Safety of Alternative Antiviral Agents for Neonatal Herpes Simplex Virus Encephalitis and Disseminated Infection

Yu Wang, PharmD and Katherine P. Smith, PharmD

College of Pharmacy, Roseman University of Health Sciences, South Jordan, Utah

OBJECTIVE: To review the evidence describing the safety of ganciclovir and foscarnet in neonates in order to guide treatment for central nervous system or disseminated herpes simplex infections in cases of acyclovir shortage or resistance.

METHODS: PubMed, Ovid Medline, and International Pharmaceutical Abstracts were searched using the thesaurus and text-word terms “ganciclovir” and “foscarnet,” with birth to 1 month age limits. Thirty-two eligible publications describing safety in neonates were identified.

RESULTS: In 340 neonates treated for cytomegalovirus (CMV), life-threatening neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$) was reported in 8.8% of patients following up to 12 months of ganciclovir administered intravenously. Neutropenia and thrombocytopenia occurred in 25.6% and 6.2% of neonates, respectively. Changes in serum creatinine concentration of >0.2 mg/dL occurred in $<1\%$ of neonates. Hepatic transaminase increases or unspecified changes in liver function tests were reported in 6.2% of neonates with hyperbilirubinemia being observed in 3.5% of total neonates. Three out of four neonates receiving foscarnet for acyclovir-resistant herpes infection or CMV survived with minimal sequelae. Neither nephrotoxicity nor electrolyte or mineral imbalances were reported.

CONCLUSIONS: Similar to what is seen in adolescents and adults, ganciclovir use in neonates is commonly associated with neutropenia, and the frequency of occurrence is comparable. The link between hepatotoxicity and ganciclovir should be interpreted with caution because of overlapping clinical manifestations of CMV. Only case reports are available describing foscarnet use in neonates, but adverse drug reactions were not observed. More research on these two agents is needed to draw conclusions about adverse drug reaction rates in the neonatal population.

INDEX TERMS: foscarnet, ganciclovir, herpesvirus 1 human, herpesvirus 2 human, infant, newborn

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INTRODUCTION

High-dose acyclovir 20 mg/kg per dose intravenously (IV) every 8 hours for 21 days is the preferred regimen for empiric and directed therapy for herpes simplex virus (HSV) central nervous system (CNS) and disseminated infection in neonates.^{1–3} Despite early appropriate treatment with high-dose acyclovir in infants presenting with HSV infection of the CNS, severe neurologic sequelae—such as cortical hemorrhage; microcephaly; megacystic encephalomalacia with laminar necrosis, cortical atrophy, and gliosis; subdural egromas, infratentorial hemorrhages, or effusions; developmental delay; and epilepsy—have been reported.⁴ At the time

of this publication and since 2009, acyclovir has been in limited supply from manufacturers. The American Society of Health-System Pharmacists Drug Shortages Resource Center reports that Bedford Laboratories and American Pharmaceutical Partners both have acyclovir for injection on back order, with no estimated release date.⁵ The American Academy of Pediatrics Committee on Infectious Diseases has provided guidelines for prioritizing acyclovir use in shortage situations and recommendations regarding alternative agents when acyclovir is not available. In suspected or proven HSV disease in neonates, ganciclovir (Cytovene, Genentech, San Francisco, CA) 6 mg/kg IV every 12 hours is recommended as first-line therapy. The second-line regimen is

foscarnet (Foscavir, Hospira Inc, Lake Forest, IL) 60 mg/kg IV every 12 hours. They only recommended oral acyclovir or valacyclovir for HSV skin infection recurrence and other non-CNS and non-disseminated infections in the neonatal population.⁶

Ganciclovir is a guanosine analogue that is believed to inhibit the inclusion of deoxyguanosine triphosphate into viral DNA. It is a homologue of acyclovir, which in HSV-infected cells requires phosphorylation by thymidine kinase to be active. It is also less selective than acyclovir for viral DNA, making it more likely to cause hematologic toxicity.⁷ It is approved by the Food and Drug Administration for the treatment of cytomegalovirus (CMV) retinitis in patients who are immunocompromised and for the prevention of CMV infection in at-risk transplant recipients. It is not currently approved for use in children; however, it has been studied and is recommended for the treatment of congenital, CNS, disseminated, and retinal CMV infection.⁸ It is also recommended for prevention of CMV infection in posttransplantation and human immunodeficiency virus (HIV)-exposed or HIV-infected children. However, the largest amount of safety research involving ganciclovir comes from the adult population. Neutropenia is the most common serious adverse drug reaction linked to ganciclovir, with older studies reporting rates as high as 24% to 40% in adult patients with acquired immunodeficiency syndrome (AIDS).⁹ In a more recent large, randomized, multicenter study that included posttransplantation adolescents and adults, neutropenia, defined as an absolute neutrophil count of $<0.5 \times 10^9/L$, occurred in 11% of patients.¹⁰ The difference between rates of neutropenia in adults versus adolescents was not described, and it is generally unknown whether children, including neonates, are more susceptible or less susceptible to ganciclovir-associated neutropenia. Other adverse drug reactions in the non-AIDS population included nephrotoxicity, thrombocytopenia, hypocalcemia, hypomagnesemia, and hypokalemia. These occur at rates ranging from 2% to 6%.¹⁰

Foscarnet is a pyrophosphate analogue that blocks the pyrophosphate-binding site of DNA polymerases found in herpesviruses.¹¹ It is more selective for herpesvirus DNA polymerases compared with native cellular DNA polymerase- α at therapeutic concentrations.⁹ Unlike acy-

clovir, it does not require intracellular activation, making it useful for some acyclovir-resistant viral infections. Foscarnet is Food and Drug Administration approved for the treatment of acyclovir-resistant mucocutaneous HSV infection and CMV retinitis. Although foscarnet is also not approved for use in children, Centers for Disease Control guidelines recommend it for CMV infection, acyclovir-resistant HSV infection, and varicella zoster virus infection in infants and children who are either HIV exposed or HIV positive.¹² Nephrotoxicity is the highest concern with foscarnet, with up to a third of adult patients developing reversible but significant renal dysfunction.⁹ In a large, randomized, controlled study of adolescents and adults receiving foscarnet for transplant-related CMV prophylaxis, the rate of nephrotoxicity, defined as either an absolute increase in serum creatinine concentration (≥ 2.5 mg/dL or 100%) or a 50% decrease in creatinine clearance from baseline, was 5%, amounting to a difference of 2.6% compared with patients in the same study who received ganciclovir.¹⁰ No nephrotoxicity was reported in a similarly sized study of adults who received low-dose foscarnet for hepatitis B, but the definition of nephrotoxicity was not provided.¹³ As a chelator of divalent cations, mineral deficiencies are considered common in association with foscarnet and patients may experience symptomatic hypocalcemia.¹⁴ Reported rates of calcium imbalance have varied widely depending on the patient population receiving foscarnet. Calcium imbalance has been reported to occur in 35% of adults and adolescents with AIDS but was reported to occur in 22% of adult and adolescent transplant recipients receiving foscarnet.^{10,15} The same type of discrepancies can be found with reported rates of hypomagnesemia (18% in transplant recipients, 44% in patients with AIDS), hypophosphatemia (6% in transplant recipients, 13% in patients with AIDS), and hypokalemia (17% in transplant recipients, 10% in patients with AIDS). The reasons for these variable rates of mineral and electrolyte deficiencies are unknown, but concomitant medication use as reported in the population of patients with AIDS (for example, amphotericin B and electrolyte supplements) could have played a role. Too few children were enrolled in either type of study to draw a conclusion about adverse drug reaction rates with foscarnet.

Questions persist about whether infants and young children experience the same rates of toxicities with either ganciclovir or foscarnet. In light of The American Academy of Pediatrics recommendations to use these agents for HSV CNS and disseminated infection in neonates in the case of acyclovir shortage, further analysis into the available safety data is warranted. The purpose of this review is to summarize the published literature describing neonatal exposure to ganciclovir or foscarnet with the intent of helping practitioners select and monitor treatment.

METHODS

PubMed (1940-August 2013), Ovid Medline (1948-August 2013), and International Pharmaceutical Abstracts (1970-August 2013) databases were searched using the following search terms: "ganciclovir" (text in all fields), "ganciclovir" (thesaurus term), "foscarnet" (text in all fields), or "foscarnet" (thesaurus term). In PubMed and Ovid Medline, limits or filters were set for patient age to include only newborns aged birth to 1 month. Articles were further analyzed to ensure that studies included neonatal ganciclovir or foscarnet exposure occurring between birth and a postmenstrual age of 44 weeks. In International Pharmaceutical Abstracts, the following thesaurus terms and text in all fields terms were searched in combination with the terms above: "neonate," "newborn," "pediatric," or "infant." A total of 175 articles were found on ganciclovir and 27 articles were found on foscarnet. Review articles, *in vitro* research, non-parenteral therapy, posttransplantation studies, and publications not written in English or Mandarin Chinese were excluded. The references of relevant citations were also hand-searched for studies including neonates. To more adequately address safety, only ganciclovir studies that described treatment of more than 1 patient were included. All studies and case reports of foscarnet use in neonates were included. A total of 28 eligible ganciclovir studies and 4 case reports of foscarnet use were evaluated.

RESULTS

Ganciclovir for Neonates With CMV Infection

In several pharmacokinetic and therapeutic studies and case series publications that included neonates, adverse drug reaction data were not

described.¹⁶⁻²⁹ Another study included only long-term efficacy data because safety data had already been published elsewhere.³⁰

Studies that described adverse drug reactions in detail in the neonatal population have been summarized in the Table. Safety data are available for approximately 340 neonates who received ganciclovir for the prevention or treatment of CMV infection. Dosages used ranged from 3.6 to 15 mg/kg/day in 2 divided doses. Most neonates received 6 weeks of IV therapy followed by oral ganciclovir or valganciclovir therapy. Life-threatening neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$) was reported in 30 neonates (8.8%) and any neutropenia was reported in 87 neonates (25.6%). All cases of neutropenia were reversible upon discontinuation or dose reduction if undertaken. A total of 3 neonates (<1%) experienced increases in serum creatinine concentration of >0.2 mg/dL, but changes were small and total serum creatinine concentration did not exceed 2.0 mg/dL; however, not all studies measured changes in serum creatinine concentration. Thrombocytopenia, which was in some studies reported as a platelet count $<50,000$ cells/mm³, was experienced by 21 neonates (6.2%). Hypocalcemia, hypomagnesemia, and hypokalemia were not reported in any of the studies or case series. Increases in hepatic transaminases or non-specific liver function test changes were experienced by 21 neonates (6.2%) and hyperbilirubinemia occurred in 12 neonates (3.5%).

Foscarnet for Neonates With CMV

In a case report by Nigro et al,⁴⁵ a 41-week-gestation boy whose mother had serologic and virologic signs of recurrent CMV infection presented on day 1 of life with hepatomegaly, jaundice, and right microphthalmia with cataract. Further examination revealed liver fibrosis, interstitial pneumonitis, and hyperechoic lesions in the basal ganglia. Ganciclovir was not given because of the parents' concerns about side effects. Foscarnet 60 mg/kg IV was administered every 8 hours for 3 weeks, followed by 100 mg/kg 3 times a week for 3 months. Concentrations of electrolytes and minerals remained stable and within normal limits throughout treatment. The cerebral ultrasound and chest x-ray normalized, and a repeat liver biopsy at 5 months did not detect CMV via polymerase chain reaction (PCR) or

Table. Summary of Neonatal Ganciclovir Case Series and Study Data

Source	Study Design	Patients	Exclusion Criteria	IV Ganciclovir Treatment Regimen	ADR Assessment Schedule	ADRs Reported
Townsend et al ³¹	Retrospective surveillance of infants with congenital CMV	17 presumed newborns were tx	NA	Dose not provided; median tx was 6 wk (range, 4 days to 3 mo)	NA	1 infant with neutropenia* required DC after 4 days of tx; 1 infant developed thrombocytopenia† after 4 wk of tx; 1 infant developed "abnormal liver function tests" after 5 wk of tx‡
Amir et al ³²	Retrospective chart review of ganciclovir for CMVs	23 newborns (BW 1580-3630 g)	NA	Ganciclovir 5 mg/kg per dose q 12 hr × 6 wk	Blood counts q other wk	2 pts with reversible life-threatening neutropenia,§ 3 pts with moderate to severe neutropenia,¶ and 7 pts with 16 episodes of mild neutropenia.** Two pts had central line infections. Neutropenia occurred mainly in the first 6 wk of IV ganciclovir
He et al ³³	Prospective, randomized observational study of infants with CMV	167 newborns (BW 1350-4120 g); 79 received large dose, 88 received small dose	NA	Large dose: ganciclovir 7.5 mg/kg per dose q 12 hr × 2 wk followed by 10 mg/kg/day × 3 days q wk for a total of 2–3 mo. Small dose: ganciclovir 5 mg/kg per dose q 12 hr × 2 wk followed by 5 mg/kg/day for 5 days a wk for a total of 2–3 mo	Blood counts twice weekly, liver function tests q wk during induction; blood counts once a wk, liver function tests q other wk during the maintenance regimen	13 pts who received large-dose ganciclovir developed neutropenia vs. 5 pts who received small-dose ganciclovir and developed neutropenia.*
Lackner et al ³⁴	Prospective, controlled (tx vs. no tx),	23 pts total, 12 tx as neonates, 8 neonates not tx	None	Ganciclovir 10 mg/kg/day × 21 days	NR	2 cases of reversible mild neutropenia** without dose reduction.††
Halwachs-Baumann et al ³⁵	randomized study of asymptomatic infants with CMV	17 newborns, 12 of which were tx, 5 of which were not tx	None	Ganciclovir 10 mg/kg/day × 21 days or longer (symptom based)	NR	Among tx neonates, there was 1 case of diarrhea and 1 case of leukopenia, both responding to a dose reduction.††

IV, intravenous; ADR, adverse drug reaction; CMV, cytomegalovirus; tx, treat/treatment; NA, not applicable; BW, birthweight; q, every; pts, patients; NR, not reported; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; ULN, upper limit of normal; WBC, white blood cell; AST, aspartate aminotransferase; CNS, central nervous system; ANC, absolute neutrophil count; DC, discontinued; UA, uric acid; CBC, complete blood count; FT, full term; BUN, blood urea nitrogen; GGT, gamma-glutamyl transpeptidase; NIAID, National Institute of Allergy and Infectious Diseases

* The definition of neutropenia was not provided; † The definition of thrombocytopenia was not provided; ‡ The definition of elevated hepatic transaminases or abnormal liver function was not provided; § Historical controls were included for auditory outcome data only; ¶ Life-threatening neutropenia was defined as an ANC of $<0.5 \times 10^9/L$ (grade IV; NIAID); # Moderate to severe neutropenia (grade II or III) was defined as an ANC of $0.5 \times 10^9/L$ to $0.999 \times 10^9/L$ (NIAID); ** Mild neutropenia was defined as an ANC of $1.0 \times 10^9/L$ to $1.5 \times 10^9/L$; †† Adverse events were not reported in study patients not receiving treatment; ‡‡ The definition of anemia was not provided; §§ The definition of thrombocytopenia was $<50,000/mm^3$; ¶¶ Hyperbilirubinemia criteria were based on preterm versus term birth and on the days following birth

Table. Summary of Neonatal Ganciclovir Case Series and Study Data (cont.)

Source	Study Design	Patients	Exclusion Criteria	IV Ganciclovir Treatment Regimen	ADR Assessment Schedule	ADRs Reported
Kimberlin et al ³⁶	Prospective, controlled (2 protocols), non-randomized pharmacokinetic study of IV ganciclovir vs. oral valganciclovir for symptomatic CMV	24 newborns in both protocols; 5 newborns in the first protocol received predominantly IV ganciclovir (BW: median, 2000 g; range, 1950-3450 g)	Imminent death, other antiviral agents, immunoglobulin administration, gastrointestinal abnormalities, severe renal dysfunction, maternal HIV	6 mg/kg per dose q 12 hr × 6 wk (except 4 days where they received valganciclovir)	Hematologic laboratory data weekly and 2 wk after discontinuation	Of all 24 newborns, 2 developed life-threatening neutropenia, [¶] 7 developed severe neutropenia, [#] 3 developed anemia, ^{##} 1 experienced an increase of ALT that was 5.1× to 10× ULN, and 1 experienced hyperbilirubinemia (2.6× to 5× ULN). No pts experienced grade 3 or 4 toxicities in platelet counts, WBC count, creatinine concentration, and AST serum concentration. ³⁷
Tanaka-Kitajima et al ³⁸	Case series of ganciclovir for congenital CMV	6 infants (BW 576-2715 g)	NA	Ganciclovir 2.5-6 mg/kg per dose q 12 hr × 2-7 wk	NA	ADRs were mentioned but not observed.
Kimberlin et al ³⁹	Prospective, randomized controlled (tx vs. no tx) study of ganciclovir for congenital CMV involving the CNS	97 infants total, 47 tx and 50 not tx	Imminent death, other antiviral agents, immunoglobulin administration, a serum creatinine concentration >1.5 mg/dL, maternal HIV, hydranencephaly	Group 1: ganciclovir 6 mg/kg per dose every 12 hr × 6 wk. Group 2: no tx. If a pt developed life-threatening neutropenia, [¶] the dose was held until the ANC was >0.75 × 10 ⁹ /L; the dose was reduced by 50% and later DC if life-threatening neutropenia recurred.	CBC, ALT, bilirubin, UA, and creatinine at study entry and on days 3, 5, 7, 10, 14, 17, 21, 28, 35, and 42	In group 1, 11 developed life-threatening neutropenia [¶] (vs. 1 in group 2); 18 developed severe neutropenia [#] in group 1 (vs. 8 in group 2); 3 in group 1 developed thrombocytopenia ^{§§} (vs. 2 in group 2); and 11 experienced hyperbilirubinemia ^{¶¶} (vs. 7 in group 2). The mean onset of life-threatening or severe neutropenia in group 1 was 14.2 days (SD = 12.3; vs. 14.3 ± 13.1 days in group 2). Neutropenia resolved in an average of 12.8 days (SD = 13.6; vs. 14.2 ± 13.5 days in group 2).*
Michaels et al ⁴⁰	Retrospective chart review of ganciclovir for CMV	9 pts total, 5 were neonates ages 3-10 days (4 were FT, 1 was 33 wk gestation)	NA	Ganciclovir 10 mg/kg/day IV × 2-4 wk followed by 5 mg/kg/day IV for a total course of 5.5-12 mo	NA	9 bacterial infections, 4 catheter malfunctions, and 1 case of reversible life-threatening neutropenia [¶] that recurred when therapy was restarted at the same dose.

Table. Summary of Neonatal Ganciclovir Case Series and Study Data (*cont.*)

Source	Study Design	Patients	Exclusion Criteria	IV Ganciclovir Treatment Regimen	ADR Assessment Schedule	ADRs Reported
Liberek et al ⁴¹	Ganciclovir for CMV (design NR)	31 pts total, 5 were neonates up to 3 wk, 25 pts received ganciclovir	NA	Ganciclovir 5-7 mg/kg IV daily for 14-21 days	NR	The "tolerance of the drug was good."
Whitley et al ⁴²	Phase 2, uncontrolled, cohort study of ganciclovir for symptomatic congenital CMV	47 neonates total, 16 assigned to cohort 1 (small dose) and 31 to cohort 2 (large dose).	Imminent demise, other antiviral agents, immunoglobulin administration, a serum creatinine concentration >2 mg/dL, symptomatic disease not involving the CNS, asymptomatic congenital CMV	Ganciclovir 4 mg/kg per dose (cohort 1) or 6 mg/kg per dose (cohort 2) q 12 hr x 6 wk. In cases of life-threatening neutropenia [¶] or thrombocytopenia, ^{§§} the dose was decreased by 50%. If not resolved after a week at the lower dose, ganciclovir was held until neutrophils returned to baseline.	CBC, reticulocyte count, platelets, hepatic transaminases, serum creatinine, BUN, bilirubin, GGT, and UA on admission and on days 3, 5, 7, 10, 14, 17, 21, 28, 35, 42, and 49.	Of 42 treated neonates, 14 developed life-threatening neutropenia, [¶] 17 developed thrombocytopenia, [†] and 17 experienced elevated hepatic transaminases (AST >250 units per deciliter or ALT >150 units per deciliter). Serum creatinine increased by 0.4-0.5 mg/dL in 3 neonates. In no cases did the serum creatinine concentration exceed 2.0 mg/dL. Three children in each cohort had ganciclovir discontinued because of life-threatening neutropenia on an average of day 16.8 of therapy (range, days 7-27).
Nigro et al ⁴³	Case series of ganciclovir for CMV-associated liver disease with or without maintenance tx	6 immunocompetent infants, 2 with generalized CMV diagnosed and tx at birth	NA	Ganciclovir 5 mg/kg per dose twice daily for 14 days or 7.5 mg/kg per dose twice daily for 14 days, followed by 10 mg/kg 3 times a week for 3 mo	NR	ADRs were mentioned but not observed.
Nigro et al ⁴⁴	Randomized, prospective, pilot, dual-center, compassionate use protocol of ganciclovir for symptomatic congenital CMV	12 infants with mean age of 2.7 mo (range, 14 days to 6 mo; BW 1430-3450 g), 6 pts in each group. Pts had life- or sight-threatening disease, or they failed to show spontaneous improvement.	Not used	Group 1: ganciclovir 5 mg/kg twice daily x 2 wk. Group 2: 7.5 mg/kg twice daily x 2 wk, followed by 10 mg/kg 3 times weekly for 3 mo	NR	Group 1: no side effects were observed. Group 2: 1 infant developed moderate to severe neutropenia, [#] 1 infant developed mild neutropenia, ^{**} and 2 infants experienced elevated hepatic transaminases. [‡]

immunohistochemical staining. At the follow-up visit at 13 months of age, mental development and motor development were found to be favorable. Liver function and size were also normal.

In another case report, a 24-week-gestation child whose mother had persistent CMV infection presented on the eighth day of life with hemophagocytic lymphohistiocytosis shortly after the initiation of pumped breast milk feeding. CMV immunoglobulin G and immunoglobulin M were detected in serum, and CMV DNA was found in blood leukocytes and urine by PCR. Treatment with granulocyte colony-stimulating factor and ganciclovir (dose not provided) during 3 weeks was unsuccessful. CMV pp65 antigen was detected in bone marrow and blood at 24 weeks of age, which prompted the initiation of treatment with foscarnet 100 mg/kg/day IV and methylprednisolone 2 mg/kg/day IV. After 8 days, the patient's neutrophil and platelet counts began to increase and normalization of platelets and neutrophils was achieved following 3 weeks of treatment. Counts remained normal at the 18-month follow-up visit.⁴⁶

Foscarnet for Neonates With HSV

In a case report by Nyquist et al,⁴⁷ a 10-day-old full-term infant presented with HSV-2 infection of the larynx after an uncomplicated birth. Acyclovir 10 mg/kg IV every 8 hours was started after the patient failed to improve while on antibiotics and sympathomimetics. HSV was identified via positive viral cultures obtained on admission; later nose and throat cultures with susceptibility testing revealed HSV-2 resistant to acyclovir. Despite 18 days of acyclovir, the patient was not improving, so acyclovir was replaced with foscarnet 40 mg/kg IV every 8 hours. The patient stabilized clinically but experienced continuing intermittent stridor. At days 29 and 34 respectively, cultures of nasal washes and throat swab specimens remained positive for HSV, and CNS viral culture and HSV PCR were negative. On day 39, foscarnet was discontinued. On day 45, after the stridor and oxygen saturation had significantly improved, the infant was discharged. Adverse drug reactions linked to foscarnet or acyclovir were not discussed. At follow-up at age 3.5 months, the child was symptom-free and developmentally normal.

In another case report, a 27-week-gestation neonate was born via emergency cesarean deliv-

ery to a mother who presented with pneumonia, hepatitis, severe capillary leak syndrome, disseminated intravascular coagulation (DIC), and pancytopenia secondary to HSV infection. At birth the neonate weighed 1200 g and had Apgar scores of 5 and 7. On day 4 of life, the infant was extubated and off of vasopressors; acyclovir 10 mg/kg IV every 8 hours was started when the maternal diagnosis of disseminated HSV was made. On day 9 of life, the neonate developed respiratory and cardiac instability, thrombocytopenia, impaired liver function, and DIC. Foscarnet was started on day 11 of life at 40 mg/kg IV every 8 hours, which was day 10 of therapy against HSV. On day 14 of life, life support was discontinued because of hypotension, a grade IV intraventricular hemorrhage, and continuing DIC. On autopsy, HSV was found from cultures of the liver, brain, and cerebral spinal fluid, and the strain was acyclovir resistant because of a mutation of the thymidine kinase gene. Sensitivity to foscarnet was retained. No antiviral therapy adverse drug reactions were reported. No mention was made of the fact that the acyclovir dose was low; the explanation that was provided for acyclovir failure was the fact that the infant had received systemic corticosteroids to support blood pressure.⁴⁸

DISCUSSION

The most experience with ganciclovir in neonates comes from CMV management, where doses are similar (5-7.5 mg/kg per dose every 12 hours) but the duration of parenteral therapy is twice as long (6 weeks versus 3 weeks) compared with what is recommended for neonatal CNS and disseminated HSV infection.^{33,39,42} The adverse drug reaction profile with ganciclovir would be expected to be similar regarding neonates with HSV compared with neonates with CMV; however, symptomatic CMV infection in the neonatal period is associated with end-organ disease, which can be difficult to distinguish from adverse drug reactions of antiviral therapy. For example, thrombocytopenia, hepatitis, and jaundice have been documented in symptomatic neonates with CMV.³ Because few studies on ganciclovir use and no studies on foscarnet use for neonatal infection included a control group, the rates of these potential adverse drug reactions are unclear. Neutropenia is the most

problematic adverse drug reaction associated with ganciclovir in neonates. Although many episodes of neutropenia were severe, in most cases dose reduction and/or discontinuation resulted in reversal of neutropenia within 2 weeks.³⁹ It is not clear whether transient neutropenia resulted in additional infections or complications in the study patients, nor is it clear what measures were taken to treat neutropenia or reduce the infection risk in those patients. The few reports of IV line infections were not felt to be related to the study medications.³² Small increases in serum creatinine concentration were observed in association with ganciclovir therapy in neonates; however, the more robust prospective studies that have been conducted excluded infants with existing severe renal disease.^{39,42} From these studies, large increases in serum creatinine concentration (>0.5 mg/dL) have not been seen in the neonatal population, despite the fact that significant elevations in serum creatinine concentration (increases of ≥ 2.5 mg/dL) have been reported in adults receiving ganciclovir.⁷ It is important to note that significant amounts of adult research come from the transplantation literature, where concomitant exposure to nephrotoxic calcineurin inhibitors is common. In adult patients with AIDS, exposure to antimicrobials known to affect creatinine clearance was also allowed in studies of ganciclovir for CMV retinitis.¹⁵ Concerns regarding permanent reproductive toxicity, mutagenicity, and teratogenicity observed in animal research have yet to be confirmed or refuted because long-term data in humans are lacking.⁴⁹

Foscarnet 120 mg/kg/day IV in 2 divided doses is considered second-line therapy for neonatal CNS or disseminated HSV infection in cases of acyclovir shortage.⁶ There are currently no controlled studies in the neonatal population involving foscarnet for any infections caused by herpesviruses, including CMV. In the published case reports describing the 4 neonates or infants who received foscarnet therapy for either HSV or CMV infection, dosages ranged from 100 to 180 mg/kg/day IV in 3 divided doses during the acute infection management phase. Only 1 case report mentioned adverse drug reactions for foscarnet; neither the potential renal toxicity nor the electrolyte or mineral imbalances previously reported with foscarnet were observed.⁴⁵ Because these were case reports, it is not clear whether mineral or electrolyte monitoring occurred dur-

ing the course of therapy. However, large adult studies describing decreased electrolyte and mineral serum concentrations with foscarnet were available at the time of publication of at least 3 of the case reports.^{45,46,48} Although specific neonatal recommendations are lacking, adequate hydration prior to each dose of foscarnet has been shown to be helpful in preventing nephrotoxicity.¹⁰ No patients in the 4 case reports presented received bolus fluids, but in 1 case an infant was already receiving aggressive life support measures prior to the initiation of foscarnet,⁴⁸ and in another the patient had ascites.⁴⁵ In all cases where the infant survived the initial infection, development at follow-up occurring at ages 3 to 18 months was considered normal or unaffected.⁴⁵⁻⁴⁷

CONCLUSION

In conclusion, in the case of acyclovir for injection shortage, ganciclovir and foscarnet are currently recommended as first- and second-line therapies for neonatal HSV encephalitis and disseminated infections; however, safety data are very minimal for foscarnet. Underlying disease states in adults, older children, and neonates have the potential to affect the full appreciation of adverse drug reaction rates associated with ganciclovir or foscarnet. Ganciclovir should be avoided in cases of severe renal dysfunction, and the patient should be closely monitored for the development of neutropenia, with dose decreases or discontinuation as necessary. Although experience with foscarnet is limited, the few cases where it has been used to treat CMV or HSV infection are promising. Until larger studies are available, the adverse drug reaction profile in the neonatal population will be difficult to predict.

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Abbreviations AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; CNS, central nervous system; DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IV, intravenously; PCR, polymerase chain reaction

Correspondence Katherine P. Smith, PharmD, BCPS, Roseman University of Health Sciences College of Pharmacy, 10920 S. River Front Parkway, South Jordan, UT 84095, email: ksmith@roseman.edu

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