

## Acyclovir–Valaciclovir Equilibrium Between Peritoneal Fluid and Plasma

Acyclovir excretion via continuous ambulatory peritoneal dialysis (CAPD) is expected to be low due to the drug's extended distribution (1,2), which results in low peritoneal concentrations. Literature on oral acyclovir pharmacokinetics in CAPD is limited, but data on intravenous (IV) acyclovir in CAPD confirm a low peritoneal clearance and indicate that it is not significantly influenced by differences in dialysate osmolality (2). This finding leads to the assumption that the main physicochemical event that dominates acyclovir peritoneal excretion is diffusion, and this may be attributed to the drug's small size and low molecular weight.

Equilibrium between peritoneal fluid and plasma is reached progressively during dialysis, for endogenous substances and drugs (3). Inpatient variations in acyclovir peritoneal clearances observed in consecutive bag exchanges are expected to be a result of the equilibrium–time curve, whereas interpatient variations result from individual anatomical and functional characteristics of the peritoneum. The aim of this study was to investigate the pharmacokinetic parameters of acyclovir excretion via CAPD and, in order to individualize dosage adjustment in this renal failure population, to investigate the contribution of dialysis to the drug's total clearance.

### METHOD

Nineteen CAPD patients were recruited in this study and were divided into two groups. In the first group (group A), 10 anuric patients on three bag exchanges daily of 2 L isotonic solutions were recruited from the Royal London Hospital, in London, United Kingdom, and were administered 1 tablet of acyclovir (800 mg). Eleven serial blood samples were collected during the following 32 hours. In the second group (group B), 9 patients recruited from Laiko General Hospital, Athens, Greece, and established on their individualized bag exchange scheme, were administered a single oral dose of valaciclovir (500 mg; biotransformed to acyclovir) (1) and, after a washout period of 15 days, an equivalent single IV dose of acyclovir (350 mg). Fourteen consecutive blood samples were collected during the following 32 hours.

In both groups, peritoneal effluents were collected at the end of every exchange and, in group B, urine was collected for 32 hours in patients with residual renal function (> 200 mL/24 hours). In group A, acyclovir analysis was performed by radioimmuno-

assay (RIA) (4). In group B, high performance liquid chromatography (HPLC) (5) was used for the simultaneous detection of acyclovir and valaciclovir.

The software MWP<sub>HARM</sub> (Mediware, Groningen, The Netherlands) was used for the estimation of pharmacokinetic parameters.

Total acyclovir clearance ( $CL_{total}$ ) was measured by the area under the curve ( $AUC_{0-\infty}$ ) of acyclovir concentration versus time, from time zero to infinity:

$$CL_{total} \text{ (L/hr)} = \text{dose (mg)} / AUC_{0-\infty} \text{ (mg} \cdot \text{hrs/L)}.$$

Prediction of acyclovir serum concentration at steady state ( $c_{ss}$ ) following multiple-dose treatment was based on the observed  $CL_{total}$ :

$$c_{ss} \text{ (mg/L)} = \text{dose} / CL_{total} \times \text{dose interval (hrs)}.$$

Acyclovir bioavailability (F) from valaciclovir was calculated by measuring the  $AUC_{0-\infty}$  following oral valaciclovir and the equivalent IV acyclovir:

$$F = \text{oral } AUC_{0-\infty} / \text{IV } AUC_{0-\infty}.$$

Peritoneal clearance ( $CL_{CAPD}$ ) and renal clearance ( $CL_{renal}$ ) were calculated by measuring the total amount of acyclovir detected during 32 hours after administration, in effluents and urine respectively:

$$CL_{CAPD} \text{ (L/hr)} \\ = \text{dialysate acyclovir (mg)} / AUC_{0-32} \text{ (mg} \cdot \text{hrs/L)}$$

and

$$CL_{renal} \text{ (L/hr)} \\ = \text{urine acyclovir (mg)} / AUC_{0-32} \text{ (mg} \cdot \text{hrs/L)},$$

where  $AUC_{0-32}$  is the area under the curve of acyclovir concentration versus time, from time zero to 32 hours after administration.

Inpatient variation in  $CL_{CAPD}$  was calculated by the amount of acyclovir detected in every CAPD effluent and the corresponding dwell time AUC, which was determined using the trapezoidal method. Possible correlation of  $CL_{CAPD}$  with dialysis adequacy and transfer test (DATT), and relation of  $CL_{total}$  to  $CL_{CAPD}$  were also examined. The DATT parameters (6) were effluent/serum urea (D/P urea), effluent/dialysate glucose (D/D<sub>0</sub> glucose), effluent/serum creatinine (D/P Cr), and net ultrafiltration.

Evaluation of intra- and interpatient variation was based on the t-test and the Wilcoxon test for normal and nonnormal distribution, respectively. Comparison of pharmacokinetic parameters between valaciclovir and IV acyclovir was based on paired

t-test, and between valaciclovir and oral acyclovir, on unpaired t-test. Determination of multivariate factors was based on linear regression, and correlations were estimated by Pearson's and Spearman's correlation coefficient in normal and nonnormal distribution, respectively. Statistical significance was considered at  $p$  value less than 0.05.

## RESULTS

Ten anuric patients were enrolled in group A. There were 9 patients in group B, 3 (33%) of whom had residual renal function (0.8 L, 1.2 L, and 2 L urine/24 hours, respectively). In group A, mean age was  $55.5 \pm 14.6$  years; there were 4 males and 6 females; mean body surface area (BSA) was  $1.78 \pm 0.16$  m<sup>2</sup>; and mean excess body weight (EBW) was 23%. Mean duration on CAPD was  $4.2 \pm 1.8$  years. In group B, mean age was  $52.0 \pm 15.7$  years; there were 4 males and 5 females; mean BSA was  $1.69 \pm 0.18$  m<sup>2</sup>; and EBW was 21%. Mean duration on CAPD was  $2.9 \pm 2.8$  years. Volume of distribution was  $6.76 \pm 3.00$  L/kg,  $2.29 \pm 0.90$  L/kg, and  $0.55 \pm 0.08$  L/kg for oral acyclovir, valaciclovir, and IV acyclovir, respectively.

For valaciclovir and IV acyclovir,  $CL_{renal}$  was  $0.496 \pm 0.500$  L/hr/1.73 m<sup>2</sup> and  $0.21 \pm 0.20$  L/hr/1.73 m<sup>2</sup> respectively, with high inter- and inpatient variation between oral and IV administration despite the fact that renal creatinine clearance remained stable during the crossover period.  $CL_{CAPD}$  was significantly different for oral acyclovir versus valaciclovir ( $0.193 \pm 0.036$  L/hr/1.73 m<sup>2</sup> vs  $0.355 \pm$

$0.189$  L/hr/1.73 m<sup>2</sup>,  $p = 0.03$ ), but similar between valaciclovir and IV acyclovir ( $0.355 \pm 0.189$  L/hr/1.73 m<sup>2</sup> vs  $0.260 \pm 0.092$  L/hr/1.73 m<sup>2</sup>,  $p = 0.179$ ), with corresponding intra- versus interpatient coefficient of variation (CV): 28% versus 28%, 46% versus 53%, and 64% versus 34%, respectively.  $CL_{total}$  was  $21.54 \pm 8.10$ ,  $5.35 \pm 2.66$ , and  $1.88 \pm 0.96$  L/hr/1.73 m<sup>2</sup> for oral acyclovir, valaciclovir, and IV acyclovir, respectively.

Valaciclovir bioavailability was  $46.25\% \pm 11.78\%$ , and absolute  $CL_{total}$  (corrected for bioavailability and ester factor 0.6944) was  $1.70 \pm 0.95$  L/hr/1.73 m<sup>2</sup>, which was similar to IV administration. There was no significant difference ( $p = 0.45$ ) in absolute  $CL_{total}$  between anuric patients and patients with residual renal function. The percentage of bioavailable dose excreted via CAPD was low:  $11.6\% \pm 7.1\%$  for IV acyclovir and  $15.1\% \pm 10.2\%$  for oral valaciclovir.  $CL_{CAPD}$  correlated only with the DATT parameter that represents peritoneal creatinine clearance (D/P Cr) in effluents of 2.27% dialysates ( $p = 0.027$ ) and isotonic ( $p < 0.002$ ) dialysate effluents, exclusively in IV administration and not in oral administration, due probably to oral bioavailability fluctuations.  $CL_{total}$  did not correlate with  $CL_{CAPD}$  and/or  $CL_{renal}$  ( $p > 0.15$ ).

According to the reported acyclovir therapeutic range of 4 – 8 mmol/L (1) for herpes and varicella zoster infections, the predicted acyclovir steady state concentrations were suprathereapeutic for all participants, ranging from 10 to 24 mmol/L and from 18 to 84 mmol/L, following the recommended oral doses of 1600 mg/24 hours for acyclovir and 1000 mg/24 hours for valaciclovir, respectively.

## DISCUSSION

Differences in duration on CAPD and the diversity in medical history were not considered to contribute to the observed interpatient variations in acyclovir  $CL_{CAPD}$ . CAPD has been associated with anatomical changes in the peritoneum but does not result in its functional deterioration (7), and the literature does not confirm a homogenous influence by coexisting illness on the efficacy of the peritoneal membrane (8).

Acyclovir  $CL_{CAPD}$  following oral acyclovir administration was significantly lower ( $p = 0.03$ ) than that observed following valaciclovir administration. The differences in  $CL_{CAPD}$  and CV could be attributed to the study design, depending on which patients in group A were put on a certain scheme of CAPD bag exchanges (2 L isotonic/8 hours); whereas, in group B, patients were stabilized on their individual CAPD scheme. Acyclovir  $CL_{CAPD}$  in the IV acyclovir group, although lower compared to valaciclovir, was not considered significantly different, and both values were within the reported range for IV acyclovir (2).

The maximum acyclovir equilibrium between peri-

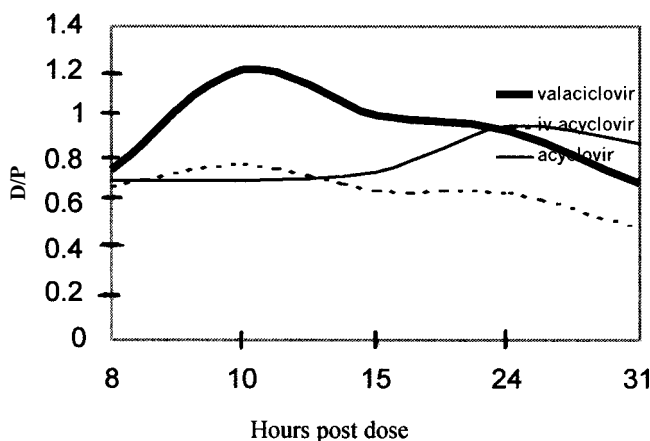


Figure 1 — The maximum acyclovir equilibrium between peritoneal and serum concentrations (D/P) was reached later following oral valaciclovir (12 hours) than IV acyclovir (10 hours), with corresponding minimum peritoneal concentrations representing 69% and 50% of serum concentrations, reaching up to 120% and 79% for oral valaciclovir and IV acyclovir respectively. Twelve hours post dose, a decline in D/P with the same profile was observed for both routes of administration.

toneal and serum concentrations (D/P) was reached later following oral valaciclovir (12 hours) than IV acyclovir (10 hours), with corresponding minimum peritoneal concentrations representing 69% and 50% of serum concentrations, and maximum peritoneal concentrations reaching 120% and 79% for oral valaciclovir and IV acyclovir respectively. Twelve hours post dose, a decline in D/P with the same profile was observed for both routes of administration (Figure 1).

Theoretically, peritoneal concentrations never exceed serum concentrations; 100% D/P is not reached, since many physicochemical factors impede the equilibration (3). The fact that 120% D/P equilibration was observed following valaciclovir administration leads to the assumption that, in the peritoneal cavity, acyclovir is distributed not only from systemic circulation after first-pass effect hepatic metabolism, but also, a substantial amount is derived from hydrolysis by enteric mucosa and absorption at the enteric site (9). The hypothesis of the contribution of enteric absorption to high peritoneal concentrations was also strengthened by (1) the observation that the D/P in oral acyclovir, although lower than in valaciclovir, reached 90% compared to 79% for IV administration; and (2) the fact that there was no significant difference in mean acyclovir peritoneal clearance between IV acyclovir and oral valaciclovir suggests that the high D/P observed following oral administration was an artifact resulting from acyclovir distribution and accumulation in peritoneal fluid due to sustained gut absorption.

In conclusion, the equilibrium–time profile exhibited maximum values during the absorption and distribution phase. However, intra- and interpatient variations observed in peritoneal clearance did not influence total clearance of acyclovir. Peritoneal clearance was low, not contributing to the prediction of dosage needs.

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