Lack of interaction between valaciclovir, the L-valyl ester of aciclovir, and digoxin

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Aims Changes in both digoxin and aciclovir renal clearance following coadministration with some other renally eliminated drugs have been reported. The potential interaction of valaciclovir, with its antiherpetic metabolite aciclovir, and digoxin was investigated.

Methods Twelve healthy volunteers (seven males, five females) participated in an open, randomized, four-period crossover study. Valaciclovir, 1000 mg, was given alone on one occasion, and on another, after the second of two 0.75 mg digoxin doses administered 12 h apart. Blood samples and all urine were collected up to 12 h following the valaciclovir dose for aciclovir radioimmunoassay. On a third occasion, digoxin was given alone and on a fourth, with 1000 mg valaciclovir three times/day for 8 days starting 12 h before the first digoxin dose. Blood samples were taken up to 168 h and all urine collected up to 24 h following the second dose for digoxin radioimmunoassay.

Results There were no clinically significant differences in digoxin or aciclovir pharmacokinetic parameters when digoxin or valaciclovir was given alone or in combination.

Conclusions No dosage adjustment is required when valaciclovir and digoxin are coadministered.

Keywords: valaciclovir, digoxin, no interaction

Introduction

Valaciclovir (Valtrex[®]), the L-valyl ester of aciclovir, is licensed for the treatment of herpes zoster (shingles), a disease occurring commonly in the elderly. After oral administration, valaciclovir is rapidly converted to aciclovir with a bioavailability 3–5 times greater than from oral aciclovir [1]. Aciclovir is renally eliminated with tubular secretion forming a significant component. Probenecid, which inhibits organic anion secretion in the renal tubule, decreases the renal clearance of aciclovir [2]. Both probenecid and cimetidine, which inhibit tubular cation secretion, decrease aciclovir renal clearance following oral valaciclovir [3].

Digoxin, a drug of low therapeutic index, is commonly prescribed in the elderly. In most patients more than 80% of digoxin is excreted unchanged in the urine [4]. Interactions with drugs which affect digoxin renal clearance have been identified, some of which may be due to effects on tubular secretion [5, 6]. As there is the potential for an interaction between digoxin and aciclovir following oral valaciclovir, we have studied the pharmacokinetics of the drugs alone and in combination in healthy volunteers.

Methods

Subjects

Twelve healthy volunteers (seven males, five females) of mean age 31 years (range 22–44 years) and mean weight 75 kg (range 51–99 kg) participated in the study. Exclusion criteria included evidence of a cardiac conduction disorder on a 12-lead ECG and an estimated creatinine clearance <70 ml min⁻¹. All subjects gave written informed consent, and the protocol was approved by the Wellcome Protocol Review Committee and the King's Healthcare Research Ethics Committee.

Study design

This open, randomized, four-period crossover study was carried out at the Wellcome Clinical Investigations Unit, King's College Hospital, London. Volunteers fasted overnight prior to drug administration on the first blood sampling day. Oral valaciclovir, 1000 mg, was administered on one occasion, and on another, with digoxin, 0.75 mg being given 12 h before and 0.75 mg being given with valaciclovir. Digoxin was not dosed to steady state because of the ethical concerns of giving multiple doses to healthy volunteers. Blood was sampled before and 15, 30, 45 and 60 min and 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 12 h after the valaciclovir dose for plasma aciclovir assay. Urine was also

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collected up to 12 h, weighed and a 10 ml aliquot was frozen at -20°C for aciclovir assay.

Digoxin was administered as 2×0.75 mg doses alone on one occasion, and on another, with oral valaciclovir, 1000 mg three times daily for 8 days, with valaciclovir started 12 h before the first digoxin dose. The valaciclovir daily dose was that recommended for the treatment of shingles. Blood samples were taken before and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 24, 32, 48, 72, 96 and 168 h following the second digoxin dose for plasma digoxin assay. Urine was collected up to 24 h after the second digoxin dose, weighed, and a 10 ml aliquot was frozen at -20°C for digoxin assay.

Adverse experiences were recorded, 12-lead ECGs were performed before dosing and at 24 h after the second digoxin dose, and continuous lead II ECG monitoring was performed on all subjects for 24 h after digoxin doses.

Assays

Plasma and urine aciclovir determinations were made using double antibody radioimmunoassay (r.i.a.), which is a modification of the original method [7]. The lower limits of quantitation (LLOQs) were $0.01\text{ }\mu\text{g ml}^{-1}$ ($0.04\text{ }\mu\text{M}$) for plasma and $0.025\text{ }\mu\text{g ml}^{-1}$ ($0.11\text{ }\mu\text{M}$) for urine, with separate inter- and intra-assay precision shown by coefficients of variation (CVs) of $<10\%$ for plasma and $<11\%$ for urine.

Plasma and urine digoxin determinations were made using a competitive r.i.a. procedure (Phoenix International Life Sciences Inc.). The LLOQ was 0.10 ng ml^{-1} for both plasma and urine, with combined inter- and intra-assay precision shown by CVs of $\leq 10\%$ for plasma and $\leq 12\%$ for urine.

Pharmacokinetic and statistical analysis

Non-compartmental pharmacokinetic parameters were determined for plasma aciclovir and digoxin. The area under the plasma concentration-time curve from zero to the last measurable plasma concentration $\text{AUC}(0, t)$ was estimated

by the linear trapezoidal rule. $\text{AUC}(0, \infty)$ was calculated as $\text{AUC}(0, t) + C_t/\lambda_z$ where C_t is the last quantifiable concentration at time t . λ_z was obtained by log linear regression, using the terminal portion of the log of the concentration-time curve. Digoxin C_{max} and $\text{AUC}(0, \infty)$ were corrected for pre-dose concentration (C_0) as the plasma profile after the second dose was not at steady state (half-life of approximately 40 h). Digoxin $\text{AUC}(0, 24\text{ h})$ was also measured, but was not corrected. The elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$. The apparent volume of distribution, V_z/F , was calculated as $\text{Dose} \cdot \text{AUC}(0, \infty)/\lambda_z$. The aciclovir dose was calculated from the molar equivalents in the valaciclovir dose. Urinary recovery (Ae) was calculated as the product of urine concentrations and weights (assuming density of 1 g ml^{-1}). Renal clearance (CL_R) was calculated as Ae/AUC where Ae is the amount of drug excreted unchanged in urine, and AUC and Ae were measured over 12 and 24 h for aciclovir and digoxin respectively.

Pharmacokinetic parameters following digoxin or valaciclovir alone or in combination were subjected to analysis of variance. All parameters except t_{max} were log-transformed prior to analysis. Data were back-transformed to provide a point estimate with 95% confidence interval (CI) for the ratio in pharmacokinetic parameters between treatments. Differences between t_{max} medians were estimated (with 95% CIs) using a method based on the Wilcoxon Signed Rank test.

Results

Pharmacokinetic and statistical analysis

Arithmetic mean $\pm$ s.d. and geometric mean digoxin pharmacokinetic parameters are given in Table 1. There were no clinically significant differences obtained when digoxin was given alone or with valaciclovir (Table 1). The total amount of drug excreted in 24 h in urine ($n=11$) was similar whether digoxin was given alone ($73.8 \pm 28.5\text{ }\mu\text{g}$) or in combination ($81.0 \pm 31.3\text{ }\mu\text{g}$).

Table 1 Arithmetic mean $\pm$ s.d., geometric mean and statistical comparisons for digoxin pharmacokinetic parameters following digoxin alone and in combination with multiple doses of valaciclovir ($n=12$).

Parameter	Treatment	Arithmetic mean	Geometric mean	Geometric mean ratio combination/alone (95% CI)
C_{max} (ng ml^{-1}) ^a	Digoxin alone	3.45 ± 0.95	3.35	96% (79, 117%)
	Combination	3.32 ± 0.88	3.23	
$\text{AUC}(0, \infty)$ ($\text{ng ml}^{-1}\text{ h}$) ^a	Digoxin alone	42.6 ± 11.5	41.3	91% (73, 115%)
	Combination	40.6 ± 15.2	37.7	
$\text{AUC}(0, 24\text{ h})$ ($\text{ng ml}^{-1}\text{ h}$)	Digoxin alone	37.2 ± 7.8	36.6	95% (89, 100%)
	Combination	35.4 ± 8.2	34.6	
$t_{1/2}$ (h)	Digoxin alone	37.8 ± 7.4	37.2	106% (96, 117%)
	Combination	40.1 ± 7.2	39.5	
CL_R (ml min^{-1}) ^b	Digoxin alone	73.8 ± 28.5	68.7	110% (73, 166%)
	Combination	81.0 ± 31.3	75.6	
V_z/F (l)	Digoxin alone	1045 ± 354	994	116% (90, 150%)
	Combination	1260 ± 576	1155	
t_{max} (h) ^c	Digoxin alone	1.0 (0.5–2.0)	1.0	–0.25 (–0.50, 0.25)
	Combination	1.0 (0.5–2.5)	1.0	

^aCorrected for pre-dose concentration. ^b $n=11$. ^cMedian (range) and median difference (95% CI) shown.

Table 2 Arithmetic mean $\pm$ s.d. geometric mean and statistical comparisons for aciclovir pharmacokinetic parameters following valaciclovir alone and in combination with digoxin ($n = 12$).

Parameter	Treatment	Arithmetic mean	Geometric mean	Geometric mean ratio combination/alone (95% CI)
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	Valaciclovir alone	4.98 ± 1.29	4.84	103% (94, 113%)
	Combination	5.14 ± 1.23	5.00	
AUC(0, ∞) ($\mu\text{g ml}^{-1} \text{ h}$)	Valaciclovir alone	19.7 ± 4.5	19.2	103% (94, 111%)
	Combination	20.1 ± 4.2	19.7	
$t_{1/2}$ (h)	Valaciclovir alone	2.27 ± 0.16	2.26	99% (97, 101%)
	Combination	2.24 ± 0.15	2.24	
CL_R (ml min^{-1}) ^a	Valaciclovir alone	279 ± 72	270	101% (89%, 116%)
	Combination	278 ± 49	273	
V_z/F (l)	Valaciclovir alone	123 ± 33	119	97% (88, 105%)
	Combination	119 ± 33	115	
$t_{\max}$ (h) ^b	Valaciclovir alone	2.5 (1.5–3.0)	2.50	−0.25 (−0.50, 0.23)
	Combination	2.0 (1.5–3.0)	2.00	

^a $n = 10$. ^bMedian (range) and median difference (95% CI) shown.

Arithmetic mean $\pm$ s.d. and geometric mean aciclovir pharmacokinetic parameters are given in Table 2. There were no statistically significant differences obtained when valaciclovir was given alone or concomitantly with digoxin (Table 2). The percentage of the dose excreted in urine ($n = 10$) was similar whether valaciclovir was given alone ($42.6 \pm 9.8\%$) or in combination ($43.5 \pm 8.0\%$).

Adverse experiences (AEs)

There were no clinically significant changes in the ECG, and no AEs following valaciclovir alone. The most common AE was nausea, a known side-effect of digoxin, with 15 reports occurring on occasions when digoxin was administered.

Discussion

This study examined any pharmacokinetic interaction between aciclovir and digoxin taking into account their very different elimination half-lives.

The use of digoxin AUC(0, ∞) or AUC(0, 24 h) for comparison was valid in this study assuming the null hypothesis of no effect of valaciclovir coadministration on digoxin plasma concentrations. AUC(0, 24 h) was a more sensitive test (95% confidence interval 89–100%) compared with either corrected $C_{\max}$ or AUC(0, ∞) (95% CI of 79–117% and 73–115% respectively). A large contribution to the variability came from the pre-dose correction. Rather than an increase in digoxin AUC(0, 24 h) (suggestive of reduced digoxin clearance) there was a very small (5%) and non-clinically significant reduction when digoxin and valaciclovir were given in combination. The results obtained contrast with the increase of 18% in digoxin peak concentrations which occurred following coadministration of a single dose only of the nucleoside analogue, famciclovir [8].

The lack of effect on aciclovir pharmacokinetic parameters indicated that aciclovir and digoxin do not share the renal tubular transport system. Previous studies also suggest that

digoxin does not share this system indicated by the lack of effect of probenecid and tolazoline on digoxin secretion [5]. This contrasts with the competitive effects of probenecid and cimetidine on aciclovir secretion following valaciclovir, resulting in reduced aciclovir renal clearance [3].

In summary, these data indicate that there is no clinically significant interaction when valaciclovir and digoxin are coadministered and that the two drugs can be co-prescribed without dosage adjustment.

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