Continuous Infusion of High-Dose Acyclovir for Serious Herpesvirus Infections

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Thirteen patients with herpesvirus infections who were unresponsive to at least 72 h of intermittent acyclovir administration received high-dose continuous infusion. Steady-state concentrations were maintained at between 20 and 98 μmol/liter. Of 12 patients who had continuous infusion for >5 days, 7 (58%) resolved their infections, as determined by clinical and virologic parameters, suggesting that continuous infusion may succeed in some patients who do not respond to conventional therapy.

Acyclovir is a purine nucleoside with in vitro activity against herpes simplex virus (HSV), varicella-zoster virus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) (1). The drug has been shown to be of clinical benefit when administered topically, orally, or parenterally for the prophylaxis and treatment of certain herpesvirus infections (1). While acyclovir is conventionally given by intermittent or intravenous routes, the method of administration that best inhibits viral replication is not known. This report describes the use of high-dose acyclovir given by continuous intravenous infusion to 13 patients with serious herpesvirus infections.

Patients hospitalized at the University of Minnesota Hospital were eligible for this study if they (i) had serious, systemic, life-threatening herpesvirus infections; (ii) had received at least 72 h of intermittent oral or intravenous acyclovir; and (iii) were judged by the attending physicians to have had poor responses to conventional, intermittent acyclovir administration. Clinical indicators of poor response included continued fever and weakness in CMV-infected individuals, progression of mucocutaneous lesions in HSV-infected individuals, and continued fever or lymphadenopathy in EBV-infected individuals.

The acyclovir dosing regimen for continuous infusion was designed by using a two-compartment pharmacokinetic model (5), with acyclovir elimination defined as a function of creatinine clearance (CLCR). Nominal values of the pharmacokinetic parameters used for simulation of concentration in plasma and dosage regimen design were as follows: volume of distribution of the central compartment, 0.32 liter/kg of body weight, and intercompartmental rate constants of 1.3 h⁻¹ (k₁₂) and 0.8 h⁻¹ (k₂₁). The elimination rate constant (k₁) was defined as a function of CLCR by the equation k₁ = k₁slope · CLCR + k₁int, where k₁slope and k₁int were 0.0096 and 0.082 h⁻¹, respectively (D. M. Brundage, B. Chinnock, B. Bean, and J. H. Rodman, Drug Intell. Clin. Pharm. 18:501, 1984). The parameter k₁slope is a dimensionless regression parameter between renal elimination and CLCR derived from the relationship between acyclovir total body clearance (CL) and CLCR developed by Blum et al. (3). The parameter k₁int represents the nonrenal elimination rate constant. Estimating k₁ from a function of CLCR allows any value of CLCR to be considered in initial dosage regimen design and facilitates empirical adjustments in the dosage regimen based on changes in CLCR. Values for CLCR in these patients were estimated by the method of Cockcroft and Gault (4). The desired concentrations in plasma for continuous infusion of acyclovir were based on in vitro susceptibility data. Steady-state concentrations in plasma (Cₚₛ) were generally targeted at 20 to 80 μmol/liter, with Cₚₛ of 20 to 40 μmol/liter for resistant HSV, 30 to 60 μmol/liter for EBV, and 40 to 80 μmol/liter for CMV. The initial continuous-infusion regimens (milligrams per hour) for acyclovir were calculated as desired Cₚₛ (milligrams per liter) · CLCR (liter per hour), where CLCR = k₁slope · V₁ and V₁ is the volume of distribution of the central compartment. Subsequent regimens were calculated on the basis of individual patient acyclovir CL estimated from actual concentration data or from model-estimated values for acyclovir CL in patients with changing renal function. All dose adjustments were made to keep Cₚₛ within target limits. Patient response and tolerance were assessed by laboratory and clinical evaluation. Serial blood samples were obtained and analyzed in our laboratory for acyclovir concentrations by radioimmunoassay (11). The radioimmunoassay for acyclovir was considered acceptable if values for the plasma controls were within 10% of the stated value and if the correlation coefficient from weighted regression of the standard line was 0.995 or greater. The usable range of this radioimmunoassay for acyclovir is 1.25 to 115.3 μmol/liter when a 1:100 dilution of the unknown is used.

Table 1 describes the 13 patients who received continuous infusions of acyclovir. Pharmacokinetic and tolerance data are presented in Table 2. The overall range of Cₚₛ during continuous infusion was 20 to 98 μmol/liter in the 81 plasma samples analyzed. The correlation was good (r = 0.91) between the initial acyclovir concentration predicted by the pharmacokinetic model and the measured value (Fig. 1). To optimize therapy, the administration rate was subsequently increased in patients 2, 3, 4, 10, and 12. Acyclovir CL (Fig. 2) ranged from 71 to 555 ml/min per 1.73 m² and correlated well with CLCR in these patients (r = 0.94). The only
The intermittent administration of parenteral acyclovir has shown widespread safety and utility in the treatment of herpes-group viral infections. However, the pharmacodynamic relationship between inhibition of viral replication and exposure to acyclovir is essentially unknown, as is the relationship between acyclovir concentrations in plasma achieved clinically and the intracellular concentration of the active metabolite acyclovir triphosphate. The usefulness of acyclovir continuous infusion has been previously suggested by Spector et al. (12), who treated HSV or varicella-zoster virus infections in 16 immunocompromised patients with low-dose continuous infusion. Mean \( C_{\text{ss}} \) ranged from 4.1 to 36.6 \( \mu \text{mol/liter} \). All patients survived, and no adverse effects were detected clinically or by laboratory tests in this study.

Our study also suggests that acyclovir continuous infusion may have some clinical usefulness. Two of five evaluable patients with CMV infection and three of three patients with HSV infection were judged improved on the basis of cessa-
tion of viral shedding and clinical resolution (which meant cessation of fever and weakness for those with CMV disease and healing of mucocutaneous lesions for those with HSV disease). EBV disease was considered improved in two of four patients: one patient had resolution of fever and decreased lymphadenopathy by computerized tomography scan, and the other had marked regression of hepatomegaly and lymphadenopathy. Our pharmacokinetic model for acyclovir dosing performed well, accommodating the wide range of renal function present in these patients. The relationship between acyclovir CL and CL\textsubscript{CR} observed in our study is consistent with that described by Blum et al. (3).

Acyclovir concentrations in plasma were achieved and maintained within the desired target limits.

All three patients infected with HSV had isolates that were deficient in thymidine kinase activity, with 50% inhibitory levels (ID\textsubscript{50}) of acyclovir exceeding 40 \textmu molar/liter. Sensitive HSV isolates had ID\textsubscript{50} of <8 \textmu molar/liter (6). These HSV infections resolved following continuous infusion of acyclovir. However, the \textit{C}_{\text{ss}} maintained only approximately the ID\textsubscript{50} for the HSV isolates as determined by plaque reduction assay on Vero cells. This observation would cast doubt on the direct application of an in vitro ID\textsubscript{50} to a clinical setting and also suggests that resistance is only a relative term. Obviously, more pharmacodynamic data are needed to correlate the in vitro ID\textsubscript{50}, plasma drug concentration, and clinical efficacy.

Acyclovir continuous infusion appears to be reasonably safe. Elevation of bilirubin, noted in patient 4, was of undetermined etiology but thought to represent progression of CMV disease rather than drug toxicity. The bilirubin returned to normal following improvement of CMV disease and discontinuation of acyclovir. Patients 5, 9, and 11 developed neutropenia while receiving acyclovir continuous infusion. Coexisting risk factors were present in all instances: patient 5 had received cyclic high-dose cyclophosphamide within 30 days prior to acyclovir, patient 9 was receiving concurrent interferon alfa-2b, and patient 11 had received vidarabine 2 days prior to the start of acyclovir continuous infusion.

The administration of acyclovir by continuous infusion is not necessary in most clinical situations. However, we believe that continuous infusion may represent a viable alternative in select situations. Continuous infusion may be useful in treating infections due to acyclovir-resistant HSV, such as those described in this report and by others (2, 10). Additionally, continuous infusion may be useful in therapy of B-cell lymphoproliferation induced by EBV. Acyclovir has been previously described as beneficial when administered in the polyclonal phase of the disease (9). The use of acyclovir for treatment of CMV remains controversial. The apparent usefulness of ganciclovir, however, probably limits further investigation of acyclovir, at least as a treatment for CMV (7). Lastly, continuous infusion of acyclovir may represent a treatment approach for patients who have severe viral infections not responding to conventional administration of the drug and at risk for the sequelae, such as neurotoxicity, of alternative agents (8). The potential risks of continuous infusion appear to be nephrotoxicity and neutropenia. Nephrotoxicity (not observed in this study) can be minimized by close attention to dose, renal function, and hydration status of the patient. Concomitant administration of other agents known to cause neutropenia should be avoided or done with extreme caution if continuous infusion is attempted. Finally, acyclovir continuous infusion should be used only by centers able to closely monitor the virologic status of their patients and periodically determine the circulating concentration of the drug.

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**LITERATURE CITED**


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**FIG. 1.** Measured versus predicted initial concentrations of acyclovir in plasma. The solid line is that of identity. The line of best fit is described by the equation \( y = 0.9x + 5.4 \).

**FIG. 2.** Acyclovir CL versus estimated CL\textsubscript{CR} (both in milliliters per minute per 1.73 m\textsuperscript{2}). The solid line represents the line of best fit.