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Effects of non-steroidal anti-inflammatory drugs on the pharmacokinetics and elimination of aciclovir in rats

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Abstract

This study aims to investigate the effect of commonly used non-steroidal anti-inflammatory drugs (NSAIDs) on the pharmacokinetics and the renal elimination of aciclovir in rats. Pharmacokinetic parameters were determined following an intravenous administration of aciclovir (5 mg kg^{-1}) to rats in the presence and absence of ketoprofen or naproxen (25 mg kg^{-1}). Compared with the control (given aciclovir alone), pre-treatment with ketoprofen or naproxen 30 min before aciclovir administration significantly altered the pharmacokinetics of aciclovir. Renal clearance of aciclovir was reduced by approximately two fold in the presence of ketoprofen or naproxen. Consequently, the systemic exposure (AUC) to aciclovir in the rats pre-treated with ketoprofen or naproxen was significantly ($P < 0.05$) higher than that from the control group given aciclovir alone. Furthermore, the mean terminal plasma half-life of aciclovir was enhanced by 4–5 fold by pre-treatment with ketoprofen or naproxen. These results suggest that NSAIDs, such as ketoprofen and naproxen, are effective in altering the pharmacokinetics of aciclovir by inhibiting the organic anion transporter-mediated tubular secretion of aciclovir. Therefore, concomitant use of ketoprofen or naproxen with aciclovir should require close monitoring for clinical consequence of potential drug interaction.

Introduction

Organic anion transporter 1 (OAT1), localized in the basolateral membrane of renal proximal tubule cells, plays an important role in the transepithelial movement of small negatively charged molecules from the systemic circulation into the tubular lumen (Hosoyamada et al 1999; Sweet & Pritchard 1999; Tojo et al 1999). Recent cloning, expression and functional characterization of OAT1 from several species has revealed the remarkably broad substrate specificity of OAT1, which is capable of handling a wide variety of chemically unrelated organic anions, such as endogenous metabolites, hormones, second messengers, toxins, xenobiotics and fluorescent dyes (Sekine et al 1997; Ullrich 1997; Uwai et al 1998; Cihlar & Ho 2000; Burckhardt et al 2003). With great efficiency, the OAT1 system is also able to interact with a spectrum of important therapeutics, including β-lactam antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and antiviral drugs, as well as a number of hippurates (Apiwattanakul et al 1999; Cihlar et al 1999; Jariyawat et al 1999; Uwai et al 2000; Burckhardt et al 2003). Organic anion transporters have been involved in the emergence of the nephrotoxicity of certain anionic drugs, such as nucleoside antiviral drugs (e.g. cidofovir, adefovir), as well as β-lactam antibiotics (e.g., cefaloridine, cephaloglycin) (Tune 1994; Takeda et al 1999; Ho et al 2000). Therefore, probenecid, a competitive inhibitor of the organic anion transporters, appears to be effective in altering the pharmacokinetics as well as in reducing the nephrotoxicity of drugs accumulated in the kidney via OAT1-mediated pathway (Berndt & Hayes 1982; Tune 1997; Lacy et al 1998). In practice, cidofovir is used in conjunction with probenecid to reduce the dose-limiting nephrotoxicity in the treatment of cytomegalovirus retinitis in AIDS patients (Hitchcock et al 1996).

Aciclovir, a potent anti-herpesvirus agent, is eliminated mainly by the renal excretion of unchanged drug, where the renal clearance of aciclovir is about 75–80% of the total body clearance (de Miranda et al 1979, 1981a; Laskin et al 1982a). Given that the

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renal clearance of aciclovir is approximately three times greater than the glomerular filtration rate, renal excretion of aciclovir has a significant tubular secretion component (de Miranda et al 1979, 1981b; Laskin et al 1982a). Subsequently, the co-administration of probenecid, a competitive inhibitor of organic anion transporters, has been shown to alter the pharmacokinetics of aciclovir in the combination therapy (Laskin et al 1982b). Aciclovir is a substrate of OAT1 (Wada et al 2000) but does not appear to interact with OAT2 and OAT3, while valaciclovir and zidovudine interact with OAT2 and OAT3 in addition to OAT1 (Cha et al 2001; Takeda et al 2002). Given that a considerable number of drugs and toxins can interact with OAT1, close monitoring may be required for potential drug interaction via OAT1-mediated renal excretion during combination therapy that includes aciclovir.

Several NSAIDs, such as naproxen and ketoprofen, have a potent inhibitory effect on the human organic anion transporter 1 (hOAT1)-specific transport pathway, implying that certain NSAIDs may be effective in altering the pharmacokinetics, as well as the emergence of nephrotoxicity, of drugs that can be accumulated in the proximal tubule primarily via OAT1 (Masuda et al 1997; Mulato et al 2000). Furthermore, due to the current use profile of NSAIDs, either as prescription or over-the-counter drugs, interactions between NSAIDs and other anionic drugs during the renal tubular secretion may occur relatively frequently and thus potentially increase the risk of adverse events. Therefore, this study has investigated the effect of those commonly used NSAIDs on the pharmacokinetics and renal elimination of aciclovir in rats.

Materials and Methods

Materials

Aciclovir, naproxen and ketoprofen were purchased from Sigma Chemical Co. (St Louis, MO). Paracetamol (acetaminophen; internal standard, IS) was obtained from Dae Heung Pharm. Co. (Seoul, Korea) and ketamine hydrochloride from Yuhan Co. (Seoul, Korea). All other chemicals were reagent grade and all solvents were HPLC grade. The polyethylene tube (0.58 mm i.d. $\times$ 0.96 mm o.d.) used for animal studies was purchased from Naume Co. (Tokyo, Japan).

Animal studies

All animal studies were performed in accordance with the Principles for Biomedical Research Involving Animals developed by the Council for International Organizations of Medical Sciences and the experimental protocols were approved by the animal care committee of Chosun University.

Male Sprague-Dawley rats, 280–320 g, were obtained from Samtako Bio Co. Ltd (Osan, Korea). The rats were anaesthetized with 1 mL kg^{-1} of ketamine hydrochloride (50 mg mL^{-1}) and the right femoral artery was cannulated using a polyethylene tube on the day before the experiment. After surgery, each rat was housed individually in a cage and received free access to water and food. For the experiment, rats were divided into three groups, comprising 4 rats per group. Groups 1–3 were given 5 mg kg^{-1} of aciclovir intravenously (i.v. bolus) via a left femoral vein with either naproxen sodium (25 mg kg^{-1}) or ketoprofen (25 mg kg^{-1}) 30 min before the intravenous administration of aciclovir, or were given no concomitant treatment (control). Blood samples were collected from the right femoral artery at 0, 0.083, 0.16, 0.33, 0.5, 1, 2, 4, 8, 12 and 24 h following an aciclovir injection. Urine was also collected for 24 h from the same group of rats. Blood samples were centrifuged at 3000 rev min^{-1} for 10 min to obtain the plasma for the HPLC assay. Urine samples were centrifuged for 10 min at 3000 rev min^{-1} and then passed through a 0.45-μm Millipore membrane filter (Millipore Filter Co., Bedford, MA). All samples were stored at -70°C until analysed.

HPLC assay

The plasma and urine concentrations of aciclovir were determined by an HPLC assay described as follows. Briefly, 0.05 mL of the internal standard (100 μg mL^{-1} of paracetamol in methanol) was added to 0.1-mL plasma samples and then samples were deproteinized by adding 0.2 mL of acetonitrile and vortex-mixing for 5 min. After centrifugation of the samples for 10 min, the supernatant was evaporated to dryness at 45 °C under nitrogen stream. The residue was reconstituted with 100 μL of mobile phase and then a 50-μL volume was injected directly into the HPLC system. The filtered urine samples (50 μL) were injected into the HPLC system after appropriate dilution. The chromatographic system consisted of a pump (LC-10AD), an automatic injector (SIL-10A) and a UV detector (SPD-10A) (Shimadzu Scientific Instruments, Japan) set at 254 nm. An octadecylsilane column (Luna C18, 4.6 $\times$ 150 mm, 5 μm; Phenomenex, Torrance, CA) was eluted with a mixture of 0.2 M phosphate buffer (pH 2.5)–methanol (99:1, v/v) at a flow rate of 1.5 mL min^{-1} at room temperature. The calibration curve from the standard samples was linear over the concentration range of 0.3–20 μg mL^{-1}. The limit of detection was 0.3 μg mL^{-1}.

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed using Kinetica-4.3 (InnaPhase Corp., Philadelphia, PA). The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method. The terminal elimination rate constant (λz) was estimated from the slope of the terminal phase of the log plasma concentration–time points fitted by the method of least squares, and then the terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda z$. Additional estimated parameters using non-compartmental pharmacokinetic analysis were systemic plasma clearance (CL) and the volume of distribution (Vdss). Renal clearance (CL_R) was calculated as $CL_R = Ae/AUC$, where Ae (amount of unchanged drug

eliminated in urine) and AUC are measured over the same time interval.

Statistical analysis

All the means are presented with their standard deviation. The pharmacokinetic parameters were compared with a one-way analysis of variance, followed by a posteriori testing with the use of the Dunnett correction. $P < 0.05$ was considered statistically significant.

Results

The mean plasma concentration–time profiles of aciclovir in the presence and absence of ketoprofen or naproxen were evaluated in rats (Figure 1). The mean pharmacokinetic parameters of aciclovir are summarized in Table 1.

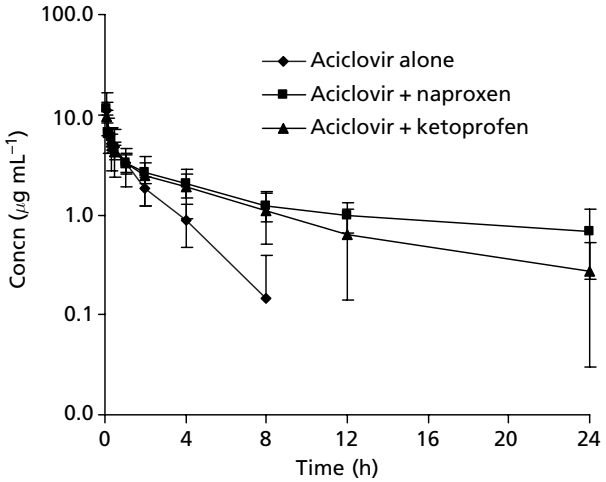

Figure 1 Mean pharmacokinetic profile of aciclovir following intravenous administration (5 mg kg^{-1}) to rats in the presence and absence of NSAIDs (mean ± s.d., n = 4).

Table 1 Mean pharmacokinetic parameters of aciclovir following intravenous administration (5 mg kg^{-1}) to rats in the presence and absence of NSAIDs

Parameter	Aciclovir alone	Aciclovir + naproxen	Aciclovir + ketoprofen
t½ (h)	2.0 ± 1.2	10.0 ± 1.7*	8.1 ± 4.1*
CL (L h^{-1} kg^{-1})	0.44 ± 0.24	0.17 ± 0.04*	0.22 ± 0.10
CL_R (L h^{-1} kg^{-1})	0.32 ± 0.17	0.14 ± 0.06*	0.17 ± 0.07
Vdss (L kg^{-1})	1.0 ± 0.52	1.70 ± 0.31	1.70 ± 0.78
AUC (μg h^{-1} mL^{-1})	13.0 ± 4.8	31.0 ± 7.6*	26 ± 12*
Ae (% dose)	71 ± 14	82 ± 20	75 ± 7

Data are mean ± s.d., n = 4. *$P < 0.05$, compared with the control (given aciclovir alone).

Total clearance of aciclovir was due almost entirely to renal clearance, which was about 70–80% of the total clearance in all cases, as consistent with previous reports (de Miranda et al 1979, 1981b; Laskin et al 1982a). As summarized in Table 1, pre-treatment with naproxen 30 min before aciclovir administration significantly ($P < 0.05$) altered the pharmacokinetics of aciclovir, compared with the control rats given aciclovir alone. Renal clearance and total clearance of aciclovir decreased by about two fold in the presence of naproxen. Consequently, systemic exposure (AUC) to aciclovir was significantly ($P < 0.05$) higher than in the control rats given aciclovir alone (Figure 1). The increase in aciclovir's AUC with administration of naproxen might be entirely accounted for by the reduction in CL_R of aciclovir. Similarly, the concurrent use of ketoprofen also reduced the renal and total clearance of acyclovir, although there was no statistical significance due to the high inter-subject variability. Ketoprofen increased the systemic exposure (AUC) to aciclovir by two fold ($P < 0.05$). The terminal plasma half-life (t½) of aciclovir increased by four to five fold in the presence of naproxen or ketoprofen. In the control group, urinary excretion of aciclovir was rapid; approximately 62% of the dose was excreted into the urine in the first 8 h and 71% of the dose was recovered in 24 h. Following the co-administration of naproxen, the urinary excretion of aciclovir was 48, 16 and 18% of the administered dose in the 8-, 12- and 24-h urine samples, respectively (Figure 2). In the presence of ketoprofen, the urinary excretion of aciclovir was similar to that after the co-administration of naproxen.

Collectively, pre-treatment with naproxen or ketoprofen (OAT1 inhibitors) before aciclovir administration significantly altered the renal elimination and pharmacokinetic profiles of aciclovir.

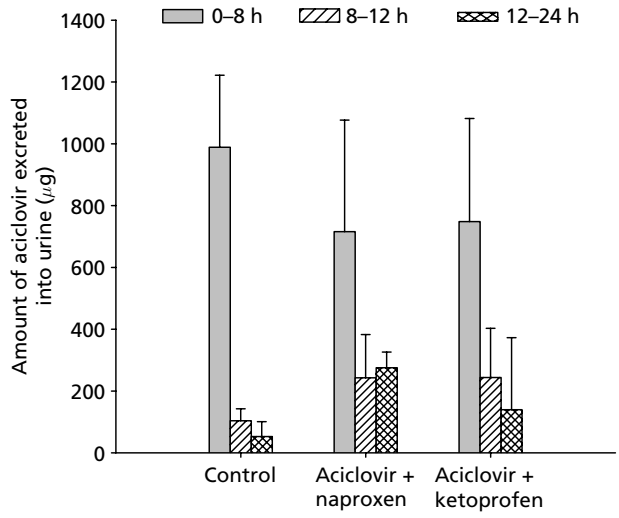

Figure 2 Mean urinary excretion profiles of aciclovir following intravenous administration (5 mg kg^{-1}) to rats in the presence and absence of NSAIDs (mean + s.d., n = 4).

Discussion

Over the past decade, a tremendous amount of work has been done for the molecular characterization of transport proteins in animals and man, which has led to a better understanding of the pathophysiological roles of a number of transport proteins (Meijer et al 1990; Müller & Jansen 1997; Kim 2000). Furthermore, there is increasing preclinical and clinical evidence to support the importance of transport proteins in the pharmacokinetics/toxicokinetics of a wide variety of structurally diverse drugs (Yamazaki et al 1996; Watkins 1999; Ayrton & Morgan 2001). As a consequence, the degree of expression and functionality of transport proteins may directly affect the therapeutic effectiveness, safety and target specificity of substrates. Traditionally, a change in the metabolic clearance of a drug, particularly via cytochrome P450-mediated metabolism, has been considered as the cause of many clinically important drug interactions (Von Moltke et al 1998; Dresser et al 2000). However, increasing evidence suggests that some drug interactions result from changes in the activity of transport proteins. For example, several clinically significant drug interactions have been reported with digoxin with ~50–300% increases in plasma concentrations after concomitant administration with P-glycoprotein inhibitors, such as quinidine, verapamil and talinolol (Angelin et al 1987; Verschraagen et al 1999; Westphal et al 2000). In addition, the decrease in renal excretion caused by probenecid co-administration with a variety of anionic drugs can be attributed to inhibition of OAT-mediated secretion at the basolateral membrane of renal proximal tubules (Laskin et al 1982b; Wada et al 2000). Therefore, transport proteins can play an important role in many clinical drug interactions.

Laskin et al (1982b) reported that tubular secretion of aciclovir is inhibited by co-administration of probenecid in man, at least in part. In their studies, after probenecid administration, there was a 32% decline in renal clearance, a 40% increase in the area under the curve and an 18% increase in the terminal plasma half-life of aciclovir. Although statistically significant, the increase in the terminal plasma half-life of aciclovir is small and the influence of probenecid on the pharmacokinetics of aciclovir appeared to be limited. This may be because the dose of probenecid given might not be adequate for the complete inhibition of a transport system (Laskin et al 1982b). Perhaps if larger doses of probenecid, repetitive doses of probenecid, or both, had been administered to the subjects, renal tubular secretion of aciclovir could have been blocked more completely. Therefore, in our studies, we tried to select more potent inhibitors than probenecid, as well as administering high doses without toxicity, to ensure more complete blocking of the OAT-mediated transport pathway. Recently, NSAIDs, such as ketoprofen, flurbiprofen, indometacin, diclofenac, naproxen and ibuprofen, were reported to be all equally, or more, effective than probenecid in inhibiting OAT1, with IC50 values (concentrations reducing transport by 50%) in the range 1.2–8 μM (Mulato et al 2000). Particularly, ketoprofen and naproxen appeared to be more potent inhibitors than probenecid against OAT1. Therefore, in our study, ketoprofen and naproxen were chosen to evaluate the potential drug interaction of aciclovir via the OAT1-mediated transport. Considering that naproxen and ketoprofen are eliminated more slowly than aciclovir, with a half-life of about 12 and 20 h, respectively, in rats (Satterwhite & Boudinot 1991, 1992), the inhibitory effect of NSAIDs on the renal secretion of aciclovir was examined following a single intravenous injection of naproxen or ketoprofen 30 min before aciclovir administration.

As summarized in Table 1, co-administration of naproxen or ketoprofen significantly altered the pharmacokinetics of aciclovir in rats, compared with the control rats given aciclovir alone. Renal clearance and total clearance of aciclovir decreased by two fold in the presence of naproxen or ketoprofen. Consequently, systemic exposure (AUC) to aciclovir was significantly ($P < 0.05$) increased by the concurrent use of naproxen or ketoprofen (Figure 1). The increases in aciclovir's AUC with co-administration of OAT1 inhibitors, such as naproxen and ketoprofen, could be entirely accounted for by the reduction in CL_R of aciclovir. The terminal plasma half-life (t½) of aciclovir increased about four to five fold in the rats pretreated with naproxen or ketoprofen, resulting in the delayed urinary excretion of aciclovir. As shown in Figure 2, the urinary excretion of aciclovir in the 8–24-h samples increased to 26–34% of the administered dose in the presence of naproxen or ketoprofen, while it was about 9% in the control group.

Aciclovir can cause an elevation in the serum creatinine level and crystal formation in the renal tubules after bolus injection, while oral aciclovir therapy in currently recommended doses does not appear to confer any nephrotoxicity (Brigden & Whiteman 1983). The pace of aciclovir-induced renal failure can be exceedingly rapid and a marked increase in serum creatinine level has been reported after treatment for only 12 h with intravenous aciclovir (Becker et al 1993). In nearly all instances of aciclovir-induced nephrotoxicity, renal function recovers when use of the drug is discontinued. In this study, the renal elimination of aciclovir was altered by OAT1 inhibitors, such as naproxen and ketoprofen, implying that the drug interaction between aciclovir and NSAIDs via the OAT1-mediated transport pathway can help to prevent aciclovir-induced nephrotoxicity. Furthermore, naproxen and ketoprofen may also prolong the duration of action of aciclovir within the body due to the increased half-life of aciclovir. Therefore, the clinical significance of this finding needs to be further evaluated at the therapeutic dose level in clinical studies.

Conclusion

Pre-treatment with naproxen or ketoprofen before aciclovir administration significantly alters the renal elimination and pharmacokinetic profiles of aciclovir, implicating drug interaction via the organic anion transporter-mediated pathway during the tubular secretion of aciclovir. Therefore, concomitant use of NSAIDs with aciclovir should require close monitoring for potential drug interaction.

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