

## **Lack of interaction between valaciclovir, the L-valyl ester of acyclovir, and Maalox antacid**

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Valaciclovir is rapidly and extensively converted to acyclovir. In this study we investigated the potential interaction between oral valaciclovir and Maalox. On each of three occasions 18 healthy volunteers received a single oral dose of 1000 mg valaciclovir, or 30 mL Maalox 65 min after valaciclovir administration, or 30 mL Maalox 30 min before valaciclovir. Acyclovir plasma concentrations and pharmacokinetic parameters were not significantly affected by administration of Maalox before or after valaciclovir. Therefore, there is no need for restriction of valaciclovir dosing in patients receiving antacid medication.

### **Introduction**

Valaciclovir, the L-valyl ester of acyclovir, is rapidly and extensively converted to acyclovir (Weller *et al.*, 1993) which has potent in-vitro activity against herpes simplex virus types 1 and 2 and varicella zoster virus and is widely used to treat infections caused by these viruses (Wagstaff, Faulds & Goa, 1994). High dose acyclovir may also have a role in the suppression of cytomegalovirus infections (Meyers *et al.*, 1988; Balfour *et al.*, 1989; Prentice *et al.*, 1994).

The bioavailability of acyclovir in man is 10–20% but with increasing doses, bioavailability falls such that plasma concentrations reach a plateau. (Wagstaff *et al.*, 1994). Valaciclovir is rapidly and extensively converted to acyclovir by a hepatic mitochondrial enzyme known as valaciclovir hydrolase (Burnette & de Miranda, 1993) and in healthy volunteers, the bioavailability of acyclovir from valaciclovir is three to five times greater than for high dose oral acyclovir. Repeat dosing with 1000 mg valaciclovir gives average concentrations comparable to those obtained with 5 mg/kg doses of intravenous acyclovir (Weller *et al.*, 1993).

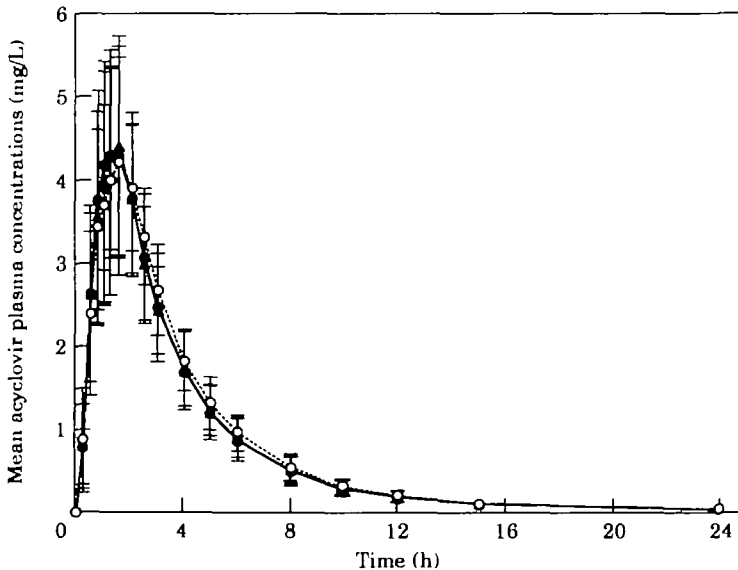
Antacids influence the absorption of many drugs either by increasing gastric pH, affecting gastric emptying or binding to the drug to form insoluble salts (Gugler & Allgayer, 1990). Concomitant administration with cimetidine, which increases gastric pH, has no effect on valaciclovir bioavailability (Rolan *et al.*, 1993) but the potential effect of antacids is unknown.

### Methods

Eighteen healthy volunteers (nine males and nine females, aged 20–29 years, weight 54.0–87.8 kg) were recruited. All volunteers were in good health, taking no regular medication and with no significant past medical history or abnormal findings on physical examination, electrocardiogram, full blood count, biochemical profile (urea, creatinine, electrolytes, liver function tests) or urinalysis. The study protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Hôtel Dieu Hospital, Paris, France and each subject gave written informed consent before inclusion.

All subjects abstained from using aspartame (an artificial sweetener that interferes with the drug assay), alcohol or caffeine-containing beverages and from smoking for at least 24 h before and after valaciclovir dosing. They also abstained from taking any medication for 1 week before and during the study, with the exception of study drugs and oral contraceptives for women. Subjects were confined to the study location between 12 h before and 24 h after administration of valaciclovir. They fasted for 8 h before valaciclovir administration and an additional 4 h following valaciclovir dosing.

On each of three occasions at least 7 days apart, subjects received a single dose of 1000 mg valaciclovir ( $2 \times 500$  mg tablets). On one occasion this was taken alone, on another occasion 30 min after taking 30 mL Maalox (1047 mg aluminium hydroxide and 1197 mg magnesium hydroxide) and on a third occasion 65 min before Maalox, according to a randomised, balanced, crossover design. Subjects received a standard lunch 4 h after valaciclovir dosing. Blood samples for acyclovir assay were taken into pre-chilled ethylene diamine tetra-acetic acid (EDTA) tubes, the plasma separated and immediately frozen at  $-20^{\circ}\text{C}$  until assay.



**Figure.** Mean ( $\pm$ s.d.) plasma acyclovir concentrations following valaciclovir administered alone and with Maalox. ●, Maalox given 30 min before VACV dosing; ▲, Maalox given 65 min after VACV dosing; ○, VACV alone

Full blood counts and biochemical profiles were determined before and 24 h after valaciclovir dosing on each occasion, and any adverse experiences were recorded. The investigator assessed any possible relationship to the study drug and severity.

Plasma acyclovir concentrations were determined by a specific double antibody radio-immunoassay (RIA) which utilises a monoclonal antibody raised to acyclovir and tritiated acyclovir as a tracer. The method separates antibody-bound from free [ $^3\text{H}$ ] acyclovir and is a modification of the original RIA acyclovir assay method (Quinn *et al.*, 1979).

Pharmacokinetic analysis of plasma acyclovir concentrations was conducted by non-compartmental methods. The peak concentration ( $C_{\text{max}}$ ) and time of peak concentration ( $T_{\text{max}}$ ) were determined from the raw data. The area under the concentration time curve (AUC) was estimated by the linear trapezoidal rule up to the last measurable concentration ( $C_t$ ) with extrapolation to infinite time by addition of the term  $C_t/\lambda$  in which  $\lambda$ , the elimination rate constant was estimated by regression of the log (concentration)-time profiles. The apparent elimination half-life ( $T_{1/2}$ ) was calculated as  $\ln 2/\lambda$ . Statistical differences between AUC,  $C_{\text{max}}$  and  $T_{1/2}$  for acyclovir in each of the treatment groups were assessed by analysis of variance (ANOVA) on log-transformed data. Median differences in  $T_{\text{max}}$  were estimated using the non parametric Friedman test.

**Table.** Geometric mean (range) and 95% confidence intervals for ratio of acyclovir pharmacokinetic parameters after valaciclovir alone and valaciclovir administered 30 min after or 65 min before Maalox

	Valaciclovir alone	Maalox given 30 min before VACV	Maalox given 65 min after VACV
$AUC_{0-\infty}$			
Mean (mg.h/L)	18.15	17.53	17.66
	(13.13-24.15)	(13.70-26.55)	(12.96-26.44)
95% Confidence intervals for ratio reported to VACV alone		95.9% (90.0-102.2%)	96.8% (90.8-103.1%)
$C_{\text{max}}$			
Mean (mg/L)	4.57	4.89	4.67
	(3.22-6.76)	(3.26-6.71)	(2.72-7.95)
95% Confidence intervals for ratio reported to VACV alone		108.2% (98.9-118.4%)	102.1% (93.3-111.7%)
$T_{1/2}$			
Mean (h)	2.67	2.73	2.70
	(2.27-3.01)	(2.33-3.22)	(2.24-3.29)
95% Confidence intervals for ratio reported to VACV alone		102.1% (99.3-104.9%)	100.8% (98.0-103.6%)
$T_{\text{max}}$			
Mean (h)	1.50	1.25	1.50
	(0.75-2.50)	(0.75-3.00)	(1.00-4.00)
95% Confidence intervals for ratio reported to VACV alone		0 (-1.00-0.00)	0 (-0.50-0.25)

### Results and discussion

There were six reports of mild to moderate adverse experiences. None was considered related to study drugs by the investigator, except for one report of heaviness in the stomach which was possibly related to the antacid. There were no clinically significant changes in vital signs, full blood counts or biochemical profiles.

Mean plasma acyclovir concentrations for each occasion are shown in the Figure and the acyclovir pharmacokinetic parameter estimates and the 95% confidence intervals for the ratio of each parameter following valaciclovir administered with Maalox compared with those after valaciclovir alone are shown in the Table. There were no significant differences in any of the acyclovir pharmacokinetic parameters between treatment groups and concentrations were consistent with previous studies (Weller *et al.*, 1993).

The lack of effect of concomitant Maalox administration on acyclovir bioavailability from valaciclovir implies that changes in gastric pH do not influence valaciclovir bioavailability and that there is no significant binding of valaciclovir to aluminium hydroxide and magnesium hydroxide. The fact that cimetidine has no significant effect on valaciclovir absorption (Rolan *et al.*, 1993) confirms the lack of effect of changes in gastric pH. Valaciclovir in solution is partly positively charged and partly neutral (pKa 1.7–7.47–9.41). The absence of significant binding of valaciclovir to Maalox is consistent with the fact that the antacid ions of magnesium ( $Mg^{++}$ ) and aluminium ( $Al^{++}$ ) are unlikely to bind to or to chelate a moiety of like charge. Similarly, it is unlikely that other antacids will affect acyclovir bioavailability from valaciclovir and there is no need for dosage adjustment when valaciclovir is given to patients also receiving antacids.

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