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The Use of Antiviral Drugs During the Neonatal Period

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Introduction

Parenteral therapy of viral infections of the newborn and infant became a reality with the introduction of vidarabine (adenine arabinoside) for the treatment of neonatal herpes simplex virus (HSV) infections in the early 1980's. Since then, acyclovir has become the treatment of choice for neonatal HSV infections, as well as a variety of other herpesvirus infections. Similarly, ganciclovir has been established as beneficial for the treatment of congenital cytomegalovirus (CMV) infections that involve the central nervous system (CNS). This chapter will review the lessons learned from treating neonatal HSV, and congenital CMV infections as it relates to the use of acyclovir and ganciclovir. While the natural history of these diseases is reviewed elsewhere in this text, a brief summary will precede a detailed discussion of available established and alternative therapeutics. The reader is referred to more extensive reviews of antiviral therapy in children and adults [1, 2].

Therapy of herpes simplex virus infections

Neonatal HSV infections occur in approximately 1 in 3200 deliveries in the USA [3] and, of these, approximately two thirds develop some form of CNS disease [4]. The majority of cases are caused by HSV-2 [5]. The risk of transmission is increased with primary maternal infection during the third trimester, being 30–50%, and can be decreased by cesarean delivery if HSV has been isolated from the cervix or external genitalia near the time of delivery [3]. As reviewed by Kimberlin, 85% of neonatal HSV cases occur due to peripartum transmission, whereas 10% occur via postnatal transmission, and only 5% are due to transmission *in utero* [6].

Infants with intrauterine HSV infection are characterized by the triad of cutaneous findings (active lesions, scarring), neurologic findings (microcephaly, hydranencephaly), and eye findings (chorioretinitis, microphthalmia) present at birth. Intrauterine HSV infection has been found to occur with both primary and recurrent maternal HSV infections [7], although the risk from a recurrent infection is less.

HSV infection acquired in the peripartum or postpartum period can be categorized as skin, eye, and/or mouth (SEM) disease, CNS disease, or disseminated disease. By definition, SEM disease does not involve the CNS. Disseminated disease may involve the CNS (75% of cases) along with multiple other organ systems including the liver, adrenals, gastrointestinal tract, and the skin, eyes, or mouth [8]. CNS disease may also have a component of SEM

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involvement, but does not involve other organ systems. Of all infants with neonatal HSV infections, approximately 33% have CNS disease, while about 25% have disseminated disease [9]. Thus, about 50% of infants with neonatal HSV infection have CNS disease.

The pathogenesis of CNS involvement in neonatal HSV infections differs depending on whether or not the infection is disseminated. Encephalitis associated with dissemination is due to hematogenous spread, whereas isolated encephalitis or encephalitis associated with only SEM involvement likely occurs due to retrograde intraneuronal transport of HSV [4]. This difference corresponds to the clinical presentations of disseminated versus CNS disease in that the blood-borne spread of disseminated disease presents earlier (9 to 11 days of life on average) and causes more diffuse brain involvement with multiple areas of hemorrhagic necrosis, while CNS disease occurring via slower axonal transport presents later (around 16 to 17 days of life) and typically causes more focal CNS involvement [10].

The early era of antiviral therapy for neonatal HSV infection was marked by improved mortality with intravenous vidarabine as well as with standard dose (SD) intravenous acyclovir (30mg/kg/day in 3 divided doses). The 1 year mortality for disseminated disease decreased from 85% with no therapy to 50% with vidarabine and 61% with SD acyclovir, while the 1 year mortality for CNS disease dropped from 35% with no therapy to 14% for both vidarabine and SD acyclovir [11]. More recently, highdose (HD) acyclovir has been shown to further improve upon these mortality figures. Using HD intravenous acyclovir (60mg/kg/day in 3 divided doses for 21 days), the one year mortality rates were 29% and 4% for disseminated and CNS diseases, respectively [12]. While HD acyclovir improved morbidity for infants with disseminated disease (83% of survivors had normal neurodevelopmental outcomes), infants with CNS disease did not have a significant improvement in morbidity (31% of survivors had normal neurodevelopmental outcomes).

Babies with SEM involvement have the best prognosis and, as noted below, only require 14 days of HD intravenous acyclovir therapy.

Recently, acyclovir suppressive therapy for babies with CNS after completing intravenous treatment significantly improved neurologic outcome as measured by Bailey Developmental Scores [13]. This regimen led to approximately 60% (as opposed to 31%) of children with CNS disease developing normally or with mild impairment. Treatment was administered at a dosage of 300/mg/m² per os tid for six months.

Therapy of Neonatal Varicella Zoster Virus Infections

Women who experience primary varicella-zoster virus (VZV) infections within 48 hours of delivery have children at risk for the development of chickenpox within the first three weeks of life. Newborns delivered to these women traditionally receive zoster immune globulin (ZIG) in order to prevent disease. However, with sporadic shortages of ZIG, some newborns will experience neonatal disease. No controlled clinical trials have evaluated acyclovir therapy of this disease; however, experts would recommend this drug for the treatment of newborn disease.

Available Therapies for HSV and VZV Infections

Acyclovir (Acycloguanosine, Zovirax, ACV)

Acyclovir is the most frequently prescribed antiviral agent for the management of HSV infections of the newborn and infant. It has been available for clinical use for nearly three decades and has demonstrated remarkable safety and efficacy against mild to severe infections caused by HSV and VZV in both normal and immunocompromised patients, including the newborn.

Chemistry & Mechanism of Action—Acyclovir is a deoxyguanosine analogue. After preferential uptake by viral-infected cells, acyclovir is phosphorylated by virus-encoded thymidine kinase (TK). Subsequent di- and triphosphorylation are catalyzed by host cell enzymes. Acyclovir triphosphate prevents viral DNA synthesis by both inhibiting viral DNA polymerase and being a chain terminator.

Spectrum & Resistance—Acyclovir is most active against HSV; activity against VZV also is substantial but approximately 10-fold less. Acyclovir is considered the treatment of choice for both neonatal HSV and VZV infections. Activity against CMV is poor because CMV does not have thymidine kinase activity and CMV DNA polymerase is poorly inhibited by acyclovir triphosphate.

Resistance of HSV and VZV to acyclovir has become an important clinical problem among immunocompromised patients exposed to long-term therapy [14]. Viral resistance to acyclovir usually results from mutations in the viral TK gene although mutations in the viral DNA polymerase gene also occur rarely. Resistant isolates can cause severe, progressive, debilitating mucosal disease in adults and, rarely, visceral dissemination [15, 16]. Isolates of HSV resistant to acyclovir also have been reported in normal hosts, most commonly in patients with frequently recurrent genital infection who have been treated with chronic acyclovir [17].

Indications—Acyclovir is effective for the treatment of infections caused by HSV and VZV in both immunocompetent and immunocompromised hosts, including the newborn. For the treatment of neonatal HSV infections, the recommended dose is 20 mg/kg/q8h. The duration of therapy for SEM disease is 14 days, while for those babies with either CNS or disseminated disease, therapy should be extended for 21 days.

Oral acyclovir is an experimental approach to suppressive therapy and is not currently approved by the Food and Drug Administration.

Pharmacokinetics—After intravenous doses of 2.5 to 15 mg/kg, steady-state concentrations of acyclovir range from 6.7 to 20.6 µg/ml. Acyclovir is widely distributed; high concentrations are attained in kidneys, lung, liver, heart, and skin vesicles; concentrations in the cerebrospinal fluid (CSF) are about 50% of those in the plasma [18]. Acyclovir crosses the placenta and accumulates in breast milk. Protein binding ranges from 9% to 33% and less than 20% of drug is metabolized to biologically inactive metabolites. No pharmacokinetic data are available in the newborn for the use of 20 mg/kg/dose.

In the absence of compromised renal function, the half-life of acyclovir is 2 to 3 hours in older children and adults and 2.5 to 5 hours in neonates with normal creatinine clearance. More than 60% of administered drug is excreted in the urine [18]. Elimination is prolonged in patients with renal dysfunction; the half-life is approximately 20 hours in persons with end-stage renal disease, necessitating dose modifications for those with creatinine clearance less than 50 ml/min/1.73 m² [19]. Acyclovir is effectively removed by hemodialysis but not by continuous ambulatory peritoneal dialysis [20, 21].

Adverse Effects—Acyclovir generally is a safe drug. Renal dysfunction results from obstructive nephropathy caused by the formation of acyclovir crystals precipitating in renal tubules. Occasionally administration of acyclovir by the intravenous route is associated with rash, sweating, nausea, headache, hematuria, and hypotension. High doses of intravenous acyclovir (60 mg/kg/day) in neonates have been associated with Neutropenia [22, 23].

Neurotoxicity can occur in subjects with compromised renal function who attain high serum concentrations of drug [24]. Neurotoxicity is manifest as lethargy, confusion, hallucinations, tremors, myoclonus, seizures, extrapyramidal signs, and changes in state of consciousness, developing within the first few days of initiating therapy. These signs and symptoms usually resolve spontaneously within several days of discontinuing acyclovir.

Although acyclovir is mutagenic at high concentrations in some *in vitro* assays, it is not teratogenic in animals. Limited human data suggest that acyclovir use in pregnant women is not associated with congenital defects or other adverse pregnancy outcomes.

Drug Interactions—The likelihood of renal toxicity of acyclovir is increased when administered with nephrotoxic drugs such as cyclosporine or amphotericin B.

Therapy of Congenital Cytomegalovirus Infection

Cytomegalovirus (CMV) commonly infects humans worldwide, with a seroprevalence of approximately 40% in adolescents and approaching 90% in adults with poor socioeconomic status [25, 26]. Congenital CMV infection is the most common congenital infection in the developed world, found in about 1% of liveborn infants in the United States [27]. Congenital CMV infections most commonly occur via intrauterine transmission, but since the virus is shed in bodily fluids, transmission can also be acquired perinatally during delivery or postnatally through breast milk.

Of all infants born with congenital CMV infection, approximately 7–10% have clinically evident disease at birth [28]. Clinical characteristics of intrauterine infection include intrauterine growth restriction, hepatosplenomegaly, jaundice, thrombocytopenia, microcephaly, periventricular calcifications, and chorioretinitis. As reviewed by Dollard, true mortality rates are difficult to obtain and have been reported to be as high as 30% for symptomatic infants [29], but more likely average about 5–10% [30]. Death usually is due to non-CNS manifestations of the infection, such as hepatic dysfunction or bleeding. An estimated 40–58% of infants with symptomatic congenital CMV infection have permanent sequelae, while infants who are asymptomatic at birth suffer permanent sequelae nearly 14% of the time [29]. Sensorineural hearing loss (SNHL), mental retardation, seizures, psychomotor and speech delays, learning disabilities, chorioretinitis, optic nerve atrophy, and defects in dentition are the most common longterm consequences [31]. As opposed to intrauterine infections, perinatally acquired CMV infections are not typically associated with long-term sequelae, although acute illness has been reported in premature very low birth weight infants [32]. In full term infants, perinatal infections are commonly asymptomatic, but may present with pneumonitis within the first few months of life [33].

Congenital CMV infection is the consequence of maternal-fetal infection with most symptomatic congenital cases occurring because of asymptomatic maternal infection. With maternal primary infection, there appears to be compromise of the placental blood flow following infection of the placental villae [34]. The pathogenesis of CNS involvement in congenital CMV infection begins with disseminated viremic spread, including the endothelial cells of the brain and epithelial cells of the choroid plexus. From the endothelial cells of the brain, the virus spreads to contiguous astrocytes. From the choroid plexus, the virus then moves to the ependymal surfaces via the cerebrospinal fluid (CSF). Once these cells are infected, the virus undergoes continuous replication, which leads to characteristic intranuclear inclusion bodies and cell death. As antibodies are produced in the face of continuous viral replication, immune complexes form as well, leading to further immune-mediated damage [31]. Although the specific pathogenesis of CMV mediated SNHL has not been elucidated, histology has shown evidence of infection in the cells of both the cochlear

and vestibular endolabyrinth [35]. CMV has also been isolated from the cochlear perilymph upon autopsy of infants with congenital CMV infection [36].

Recent studies of ganciclovir treatment of congenital CMV infections involving the CNS have been promising. Administering ganciclovir at doses of 12mg/kg/day divided every 12 hours for a duration of 6 weeks improved hearing outcomes in neonates with symptomatic congenital CMV infections involving the CNS (as evidenced by microcephaly, intracranial calcifications, abnormal CSF for age, chorioretinitis, and/or hearing deficits) [37]. The primary endpoint was improved brainstem-evoked response (BSER) between baseline and 6 month follow-up (or no deterioration at the 6 month follow-up if the baseline BSER was normal). For total evaluable ears, 69% of patients who received ganciclovir met the primary endpoint as opposed to 39% of the control group. No patients receiving ganciclovir had worsening of their hearing between baseline and 6 months. Ganciclovir recipients also had more rapid resolution of ALT abnormalities than did the control group, though they were significantly more likely to become neutropenic. Additional analyses of this randomized controlled trial suggest that ganciclovir may also reduce neurodevelopment delays [38]. Improvement of mortality has not yet been shown with ganciclovir therapy.

Treatment of CMV Infections

Ganciclovir (Cytovene)

Ganciclovir was the first antiviral available for the therapy and prevention of infections caused by CMV. It has proved to be a very valuable drug for immunocompromised patients, particularly hematopoietic stem cell transplant recipients, who suffer substantial morbidity and mortality from CMV infections and, more recently, in children with congenital CMV infection, albeit it not approved by US Food and Drug Administration (FDA) at this time.

Chemistry & Mechanism of Action—Ganciclovir is structurally similar to acyclovir except for an hydroxymethyl group on its acyclic side chain. The initial phosphorylation step is carried out by pUL97, which is a viral protein kinase. Cellular kinases then phosphorylate the agent two additional times to convert it into its triphosphate derivative, which is able to inhibit the CMV DNA polymerase encoded by *UL97* as well as incorporate into and terminate viral DNA.

Ganciclovir triphosphate is a competitive inhibitor of herpesviral DNA polymerases, resulting in cessation of DNA chain elongation [1, 20].

Spectrum & Resistance—Ganciclovir has similar activity to acyclovir against HSV-1, HSV-2, and VZV but, in contrast with acyclovir, its greatest activity is against CMV. Resistance of CMV isolates usually results from mutations in the *UL97* gene [39]. Mutations in the CMV DNA polymerase gene occur less often. **Indications.** Ganciclovir is licensed for several indications outside of the newborn. Several reviews summarize these clinical outcomes [2]. For the treatment of neonates congenitally infected with CMV a controlled trial has been performed [40]. As noted above, compared to no treatment, ganciclovir therapy prevented hearing deterioration at two years, although about two-thirds of treated infants developed neutropenia, often requiring dose modification.

Pharmacokinetics—Oral bioavailability of ganciclovir is poor, with less than 10% of drug being absorbed following oral administration [41, 42]. The oral formulation of ganciclovir is no longer marketed. Peak serum concentrations of ganciclovir after 6 mg/kg (newborn dose) of intravenously-administered drug range from 8 to 11 µg/ml, with concentrations sufficient to inhibit sensitive strains of CMV in aqueous humor, subretinal fluid, CSF, and brain tissue [1]. The elimination half-life of ganciclovir is 2 to 3 hours and

most of the drug is eliminated unchanged in the urine. The pharmacokinetics of ganciclovir in the neonatal population are similar to those of adults [43, 44]. Dose reduction, proportional to the degree of reduction in creatinine clearance, is necessary for persons with impaired renal function. A supplemental dose is recommended after dialysis because it is efficiently removed by hemodialysis [45].

Adverse Effects—Myelosuppression is the most common adverse effect of ganciclovir; dose-related neutropenia (less than 1,000 WBC/ μ l) is the most consistent hematologic aberration, with an incidence of about 40% [42]. Neutropenia is dose limiting in about one of seven courses and reverses after drug is stopped. Neutropenia is less frequent following oral administration of ganciclovir. Thrombocytopenia (less than 50,000 platelets/ μ l) occurs in approximately 20% and anemia in about 2% of ganciclovir recipients. Two to 5% of ganciclovir recipients experience headache, confusion, altered mental status, hallucinations, nightmares, anxiety, ataxia, tremors, seizures, fever, rash, and abnormal levels of serum hepatic enzymes, either singly or in some combination.

Dosage—The dose of ganciclovir for therapy of symptomatic congenital CMV infection is 12 mg/kg/day, given by intravenous infusion twice a day for 6 weeks.

Investigational Drug

Valganciclovir (Valcyte)

Valganciclovir was approved by the FDA in March, 2001 for the treatment of CMV retinitis. Because it is well absorbed after oral administration, it may represent a favorable option to intravenously-administered ganciclovir for the treatment of congenital CMV infection. Currently, it is licensed for the treatment of CMV infections in selected transplant populations and for CMV retinitis in patients with HIV/AIDS.

Chemistry, Mechanism of Action, Spectrum, & Resistance—Valganciclovir is the L-valine ester prodrug of ganciclovir and as such has the same mechanism of action, antiviral spectrum, and potential for development of resistance as ganciclovir [1, 20].

Indications—Valganciclovir has similar indications to ganciclovir. However, based upon limited controlled trials published to date, it currently is approved for the induction and maintenance therapy of CMV retinitis and select transplant populations [46]. It is currently under investigation for the treatment of congenital CMV infection. This randomized controlled trial, being performed by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) employs SNHL as its primary endpoint.

Pharmacokinetics—Valganciclovir is rapidly converted to ganciclovir, with a mean plasma half-life of about 30 minutes [46]. The absolute bioavailability of valganciclovir exceeds 60% and actually is enhanced by about 30% with concomitant administration of food [47]. The area under the curve of ganciclovir after oral administration of valganciclovir is one-third to one-half of that attained after intravenous administration of ganciclovir. Patients with impaired renal function require dosage reduction that is roughly proportional to their reduction in creatinine clearance.

Adverse Effects—The most common side effects associated with valganciclovir therapy in adult populations include diarrhea (41%), nausea (30%), neutropenia (27%), anemia (26%), and headache (22%) [46]. Only a limited number of newborns have received

valganciclovir therapy. The only significant finding was that of neutropenia in 15% of patients.

Dosage—The dose of valganciclovir is tailored to the patient's age and renal function. At this time the drug is not approved for administration to newborns with congenital CMV infection.

Unproven and Untested Therapies for Neonatal HSV, VZV and Congenital CMV Infections

The following two medications are utilized to treat HSV, VZV and CMV infections in older children and adults. Data on these medications is provided should antiviral resistance occur with either HSV or CMV infections of the newborn. Neither drug has been evaluated in proof-of principle studies in the newborn, and both are associated with significant toxicity. In addition, valacyclovir may become available for pediatric administration, particularly for babies with HSV infection limited to the skin, eye and mouth

Cidofovir (HPMPC, Vistide)

Cidofovir was first approved for use in the United States for the therapy of AIDS-associated retinitis caused by CMV. This remains the main indication for this antiviral.

Chemistry & Mechanism of Action—Cidofovir is a novel acyclic phosphonate nucleoside analog with a mechanism of action similar to that of other nucleoside analogues. In contrast to acyclovir, viral enzymes are not required for initial phosphorylation because native cidofovir has a single phosphate group already attached. Following diphosphorilation by cellular kinases cidofovir competitively inhibits DNA polymerase [48]. The active form of cidofovir exhibits a 25- to 50-fold greater affinity for viral DNA polymerase compared to the cellular DNA polymerase.

Spectrum & Resistance—Cidofovir is active against HSV and CMV, including acyclovir- and foscarnet-resistant HSV isolates and ganciclovir- and foscarnet-resistant CMV mutants [49]. It also is active *in vitro* against VZV, EBV, human herpesvirus-6, human herpesvirus-8, polyomaviruses, adenovirus, and human HPV.

A small number of cidofovir-resistant CMV isolates that also are resistant to ganciclovir on the basis of mutations within the DNA polymerase gene have been described [50]. A CMV mutant resistant to ganciclovir, foscarnet, and cidofovir also has been reported [51].

Indications—Cidofovir delays retinal disease progression in patients with AIDS [52, 53]. Cidofovir also has been useful in the management of disease caused by acyclovir-resistant HSV isolates [54]. Anecdotal reports of improvement of laryngeal papillomatosis following intralesional injection of cidofovir have been published, but a definitive conclusions regarding efficacy is not possible based upon this limited experience [55, 56].

Pharmacokinetics—Only 2–26% of cidofovir is absorbed after oral administration, therefore it is given intravenously. The plasma half-life of cidofovir is 2.6 hours, but active intracellular metabolites of cidofovir have half-lives of 17 to 48 hours [57]. Ninety percent of the drug is excreted in the urine, primarily by renal tubular secretion [58]. Importantly, the drug does not cross the blood-brain barrier and, therefore, should not be used to treat CNS infections.

Adverse Effects—Because cidofovir concentrates in renal cells in amounts 100 times greater than in other tissues, nephrotoxicity is the main adverse effect, especially if hydration is not well maintained [57, 58]. Manifestations of renal toxicity include proteinuria and glycosuria. Aggressive intravenous prehydration, coadministration of probenecid, and avoidance of other nephrotoxic agents reduce the likelihood of toxicity. Cidofovir is contraindicated in patients with a serum creatinine > 1.5 mg/dL, a calculated creatinine clearance ≤ 55 mL/min, or a urine protein ≥ 100 mg/dL and drug should be discontinued if serum creatinine increases ≥ 0.5 mg/dL above baseline.

Dosage—Cidofovir is administered intravenously to older children and adults as a 5 mg/kg dose once per week with probenecid. Patients with compromised renal (calculated creatinine clearance < 55 mL/min) are treated every 2 weeks. The dose should be reduced from 5 mg/kg to 3 mg/kg if serum creatinine increases > 0.3 mg/dL above baseline. There are no data for dosing the newborn with cidofovir.

Foscarnet (PFA, Foscavir)

Foscarnet is the only anti-herpes drug that is not a nucleoside analog. It is not a first line drug but is useful for the treatment of infections caused by resistant herpes viruses.

Chemistry & Mechanism of Action—Foscarnet is an inorganic pyrophosphate analogue that directly inhibits DNA polymerase by blocking the pyrophosphate binding site [20, 59].

Spectrum & Resistance—Foscarnet inhibits all known human herpesviruses, including most ganciclovir-resistant CMV isolates and acyclovir-resistant HSV and VZV strains. It also is active against HIV. Resistance occurs as a result of DNA polymerase mutations. Strains of CMV, HSV, and VZV with reduced sensitivity to foscarnet have been reported [59, 60].

Indications—Foscarnet is as effective as ganciclovir for therapy of sight-threatening chorioretinitis caused by CMV in adult patients with AIDS [61]. Because of its inherent activity against HIV, it may even offer a survival advantage for treated patients [62]. Refractory cases of chorioretinitis may respond to a combination of foscarnet and ganciclovir. Foscarnet also is effective in the therapy of CMV infections caused by ganciclovir-resistant strains of virus [62]. Limited data also suggest that foscarnet may be of benefit when administered to patients with AIDS who have gastrointestinal and pulmonary infections caused by CMV.

Infections caused by acyclovir-resistant strains of HSV and VZV have been successfully controlled with foscarnet [63, 64].

Pharmacokinetics—Only about 20% of foscarnet is absorbed after oral administration. Maximum serum concentration attained after an intravenous dose of 60 mg/kg is approximately 500 μmol/L [59]. CSF concentrations are about two-thirds of those in serum. The half-life of foscarnet is about 48 hours and 80% of an administered dose is eliminated unchanged in the urine. Dose reduction, proportional to reduction in creatinine clearance, is necessary. Hemodialysis efficiently eliminates foscarnet and therefore a supplemental dose is recommended after dialysis [65]. There are no data on the use of foscarnet in the newborn.

Adverse Effects—The most common adverse effects of foscarnet are nephrotoxicity and metabolic derangements. Evidence of nephrotoxicity includes azotemia, proteinuria, acute tubular necrosis, crystalluria, and interstitial nephritis. Serum creatinine concentrations

increase in up to 50% of patients. Fortunately, renal function returns to normal within 2 to 4 weeks of discontinuing therapy. Pre-existing renal disease, concurrent use of other nephrotoxic drugs, dehydration, rapid injection or continuous intravenous infusion of drug are risk factors for developing renal dysfunction [66]. Metabolic disturbances associated with foscarnet therapy include hypo- and hypercalcemia and hypo- and hyperphosphatemia [67]. Hypocalcemia can be associated with paresthesias, tetany, seizures, and arrhythmias. Metabolic disturbances are minimized if foscarnet is administered by slow infusion. CNS symptoms associated with foscarnet therapy include headache, tremor, irritability, seizures, and hallucinations. Fever, nausea, vomiting, abnormal serum hepatic enzymes, anemia, granulocytopenia, and genital ulcerations also have been reported.

Drug Interactions—Concomitant use of amphotericin B, cyclosporine, gentamicin, and other nephrotoxic drugs increases the likelihood of renal dysfunction. Co-administration of pentamidine increases the risk of hypocalcemia. Anemia and neutropenia are more common when patients also are receiving zidovudine.

Dosage—The usual dose of foscarnet for CMV infection is 180 mg/kg/day in three divided doses for 14 to 21 days, followed by a daily maintenance dose of 90 to 120 mg/kg. The dosage of foscarnet used for infections caused by acyclovir-resistant HSV and VZV infections is 120 mg/kg/day in three divided doses.

Summary

While significant progress has been achieved in the management of congenital CMV and neonatal HSV infections, further advances are mandatory. With the appearance of new antiviral drugs that have a different mechanism of action, the opportunity for combination therapy arises, so long as medications can be proven safe.

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