

# Therapeutic Drug Monitoring in Neonatal HSV Infection on Continuous Renal Replacement Therapy

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## abstract

Optimal acyclovir dosing under continuous renal replacement therapy (CRRT) in neonates is unknown. We monitored serum acyclovir levels and herpes simplex virus 1 (HSV-1) DNA levels in a neonate with disseminated HSV-1 infection and renal failure undergoing CRRT. A full-term, 5-day-old female presented with a 2-day history of lethargy and fever. She developed fulminant hepatitis and was diagnosed with HSV-1 infection by real-time polymerase chain reaction. Acyclovir was initiated at 60 mg/kg/day, which was lowered to 20 mg/kg/day because of development of renal failure. She was placed on continuous hemodialysis. Acyclovir dosing was adjusted according to serum acyclovir levels, and HSV-1 viral load was sequentially monitored. Semiquantification of serum HSV-1 levels was performed by real-time polymerase chain reaction. Acyclovir levels were measured by using liquid chromatography-tandem mass spectrometry. Acyclovir was administered at 20 mg/kg intravenously over 1 hour; peak concentration was 18.9  $\mu\text{g/mL}$ . The half-life of acyclovir was estimated to be 2 to 3 h. Viral load remained high during dosing every 24 hours, with a decline of 0.17 log copies/24 hours. Acyclovir dosing was changed to 20 mg/kg/dose every 8 hours, with an average viral load decline of 0.44 log copies/24 hours. Despite the guideline recommendation of 24-hour redosing, acyclovir was dialyzed at a rate that resulted in suboptimal treatment. Individual therapeutic drug monitoring for acyclovir and dosing adjustment may be required to optimize therapy for patients undergoing CRRT.

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Dr. Miyairi initiated, conceptualized, and supervised the study; Dr Enomoto was responsible for patient data collection and analysis of the intensive care treatment of the patient; Dr Funaki was involved in specimen collection and analyzed patient charts; Dr Miyata was involved in virological examination of specimen by real-time polymerase chain reaction assay; Drs Sakamoto and Kasahara were involved in analysis of the intensive care of the patient for liver failure; Dr Shoji was involved in patient data collection; Drs Funaki and Miyairi wrote the manuscript; Drs Miyata and Shoji were involved in revision of the manuscript; and all authors approved the final manuscript as submitted.

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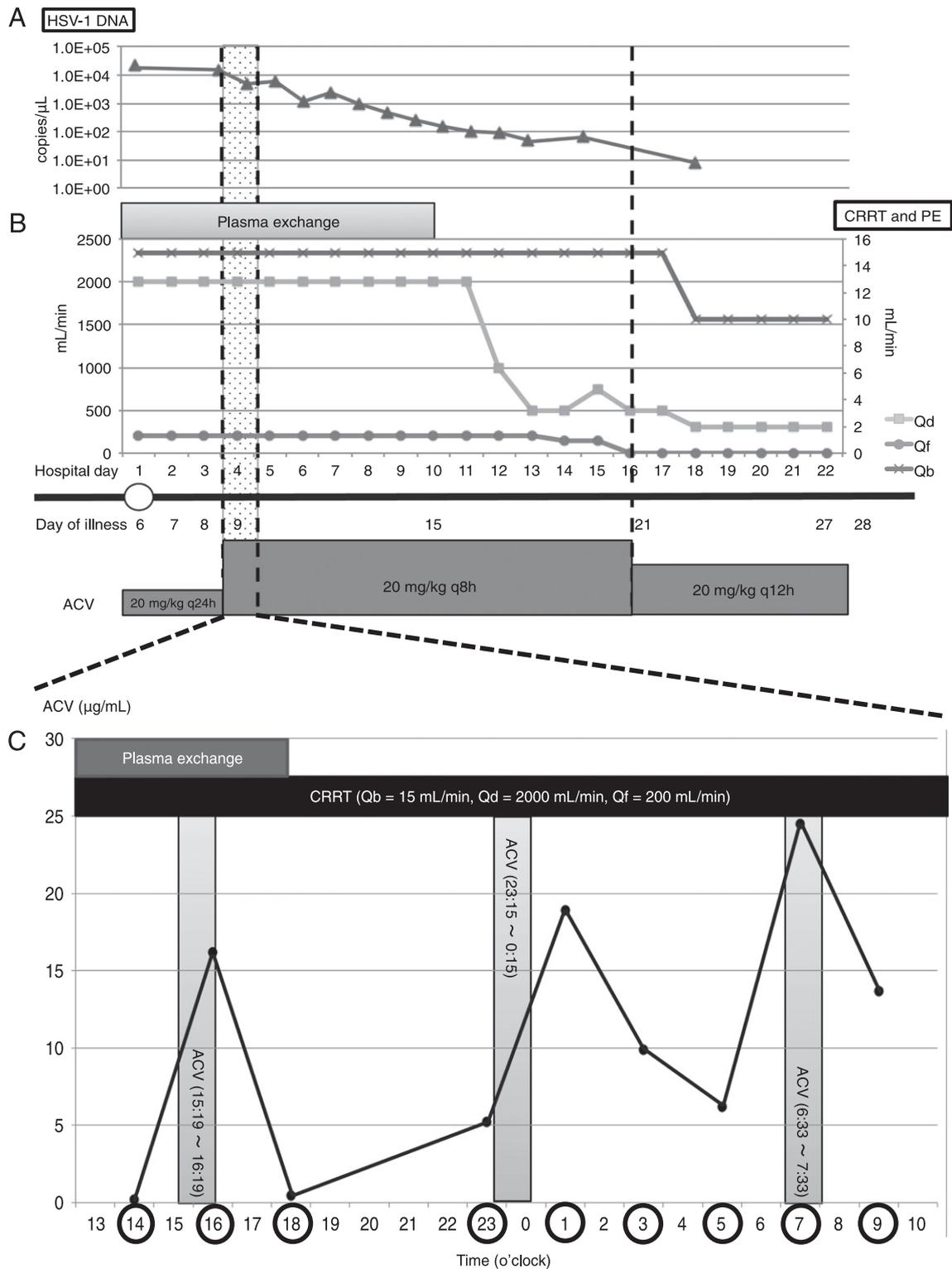
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Neonatal herpes simplex virus (HSV) infections are associated with high morbidity and mortality. Acyclovir is the treatment of choice for such infections. It is generally prescribed at a dose of 20 mg/kg every 8 hours (q8h) for neonatal disseminated and central nervous system HSV infections.<sup>1</sup> In a previous study, it was suggested that optimal dosing is a critical factor for the outcome.<sup>2</sup>

Acyclovir is eliminated by renal excretion and has a narrow therapeutic index in patients with renal impairment. Therefore, acyclovir dosage has to be adjusted according to

the individual's renal function and hemodialysis conditions.<sup>3-5</sup> Optimal dosing for acyclovir under continuous renal replacement therapy (CRRT) in neonates, however, remains unknown. Melvin et al reported that plasma quantitative HSV levels were associated with clinical presentation of neonatal HSV and mortality. Therefore, optimal dosing for acyclovir was considered to be a critical factor for controlling HSV viral load and mortality.<sup>6</sup> We monitored serum acyclovir levels and HSV-1 DNA levels in a neonate with disseminated HSV-1 infection who developed renal failure and underwent CRRT.



**FIGURE 1**

HSV-1 viral load (A) and acyclovir (ACV) concentration (C) monitoring under CRRT and PE (B). A, Semiquantification of HSV-1 DNA level. B, Scale marks on left-side y-axis represent conditions of Qd (dialysate flow rate) and Qf (filtration flow rate), and those on right-side y-axis represent conditions of Qb (blood flow rate). Timing of blood sampling in black circles.

## CASE REPORT

A full-term, 5-day-old female (gestational age 37 weeks and 5 days, birth weight 2950 g), presented with a 2-day history of lethargy and fever. She developed fulminant hepatic failure with hepatic encephalopathy and was diagnosed with HSV-1 infection by serum real-time polymerase chain reaction (PCR) on her eighth day of life. Intravenous acyclovir was initiated at 20 mg/kg q8h. On the second day of illness, however, she developed renal failure and was started on CRRT by high-flow continuous venovenous hemodiafiltration (CVVHDF). Acyclovir dosing was lowered to 20 mg/kg q24h on the fourth day of illness. She also received plasma exchange (PE) for the management of hepatic failure; however, her condition continued to deteriorate. She was transferred to our hospital for further intensive care on the sixth day of illness (first hospital day).

On arrival at our hospital, her serum HSV-1 level was  $2.3 \times 10^4$  copies/ $\mu\text{L}$ , and acyclovir was continued at a dose of 20 mg/kg q24h. On the eighth day of illness, her serum HSV-1 still remained at  $1.4 \times 10^4$  copies/ $\mu\text{L}$ . Therefore, we considered the possibility of undertreatment due to expedited elimination of acyclovir through high-flow CVVHDF that uses UT filter<sup>®</sup> cellulose triacetate membranes (Nipro, Osaka, Japan) and PE. The dosage of acyclovir administration was then changed from 20 mg/kg q24h to 20 mg/kg q8h on the eighth day of illness. We also monitored serum acyclovir levels and HSV-1 DNA levels (Fig 1). Coagulopathy due to hepatic failure improved, and PE was discontinued on the 15th day of illness. CRRT was changed from CVVHDF to continuous venovenous hemodialysis on the 21st day of illness because of improving renal function, and acyclovir dosing was changed to 20 mg/kg q12h. Serum HSV-1 DNA levels measured by real-time PCR eventually became

undetectable on the 28th day of illness. Upon completion of a 21-day course of acyclovir at an appropriate dose for disseminated HSV-1 infection, intravenous acyclovir (15 mg/kg/day) was initiated as suppression therapy (Table 1).

Quantification of serum HSV-1 viral DNA load was performed with real-time PCR.<sup>7</sup> Briefly, total nucleic acid from 400  $\mu\text{L}$  serum was extracted and reconstituted into 100  $\mu\text{L}$ , 4  $\mu\text{L}$  of which was subjected to 20- $\mu\text{L}$  real-time PCR reactions, along with positive controls of known DNA concentrations, which served as quantification standards. Serum acyclovir concentrations were measured by using liquid chromatography-tandem mass spectrometry at Epoch Medical International (Osaka, Japan) on hospital days 3 and 4.

HSV-1 viral load remained high during q24h dosing, with a decline of 0.17  $\log_{10}$  copies/24 hours; however, the average decline of HSV-1 DNA level increased to 0.44  $\log_{10}$  copies/24 hours after changing acyclovir dosage to 20 mg/kg q8h (Fig 1). HSV-1 DNA levels finally became undetectable by real-time PCR on the 23rd day of illness.

Serum drug concentrations of acyclovir under CRRT and PE were measured on the ninth and 10th days of illness. PE was performed for 5 hours, using 480 mL fresh-frozen plasma. CRRT conditions were as follows: (1) blood flow rate,

15 mL/min; (2) dialysate flow rate, 2000 mL/min; and (3) filtration flow rate, 200 mL/min. Peak acyclovir concentration ( $C_{\text{max}}$ ) was 16.2  $\mu\text{g}/\text{mL}$ , and trough level was 0.22  $\mu\text{g}/\text{mL}$  under CRRT and PE. Meanwhile,  $C_{\text{max}}$  was 18.9 to 24.5  $\mu\text{g}/\text{mL}$  under CRRT alone. The half-life of acyclovir ( $T_{1/2}$ ) was estimated at  $\sim 2$  to 3 hours under this CRRT condition and  $< 2$  hours under this CRRT condition with PE (Fig 1).

## DISCUSSION

To date, the pharmacokinetic and pharmacodynamic parameters of acyclovir in neonates with HSV infection remain unclear. Pharmacokinetic studies in neonates described a protein-binding capacity of 15% (9% to 33%), volume of distribution of 0.6 L/kg, and primary renal elimination with a half-life of 2 to 5 hours under normal renal function.<sup>8</sup> Neonates who were given acyclovir by 1-hour infusion in dosages of 5, 10, and 15 mg/kg q8h achieved predictable and consistent serum levels, with mean peak (trough) serum levels of 7.5 (1.3), 15.3 (2.5), and 21.5 (3.4)  $\mu\text{g}/\text{mL}$ , respectively.<sup>3</sup> In another study in which neonates were given intravenous acyclovir at a dose of 15 mg/kg, the mean  $\pm$  SD acyclovir peak concentration was  $18.82 \pm 5.22$   $\mu\text{g}/\text{mL}$ , trough concentration  $3.18 \pm 2.62$   $\mu\text{g}/\text{mL}$ , and acyclovir half-life  $3.03 \pm 1.06$  hours.<sup>2</sup> In our case, the patient received acyclovir at

**TABLE 1** Timeline of the Case

Day of life	Day of Illness	Hospital Day	Event	Acyclovir
5	1	NA	Onset of illness	NA
6	2	NA	Admission to first hospital	Initiate acyclovir 20 mg/kg q8h
8	4	NA	HSV-1 detection by PCR	20 mg/kg q24h
		NA	PE and CRRT (CVVHDF)	20 mg/kg q24h
10	6	1	Transfer to our hospital	20 mg/kg q24h
			PE (6 h per day) and CVVHDF continued	20 mg/kg q24h
12	8	3	NA	20 mg/kg q8h
19	15	10	PE discontinued	20 mg/kg q8h
25	21	16	Change CVVHDF to CVVHD	20 mg/kg q12h
32	28	23	HSV-1 (serum) undetectable	Switch to suppression therapy

NA, not applicable

20 mg/kg/dose with a peak concentration of 18.9 to 24.5  $\mu\text{g/mL}$ , which appears to be consistent with these previous reports.

Current guidelines and authoritative textbooks state that the clearance of acyclovir during a 24-hour CRRT is equivalent to a single session of intermittent hemodialysis. An acyclovir dosing of 3.5 to 10 mg/kg q24h in patients receiving CRRT regardless of modality is recommended.<sup>3-5,8-11</sup> However, our findings demonstrated a half-life of  $\sim 2$  hours, necessitating dosing at near-normal renal condition. The current recommended dosages were only 6% to 17% of the actual administered dosage, which prompts significant concern. Furthermore, the efficiency of the rate of acyclovir removal may be dialyzer specific. In our case, the dialyzer used was made of cellulose triacetate membranes, which have a high solute permeability, allowing the removal of  $\beta_2$ -microglobulin by diffusion. Cellulose triacetate membranes have also been shown to have high adsorption of albumin; therefore, acyclovir, a relatively small molecule with a protein-binding capacity of 15%, may be removed at a constant rate according to CRRT condition. In a report describing the removal of acyclovir during CRRT, the percentage of acyclovir extraction was 84% and 60% during continuous venovenous hemodialysis and CVVHDF with commonly used high-efficiency membranes (F-8 and CA-210 dialyzers, respectively).<sup>11</sup> Meanwhile, PE also clearly affected the pharmacokinetics of acyclovir.

Although the pharmacodynamic characteristics of acyclovir are not fully elucidated, studies have indicated a time-dependent activity.<sup>8</sup> In our study, HSV susceptibility to acyclovir was not evaluated. In general, in vitro resistance to acyclovir can be defined by using the concentration of acyclovir that reduces the plaque number by

50% (half maximal inhibitory concentration) and a widely accepted breakpoint value of  $\geq 2 \mu\text{g/mL}$  for acyclovir.<sup>12</sup> In addition, half maximal inhibitory concentration values of HSV-1 and -2 with acyclovir are 0.02 to 0.9 and 0.03 to 2.2  $\mu\text{g/mL}$ , respectively.<sup>12</sup> According to these data, our dosing regimen during CRRT appears to be reasonable in attaining the desired serum acyclovir concentrations.

Documentation of actual HSV viral load and acyclovir dosing in the clinical setting is limited. According to data regarding the clearance of HSV from patients with primary genital lesions who were treated with intravenous acyclovir at a daily dose of 15 mg/kg, the median time for clearance from genital lesions was 2 days.<sup>3</sup> For children, quantitative PCR assays have been used to diagnose herpes simplex encephalitis and monitor the response to acyclovir.<sup>13</sup> In that study, HSV DNA was quantified in 10 patients, and the number of HSV DNA copies was demonstrated to decrease gradually with antiviral therapy to an undetectable level. Subsequently, 2 weeks from onset of illness, HSV DNA was detectable in 3 of the 5 neonates. In addition, in 1 patient with severe complications, HSV DNA was continuously detectable until the 31st day after onset.<sup>13</sup> In our case, serum HSV-1 DNA persisted at high copy numbers during acyclovir administration at 24-hour intervals but decreased upon more frequent dosing, suggesting that maintaining adequate serum acyclovir concentrations may be important for virological control.<sup>6</sup> However, the possibility of spontaneous resolution cannot be excluded, and additional studies involving a greater number of patients are required for validation of this concept.

The generalizability of our findings is limited given that this is a case report of a single patient and may be influenced by the type and setting of

the dialyzer used. Inconsistent timing of blood sampling is also a limitation in interpreting the results. Nonetheless, this case should raise concern for the applicability of the current recommendations of acyclovir dosage.

In summary, efficient filtration of acyclovir during CRRT may lead to suboptimal therapeutic levels in HSV infections. Until further formal studies that go beyond a case report outline the correct dosing regimen for neonates who require acyclovir on CRRT, individual monitoring for acyclovir levels should be performed to optimize the therapy for patients undergoing continuous hemodialysis.

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## ABBREVIATIONS

CRRT: continuous renal replacement therapy  
CVVHDF: continuous venovenous hemodiafiltration  
HSV: herpes simplex virus  
PCR: polymerase chain reaction  
PE: plasma exchange

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