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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 oral 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 (CL_{CR}). 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} (k_{12}) and 0.8 h^{-1} (k_{21}). The elimination rate constant (k_{el}) was defined as a function of CL_{CR} by the equation $k_{el} = k_{slope} \cdot CL_{CR} + k_{int}$, where k_{slope} and k_{int} 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 k_{slope} is a dimensionless regression parameter between renal elimination and CL_{CR} derived from the relationship between acyclovir total body clearance (CL) and CL_{CR} developed by Blum et al. (3). The parameter k_{int} represents the nonrenal elimination rate constant. Estimating k_{el} as a function of CL_{CR} allows any value of CL_{CR} to be considered in initial dosage regimen design and facilitates empirical adjustments in the dosage regimen based on changes in CL_{CR}. Values for CL_{CR} 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 (C_{ss}) were generally targeted at 20 to 80 μmol/liter, with C_{ss} 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 C_{ss} (milligrams per liter) · CL (liter per hour), where $CL = k_{el} \cdot V_1$ and V_1 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 C_{ss} within targeted 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 C_{ss} 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 m^2 and correlated well with CL_{CR} in these patients ($r = 0.94$). The only

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TABLE 1. Patient characteristics

Patient no.	Age (yr)	Condition[a]	Herpesvirus infection	Acyclovir					Infection resolved
				Intermittent		Continuous infusion			
				Dose (mg/kg per day)	Duration (days)	Dose		Duration (days)	
						mg/h	mg/kg per h		
1	43	Renal transplant	CMV	30	4	175	2.19	9	Yes
2	31	Renal transplant	CMV	10	4	25–53	0.45–0.96	29	No
3	36	Renal transplant	CMV	30	5	60–126	1.02–2.14	7	No
4	31	Renal transplant	CMV	20	6	75–110	1.1–1.62	6	Yes
5	50	Non-Hodgkin's lymphoma	CMV	30	7	250	3.3	2	NE[b]
6	18	Marrow transplant, ALL	CMV	30	6	100	2.08	15	No
7	2	Immunodeficiency syndrome	EBV	100[c]	5	70	6.09	21	Yes
8	12	Marrow transplant, CML	EBV	30	8	270	6.1	5	No
9	30	Marrow transplant, CML	EBV	30	7	280–70	5.8–1.46	12	Yes
10	4.5	Immunodeficiency syndrome	EBV	30	12	100–160	6.06–9.7	12	No
11	8	Wiskott-Aldrich syndrome, marrow transplant	HSV	40	13	125	6.25	8	Yes
12	25	AIDS	HSV	30	17	75–100	1.22–1.63	40	Yes
13	57	AIDS	HSV	30	21	100	1.44	46	Yes

[a] ALL, Acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; AIDS, acquired immune deficiency syndrome.
[b] NE, Not evaluable.
[c] Oral acyclovir; all other regimens were intravenous.

dose-limiting adverse event observed was neutropenia (absolute count, <1,000/mm^3), which occurred in patients 5, 9, and 11. No patient experienced renal insufficiency as a result of these high levels of acyclovir. Urine output remained above 0.5 ml/mg of drug administered in all patients except patient 2, who was in acute renal failure and undergoing continuous peritoneal dialysis (0.5 to 1 liter of glucose [4.25%] per hour) prior to and throughout her course of continuous infusion. Peritoneal dialysis did not appear to affect acyclovir CL, as we have previously observed (D. M. Brundage, C. V. Fletcher, B. Chinnock, B. Bean, J. H. Rodman, and H. H. Balfour, Jr., Drug Intell. Clin. Pharm. **19**:453, 1985). Seven patients were judged by clinical and virologic parameters to have resolved their herpesvirus infections at the time the acyclovir continuous infusion was discontinued. Patient 5 was not considered evaluable because neutropenia forced discontinuation of the continuous-infusion regimen 2 days after initiation.

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_{ss} ranged from 4.1 to 36.6 μmol/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-

TABLE 2. Pharmacokinetics and tolerance

Patient no.	Clearance (ml/min per 1.73 m^2)		Measured C_{ss} (range, μmol/liter)	Serum creatinine (mg/dl)		Total bilirubin (mg/dl)		Absolute neutrophils (1,000/mm^3)	
	Creatinine	Acyclovir (mean)		Start	Stop	Start	Stop	Start	Stop
1	72	302	40–65	1.1	1.2	0.2	0.1	14.8[a]	12.9[a]
2	11	71	43–98	5.0	4.7	0.4	0.5	9.8	14.9
3	68	144	49–75	1.1	1.5	1.0	1.2	6.8[a]	5.8[a]
4	24	104	37–49	2.8	3.3	6.4	19.8	1.7	2.5
5	51	225	71	1.1	1.0	0.3	ND[b]	1.7	0.5
6	59	155	55–61	0.7	0.8	2.8	3.7	3.9	4.4
7	120	472	31–53	0.3	0.3	0.3	0.4	5.1	4.8
8	65	302	82	0.8	1.0	2.6	2.1	4.0	5.8
9	130	460	20–26	0.5	0.6	1.2	0.8	2.1	0.8
10	170	555	34–59	0.2	0.2	0.5	0.8	1.9	2.6
11	160	444	40–46	0.4	0.5	0.3	0.2	1.2	0.5
12	59	251	20–35	1.2	1.1	0.3	0.3	1.3	1.0
13	86	329	19–27	0.9	0.8	0.5	ND	3.0	2.8

[a] Leukocytes only; absolute neutrophil count not available.
[b] ND, Not done.

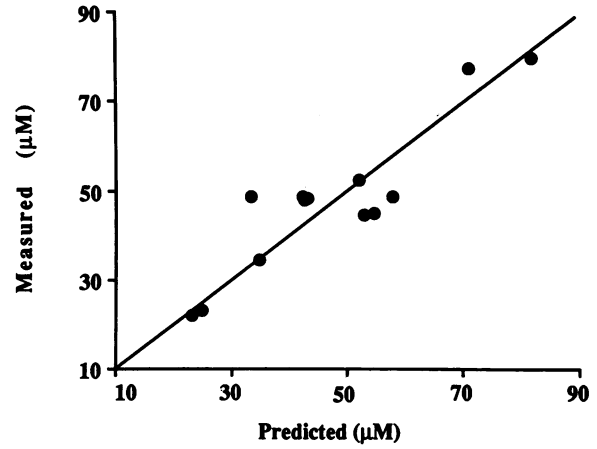

FIG. 1. Measured versus predicted initial concentrations of acyclovir in plasma. The solid line is that of identity. The line of best fit is described by the equation $y = 0.9x + 5.4$.

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_{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 targeted limits.

All three patients infected with HSV had isolates that were deficient in thymidine kinase activity, with 50% inhibitory levels (ID_{50}s) of acyclovir exceeding 40 μmol/liter. Sensitive HSV isolates had ID_{50} of <8 μmol/liter (6). These HSV infections resolved following continuous infusion of acyclovir. However, the C_{ss} maintained only approximated the ID_{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_{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_{50}, plasma drug concentration, and clinical efficacy.

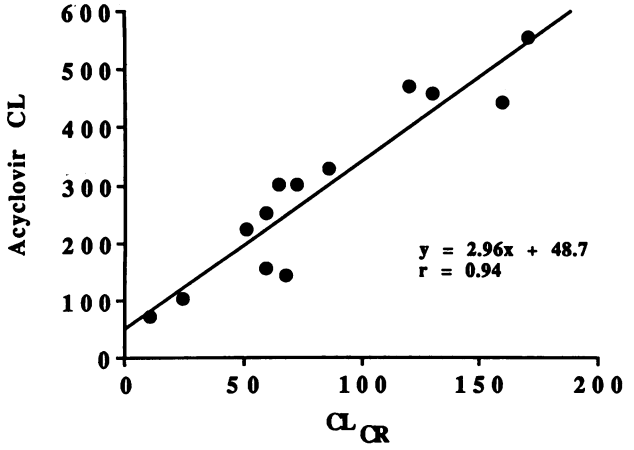

FIG. 2. Acyclovir CL versus estimated CL_{CR} (both in milliliters per minute per 1.73 m^2). The solid line represents the line of best fit.

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 are 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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