Antivirals for Cytomegalovirus Infection in Neonates and Infants
Focus on Pharmacokinetics, Formulations, Dosing, and Adverse Events

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Abstract
Cytomegalovirus (CMV) infection is very common throughout the world, and has become more of a pediatric clinical concern given the high incidence of congenital CMV infections as well as the increasing numbers of immunocompromised patients. Because of this, the need for antiviral therapies in infants and neonates is growing.
Cytomegalovirus (CMV) is a ubiquitous virus first isolated in the late 1950s from infants experiencing congenital infection, then termed cytomegalic inclusion disease. It is a member of the family of eight human herpesviruses and thus shares many similar characteristics with these viruses, including its physical structure as well as features such as latency and the potential for reactivation.

CMV itself is most often of minor clinical importance, as most infections in healthy children and adults go unnoticed, or manifest as a self-limited mononucleosis-type syndrome. The virus is common in all areas of the world, and in fact in the US by the age of 80 years, >90% of healthy adults have become infected with CMV. It is in situations where the immune system is compromised that CMV becomes much more of a clinically significant infection. Such scenarios may include those seen with primary immunodeficiencies or with secondary immunodeficiencies, such as with HIV infection, or with iatrogenic immune suppression, such as following bone marrow or solid organ transplant.

One particular instance of natural immune suppression is during fetal life. During this time in utero, if a mother sustains either a primary infection with CMV or a secondary infection with a different CMV strain, often neither she nor the fetus has an immune response sufficient to prevent transmission to and infection in the developing infant. The result is the syndrome of congenital CMV infection.

Congenital CMV infection is the most common congenitally acquired viral infection in newborns in the developed world, and is estimated to occur in 1% of all live births in the US (approximately 40,000 infants per year). Symptomatic neonatal infections often have significant sequelae with life-long impact, as affected children frequently have severe cognitive disability and developmental delays. Congenital CMV infection is also the leading infectious cause of sensorineural hearing loss; this frequently occurs in those infants symptomatic at birth, but may also occur in up to 15% of infants without clinical evidence of congenital infection.

Even though the syndrome and potentially devastating outcomes of congenital CMV infections have been understood for decades, it is only since the early 1980s that there has been even a potential pharmaceutical therapeutic option that is active against CMV. Furthermore, since this time, technologic advances in the treatment of numerous conditions (such as malignancies, autoimmune disorders, and solid-organ and bone marrow transplantation) have been made, many of which require significant immunosuppression for success. Likewise, the emergence of the HIV/AIDS epidemic has introduced
another large group of chronically immunosuppressed patients. Because of all of this, CMV, either as a primary infection or as a disease of viral reactivation, has become much more of a clinical concern. Over time and with this changing medical climate, these groups of immunocompromised patients have come to include neonates and infants who, alongside those infants with congenital disease, may require therapy against CMV.

Given these clinical scenarios, the need for antiviral therapy active against CMV in neonates and infants has intensified; however, thus far there have been few therapeutic drug options that have been studied in this group. This review presents a systematic look at the potential pharmacologic options that are available to treat CMV in infants, and the data that are available regarding the formulations, dose, pharmacokinetics (PK), and potential adverse events of each of these drugs.

A literature search was conducted using MEDLINE/PubMed and all available and pertinent literature was utilized for the preparation of this review. Search terms included the names of the individual antivirals used to treat CMV; these were used in combination with 'pediatric,' 'child,' 'infant,' and 'neonate'. Searches for individual antivirals were also conducted using the Pubmed infant and pediatric age range limits. Focus was placed on studies reporting neonatal and infant pharmacokinetics; however, when data were limited, studies including older children were also used. Many additional references were identified from the reference lists of the published articles identified by the electronic searches.

1. Ganciclovir

1.1 Mechanism of Action

The first agent found to have significant anti-CMV activity and to be approved for its treatment was ganciclovir. Previously termed DHPG on the basis of its chemical structure (9-[1,3-dihydroxy-2-propoxy-methyl]guanine), ganciclovir is similar to aciclovir in that it acts as a nucleoside analog of guanosine, and structurally differs only by an additional hydroxyl group. Both drugs must undergo triphosphorylation once inside infected cells to become active; however, unlike in herpes simplex virus (HSV)-infected cells, CMV-infected cells have no thymidine kinase for the initial phosphorylation step. It is the enzyme product of the CMV viral open reading frame (orf) UL97, phosphotransferase, that first converts ganciclovir to 5' monophosphate ganciclovir. Subsequent to this, cellular kinases diphosphorylate this monophosphate intermediate to ganciclovir triphosphate. In this triphosphorylated form, the drug is able to inhibit viral DNA synthesis by two mechanisms. First, the drug competitively inhibits the incorporation of deoxyguanine triphosphate by DNA polymerase, and has higher affinity for the viral polymerase over the host cell enzyme, thus reducing (but not eliminating) inhibition of host cell DNA production. Second, the drug becomes directly incorporated into the viral DNA chain, and, given the instability afforded by the acyclic sugar side chain, it serves to inhibit the addition of other nucleotides for chain elongation. Although aciclovir triphosphate is highly active against CMV DNA polymerase in cells, ganciclovir triphosphate is able to reach concentrations 10-fold higher and thus has much greater inhibition of CMV replication.

1.2 Spectrum of Activity

In in vitro studies, ganciclovir has been shown to have significant activity against CMV, inhibiting laboratory strains and clinical isolates from growth in concentrations from 0.1 to 1.6 μg/mL. It has also been shown to be active in tissue culture against other herpesviruses, including HSV-1 and -2, Epstein-Barr virus, human herpesvirus-6, and varicella-zoster virus (VZV).

1.3 Mechanism of Resistance

The primary mechanism of viral resistance to ganciclovir is through mutations in the UL97 gene. As this gene encodes the viral kinase, mutations in two major regions of UL97 render the enzyme less able or unable to phosphorylate ganciclovir; thus, the drug cannot be activated. As ganciclovir is the only one of the currently available antivirals against CMV requiring an initial phosphorylation step, this mechanism of resistance is fairly specific to ganciclovir, and UL97 mutations alone do not predict resistance to other agents active against CMV, such as foscarin or cidofovir. UL97 mutations account for 95% of ganciclovir-resistant viral strains.

Another site for mutations that may confer viral resistance to ganciclovir is that in the viral DNA polymerase. UL54 is the CMV gene that encodes the viral DNA polymerase, so unlike the case with mutations in UL97, mutations in this area may confer cross-resistance to the other antivirals, most commonly cidofovir. However, these mutations represent only 5% of the ganciclovir-resistant isolates.

It is generally believed that UL97 mutations arise first, and produce moderate-level ganciclovir-resistance at dose levels that are infectious to 50% of those exposed (ID₅₀) of 8–30 μM/L (the normal ID₅₀ for CMV is 0.5–3 μM/L). High-level resistance via UL54 and other mutations in the DNA
Table I. Pharmacokinetic data for intravenous ganciclovir administered every 12 hours to neonates in published studies and compared with adults

<table>
<thead>
<tr>
<th>Study (y)</th>
<th>Dose (mg/kg)</th>
<th>Vd (mL/kg)</th>
<th>CL (mL/h/kg)</th>
<th>t½ (h)</th>
<th>Cmax (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trang et al.[12] (1993)</td>
<td>4</td>
<td>669±70 (399–1341)</td>
<td>189±28 (53–479)</td>
<td>2.4 (1.6–7.2)</td>
<td>5.5±1.6</td>
</tr>
<tr>
<td>Trang et al.[12] (1993)</td>
<td>6</td>
<td>749±59 (524–1260)</td>
<td>189±28 (53–479)</td>
<td>2.4 (2.1–6.9)</td>
<td>7.0±1.6</td>
</tr>
<tr>
<td>Zhou et al.[13] (1996)</td>
<td>4-6</td>
<td>694±69</td>
<td>172±45</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Anderson et al.[14] (1995) [adults]</td>
<td>5</td>
<td>750±102</td>
<td>231±35</td>
<td>2.9</td>
<td>8.3</td>
</tr>
</tbody>
</table>

a Values are means ± standard error of the mean (range) except where otherwise stated.
b Values are means (range).
c Values are means ± standard error of the mean.
d Values are means ± standard deviation.
e Values are for Vss.
f Converted from mL/min/kg.
g Values are means.

CL = clearance; Cmax = maximum plasma concentration; ND = data not available; t½ = half-life; Vd = volume of distribution; Vss = Vd at steady state.

polymerase is reported at >30 µmol/L.[9,11] Clinical testing using restriction enzyme analysis to detect mutations in the UL97 and viral DNA polymerase genes to predict drug resistance is commercially available and often used when expected clinical response is not achieved.

1.4 Formulations

Intravenous (IV) ganciclovir is available as a powder for reconstitution in 100 mL of 5% dextrose in water, normal saline, or lactated ringers that must be infused over 1 hour. The oral formulation of ganciclovir is available as a 250 mg capsule (available as a generic formulation only). Currently, there is no commercially prepared suspension of ganciclovir available.

1.5 Pharmacokinetics of Intravenous Ganciclovir in Infants

Although the PK of ganciclovir in adults has been well studied, such data for the pediatric population are minimal. Furthermore, PK information for infants and neonates is particularly sparse as pediatric drug PK studies are subject to the significant limitations of small blood volumes and few sampling times allowed in clinical studies in children. Most of the information known about ganciclovir PK in infants derives from three studies originating from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (NIAID CASG).

The first study of ganciclovir PK in neonates was reported by Trang et al.[12] in 1993. In this open-label, phase I–II trial, the PK of IV ganciclovir were studied in 27 neonates, aged 2–49 days, with symptomatic congenital CMV infection. All had evidence of CNS involvement with or without concurrent disease in other organ systems. These neonates were randomized to ganciclovir therapy at either 4 or 6 mg/kg per dose every 12 hours for 6 weeks. Serial blood sampling provided PK data, and analyses were based on a single-compartment open model assuming zero-order input and first-order elimination.

Specific PK data for each of the doses studied are presented in table I.[12] The mean values obtained for the apparent volume of distribution (Vd), clearance (CL), and half-life (t½) did not differ significantly between the dose groups, and when normalized for bodyweight, were found overall to be similar to those reported in adults. There was wide variation in the values of Vd and Vss (Vd at steady state) found for individual infants, reflecting the variation in infant bodyweight; these parameters increased with an increase in bodyweight. Likewise, CL increased with patient age, reflecting the well known changing renal function in newborns; however, this change was not significant enough for the authors to recommend dose alterations with age, even for premature infants.

As seen with Vd and CL, mean residence time and area under the plasma concentration-time curve normalized for dose given (AUC/dose) were also similar between both dose groups.[12]

Plasma concentrations of ganciclovir decreased monoexponentially in each neonate, and the mean maximum plasma concentration (Cmax) peaks in groups receiving 4 mg/kg and 6 mg/kg were 5.5 µg/mL and 7.0 µg/mL, respectively.[12] This was somewhat lower than in adults, who demonstrated a mean peak range of 8–11 µg/mL after a dose of 5 mg/kg.[13] The mean t½ for both dose groups was 2.4 hours, consistent with the reported t½ in adults (2.9 hours).[14]

Urinary excretion of ganciclovir over a 24-hour time period was measured in 12 of the infants, with recovery of unchanged ganciclovir found at 117.1% of the total administered dose of
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8 mg/kg/day (n = 7) and 95.4% of the total administered dose of 12 mg/kg/day (n = 3). Further evaluation of urinary excretion at days 1, 2, and 10 after completion of therapy found no residual ganciclovir present in the urine. This confirmed that, as in adults, ganciclovir is entirely excreted, unchanged, by the kidneys.

Overall, the conclusions from this study, although potentially limited by the small number of sampling times, included the finding that a one-compartment model with linear PK satisfactorily described ganciclovir disposition in these neonates with congenital CMV infection. This conclusion was different from that of adult PK studies that demonstrated that disposition and CL in this population are multicompartmental.

In another study published 3 years later, Zhou et al. reanalyzed the same 27 infants examined by Trang et al. to perform a population-based PK analysis (using non-linear mixed-effects modeling analysis). This modeling analysis attempted to identify individual characteristics of infants that may account for individual variations in drug PK. In all, 13 co-variates were analyzed that potentially impacted PK parameters. Of the characteristics studied, the authors found that the approximate serum creatinine CL (ASC) for each infant affected ganciclovir CL, and bodyweight altered drug Vd. Regression equations were subsequently formulated to model these relationships, and the final CL and Vd were quite similar to those obtained by Trang et al. (see table 1).

These authors concluded, as did Trang et al., that ganciclovir CL increases linearly with increased ASC and that Vd is a linear function of the weight of the infant. However, given the similarities in the findings, no basis for dose alterations could be made. Again, however, the significant impact of renal function on drug disposition was found, suggesting that keen attention must be paid to alterations in dose in those with renal impairment.

In the largest PK study of ganciclovir in infants to date, Whiteley et al. evaluated 42 infants with symptomatic congenital CMV infection who received IV ganciclovir at one of two doses for 6 weeks in a phase II trial. These infants included those reported on by Trang et al. and Zhou et al. Fourteen infants received a dose of 4 mg/kg every 12 hours while 18 received 6 mg/kg every 12 hours. All infants were <1 month of age, 70% were White, and over one-third were premature. Blood samples for PK analysis were obtained at times 0, 0.5, 2, 3, 4, 6, 8, 24, and 48 hours of administration; weekly peaks and troughs were obtained thereafter. Again, based on the previous CASH studies, a one-compartment model, with zero-order input and first-order elimination was used. The ganciclovir dose was changed (reduced by 50%) if the absolute neutrophil count (ANC) fell below 500 cells/µL or platelets below 50,000/µL. Although this was largely a safety and tolerability study for infants with congenital CMV infection, as with previous studies, this study found that plasma drug CL was proportionate to renal function in these infants, and Vd was proportionate to bodyweight.

Data regarding ganciclovir tissue penetration data are incomplete, particularly for the pediatric population. Despite this, it does appear that ganciclovir crosses the blood-brain barrier to gain CNS penetration. One study showed that at a serum concentration of 2.2 µg/mL (3.5 hours after an IV dose of 2.5 mg/kg in adults), a cerebrospinal fluid concentration of 0.7 µg/mL was obtained. The fraction of the administered dose of ganciclovir that is able to penetrate the CNS is unknown.

1.6 Pharmacokinetics of Oral Ganciclovir in Infants

In the only large pediatric study evaluating the PK of oral ganciclovir, children with HIV and CMV disease (aged 2 weeks–20 years) were administered varying doses of oral ganciclovir in either tablet form or a compounded suspension; ganciclovir powder used for the IV formulation was dissolved in sterile water and mixed with cherry syrup for administration to children unable to swallow pills. Only two of the children in this study were aged <2 years. Both of these children received ganciclovir 30 mg/kg and had the lowest AUCs of the children studied at 1.0 and 2.9 µg • h/mL. The third-youngest child (25 months of age) had an AUC of 7.0 µg • h/mL at a dose of 50 mg/kg. Overall, the median AUC for the children studied (largely represented by older children) was 4.9 µg • h/mL at a dose of 30 mg/kg, which is comparable to the AUC of 4.29 µg • h/mL found in adults administered –15 mg/kg (1000 mg dose). However, the extent of absorption was generally limited.

1.7 Toxicity and Adverse Events

In adult studies, the most frequently encountered and serious drug toxicity associated with ganciclovir is bone marrow suppression, particularly neutropenia, occurring in about 40% of patients. Thrombocytopenia may also occur in about 20% of ganciclovir-treated adults, and anemia in about 2% of these patients. However, all of these blood-count...
abnormalities may also occur as a result of CMV infection and if one of these is present prior to starting ganciclovir, it may actually improve with therapy.

In the phase II study by Whitley et al.,[17] neutropenia (defined as >50% decrease in ANC from baseline or ANC <1000 cells/μL) was also the most significant adverse event seen in infants. Sixty-three percent of infants treated with a total daily dose of 8 mg/kg and 19% of infants treated with a total daily dose of 12 mg/kg demonstrated neutropenia, giving rise to an overall rate of neutropenia of 34% in all infants treated with ganciclovir. Three of the children in the 8 mg/kg dose group had to discontinue the drug because of persistent neutropenia despite dose reduction. In this group of infants, neutropenia was not dependent on dose; however, in adult studies, this toxicity has appeared to be dose dependent. In adult studies, the neutropenia may be dose-limiting in 15% of courses[19], however, as is also seen in pediatric data, this toxicity is reversible on discontinuation of the drug.

Neutropenia associated with ganciclovir was also noted in an efficacy study published in 2003 involving congenitally infected infants.[20] Overall, 63% of infants who received ganciclovir experienced grade 3 or 4 neutropenia compared with 21% of infants who were not treated. Fourteen of the 29 infants treated with ganciclovir who developed neutropenia required dose reduction and four ultimately had to discontinue ganciclovir to resolve the neutropenia.

In the study of oral ganciclovir in children,[18] 22% had neutropenia (defined as an ANC <400 cells/μL), but an additional 13.9% had an ANC of 400–1200 cells/μL. This is similar to the less-frequent occurrence of this toxicity seen in adults. Again, this adverse event was not found to be dose-related but reversible on discontinuation of GCV.

As in adults, another adverse event seen in infants treated with IV ganciclovir[17] was thrombocytopenia; overall, 38% of children in this study developed platelet counts <50,000 cells/μL. Adult studies have reported about a 15% incidence of thrombocytopenia.[21] Only 2% of children in this study[17] developed anemia.

Another concern in adult studies is that of other laboratory abnormalities, including elevations in creatinine and liver-function test results. In the study by Whiteley et al.,[17] 68% of the infants studied had no changes in serum creatinine levels. Of those that had changes in serum creatinine levels, no child had more than a 0.5 mg/dL increase from baseline, and none developed a creatinine level >2.0 mg/dL. A total of 36% had increases in hepatic enzymes (AST >250 IU/dL and ALT >150 IU/dL) and 66% had elevations in direct bilirubin.

There are a host of other adverse events of ganciclovir reported primarily in adult patients, including CNS disturbances (including headache and psychosis) as well as fever and rash.[15] Data on the occurrence of these adverse events in children are lacking.

One concerning toxicity found with ganciclovir administration in animal studies is that of azospernia and the potential for permanent reproductive toxicity that may occur in males (and possibly females).[21] Preclinical studies have also demonstrated teratogenicity and mutagenicity in animals.[22] Thus, long-term concerns for impairment of fertility as well as carcinogenesis must be considered when treating children with ganciclovir, notwithstanding the fact that data regarding these toxicities in humans are incomplete.

2. Valganciclovir

2.1 Mechanism of Action

Valganciclovir is an L-valine ester prodrug of ganciclovir developed to increase the bioavailability of orally administered ganciclovir[23] and to avoid the inconvenience and risks associated with IV administration and catheter-related complications. Oral ganciclovir has a bioavailability of only 6%,[23] whereas valganciclovir has been shown to have a 10-fold increased bioavailability over this (~60%) in adult studies.[23]

After ingestion, valganciclovir is transported from the intestine to the bloodstream by a peptide transporter, and subsequently liver and intestinal esterases rapidly convert valganciclovir to ganciclovir. The mechanism thereafter is assumed to be as described for ganciclovir.

2.2 Formulations

Currently, valganciclovir is commercially available only as a hydrochloride in a 450 mg tablet form. Although there is a suspension formulation in development, it is not available at this time, and there are no current US FDA-approved indications for the use of valganciclovir in children. Extemporaneous preparations have been proposed and found to be stable for up to a month when refrigerated;[24] however, use of these compounded solutions is controversial and not generally recommended given the potential lack of consistency in the formulation and the potential variability in their preparation. Although not yet commercially available, a pharmaceutical grade suspension of valganciclovir is currently being evaluated.[25,26]

2.3 Pharmacokinetics in Infants

As with most newly introduced medications, the majority of available PK data for valganciclovir thus far are derived from
studies in adults. In these studies, concentrations of valganciclovir have been found to be transient: the mean t\textsubscript{1/2} is <1 hour after dose administration, and ganciclovir C\textsubscript{max} usually occurs 2–3 hours after administration. Studies in adults have shown that although the drug is well absorbed, a high-fat meal increases the AUC by 24–56%; therefore, it is recommended that ganciclovir be administered with food. These PK data in adults have shown that valganciclovir 900 mg/day achieves similar AUC to the standard ganciclovir 5 mg/kg/day maintenance dose.[27]

There are several individual case reports of infants treated with valganciclovir compounded as a suspension for the treatment of congenital CMV or CMV disease in the perinatal period;[28–31] however, few PK studies exist in the pediatric population in general. Most reports of the use of valganciclovir in children have been either in patients with HIV infection or in those immunocompromised after transplantation.

In the first study examining valganciclovir plasma concentrations specifically in infants, eight neonates between the ages of 4 and 90 days with symptoms of CNS involvement of congenital CMV infection were studied.[32] After an initial first week of IV ganciclovir treatment (5 mg/kg every 12 hours), the parents of these infants refused to consent to central catheter placement for the additional 5 weeks of therapy; thus, oral ganciclovir (as a compounded suspension) was initiated. Based on reports of 40–60% bioavailability of ganciclovir from valganciclovir,[31,33] the first four infants enrolled received valganciclovir 15 mg/kg once daily. This dose resulted in low plasma concentrations of ganciclovir and the next four infants accordingly received valganciclovir 15 mg/kg twice daily.

Trough (immediately before dosing) and peak (1 hour after IV ganciclovir and 1.5 hours after valganciclovir) plasma concentrations were obtained once drug concentrations were at a steady state (after 3 days for IV ganciclovir and after 7 days for oral valganciclovir).[33] Only the infants treated with valganciclovir 15 mg/kg twice daily had drug concentrations that were statistically not different from those for IV ganciclovir: a peak concentration of 3.1 µg/mL was measured in the valganciclovir-treated infants and a peak concentration of 1.95 µg/mL was measured in the IV ganciclovir-treated infants. In addition, this study demonstrated that the significant decrease in CMV viruria seen with IV ganciclovir therapy was similar to that seen with both dose levels of valganciclovir; however, the higher total dosage of 15 mg/kg twice a day resulted in less quantitative viral shedding compared with the lower dose of 15 mg/kg once a day.

In the largest study of valganciclovir in pediatric patients reported thus far, investigators from the NIAID CASG performed a phase I–II study of population PK in 24 neonates using the commercial oral suspension of valganciclovir that is not yet available for clinical use.[33] This study was conducted in anticipation of the use of the oral preparation in studies designed to determine the optimal duration of therapy to achieve the best outcome in infants with CNS involvement with symptomatic congenital CMV infection.

In this study,[33] infants received some combination of IV ganciclovir and oral valganciclovir for 6 weeks. The first five patients (version 1) received 6 mg/kg of IV ganciclovir every 12 hours with interruptions on days 5–6 and days 35–36, at which time oral valganciclovir (14 mg/kg twice daily) was given with PK data collected on days 4, 6, 34, 35, and 36. Accrual in this initial version of the study was difficult, resulting in only five patients over a 22-month period. Accordingly, a second version of the study was commenced to enrol greater numbers. Over the next 11 months, 19 more infants were enrolled in the more permissive (version 2) protocol: infants received a single dose of valganciclovir followed by serial blood sampling to assess PK data, and were then started on IV ganciclovir for 2 weeks. PK data on IV ganciclovir (again administered at 6 mg/kg every 12 hours) were obtained after the second dose was given. After the infants had received 2 weeks of IV therapy and their PK data on the initial oral valganciclovir had been analyzed, the infants began 4 weeks of oral therapy at home.

During the oral valganciclovir phase, samples were obtained 1 week and 2 weeks after starting this therapy; dosing started at 14 mg/kg but could be changed based on the PK determinations for each infant.[33] The goal of therapy for this version was an AUC from time 0 to 12 h (AUC\textsubscript{12}) of 27 mg·h/L, based on the pilot study by Trang et al.[12] Data from both versions were analyzed together.

In version 2, nine patients received 14 mg/kg/dose, six received 16 mg/kg/dose, and four received 20 mg/kg/dose, all twice daily.[33] All PK data were consistent with a one-compartment model, and bodyweight was the most significant factor (postnatal age, sex, and body surface area did not provide different information once weight was taken into account). Overall, the findings of this study were very comparable to previous studies of IV ganciclovir PK. Previous studies of infants receiving 6 mg/kg of IV ganciclovir reported an AUC (AUC to time infinity by the trapezoidal rule) of 27 mg·h/L,[33] and, in adults, 5 mg/kg of IV ganciclovir provided an AUC of 25.4 mg·h/L.[33] In the study by Acosta et al.[33] 6 mg/kg of IV valganciclovir provided an AUC of 21 mg·h/L and 16 mg/kg of valganciclovir suspension provided an AUC of 27 mg·h/L. Thus, a 16 mg/kg dose of the pharmaceutical grade valganciclovir
suspension twice daily appears to adequately establish ganciclovir concentrations similar to those achieved with the 6 mg/kg twice daily IV ganciclovir formulation.

Another important finding of this study was that in this population of neonates, valganciclovir demonstrated an overall 54% bioavailability. In another evaluation of valganciclovir tablets, a bioavailability of 43% was found in a 6-year-old child. Adult data have demonstrated a bioavailability of 60%, and it is therefore important to recognize that drug availability might not be equivalent in this younger population, at least until further data are obtained.

In a recent publication by Kimberlin et al., additional PK data from the same infants evaluated in the previous report showed that in the five infants treated with IV ganciclovir the AUC12 for ganciclovir was reduced by almost one-half (41% reduction), whereas the CL of IV ganciclovir nearly doubled (73% increase) in the first 6 weeks of life. By contrast, only a small decrease in AUC12 was seen with oral valganciclovir (15% decrease) over the same time period. The investigators attributed this relative stability in AUC12 to the increase in drug bioavailability (32% increase) that occurred during this time when a concurrent increase in CL was also taking place.

Given the significant impact of CMV disease on transplant patients, many pediatric transplant centers are using valganciclovir both prophylactically and therapeutically in their patients because of the need for long-term therapy and the advantage of oral formulations. The majority of the published studies in these groups of patients are in older children and therefore outside the neonatal/infant age group pertinent to this review. However, given the differences in some of the data that have been reported, it is important to note that the PK of both ganciclovir and valganciclovir in this special population may differ somewhat from the studies reviewed here and this may also impact infant dosing in this clinical situation.

In a review of 20 children post-solid organ transplant (mostly renal transplants, mean age 8.6±5.5 years), 15 of whom were treated with oral valganciclovir, a similar bioavailability compared to that mentioned previously for valganciclovir of 42% was found. Despite the similarity to previously reported data, this study, together with another that preceded it (also in pediatric renal transplant patients), found significant interpatient variability in ganciclovir concentrations, as high as 83%, with valganciclovir. Even when comparing the findings of these two studies with one another, trough concentrations of IV ganciclovir administered at the same dose varied by over 70% between the populations. The major difference in these studies was the mean age of the patients; the study reporting the lower measured troughs evaluated children with a mean age of 4.5±3.1 years whereas the study reporting the higher troughs studied children with a mean age of 11.0±3.9 years. In addition to the age of the patient acting as a major factor in drug concentration and PK variability, the authors of these studies also suggested that variable function of the transplanted kidney (sometimes from an adult donor) plus significant potential drug-drug interactions in these post-transplant patients may significantly alter disposition of valganciclovir (as well as ganciclovir and other antivirals) from what is expected.

Although not yet available, results from studies of the pharmaceutical grade oral suspension of valganciclovir in general appear to be promising. While such studies have also been conducted primarily in the pediatric transplant population, recent reports suggest that the safety and overall PK of the suspension are bioequivalent to those of the tablet formulation.

2.4 Toxicity and Adverse Events

The toxicity and adverse events of valganciclovir seen in adults are essentially the same as those for ganciclovir, given that valganciclovir is a prodrug of the latter. In individual case reports of the use of valganciclovir in neonates and infants, toxicities have varied from none to neutropenia (after 5 weeks of therapy on 15 mg/kg three times daily in a 7-month-old). In a retrospective review of pediatric liver transplant recipients (mean age 4.9±5.6 years) who received valganciclovir 15-18 mg/kg/day for 100 days post-operatively for CMV prophylaxis, no CMV disease was encountered and no valganciclovir-related toxicities were reported.

In the recently published valganciclovir PK study by Kimberlin et al., of the 24 infants enrolled, 38% (n=9) developed grade 3 or 4 neutropenia on therapy (seven developed grade 3; two developed grade 4). Of these nine infants, one required dose adjustment and one required discontinuation of the drug. Other toxicities seen included grade 3 anemia in 13%; grade 3 hyperbilirubinemia in 1%; and grade 3 increased ALT in 1%.

3. Foscarnet

3.1 Mechanism of Action

Foscarnet (trisodium phosphonoformate) is an inorganic pyrophosphate analog that binds reversibly to viral DNA polymerase and blocks cleavage of the pyrophosphate from deoxynucleotide triphosphates, thus halting DNA chain elongation.
Since foscarnet has a higher affinity for viral polymerase, inhibition of host DNA polymerase requires 100-fold greater concentrations of the drug. Unlike ganciclovir, foscarnet requires no modifications once in the host to become active.

3.2 Spectrum of Activity

Foscarnet has been shown to be active in vitro against many members of the herpesvirus family, including HSV-1 and -2, CMV and VZV. It also has activity against hepatitis B, and given that it may also inhibit reverse transcriptase, it is also active against HIV, although it is rarely used clinically to treat these viruses.

3.3 Mechanism of Resistance

Unlike ganciclovir (and valganciclovir), foscarnet does not require activation (phosphorylation) by the viral kinase; therefore, resistance to these agents via UL97 mutations does not result in cross-resistance to foscarnet. Since all current antivirals active against CMV ultimately act on the viral DNA polymerase as an end-target, mutations in the region encoding this enzyme could potentially confer resistance to any of these antivirals, and certain patterns of resistance have been seen. Although less common than the well recognized cross-resistance that can be seen between ganciclovir and cidofovir, cross-resistance between foscarnet and cidofovir has also recently been described.

3.4 Formulations and Administration

Given its poor bioavailability, foscarnet can be administered only as an IV formulation; it is available as a solution in a concentration of 24 mg/mL. Careful administration is required, at a rate not exceeding 1 mg/kg/minute, and dilution is required for peripheral administration. Given the renal complications that may occur (see section 3.6), prehydration with normal saline or 5% dextrose in water is recommended. Careful attention must also be made to solutions being administered concurrently: foscarnet is incompatible with lactated ringsers, total parenteral nutrition (TPN), vancomycin, or any solutions containing calcium or magnesium. Currently, there are no FDA-approved indications for the use of foscarnet in pediatric patients.

3.5 Pharmacokinetics

PK data on foscarnet derive almost exclusively from adult studies as no such studies in infants or children have been reported to date. There are numerous small case series or reports of children who have been treated with foscarnet, usually in the case of presumed or proven infection with CMV, VZV, or HSV, and most have had fairly favorable outcomes. However, most of these children have been older, and most have been immunocompromised by chemotherapy or stem-cell transplantation; therefore, evaluation of foscarnet toxicities is difficult in light of concurrent disease and therapies. The only report of foscarnet use in a neonate with congenital CMV disease and extensive liver pathology resulted in a favorable outcome.

Data from adult studies have shown that 80% of the administered foscarnet dose is renally excreted metabolically unchanged, indicating that dose adjustments for any degree of renal impairment must be made. Roughly 20% of the administered drug is taken up into bone and cartilage and this may have serious implications, particularly for pediatric patients. The t½ of foscarnet has been estimated at 48 hours, and although data regarding tissue distribution are lacking, cerebrospinal fluid levels are about two-thirds of serum concentrations.

3.6 Toxicity and Adverse Events

The most significant and worrisome toxicities associated with foscarnet are renal insufficiency and electrolyte disturbances. In adult studies, 27% of AIDS patients receiving foscarnet experienced a decrease in renal function, most likely as a result of renal tubular damage. This adverse finding most often occurs 6–15 days after starting on the medication and is reversible in patients with normal underlying renal function; thus, frequent monitoring of renal function tests (creatinine, blood-urea nitrogen) is prudent. Occasionally this tubular dysfunction may manifest as nephrogenic diabetes insipidus without evidence of rising creatinine levels; therefore, monitoring for clinical symptoms, such as polyuria and polydipsia, is also recommended. Careful attention to hydration status appears to limit renal toxicities significantly.

Electrolyte abnormalities also occur quite frequently in patients taking foscarnet, and these also must be carefully and continually monitored. Hypocalcemia occurs often and is most likely due to complex formation between free calcium and the drug (thus, foscarnet may not be co-administered with TPN or other calcium-containing solutions such as vancomycin). Additionally, hypomagnesemia may occur (contributing to the hypocalcemia and also to hypokalemia) in addition to hypo- or hyperphosphatemia.

About 10% of adult AIDS patients treated with foscarnet were reported to have developed seizures; however, many of these were due to electrolyte abnormalities, impaired renal...
function, or a baseline seizure disorder. This adverse event, like many others noted for foscarnet as well as cidofovir, is difficult to evaluate because most patients treated with these agents have significant underlying disease states and are taking concurrent medications that may have played a role in toxicity. As a significant portion of the administered dose of foscarnet deposits in bone and cartilage, the potential for bone and dental toxicity is a significant concern, particularly for the pediatric population.

4. Cidofovir

4.1 Mechanism of Action

Cidofovir (HPMPC, or 1-(S)-3-hydroxy-2-(phosphonomethoxy)-propylcytosine dihydrate) is a monophosphate nucleotide analog of cytosine. Once inside the host cell, cidofovir must undergo diphosphorylation via cellular enzymes. Because the drug is itself a phosphonate, cidofovir is not dependent on viral kinases as is ganciclovir. Once diphosphorylated to its active state, cidofovir acts to competitively inhibit incorporation of host deoxyctydine into the viral DNA by viral DNA polymerase. Once incorporated into the DNA chain, cidofovir significantly impairs further chain elongation, and incorporation of two consecutive diphosphorylated cidofovir molecules halts DNA synthesis.

4.2 Spectrum of Activity

Cidofovir has in vitro antiviral activity against a very broad spectrum of DNA viruses. It has demonstrated activity against all of the human herpesviruses as well as numerous animal herpesviruses, and its activity against guinea pig CMV has facilitated studies of its use in the potential prevention of congenital disease because this animal model is used in the study of maternal-fetal transmission of CMV.

Additionally, cidofovir has been shown to have activity against poxviruses, polyomaviruses, papovaviruses, and adenoviruses. As a systemic agent, it has historically been used most often to treat CMV, particularly CMV retinitis in AIDS patients or in refractory or resistant infections. More recently, it has increasingly been used to treat some other viral infections, particularly when they are life threatening.

4.3 Mechanism of Resistance

As with foscarnet and less frequently with ganciclovir, mutations in viral DNA polymerase may confer resistance to cidofovir. Resistance via this mechanism may often occur concurrently with ganciclovir resistance. Since cidofovir does not require phosphorylation by the CMV phosphotransferase, viral resistance to ganciclovir via these mutations does not imply cross-resistance to cidofovir.

4.4 Formulations and Administration

Cidofovir is available only as an IV solution at a concentration of 75 mg/mL. Similar to foscarnet, patients must be well hydrated prior to cidofovir administration to minimize renal complications. In adults, prehydration with 1 L of normal saline is generally recommended, and, if the patient is able to tolerate it, again 2–3 hours after the infusion. Because there are no FDA-approved indications for use of cidofovir in children, these recommendations must be adjusted by each practitioner according to the size of the patient.

4.5 Pharmacokinetics

As with foscarnet, PK data for cidofovir in children are extremely limited, and information regarding the disposition of the drug derives from adult literature, mostly on immunocompromised patients.

Most (over 80%) of the drug is renally excreted unchanged within 24 hours after administration. There is an active metabolite, cidofovir diphosphate, which is eliminated more slowly in a diphasic manner, with a first phase intracellular t1/2 of 24 hours and a second phase intracellular t1/2 of 65 hours. Because of the slow elimination of this metabolite, cidofovir is able to be administered every 2 weeks. One report of a single pediatric cancer patient (age not given) found significantly greater CL of cidofovir (with a resultant markedly reduced t1/2 and Cmax), which suggests that pediatric patients may require higher doses. However, further investigation is required.

4.6 Toxicity and Adverse Events

As with foscarnet, the most commonly encountered toxicity found with cidofovir administration is renal impairment, which is seen in approximately 50% of adults in clinical trials. This effect may initially manifest as proteinuria, increased serum creatinine, or a Fanconi-type syndrome (proteinuria, glycosuria, bicarbonate wasting), and may result in permanent renal impairment or failure. Thus, great care must be taken when administering cidofovir to individuals with proteinuria and/or elevated creatinine levels at baseline, or to patients taking concurrent nephrotoxic medications.
In one case series of pediatric stem-cell transplant patients (median age [range] 10 [2–14] years), ten patients received the dose recommended for adult patients\(^7\). Only one patient demonstrated renal toxicity, and he had concurrent, significantly elevated tacrolimus concentrations that may have served as a predisposing impairment.

Two interventions have been recommended in attempts to prevent this renal toxicity: hydration and probenecid administration. Hydration, preferably with normal saline, before and after cidofovir administration is recommended and has been shown to significantly reduce renal toxicity.\(^8\) Probenecid, which blocks active renal tubular secretion, prevents drug uptake into the proximal tubular epithelial cells and hence drug-induced damage. In this way, probenecid also acts to slow renal excretion of the drug and maintain drug concentrations.\(^9\) Probenecid should be given prior to as well as after cidofovir administration and may itself cause nausea/vomiting and/or rash.

As with foscarnet, careful monitoring of renal function, including proteinuria, glycosuria, and serum creatinine levels, should be performed prior to each subsequent dose of cidofovir. Renal dysfunction is usually reversible with discontinuation of the drug; however, permanent renal impairment has been seen in several HIV-infected patients.\(^6\)

Other toxicities seen with cidofovir include neutropenia, metabolic acidosis, and ocular hypotony.\(^6\) The frequency of neutropenia seen with cidofovir (approximately 20% of patients) has been difficult to assess as direct drug toxicity since CMV disease itself often produces low white blood cell counts.

Also similar to ganciclovir, animal data have shown that cidofovir has carcinogenic and teratogenic potential.\(^11\) Additionally, cidofovir also has been found to cause hypospermatism in these preclinical studies. Although there is no evidence of these effects in humans at this time, these findings indicate that care should be taken when administering the drug to children.

### 5. Dose Recommendations

Formulating dose recommendations for children for the antivirals discussed in this review is difficult because of the paucity of available data. Table II represents the best current recommendations for neonates and infants, with doses for ganciclovir being dose- and weight-dependent and those for foscarnet being based on weight alone.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and administration</th>
<th>Notes</th>
<th>Approved Indications</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir (IV)</td>
<td>6 mg/kg IV every 12 h</td>
<td>Monitor complete blood count weekly (neutropenia, thrombocytopenia, rarely anemia); monitor liver enzymes; requires dose adjustment for renal impairment</td>
<td>Life- or sight-threatening infections in immunocompromised patients; prophylaxis in immunocompromised patients*</td>
<td>17</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>16 mg/kg PO every 12 h(^a)</td>
<td>Same as for ganciclovir</td>
<td>None</td>
<td>25, 26</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>60 mg/kg IV every 8 h or 90 mg/kg every 12 h for 14–21 d (induction) then 50–120 mg/kg every 24 h (maintenance)</td>
<td>Prehydrate with normal saline; monitor renal function carefully during therapy; monitor electrolytes including potassium, phosphate, calcium; requires dose adjustment for renal impairment (creatinine clearance ≤1.4 mL/kg/min)</td>
<td>None</td>
<td>No established guidelines for pediatric dosage and administration</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>5 mg/kg IV daily for 2 wk (induction) then 5 mg/kg every other wk (maintenance)</td>
<td>Monitor renal function carefully during therapy; requires dose adjustment for renal impairment (serum creatinine &gt;1.5 mg/dL; creatinine clearance ≤55 mL/min, urine protein &gt;100 mg/dL [≥2+ protein]); probenecid should be administered prior to dose</td>
<td>CMV retinitis</td>
<td>No established guidelines for pediatric dosage and administration</td>
</tr>
</tbody>
</table>

\(^a\) Although not approved, many experts consider symptomatic congenital CMV infection with CNS involvement an indication for IV ganciclovir therapy.

\(^b\) Recommendations are for the pharmaceutical grade suspension only.

**Table II. Dosage and administration recommendations for antivirals against cytomegalovirus (CMV) in neonates/infants**

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and valganciclovir (pharmaceutical grade suspension) being best supported by data in this subgroup of pediatric patients in the setting of congenital CMV infection. Dose information for foscarnet and cidofovir, which are clearly second-line agents for anti-CMV therapy, is based on recommendations for the treatment of adults with HIV infection.

6. Conclusion

Although antiviral options for children with CMV disease have progressed significantly over the past several decades, data regarding the disposition and, thus, optimal dosing for this population, particularly with respect to second-line drug options, are still lacking. It is fortunate that advances have been made with these data for the first-time therapy of IV ganciclovir in children, and more recently for the more desirable oral formulation valganciclovir. However, the potential need for alternative therapies such as cidofovir and foscarnet still exists because of the ever-advancing field of transplantation, the growing number of children living with HIV infection, and the fact that both of these groups are expanding to include infants.

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References


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