated successfully.

Measurement of [^{14}C]TEA transport

The uptake of [^{14}C]TEA by BBMV and BLMV was measured by a rapid filtration technique (Takano et al 1984; Griffiths et al 1991, 1992). Briefly, BBMV (40 μL; 4·6–8·1 mg protein mL^{-1}) or BLMV (20 μL; 9·2–10·4 mg protein mL^{-1}) suspension was placed in a silanized glass tube and incubated at 25°C for 20 min. Uptake was then initiated by adding 4 vols buffer (buffer E for BBMV, buffer H for BLMV) containing [^{14}C]TEA (250 μM) with or without another drug (lamivudine, cimetidine, trimethoprim or probenecid) and the solution was incubated at 25°C until uptake was terminated by addition of ice-cold stop solution (0·1 mM $HgCl_2$ in buffer C for BBMV and buffer H for BLMV). The reaction mixture was poured immediately on to a pre-wetted filter (0·45 μm) and the filter was washed with ice-cold buffer B for BBMV and buffer G for BLMV. The filter was placed in a glass vial and dissolved in scintillation cocktail (10 mL) to measure radioactivity.

To correct for non-specific adsorption of [^{14}C]TEA on to the BBMV and BLMV, a sample of each vesicle suspension was filtered immediately after addition of [^{14}C]TEA and the radioactivity present on the filter was determined as described. The control radioactivity on the filter was determined each time an experiment was performed, and subtracted from the radioactivity detected when estimating [^{14}C]TEA uptake. [^{14}C]TEA uptake (nmol (mg protein)$^{-1}$) was evaluated from the amount of [^{14}C]TEA (nmol) calculated from the specific radioactivity, and the total protein content (mg protein) of each vesicle suspension.

Analytical methods

The protein content of the BBMV and BLMV preparations was determined by use of a commercial kit (BCA Protein Assay Reagent Kit; Pierce). Radioactivity on the filters was measured by liquid scintillation counting (Wallac 1410; Pharmacia). The activity of alkaline phosphatase was determined by use of a commercial kit (Alkaline phospha-B-test Wako; Wako Pure Chemical Industries) and the activity of Na^+-K^+ ATPase was determined as the activity of ATPase inhibited by ouabain, according to the method of Jørgensen (1974).

Statistical analysis

Data, expressed as means ± s.d. of results from separate experiments, were compared by use of Student's two-tailed *t*-test, statistical significance being set at $P < 0{\cdot}05$. The concentration of concomitant drugs causing 50% inhibition of TEA uptake (IC50) was calculated from the correlation between the percentage uptake of TEA in the presence of a drug, compared with the control and the log of the drug concentration.

Results

Effect of lamivudine on TEA uptake by BBMV

Uptake of TEA by BBMV was determined ≤15 min after addition of [^{14}C]TEA (250 μM) to the BBMV suspension (Figure 2). Whereas TEA uptake increased gradually in the absence of a pH gradient ($pH_{in} = 7{\cdot}5$, $pH_{out} = 7{\cdot}5$), uptake of TEA was stimulated against its concentration gradient in the presence of an outward pH gradient ($pH_{in} = 6{\cdot}0$, $pH_{out} = 7{\cdot}5$), and reached a peak after 1 min. The maximum uptake accounted for 1·117 ± 0·103 nmol (mg protein)$^{-1}$ and was about 4·5-fold that in the absence of a pH gradient. Stimulation of TEA uptake under an outward pH gradient was inhibited by 5 mM lamivudine and uptake of TEA after 1 min decreased to 0·551 ± 0·079 nmol (mg protein)$^{-1}$. Uptake of TEA after 15 min reached a plateau of 0·3 nmol (mg protein)$^{-1}$ (approx.) under all conditions tested.

The effect of lamivudine, trimethoprim, cimetidine and probenecid on uptake of TEA by BBMV 30 s after addition of 250 μM [^{14}C]TEA is summarized in Figure 3. TEA uptake was strongly

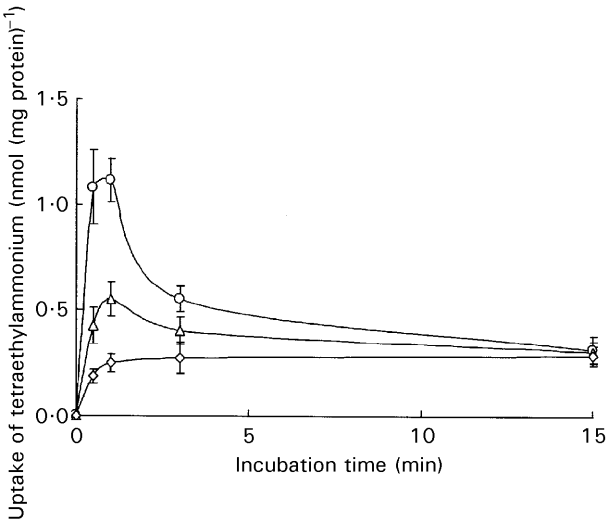

Figure 2. The effect of lamivudine on uptake of tetraethylammonium by renal brush-border membrane vesicles: ○, pH_{in} 6·0, pH_{out} 7·5; △, pH_{in} 6·0, pH_{out} 7·5 + 5 mM lamivudine; ◇, pH_{in} 7·5, pH_{out} 7·5. Brush-border membrane vesicles were incubated at 25°C with 250 μM [^{14}C]tetraethylammonium. Data are means ± s.d. of results from four preparations.

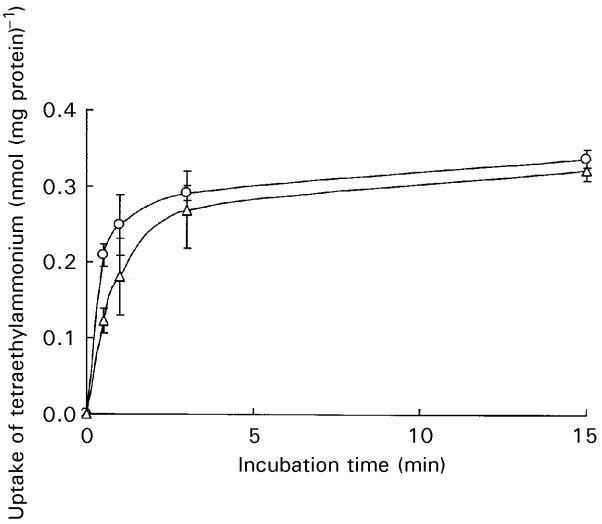

Figure 4. Effect of lamivudine on uptake of tetraethylammonium by renal basolateral membrane vesicles: △, ○, control. Basolateral membrane vesicles were incubated at 25°C lamivudine (5mM) with 250 μM [^{14}C] tetraethylammonium. Data are means ± s.d. of results from three preparations.

inhibited by trimethoprim and cimetidine, with IC50 values of $< 25\,\mu$M and $< 2{\cdot}5\,\mu$M, respectively (Table 1). TEA uptake was also reduced by lamivudine, but the effect of this drug was much weaker, as indicated by an IC50 value of 2668 μM. The uptake of TEA by BBMV was not affected significantly by the presence of probenecid.

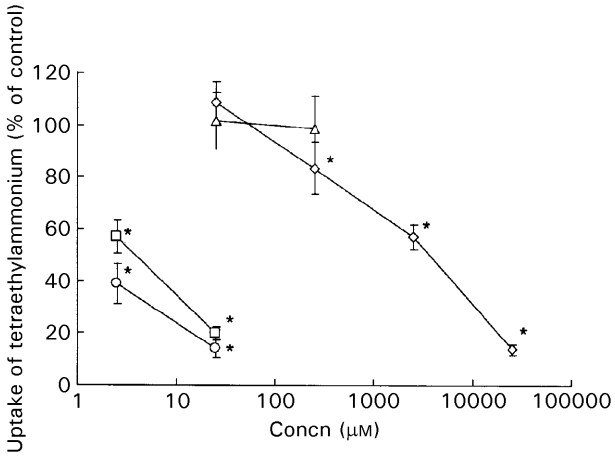

Figure 3. Effect of lamivudine (◇), trimethoprim (○), cimetidine (□) and probenecid (△) on uptake of tetraethylammonium by renal brush-border membrane vesicles. Brush-border membrane vesicles (pH_{in} 7·5, pH_{out} 7·5) were incubated at 25°C with 250 μM [^{14}C]tetraethylammonium. Data are means ± s.d. of results from four preparations. *$P < 0{\cdot}05$ compared with control.

Effect of lamivudine on TEA uptake by BLMV

Uptake of TEA by BLMV was determined ≤15 min after addition of [^{14}C]TEA (250 μM) to the BLMV suspension (Figure 4). Uptake of TEA by BLMV was $0{\cdot}208 \pm 0{\cdot}015$ nmol (mg protein)$^{-1}$ after 30 s, and then increased gradually and reached $0{\cdot}338 \pm 0{\cdot}012$ nmol (mg protein)$^{-1}$ after 15 min. Although TEA uptake by BLMV after 30 s was reduced to $0{\cdot}123 \pm 0{\cdot}017$ nmol (mg protein)$^{-1}$ in the presence of 5 mM lamivudine, uptake increased gradually and reached $0{\cdot}323 \pm 0{\cdot}014$ nmol (mg protein)$^{-1}$ after 15 min. There was no significant difference between uptake after 15 min in the presence or absence of lamivudine.

The effect of lamivudine, trimethoprim, cimetidine and probenecid on TEA uptake by BLMV 30 s after addition of 250 μM [^{14}C]TEA is summarized in Figure 5. Trimethoprim resulted in the most potent inhibition of TEA uptake with an IC50 value of 445 μM. TEA uptake was also reduced by cimetidine, with an IC50 value of 2116 μM. The effect of lamivudine on TEA uptake was much weaker—IC50 > 25 mM. TEA uptake by BLMV was not significantly affected by the presence of probenecid.

Discussion

To predict the effect of lamivudine on renal tubular excretion of co-administered cationic drugs, the uptake of TEA by BBMV and BLMV was determined, and the effect of lamivudine and other drugs on TEA uptake was compared.

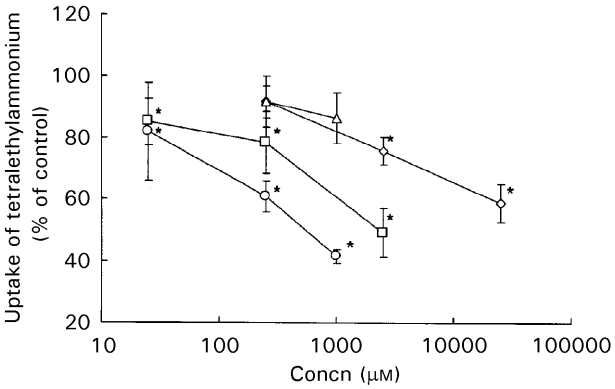

Figure 5. Effect of lamivudine (◇), trimethoprim (○), cimetidine (□) and probenecid (△) on uptake of tetraethylammonium by renal basolateral membrane vesicles. Basolateral membrane vesicles were incubated at 25°C for 30 s with 250 μM [^{14}C]tetraethylammonium. Data are means ± s.d. of results from three preparations. $*P < 0{\cdot}05$ compared with control.

Table 1. Drug concentrations inhibiting tetraethylammonium uptake by 50%.

	Drug concentrations inhibiting tetraethylammonium uptake by 50% (μM)	
	Brush-border membrane vesicles	Basolateral membrane vesicles
Lamivudine	2668	> 25000
Trimethoprim	< 25	445
Cimetidine	< 2·5	2116

Uptake by brush-border and basolateral membrane vesicles was estimated at 250 μM [^{14}C]tetraethylammonium.

The calcium precipitation method (Takano et al 1984; Maegawa et al 1988; Griffiths et al 1992) was used to prepare BBMV in this study. TEA uptake by the BBMV was similar to that in the references and uptake at an early stage was stimulated by an outward H^+ gradient. Addition of lamivudine was found to inhibit the transient increase in TEA uptake. The uptake of TEA by BBMV under an outward H^+ gradient is known to be mediated by an H^+/organic cation anti-port system (Takano et al 1984; Wright 1996; Pritchard & Miller 1997), indicating that lamivudine might inhibit transport of organic cations by the anti-port system. As found previously, the stimulated uptake of TEA by BBMV under an outward H^+ gradient was reduced significantly by cimetidine, a representative cationic drug, but not by probenecid, a representative anionic drug (Takano et al 1985; Griffiths et al 1992). IC50 for cimetidine was $< 2{\cdot}5$ μM in this study, similar to the value (1·07 μM) measured in a similar study by Somogyi et al (1994). Trimethoprim, which has previously been found to reduce renal clearance of lamivudine in rat isolated perfused kidneys (Sweeney et al 1995), also inhibited uptake of TEA by BBMV; the IC50 was < 25 μM. The IC50 for the action of lamivudine on TEA uptake by BBMV was much higher than that for cimetidine or trimethoprim. Takano et al (1985) reported that the affinity of cimetidine for the H^+/organic cation anti-port system was greater than that of TEA. It was suggested that the affinity of trimethoprim for the anti-port system would be almost equal to that of cimetidine whereas the affinity of lamivudine would be much lower. It is unlikely that lamivudine would cause potent competitive inhibition of organic cation transport by the anti-port system at the renal brush-border membrane.

The uptake of TEA by BLMV increased gradually and became saturated as shown in previous reports (Takano et al 1984). At an early stage this uptake was reduced by lamivudine. TEA uptake by BLMV was reported to involve a carrier-mediated system and it was suggested that lamivudine might inhibit transport of organic cations by this system (Takano et al 1984; Wright 1996; Pritchard & Miller 1997). The uptake of TEA by BLMV at an early stage was reduced significantly by the presence of cimetidine or trimethoprim; the IC50 of trimethoprim was fourfold (approx.) that of cimetidine. The IC50 values for the action of cimetidine or trimethoprim on TEA uptake by BLMV were higher than those for TEA uptake by BBMV. Katsura et al (1993) indicated that, with regard to their affinity for different substrates, the characteristic organic cation transport systems in the basolateral and brush-border membranes of the renal tubule epithelium were different. This is consistent with differences between the affinities of the organic cation transport systems of BBMV and BLMV for cimetidine and trimethoprim observed in this study. The IC50 for the action of lamivudine on TEA uptake by BLMV was much higher than that for cimetidine or trimethoprim, suggesting that the affinity of lamivudine for the carrier-mediated system is lower than that of the other drugs, as observed with BBMV. Lamivudine would have little effect on competitive inhibition of organic cation transport at the renal basolateral membrane.

As already discussed, trimethoprim would be a potent inhibitor of renal tubular excretion of organic cations, with a potency equal to that of cimetidine. This seems reasonable because trimethoprim is a cationic drug, and it has already been reported that the in-vivo renal clearance of

TEA was reduced significantly by co-administration of trimethoprim (Cacini 1987). Conversely, lamivudine would be a very weak inhibitor of renal tubular excretion of organic cations and has a much lower affinity than other cationic drugs for the system involved in the transport of organic cations at the basolateral and brush-border membrane of the renal tubule epithelium. We observed that the concentration of lamivudine detected in the renal cortex of rats was 40 μM (approx.) when the plasma concentration of lamivudine in the rats was almost maintained at the maximum plasma concentration observed in healthy volunteers given clinical doses (unpublished data). Because the concentration of lamivudine in the renal cortex is much lower than the IC50 for the action of lamivudine on the uptake of TEA by BLMV or BBMV, it can be speculated that although the renal clearance of lamivudine is reduced by co-administered cationic drugs, clinical use of lamivudine would not significantly affect the renal clearance of other cationic drugs. This is supported by a previous clinical study showing that whereas lamivudine did not affect renal clearance of trimethoprim, trimethoprim reduced renal clearance of lamivudine when the two drugs were co-administered (Moore et al 1996).

The effect of 3′-azido-3′-deoxythymidine (AZT), often co-administered with lamivudine in patients with AIDS, on transport of TEA and *N*-methylnicotinamide in BBMV and BLMV was investigated by Griffiths et al (1991, 1992). These authors found that AZT could be a substrate and a competitive inhibitor of both organic cation transport in BBMV and organic anion transport in BLMV. Similar findings were observed by Aiba et al (1995) in rats in-vivo, suggesting that AZT can be transported by anion transport systems in the basolateral membrane of the renal tubule epithelium, whereas it is excreted by cation transport systems in the brush-border membrane. The results of our study suggest that AZT might affect renal clearance of lamivudine by competitive inhibition of transport at the brush-border membrane. Johnson et al were, however, unable to find any significant difference between the pharmacokinetics of lamivudine in healthy volunteers receiving single doses of lamivudine (150 mg tablet) alone and lamivudine (150 mg) and AZT (300 mg) combination tablet. Their clinical study also indicated no significant difference between the pharmacokinetics of lamivudine, AZT or AZT glucoronide, the main metabolite of AZT, in HIV infected patients receiving lamivudine (300 mg) or AZT (200 mg) alone, or in those receiving combination therapy (lamivudine 300 mg and AZT 200 mg: unpublished data). These findings suggest that the transport system for lamivudine and AZT at the brush border mambrane of the renal tubule epithelium has a high capacity for the efflux of these two drugs, or is not shared.

It has been suggested that the hydrophobicity of substrates would be closely related to their affinity for the organic cation transport system at renal proximal tubules. David et al (1995) showed that the affinity of substrates for the organic cation transport system increased with increasing hydrophobicity and the influence was more marked for their luminal transport than for their contraluminal transport. Wright & Wunz (1998) also suggested that interaction of hydrophobic organic cations with a H^+/organic cation anti-port system resulted in the formation of a substrate–anti-porter complex with a comparatively low rate of turnover, because the high affinity of substrates for the anti-port system correlated with increasing hydrophobicity. Because lamivudine is a hydrophilic compound—its partition coefficient (log P) is $-1{\cdot}0$ (approx.) at pH 4–8 (unpublished data)—its affinity for organic cation transport system at the renal brush-border and basolateral membranes would be much weaker than that of other cationic drugs such as trimethoprim and cimetidine, as described above.

In conclusion, the uptake of TEA by BBMV and BLMV was inhibited by lamivudine but, because the IC50 for lamivudine was much higher than those for cimetidine or trimethoprim, it is unlikely that lamivudine will have any significant effect on the excretion of co-administered cationic drugs by the renal tubules.

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