SciMedCentral

Journal of Drug Design and Research

Review Article

Clinical Pharmacology of Aciclovir in Infants and Children

Gian Maria Pacifici*

Associate Professorof Pharmacology, Italy

***Corresponding author**
Gian Maria Pacifici,Associate Professorof Pharmacology,via Sant'Andrea 32,56126 Pisa,Italy,
Email: pacifici44@tiscali.it

Submitted: 24 March 2021

Accepted: 09 April 2021

Published: 12 April 2021

ISSN: 2379-089X

Keywords
- Aciclovir
- Breast-milk
- Dosing
- Placental-transfer
- Prophylaxis
- Treatment

Abstract

Aciclovir is an acyl guanine nucleoside analogue that lacks the 2' and 3' positions normally supplied by ribose. Aciclovir is the prototype of a group of antiviral agents that are nucleoside congeners that are phosphorylated intracellularly by a viral kinase and subsequently by host cell enzymes to become inhibitors of viral DNA synthesis. Aciclovir is most active against herpes simplex virus-1 and has been used to treat varicella zoster and Epstein-Barr viruses. The intravenous dose of acyclovir is 30 mg/kg thrice-daily in infants. In children the dose varies according to the virus to be treated and the oral dose ranges from 200 to 800 mg 4 or 5 times-daily to treat varicella zoster infection and increases with child age. Aciclovir elimination half-life ranges from about 10 to 3 hours in infants, decreases with infant maturation, and in children it is about 1.5 hours. Aciclovir interacts with drugs and may induce nephrotoxicity. The treatment and the prophylaxis with aciclovir have been extensively studied in infants and children. Aciclovir penetrates into the cerebrospinal fluid in significant amounts and cured encephalitis caused by herpes simplex virus and meningitis due to herpes zoster virus. This drug crosses the placenta and migrates into the breast-milk. The aim of this study is to review of acyclovir dosing, efficacy, safety, adverse-effects, pharmacokinetics, metabolism, drug-interactions, toxicity, treatment, prophylaxis, penetration into the cerebrospinal fluid, treatment of meningitis, in infants and children, placental transfer, and migration into the breast-milk.

INTRODUCTION

Aciclovir is an acyl guanine nucleoside analogue that lacks the 2' and 3' positions normally supplied by ribose. Aciclovir is the prototype of a group of antiviral agents that are nucleoside congeners that are phosphorylated intracellularly by a viral kinase and subsequently by host cell enzymes to become inhibitors of viral DNA synthesis.

MECHANISM OF ACICLOVIR ACTION IN LOW CASE

Aciclovir inhibits viral DNA, its selectivity of action depends on interaction with herpes simplex virus thymidine kinase and thus occurs only in the cells infected with the virus. The affinity of aciclovir for herpes simplex virus thymidine kinase is about 200 times greater than for the mammalian enzyme. Cellular enzymes convert the monophosphate to aciclovir triphosphate, which competes for endogenous dGTP. The immunosuppressive agent mycophenolate mofetil potentiates the antiherpes activity of aciclovir and related agents by depending intracellular dGTP pools. Aciclovir triphosphate competitively inhibits viral DNA, where it acts as chain terminator because of the lack of a 3'-hydroxyl group. By a mechanism termed suicide inactivation, the terminated DNA template containing aciclovir binds to the viral DNA polymerase and leads to its irreversible inactivation [1].

Absorption, distribution, metabolism and excretion of aciclovir

The oral bioavailability of aciclovir is about 10 to 30% and decreases with increasing dose. Delivery of an oral dose can be enhanced by administration of the prodrug form valaciclovir. Valaciclovir is an esterified version with higher bioavailability (55 to 70%) than aciclovir; desertification occurs rapidly and nearly completely following an oral administration. Unlike aciclovir, valaciclovir is a substrate for intestinal and renal peptide transporters. Aciclovir distributes widely in body fluids, including vesicular fluid, aqueous humor, and cerebrospinal fluid (see references 40-42]. Compared to plasma salivary concentrations are low, and concentrations in vaginal secretion vary widely. Aciclovir is concentrated in beast-milk (see references 48-52), amniotic fluid, and placenta (see references 46, 47). Newborn plasma concentrations are similar to maternal ones. Percutaneous absorption of aciclovir after topical administration is low. Renal excretion of non-metabolized aciclovir by glomerular filtration and tubular secretion is the principal route of elimination. The elimination half-life is about 2.5 hours (range, 1.5 to 6) in adults with normal renal function. In infants, the elimination half-life is about 4 hours (see the reference 15) and increases to 20 hours in anuric infants [1].

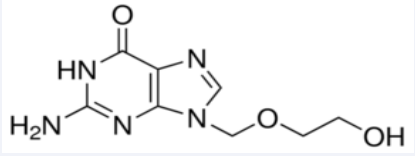

Figure 1 Aciclovir molecular structure (molecular weight = 225.20 grams/mole).

Therapeutic uses of aciclovir

Aciclovir's clinical use is mainly limited to herpesviruses. Aciclovir is most active against herpes simplex virus-1 (effective plasma concentration ranges from 0.02 to 0.9 μg/ml), approximately half as active against herpes simplex virus-2 (effective plasma concentration ranges from 0.03 to 2.2 μg/ml), a tenth as potent against varicella zoster virus (effective plasma concentration ranges from 0.8 to 4.0 μg/ml), and Epstein-Barr virus, and least active against cytomegalovirus (effective plasma concentration > 20 μg/ml) and human herpesvirus [6]. Uninfected mammalian cell growth generally is unaffected by high aciclovir concentrations (> 50 μg/ml). In immunocompetent people, the clinical benefits of aciclovir and valaciclovir are greater in initial herpes simplex virus infections than is recurrent ones. These drugs are particularly useful in immunocompromised patients because these individuals experience both more frequent and more severe herpes simplex virus and varicella zoster virus infections. Because varicella zoster virus is less susceptible than herpes simplex virus to aciclovir, higher doses must be used for treating varicella zoster virus. Oral valaciclovir is as effective as oral aciclovir in herpes simplex virus infections and more effective for treating herpes zoster virus. Aciclovir is ineffective therapeutically in established cytomegalovirus infections, but ganciclovir is effective in cytomegalovirus prophylaxis in immunocompromised patients. Epstein-Barr virus-related oral hairy leukoplakia may improve with aciclovir. Oral aciclovir in conjugation with systemic corticosteroids appears beneficial in treating Bell palsy; valaciclovir is ineffective in acute vestibular neuritis [1].

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "aciclovir dosing infants, children", aciclovir efficacy, safety infants, children", "aciclovir adverse-effects infants, children", "aciclovir pharmacokinetics infants, children", "aciclovir metabolism", "aciclovir drug interactions", "aciclovir toxicity infants, children", "aciclovir treatment infants, children", "aciclovir prophylaxis infants, children", "aciclovir penetration into the cerebrospinal fluid", "aciclovir treatment of meningitis infants, children", "aciclovir placental transfer", and "aciclovir migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] were consulted.

RESULTS

Administration schedule of aciclovir to infants [2]

Dose: The standard regimen for aciclovir, irrespective of prematurity, is 30 mg/kg thrice-daily given intravenously. The dose frequency may be adjusted in premature infants as follows: 20 mg/kg intravenously twice-daily in infants with a postmenstrual age < 30 weeks; thrice-daily in infants with 30 to 35 weeks of postmenstrual age; 4 times-daily in infants of ≥ 36 weeks of postmenstrual age. However, this proposed dosing guidance needs prospective validation and safety analysis. In infants older than three months of age, dosing changes from a weight related dose to that of surface area and the dose for these infants is 250 mg/m^2 thrice-daily, doubled to 500 mg/m^2 in the immunocompromised infants or in herpes simplex encephalitis. The dosing interval must be at least doubled if there is renal failure.

Duration of therapy. Treat chickenpox for one week, and neonatal herpes simplex infection for two weeks if there is only skin, eye, and/or mouth disease but increase this to three weeks in all other cases (especially if there could be central nervous system involvement it is essentially to confirm that the cerebrospinal fluid is negative for herpes simplex virus before stopping treatment). Long-term oral suppression treatment in surviving infants with central nervous system herpes simplex can be given 300 mg/m^2 of body-surface area thrice-daily for six months.

Eye ointment. Apply five times-daily under ophthalmic supervision until three days after resolution is complete.

Adverse-effects and precautions: Neutropenia occurs in approximately 20% of infants. Phlebitis may occur at intravenous site due to alkaline pH of 10. Risk of transient renal dysfunction and crystalluria is minimized by slow infusion rate and adequate infant hydration. Resistant viral strains may emerge during long-term therapy; these infants are at high risk for progressive life-threatening disease. Aciclovir is incompatible with fat emulsion, aztreonam, caffeine citrate, caspofungin, cefepime, dopamine, meropenem, and piperacillin-tazobactam [3].

Administration schedule of aciclovir to children [3]

Oral suppression of herpes simplex virus:

- **Children aged 12 to 17 years.** Give: 400 mg twice-daily, alternatively 200 mg 4 times-daily; increase the dose to 400 mg thrice-daily. The dose may be increased if recurrences occur on standard suppressive therapy of for suppression of genital herpes during pregnancy (from 36 weeks gestation), the therapy interrupted every 6 to 12 months to reassess recurrences frequency, consider restarting after two or more recurrences.

Oral treatment of herpes simplex virus and prophylaxis in immunocompromised children:

- **Children aged 1 to 23 months.** Give: 100 to 200 mg 4 times-daily.
- **Children aged 2 to 17 years.** Give: 200 to 400 mg 4 times-daily.

Oral treatment of herpes simplex virus:

- **Children aged 1 to 23 months.** Give: 100 mg 5 times-daily for 5 days (longer treatment if new lesions appear during treatment of if healing incomplete).
- **Children aged 2 to 17 years.** Give: 200 mg 5 times-daily usually for 5 days (longer treatment if new lesions appear during treatment of if healing incomplete).

Intravenous treatment of herpes simplex virus

Children aged 1 to 2 months. Give: 20 mg/kg thrice-daily for 14 days (for at least 21 days if central nervous system is involved.

Confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment).

Children aged 2 to 17 years. Give: 5 mg/kg thrice-daily usually for 5 days.

Oral treatment of herpes simplex virus in immunocompromised or if the absorption is impaired

Children aged 1 to 23 months. Give: 200 mg 5 times-daily usually for 5 days (longer treatment if new lesions appear during treatment or if healing incomplete).

Children aged 2 to 17 years. Give: 400 mg 5 times-daily usually for 5 days (longer treatment if new lesions appear during treatment or if healing incomplete).

Intravenous treatment in immunocompromised children or in herpes simplex virus encephalitis

Children aged 3 months to 11 years. Give: 500 mg/m^2 thrice-daily usually for 5 days (given for at least 21 days in encephalitis. Confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment).

Children aged 12 to 17 years. Give: 10 mg/kg thrice-daily usually for 5 days (given for at least 14 days in encephalitis and for at least 21 days if also immunocompromised. Confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment).

Oral treatment of varicella zoster virus (chickenpox), herpes zoster virus (shingles)

Children aged 1 to 23 months. Give: 200 mg 4 times-daily for 5 days.

Children aged 2 to 5 years. Give: 400 mg 4 times-daily for 5 days.

Children aged 6 to 11 years. Give: 800 mg 4 times-daily for 5 days.

Children aged 12 to 17 years. Give: 800 mg 5 times-daily for 7 days.

Intravenous treatment of varicella zoster virus (chickenpox), herpes zoster virus (shingles)

Children aged 1 to 2 months. Give: 10 to 20 mg/kg thrice-daily for at least 7 days.

Children aged 3 months to 11 years. Give: 250 mg/m^2 thrice-daily usually for 5 days.

Children aged 12 to 17 years. Give: 5 mg/kg thrice-daily usually for 5 days.

Intravenous treatment of varicella zoster virus (chickenpox), in immunocompromised children, of herpeszostervirus(shingles)inimmunocompromised children

Children aged 3 months to 11 years. Give: 500 mg/m^2 thrice-daily usually for 5 days.

Children aged 12 to 17 years. Give: 10 mg/kg thrice-daily usually for 5 days.

Oral treatment of varicella zoster virus (shingles) in immunocompromised children

Children aged 1 to 23 months. Give: 200 mg 4 times-daily continued for 2 days after crusting the lesion.

Children aged 2 to 5 days. Give: 200 mg 4 times-daily continued for 2 days after crusting the lesion.

Children aged 6 to 11 years. Give: 800 mg 4 times-daily continued for 2 days after crusting the lesion.

Children aged 12 to 17 years. Give: 800 mg 5 times-daily continued for 2 days after crusting the lesion.

Intravenous treatment of herpes zoster virus and varicella zoster virus in encephalitis

Children aged 1 to 2 months. Give: 10 to 20 mg/kg thrice-daily for 10 to 14 days in encephalitis, possibly longer if also immunocompromised.

Children aged 3 months to 11 years. Give: 500 mg/m^2 trice-daily given for 10 to 14 days in encephalitis, possibly longer id also immunocompromised.

Children aged 12 to 17 years. Give: 10 mg/kg thrice-daily given for 10 to 14 days in encephalitis, possibly longer if also compromised.

Oral treatment of varicella zoster virus (chickenpox), attenuation of infection if varicella zoster virus immunoglobulin not indicated

Children. Give: 10 mg/kg 4 times-daily for 7 days, to be started 1 week after exposure.

Efficacy and safety of aciclovir in infants and children

Eight-nine infants, aged 4 months, suffering from herpes simplex virus were treated with aciclovir intravenously at a dose of 60 mg/kg daily for ≥ 14 days. This treatment was found efficacy and safe, the adverse-effects were common but were not severe and many of the adverse-effects were related to the underlying infection rather than due to aciclovir exposure [5]. Infants, aged ≤ 28 days, had infection caused by herpes simplex virus in the central nervous system (N = 28), or disseminated infections which occurred in 41 infants or skin, eyes, or mouth infection (N = 10) who were treated with aciclovir intravenously at 30, or 45, or 60 mg/kg daily, respectively. The use of aciclovir at a dose of 60 mg/kg for treating central nervous system or disseminate infections was found efficacy and safe [6]. The prodrug valaciclovir was administered at an oral dose of 1,000 mg daily and aciclovir was administered at an oral dose of 800 mg daily to children. Extensive sensitivity monitoring of herpes simplex virus isolates confirmed a very low rate of aciclovir resistance among immunocompetent children (< 0.5%). The incidence of resistance among immunocompromised children remained low at about 5%. Both valaciclovir and aciclovir treatments were found safe and efficacy for curing the infection caused by herpes simplex virus [7]. Polish children, infected by varicella zoster virus or by herpes simplex virus were treated with high dose of aciclovir. In immunocompetent children with varicella zoster or herpes simplex infection received oral aciclovir to treat genital,

skin, severe gingivostomatitis, paronychia, and pharyngitis. Intravenous aciclovir should be administered for treating these infections in immunocompromised children. The treatment was efficacy and safe but neurological complications were observed in some children [8].

Adverse-effects caused by aciclovir in infants and children

Sixteen infants suffering from herpes simplex virus infection in the central nervous system and/or disseminated infection received oral aciclovir therapy for two years. During this treatment, 5 children (31.2%) had brief recurrences of dermal lesions, and none had evidence of neurologic deterioration. A minority of these infants exhibited mild or significant development delays [9]. Fifty-one infants and children had proven herpes simplex encephalitis and were treated with aciclovir. The initial dose of aciclovir was incorrect in 38 cases (74.5%) and the median duration of intravenous aciclovir was 4 days (range, 1 to 21). Six children (11.8%) received a full course of aciclovir for 10 days and for more days was given to 14 children (27.4%) there appeared to be no real indication for starting aciclovir. The management of infants and children with suspected viral encephalitis appears hazard in many cases and guidance for the management of subjects with suspected viral encephalitis are needed [10]. Thirty-one children, aged 2 to 15 years, were infected by varicella infection and were treated with aciclovir. Eighteen children (58.1%) had moderate rash, six children (19.3%) had severe rash while seven children (22.6%) had a mild itch. Complications were noted in three children (6.9%) and included otitis media, pneumonia, and secondary bacterial infection of vesicular lesion. The use of oral aciclovir for treating varicella infection seems to limit new rash formation and the total duration of illness averaged to < 5 days [11]. Forty-nine children with neuropsychiatric symptoms and 44 children without neuropsychiatric symptoms were enrolled. Aciclovir-related neuropsychiatric were observed in 77 children. The characteristic curve analysis for 9-carboxymethoxymethylguanine, the main metabolite of aciclovir, demonstrated that the neuropsychiatric symptoms could be predicted with a sensitivity of 91% and a specificity of 93%. Thirty-nine of 49 children (79.6%) with neuropsychiatric symptoms showed levels exceeding this concentration compared to only three of the 44 children (6.8%) without neuropsychiatric symptoms (P-level < 0.001). Aciclovir exposure, aciclovir plasma concentration, creatinine clearance, and creatinine concentration were statistically significant predictor of adverse-effects caused by aciclovir in these children [12]. Seventy-two children, aged 1 to 6 years, had culture positive for herpes simplex virus and were treated with aciclovir at an oral dose of 15 mg/kg 5 times-daily. These children had oral skin lesions, fever, lesions around the mouth but not outside the oral cavity, eating and drinking difficulties, and these are the adverse-effects caused by aciclovir [13]. One-hundred-two children, aged 5 to 16 years, had varicella infection. Fifty children (49.0%) received aciclovir at doses 20 mg/kg (infants were aged 5 to 7 years), 15 mg/kg (infants were aged 7 to 12 years), and 10 mg/kg (infants were aged 12 to 16 years). The remaining 52 children received placebo. Treated children experienced cutaneous healing, and numerous lesions. Aciclovir did not significantly change the rate of varicella complications. Aciclovir recipients had lower geometric mean serum antibody titers to varicella zoster virus than their placebo counterparts 4 weeks after the onset of illness, but antibody titers in both groups were similar 1 year later [14].

Pharmacokinetics of aciclovir in infants

Sampson et al. [15] studied the pharmacokinetics of aciclovir in 28 preterm and term infants with postmenstrual, postnatal ages and body-weight of: 31 weeks (range, 25 to 41), 3 days (range, 1 to 30), and 1,295 grams (range, 578 to 5,720), respectively. Two studies contributed the data for the Sampson et al. [15] investigation. Aciclovir was administrated intravenously at a dose of 500 mg/m^2 thrice-daily (study 1) or 10 mg/kg twice-daily (study 2). The pharmacokinetic parameters of aciclovir (Table 1).

TBC = total body clearance. DV = distribution volume, %RSE = %relative standard error.*Relation between total body clearance and postmenstrual age. **Correlation coefficient between total body clearance and distribution volume.

This table shows that the distribution volume is larger than the water volume and there is a remarkable interindividual variability in the total body clearance and in the distribution volume (Table 2).

TBC = total body clearance. DV = distribution volume. Conc. 50_{ss} = concentration in the half of dosing interval at steady-state. This table shows that there is a remarkable interindividual variability in the pharmacokinetic parameters of aciclovir. In addition, the median empirical Bayesian post-hoc parameter estimates for the total body clearance, 0.278 L/h/kg, was within 10% of the typical population model estimate of 0.305 L/h/kg. Comparing the youngest and oldest postmenstrual age cohorts, the total body clearance increased 2.8-fold, the distribution volume estimates were unchanged, and the half-life estimates decreased 3.4-fold.

Tod et al. [16] investigated the pharmacokinetics of aciclovir 102 infants. Seventy-nine infants (77.4%) had postmenstrual, postnatal ages and body-weight of 15.4 months (range, 8.0 to 33.1), 5.4 months (range, 0.1 to 23.1), and 6.90 kg (range, 1.8 to 13.0), respectively, and received oral aciclovir at a dose of 21.7 to 32.6 mg/kg. Five infants (4.9%) had postmenstrual, postnatal ages and body-weight of 41.8 months (range, 34.7 to 79.9), 32.8 months (range, 25.7 to 70.9), and 13.6 kg (range, 11.0 to 16.0), respectively, and received oral aciclovir at a dose of 21.7 to 32.6 mg/kg. Eighteen infants (17.6%) had postmenstrual, postnatal ages and body-weight of 81.0 months (range, 10.0 to 213), 72.0 months (range, 3.0 to 204), and 17.8 kg (range, 2.4 to 62.0), respectively, and received aciclovir intravenously at a dose of 83 to 500 mg/m^2. Summarizes the pharmacokinetic parameters of aciclovir administered orally (Table 3).

TBC = total body clearance. F = bioavailability. DV = distribution volume. %CV = %coefficient of variation. The bioavailability of aciclovir is about 12%

This table shows that the distribution volume is larger than the water volume and there is a wide interindividual variability in the total body clearance and in the distribution volume.

Table 1: Final model and bootstrap pharmacokinetic parameters of aciclovir obtained in preterm and term infants.

			Bootstrap confidence interval		
Parameter	**Point estimate**	**%RSE**	**2.5%**	**Median**	**97.5%**
TBC (L/h/kg)	0.305	13.9	0.237	0.307	0.379
DV (I/kg)	2.80	14.8	1.82	2.80	3.67
*TBC, PMA	3.02	11.5	2.39	3.02	4.18
Interindividual variability (%coefficient of variation)					
TBC	52.8	36.2	35.6	53.2	84.4
DV	85.0	51.5	4.89	81.3	140
**TBC versus DV	0.98	45.7	0.62	1.00	1.02
Proportional residual variability (%coefficient of variation)					
---	34.5	35.0	21.2	32.0	43.3

Median and range of individual pharmacokinetic parameter post hoc estimates for aciclovir after intravenous administration, Tod et al [16] (Table 4).

TBC = total body clearance. DV = distribution volume. DVc = distribution volume obtained with one single compartment model. TBCd = total body clearance obtained with two compartments model. DVp = distribution volume obtained with two compartment model. %CV = %coefficient of variation. This table shows that there is a wide interindividual variability in the total body clearance and in the distribution volume.

Sullender et al. [17] explored the pharmacokinetics of aciclovir in 18 infants and children aged from 3 weeks and 24.3 years with a body-weight and body-surface area ranging from 3.8 to 24.3 kg and 0.25 to 0.90 m^2, respectively. Subjects were suffering for infections caused by herpes simplex virus or varicella zoster virus and aciclovir was administered orally at a dose of 300 or 600 mg/m^2 4 times-daily for 5 to 7 days. Blood samples were obtained at 6 times ranging from 1 to 8 hours. Summarizes the plasma concentration of aciclovir (Table 5).

m = months. y = years. [a]Samples were drown on day 2, 3 or 4 just before and 2 hours after the 2nd, 3rd or the 4th dose. [b]One patient received an extra dose on the last day 3.5 hours after the scheduled last dose; 4- to 8- hours points were excluded from the mean. [c]Data for one subject for whom there were substantial deviations from the protocol dosing regimen were excluded from the means.

This table shows that aciclovir is slowly eliminated in infants and children and there is a wide interindividual variability in aciclovir plasma concentration (Table 6).

m = months. y = years. Cl_{cr} = creatinine clearance. [a]One subject received an extra dose 3.5 hours after the last scheduled dose. The AUC was excluded from the mean calculation. [b]One subject was not included in the mean calculation because of substantial deviation from the protocol dose schedule. The elimination rate was indeterminable for one subject who had identical concentration at 3.0 hours and at the last sampling time (8.0 hours). Therefore, the time to peak concentration, AUC, and the elimination half-life were not included. [c]The data for one subject were insufficient for determination of the Kel; therefore, AUC and the elimination half-life were not reported; in this instance, the peak to plasma was set equal to the mean at consecutive time points (3.083 and 4.167) at which the peak concentration occurred.

This table shows the time to peak concentration occurs rapidly, and the elimination half-life is short.

Bomgaars et al. [18] investigated the pharmacokinetics of aciclovir following oral valaciclovir in 32 immunocompromised children aged 9 years (range, 3 to 18), weighing 31 kg (range, 13 to 103), and having a body-surface area of 1.07 m^2 (range, 0.6 to 2.33). Children in study A received a single dose of valaciclovir of 15 mg/kg (maximum dose was 2 grams) and children in study B were treated with valaciclovir at a dose of 45 mg/kg daily (maximum dose was 6 grams daily) for 5 to 10 years (Table 7).

This table shows that the peak concentration of aciclovir occurs rapidly (129 min, thus 2.1 hours), the distribution volume is similar to the water volume and it is lower than that found in infants. For comparison of aciclovir pharmacokinetic parameters obtained in infants see the tables 2 and 6. The elimination half-life is shorter than that found in infants, and the renal clearance is lower than the total body clearance (Table 8).

The values of $AUC_{0-\infty}$ are significantly different (*P-value = 0.0261) and the values of total body clearance are significantly different (*P-value = 0.0003) among these children. *One-way analysis of variance.

This table shows that oral valaciclovir administered at a dose of 15 mg/kg produced non different peak concentration and AUC values than intravenous aciclovir administered at a dose of 10 mg/kg (Table 9).

Metabolism of aciclovir in humans

The major route of aciclovir elimination is the renal excretion of unchanged drug. Urinary recovery data after aciclovir administration to healthy volunteers indicate that <15% and 1% of the aciclovir dose is metabolized to 9-[(carboxymethoxy) methyl]guanine and to 8-hydroxy-aciclovir, respectively [19]. The metabolism of 8-^{14}C-aciclovir was studied in humans and the radioactive dose was excreted predominantly in the urine (71 to 99%) with less than 2% excretion in the faeces. The 9-carboxymethoxymethylguanine was the only significant urinary metabolite of aciclovir accounting for 8.5 to 14.1% of the administered dose. A minor metabolite (< 2% of the administered dose) was 8-hydroxy-aciclovir and unchanged urinary aciclovir ranged from 62 to 91% of the dose [20].

Interactions of aciclovir with drugs

In healthy subjects, interactions are observed after co-administration of mycophenolate mofetil and aciclovir, but the extent of the interactions is unlikely to be of clinical significance [21]. Increased risk of acute kidney injury was likely associated with the concomitant use of valaciclovir and some non-steroidal anti-inflammatory drugs such as loxoprofen, diclofenac, etodolac, ketorolac, piroxicam or lornoxicam. The case series from the adverse-effects indicated that compared with aciclovir, valaciclovir is more likely to be affected by non-steroidal anti-

Table 2: Individual empirical Bayesian post-hoc parameter estimates for acyclovir.

Postmenstrual age (weeks)	Number of infants	TBC (L/h/kg)	DV (L/kg)	Elimination half-life (h)	Peak conc. (µg/ml)	Conc. 50_{ss}	Trough conc. (µg/ml)
< 30	13	0.211 (0.095-0.310)	2.88 (0.646-5.30)	10.2 (4.73-13.2)	10.3 (4.59-110)	7.12 (3.38-65.7)	3.92 (2.38-39.3)
30 to <36	9	0.449 (1.87-10.85)	4.49 (1.87-10.85)	6.55 (4.28-9.26)	8.83 (5.44-29.8)	6.80 (3.72-16.9)	5.10 (2.54-9.62)
36 to 41	6	2.55 (0.293-4.09)	2.55 (0.293-4.09)	3.00 (1.61-3.69)	12.4 (10.8-86.1)	5.82 (5.23-22.0)	2.90 (2.19-7.46)
Overall	28	3.34 (0.293-10.85)	3.34 (0.293-10.85)	7.07 (1.61-13.2)	11.1 (4.59-110)	6.33 (3.38-65.7)	4.15 (2.19-39.3)

Table 3: Median and 5th to 95th percentiles of individual pharmacokinetic parameters post hoc estimates for aciclovir after oral administration.

Value	TBC/F (L/h)	TBC/F (L/h/kg)	TBC/F ($L/h/m^2$)	DV (L)	DV (L/kg)	DV (L/m^2)	Ka (h^{-1})
Median	20.9	3.1	56.3	37.3	5.4	93.2	0.28
5th to 95th percentiles	1.7 – 93.9	0.6 – 9.8	7.5 – 201	12.1 – 81.4	3.5 – 8.2	54.1 – 170	0.28 – 0.28
%CV	98	79	86	53	27	31	---

Table 4: Median and range of individual pharmacokinetic parameter post hoc estimates for aciclovir after intravenous administration.

Value	TBC /L/h)	TBC (L/h/kg)	DVc (L)	DVc (L/kg)	TBCd (L/h)	TBCd (L/h/kg)	DVp (L)	DVp (L/kg)
Median	9.7	0.44	10.0	0.57	4.79	0.21	13.7	0.62
Minimum	0.76	0.24	1.7	0.28	0.12	0.02	1.4	0.40
Maximum	22.5	0.79	27.1	0.71	18.2	0.45	25.6	1.24
%CV	59	32	67	20	100	62	62	27

Table 5: Plasma concentrations of acyclovir.

Age group	Dos (mg/m^2)	Plasma concentration of aciclovir (µg/ml)								
		Day 2, 3, or 4[a]		Before last dose	Time (hours) after the last dose					
		Before	2 hours		1	2	3	4	6	
6 m-4y[b] (N = 6)	600	0.31±0.07	1.03±0.30	0.22±0.20	0.53±0.23	0.84±0.35	0.90±0.44	0.95±0.49	0.60±0.35	0.35±0.17
4 -7 y[c] (N = 7)	600	0.59±0.44	0.97±0.60	0.30±0.14	0.73±0.31	0.84±0.30	0.85±0.29	0.73±0.29	0.51±0.19	0.35±0.20
6 m-7 y (N = 3)	600	0.45±0.35	1.00±0.47	0.25±0.18	0.62±0.28	0.84±0.32	0.88±0.34	0.85±0.41	0.56±0.27	0.35±0.17
< 2 m	300	1.56±1.51	1.87±1.34	0.6±0.27	0.61±0.16	1.48±0.55	1.82±1.16	1.88±1.11	1.32±0.90	0.84±0.60
6 m-4 y (N = 2)	300	1.05±0.10	1.31±0.09	0.49±0.55	0.61±0.19	0.77±0.13	0.73±0.14	0.52±0.13	0.29±0.13	0.21±0.02

inflammatory drugs, and the concomitant use of valaciclovir with some non-steroidal anti-inflammatory drugs might be associated with increased risk of acute kidney injury. The drug interactions with this specific combination of medications are worth exploring further [22]. Probenecid and cimetidine increased the plasma concentration of aciclovir [23]. There is a significant increase in urinary theophylline and a decrease in urinary 1,3-dimethyluric acid and 1-methyluric acid metabolites after the co-administration of aciclovir. The decrease in total body clearance is likely to have resulted from inhibition of metabolism via the oxidation pathway. These results indicated that aciclovir therapy lowers the dose of theophylline and is necessary a careful monitoring of theophylline plasma concentrations [24].

Toxicity caused by aciclovir in infants and children

Among the cohort of infants exposed to aciclovir, the rate of acute kidney injury was low. Sicker infants, and those exposed to additional nephrotoxic medications, are at a greater risk for aciclovir-induced toxicity and warrant closer monitoring [25]. Nephrotoxicity associated with intravenous aciclovir is common and necessitates renal function monitoring. Risk factors include greater dose, older age, and concomitant ceftriaxone administration. Outside the neonatal period, renal dysfunction may be minimized by dosing intravenous aciclovir below thresholds associated with nephrotoxicity (ie, ≤ 500 mg/m^2 per dose or ≤ 15 mg/kg per dose), particularly in older patients [26]. One of nine infants (11.1%) treated with aciclovir developed

Table 6: Non-compartmental analysis of aciclovir plasma concentrations after the last oral dose of aciclovir suspension.

Age group	Dose (mg/m²)	Peak conc. (µg/ml)	Time to peak (h)	AUC (µg*h/ml)	Elimination half-life (h)	Cl_{cr} (ml/min/1.73 m²)
6 m – 4 y (N=7)[a]	600	1.07±0.44	3.21±0.99	5.68±2.40	2.61±0.75	88±27
4 – 7 y (N=6)[b]	600	0.89±0.30	2.64±0.47	5.38±2.12	2.57±0.95	99±19
6 m – 7 y (N=3)	600	0.99±0.38	3.00±0.86	5.56±2.17	2.59±0.78	93±24
< 2 m (N=3)[c]	300	1.88±1.11	4.10±0.48	6.54±4.32	3.25±0.33	50±14
6 m – 4 y (N=2)	300	0.77±0.13	2.0±0.00	2.87±0.85	2.75±0.17	92±8.5

Table 7: Pharmacokinetic parameters of aciclovir following oral administration of valaciclovir at a dose of 15 mg/kg.

Parameter	Mean±SD	Median (range)
Peak concentration (µM)	18.8±7	17.1 (7.9 – 40.3)
Tmax (min)	129±57	120 (60 – 250)
$AUC_{0-\infty}$ (µM*min)	4106±1519	3934 (1672 – 8510)
Total body clearance (ml/min/kg)	11.4±4.4	10.7 (5.2 – 23.4)
Elimination half-life (min)	87.5±29	80.0 (41.3 – 173)
Elimination half-life (h)	1.4±0.48	1.3 (0.68 – 2.9)
Distribution volume (L/kg)	1.34±0.65	1.23 (0.33 – 3.3)
Tau (min)	23.0±12.4	25.8 (1.2 – 70.0)
Renal clearance (ml/min/kg)	3.03±2.2	2.3 (0.35 – 8.2)

Table 8: Age comparison pharmacokinetic parameters of aciclovir following oral valaciclovir.

Age (years) mean and (range)	Number of children	$AUC_{0-\infty}$ (µM*min)	Total body clearance (ml/min/kg)
3.75 (3 – 5)	8	2925±974	16.2±4.5
8.3 (6 – 11)	12	4292±1105	10.4±2.9
15 (12 – 18)	12	4707±1797	9.1±3.1

Table 9: Comparison of pharmacokinetic parameters obtained following oral valaciclovir and intravenous aciclovir in 11 children.

Oral administration of valaciclovir (15 mg/kg)					Intravenous administration of aciclovir (10 mg/kg)		
Peak conc. (µM)	$AUC_{0-\infty}$ (µM*min)	TBC (ml/min/kg)	Elimination Half-life (min)	Bioavailability (%)	Dose (mg/kg)	Peak conc. (µM)	$AUC_{0-\infty}$ (µM*min)
18±4	4294±1635	10.7±5.0	80.8±29	63.8±13.5	9.2±3.0	42.3±17	6446±4110
*P-value (One-way analysis of variance)						0.2083	0.0625

symptomatic recurrence of the central nervous system disease and none of the remaining eight patients experienced dermal or neurologic recurrence caused by herpes simplex disease. Renal and neurologic statuses were routinely monitored and no signs of aciclovir toxicity were observed [27]. A newborn infant whose condition was diagnosed as herpes simplex encephalitis and who had subsequent recurrences of skin disease had repeated episodes of neutropenia while receiving therapy with intravenous 30 mg/kg daily or oral 30 mg/kg daily aciclovir. The neutropenia did not recur when the dosage of oral aciclovir was reduced to 10 mg/kg daily. This case represents the first well-documented report of aciclovir-induced neutropenia [28].

Treatment of infants and children with aciclovir

Infants surviving neonatal herpes simplex virus disease with central nervous system involvement had improved neurodevelopmental outcomes when they received suppressive therapy with oral aciclovir for 6 months [29]. A boy, aged 2 years, who was diagnosed with herpes simplex virus and opercula syndrome was studied. The child recovered without sequela as a result of 30 days of intravenous and 10 days of oral aciclovir treatment [30]. Aciclovir appears to be effective in reducing the number of days with fever among healthy children with chickenpox. The results were inconsistent with respect to the number of days, new lesions, the maximum number of lesions, and the relief of itchiness. The clinical importance of aciclovir treatment in healthy children remains controversial [31]. Forty children had cerebrospinal fluid analysis, but basic results were incomplete in 13 cases. The initial dose of aciclovir was incorrect in 38 cases (95.0%). The median (range) length of intravenous aciclovir treatment was 4 days (range, 1 to 21). Six children were given a full course of aciclovir for 10 days or more. For

14 children (35.0%), there appeared to be no real indication for starting aciclovir. Case note documentation was generally inadequate. The management of children with suspected viral encephalitis appears hazard in many cases. Guidelines for the management of children with suspected viral encephalitis are needed [32]. Aciclovir is licensed for treatment of varicella and herpes zoster virus, and aciclovir, valaciclovir, and famciclovir are approved for treatment of herpes zoster infection. Passive antibody prophylaxis with varicella-zoster immune globulin is indicated for susceptible high-risk patients exposed to varicella, and a live attenuated varicella vaccine is now recommended for routine childhood immunization [33]. Oral aciclovir treatment for herpetic gingivostomatitis, started within the first three days of onset, shortens the duration of all clinical manifestations and the infectivity in affected children [34]. Aciclovir is not recommended for healthy individuals without severe disease, and as a prophylactic agent against varicella in asthmatic patients receiving aerosolized or low-dose oral steroids and/or as treatment of the post-varicella syndromes. When aciclovir is prescribed should be given intravenously for treating severe disease, to those at risk of disseminated infection, and to children aged < 2 years [35].

Prophylaxis with aciclovir in infants and children

The combination of intravenous immunoglobulin given soon after birth and prophylactic aciclovir intravenously administered 7 days after the onset of maternal rash can effectively prevent perinatal varicella infection [36]. Prophylaxis with oral aciclovir started at a dose of 400 mg daily in children, aged < 2 years, and 800 mg daily in older children, divided in 5 doses, showed good results for the control of herpes simplex virus infection [37]. Oral aciclovir administration to healthy susceptible subjects at the beginning of secondary viremia in the late incubation period (9 days after exposure) can effectively prevent or modify clinical varicella infection [38]. Prophylaxis with aciclovir at an oral dose of 40 or 80 mg/kg in four divided doses controlled the infection caused by varicella in infants and children [39].

Penetration of aciclovir in the cerebrospinal fluid (CSF)

In patients with central nervous system infection caused by herpesvirus, the blood-brain-barrier disruption is associated with increased concentration of aciclovir and its metabolite 9-carboxymethoxymethylguanine in the CSF. Evaluation of the CSF to serum albumin concentration ratio, normal renal function, CSF concentrations of aciclovir and its metabolite 9-carboxymethoxymethylguanine may contribute to optimize aciclovir dosing and avoidance of aciclovir-induced neuropsychiatric symptoms [40]. The penetration of aciclovir into the CSF, in patients with herpes simplex encephalitis, following the oral administration of the prodrug valaciclovir at a dose of 1,000 mg thrice-daily, cured the infection. The oral therapy achieved with adequate aciclovir concentrations in the CSF may be an acceptable as early treatment for suspected herpes simplex encephalitis in resource-limited settings [41]. Aciclovir concentrations in CSF at 2 and 8 hours after dosing were essentially stable, with the mean ±SD levels being 2.5±0.9 and 2.3±0.7 μM, respectively. Similar levels were recorded in serum and CSF samples from five other multiple sclerotic patients after 6 months of oral treatment with valaciclovir at identical dosages. The AUC for aciclovir in CSF to the AUC for aciclovir in serum is approximately 20% [42].

Treatment of meningitis with aciclovir in infants and children

Four infants with encephalitis caused by herpes simplex virus were treated with aciclovir at a dose of 60 mg/kg daily and this disease was cured [43]. Twenty-nine infants and 17 children had meningitis or encephalitis and were treated with aciclovir which cured both the meningitis and the encephalitis [44]. A 7-years-old boy had the meningitis caused by herpes zoster virus and was treated with aciclovir at a dose of 15 mg/kg thrice-daily for 10 days and rapidly improved [45].

Transfer of aciclovir across the human placenta

The antiviral agents ganciclovir and aciclovir appear to cross the human placenta by simple diffusion, at least at therapeutic levels, and this transfer is not affected by the nucleoside transport inhibitor dinitrobenzylthioinosine [46]. Overall transfer of aciclovir at therapeutic concentrations from maternal to fetal compartment occurred at a rate of about 30% that of a freely diffusible marker, antipyrine. The overall transport was not saturable, was not inhibited by 50-fold adenine concentration, and did not proceed against a concentration gradient. There was no placental metabolism of aciclovir. Fetal-to-maternal transfer of aciclovir occurred at a similar rate. In maternal-facing microvesicles net uptake of aciclovir was not saturable, but was temperature dependent and was inhibited by high concentrations of adenine and ganciclovir, but not by nucleosides adenosine, cytidine, and cytosine. These data are most consistent with a carrier-dependent nucleobase-type uptake of aciclovir. Passive overall net transfer of aciclovir depends on its solubility characteristics [47].

Migration of aciclovir into the human breast-milk

One hundred forty-eight women were randomized and 146 mother-infant pairs were followed postpartum. Aciclovir was detected in 35 (79.5%) of 44 breast-milk samples collected at 2 weeks postpartum. Median and maximum aciclovir levels were 2.62 and 10.15 mg/ml, respectively (interquartile range, 0.6 to 4.19) [48]. Valaciclovir (500 mg twice-daily for 7 days) was given to 5 women after delivery who were breast-feeding healthy term infants. Valaciclovir was rapidly converted to aciclovir. The peak serum aciclovir concentration occurred 3 hours before the peak breast-milk concentration (2.7 μg/ml at 1 hour versus 4.2 μg/ml at 4 hours). The ratio of breast-milk to serum aciclovir concentration was highest 4 hours after the initial dose at 3.4 mg/kg and reached steady-state ratio at 1.85 mg/kg. The amount of aciclovir in breast-milk after valaciclovir administration is considerably less (2%) than that used in therapeutic dosing of neonates [49]. Aciclovir concentrations in breast-milk ranged from 18.5 pmol (4.16 μg/ml) to 25.8 pmol (5.81 μg/ml). An estimate of the infant's dosage ingested through nursing was 0.73 mg/kg daily or approximately 1 percent of the maternal dose in mg/kg daily. The infant was nursed without any signs of adverse-effects. Aciclovir was measured in clinically insignificant

concentrations in the milk of a woman receiving large dosages of aciclovir for herpes zoster virus infection. Breast-feeding continued without adverse-effects to the nursing infant [50]. Aciclovir concentration was measured by radioimmunoassay in the serum and in the beast-milk of a lactating woman who was treated with oral acyclovir for herpes zoster virus infection. Daily serum and milk samples showed milk concentrations that averaged 3.2-fold higher than serum levels and the elimination phase had a half-life of 2.8 hours in the breast-milk [51]. Maternal plasma, breast-milk, and infant urine were collected following a 200 mg oral dose of aciclovir. The drug concentration in the breast-milk exceeded the corresponding plasma concentration except at the time of peak plasma concentration. This would not be expected on the basis of simple diffusion, and might be caused by a facilitated or active transport mechanism [52].

DISCUSSION

Aciclovir is an acyl guanine nucleoside analogue that lacks the 2' and 3' positions normally supplied by ribose. Aciclovir is the prototype of a group of antiviral agents that are nucleoside congeners that are phosphorylated intracellularly by a viral kinase and subsequently by host cell enzymes to become inhibitors of viral DNA synthesis. Aciclovir inhibits viral DNA; its selectivity of action depends on interaction with herpes simplex virus thymidine kinase and thus occurs only in the cells infected with this virus. The oral bioavailability of aciclovir is about 10 to 30% and decreases with increasing dose thus it is preferentially administered intravenously. Delivery of an oral dose can be enhanced by administration of the prodrug valaciclovir. Aciclovir's clinical use is mainly limited to herpes viruses. Aciclovir is most active against herpes simplex virus-1 (effective plasma concentration ranges from 0.02 to 0.9 μg/ml), approximately half as active against herpes simplex virus-2 (effective plasma concentration ranges from 0.03 to 2.2 μg/ml), a tenth as potent against varicella zoster virus (effective plasma concentration ranges from 0.8 to 4.0 μg/ml), and Epstein-Barr virus, and least active against cytomegalovirus (effective plasma concentration > 20 μg/ml) and human herpesvirus 6. Uninfected mammalian cell growth generally is unaffected by high aciclovir concentrations (> 50 μg/ml) [1]. In infants, the standard regimen for aciclovir, irrespective of prematurity, is 30 mg/kg thrice-daily given intravenously. In infants aged > 3 months, the dose is 250 mg/m^2 thrice-daily, doubled to 500 mg/m^2 in the immunocompromised or in herpes simplex encephalitis. The dose interval must be at least doubled if there is renal failure [2]. In children, suffering from herpes simplex virus infection, the intravenous dose is 20 mg/kg thrice-daily given for 14 days, but it must be prolonged to 21 days if the central nervous system is involved. In children the aciclovir dose depends on the infective virus, may be administered intravenously or orally, and the oral treatment of varicella zoster virus infection consists of 200 to 800 mg 4 or 5 times-daily and the dose increases with child age [4]. Aciclovir administered at a dose of 60 mg/kg for ≥ 14 days has been found efficacy and safe for the treatment of herpes simplex virus infection [5]. The use of aciclovir, given at a dose of 60 mg/kg for treating nervous system infection, has been found efficacy and safe [6], and the prodrug valaciclovir given at an oral dose of 1,000 mg daily or an aciclovir oral dose of 800 mg daily successfully treats infection caused by herpes simplex virus and the incidence of resistance is 5% [7]. Aciclovir is efficacy in treating genital, skin, severe gingivitis, paronychia, and pharyngitis caused by varicella zoster virus of herpes simplex virus infections [8]. Treatment of infants suffering from central nervous system and/or disseminate infection were treated with aciclovir for 2 years, this treatment causes dermal lesions, and a minority of these infants exhibited mild development delays [9]. Infants and children with proven encephalitis caused by herpes simplex virus were treated with aciclovir but the treatment was incorrect in some cases and it appeared hazard in many cases [10]. Children with varicella infection were treated with aciclovir. About half of children has moderate rash, 20% has severe rash and has complications including otitis media, pneumonia and vesicular lesions which occurs in about 7% of children [11]. Treatment with aciclovir causes neuropsychiatric adverse-effects in children [12]. Children with culture positive for herpes simplex virus were treated orally with aciclovir at a dose of 15 mg/kg 5 times-daily and reported oral skin lesions, fever, and lesions around but not outside the oral cavity, eating and drinking difficulties which were caused by aciclovir [13]. Children treated with aciclovir for varicella infection experience cutaneous and other numerous lesions [14]. The pharmacokinetics of aciclovir have been studied in infants [15] and the elimination half-life ranges between about 10 to 3 hours and decreases with infant maturation. In children, the elimination half-life ranges between 2.5 to 3.2 hours and decreases with child age [17]. Bomgaars et al. [18] reported an aciclovir half-life of 1.4 hours in children, and the total body clearance is 16.2, 10.4, and 9.1 ml/min/kg in children with a mean age of 3.7, 8.3, and 15 years, respectively, indicating that the total body clearance decreases with child development. A small fraction of aciclovir is metabolized to 9-[(carboxymethoxy)methyl]guanine and to 8-hydroxy-aciclovir [19]. Radioactive aciclovir was administered to humans and most of radioactivity was found in urines with only 2% in the faeces [20]. Aciclovir interacts with mycophenolate mofetil but the interaction has limited clinical significance [21]. Valaciclovir associated with non-steroidal anti-inflammatory drugs induces acute kidney injury [22]. Probenecid and cimetidine increase the plasma concentration of aciclovir [23], and aciclovir decreases the metabolism of theophylline [24]. Aciclovir induces nephrotoxicity in infants [25] and this toxicity increases with greater dose of aciclovir, is associated with older age, and by concomitant administration of ceftriaxone [26]. Only 11% of infants treated with aciclovir develop central nervous system disease [27]. A newborn infant treated with oral aciclovir developed neutropenia and this adverse-effect disappears with oral aciclovir at a dose of 10 mg/kg [28]. Treatment with aciclovir has been studied in infants and children [29-35]. Aciclovir improves neurodevelopment outcomes in infants [29]. A boy, aged 2 years, suffering from herpes simplex virus infection recovered following treatment with aciclovir [30]. Aciclovir reduces the number of days with fever in healthy children with chickenpox but the treatment was inconsistent with respect to the number of treatment days [31]. The treatment of viral encephalitis with aciclovir may be a hazard and guidelines for treating viral encephalitis in children are needed [32]. Aciclovir, valaciclovir, and famciclovir are approved for treating varicella and herpes zoster virus infections however attenuated varicella vaccine is recommended [34]. Oral aciclovir is recommended to

treat varicella infection and intravenous treatment should be given for severe disease [35]. Prophylaxis with aciclovir has been performed in infants and children [36-39]. The combination of intravenous immunoglobulin and prophylactic aciclovir has been suggested to prevent perinatal varicella in infected mothers [36]. Prophylaxis with aciclovir is recommended at an oral dose of 400 mg daily in young children and at a dose of 800 mg daily in older children to prevent varicella infection [37]. Oral aciclovir administered to healthy subjects at the beginning of secondary viremia infection prevents and modifies clinical varicella infection [38] an oral dose of 40 or 80 mg/kg aciclovir given in four divided doses controls varicella infection in infants and children [39]. Aciclovir penetrates into the cerebrospinal fluid in significant amounts [40-42]. The disruption of the blood-brain-barrier increases the penetration of aciclovir into the cerebrospinal fluid [40], high aciclovir concentration in the cerebrospinal fluid is obtained by the administration of 1,000 mg of valaciclovir [41], and the concentration of aciclovir in the cerebrospinal fluid decays slowly [42]. An intravenous aciclovir dose of 60 mg/kg cures the encephalitis caused by the herpes simplex virus [43]. Aciclovir successfully cures the meningitis or encephalitis in infants [44], and an intravenous dose of 15 mg/kg thrice-daily cures the meningitis caused by herpes zoster virus infection [45]. In-vitro studies showed that aciclovir crosses the human placenta by simple diffusion [46] and the overall transport is not saturable [47]. Aciclovir migrates into the human breast-milk in significant amounts [48-52]. Aciclovir is detectable in the breast-milk 2 weeks postpartum [48] and also after administration of valaciclovir [49]. Following high aciclovir dose administered to the mothers, the dose ingested by the infants is about 1% of the maternal dose [50]. The elimination half-life of aciclovir in the human breast-milk is 2.8 hours and the migration of aciclovir into the breast-milk may occur by facilitate or active transport mechanism [52].

In conclusion, aciclovir cures the infections caused by herpes simplex, varicella zoster, and Epstein Barr viruses. In infants, the aciclovir dose is 30 mg/kg thrice-daily given intravenously irrespective of prematurity. In infants, aged > 3 months, the dose is 250 mg/m^2 trice-daily and is doubled to 500 mg/m^2 in immunocompromised infants with herpes simplex encephalitis. In children the dose depends on the virus causing the infection, may be administered intravenously or orally, and the oral dose to treat varicella zoster infection is 200 to 800 mg given 4 or 5 times-daily. Aciclovir has been found efficacy and safe in infants and in children but it may cause adverse-effects. Aciclovir is eliminated mostly by renal route and the elimination half-life of aciclovir ranges from about 10 to 3 hours in infants and decreases with infant maturation. In children the aciclovir elimination half-life is about 1.5 hours. Aciclovir may cause nephrotoxicity, the treatment and the prophylaxis with aciclovir has been extensively studied. This dug penetrates into the cerebrospinal fluid in significant amounts and cures encephalitis caused by herpes simplex virus and the meningitis due to herpes simplex and herpes zoster viruses. Aciclovir crosses the human placenta and migrates into the human breast-milk. The aim of this study is to review the clinical pharmacology of aciclovir in infants and children.

REFERENCES

1. Acosta EP."Antiviral Agents (Nonretroviral)". In The Goodman & Gilman's. Pharm BasTherap. 2018; 13: 1018-1035.
2. Sean Ainsworth. Neonatal Formulary. Aciclovir. Oxford University Press. 2020; 8 : 61-63.
3. Young TE, Mangum B. NEOFAX®. Aciclovir. Thomas Reuters Clinical Editorial Staff. 2010; 23: 2-3.
4. The British national formulary for children. 2020-2021; 78: 420-421.
5. Ericson JE, Gostelow M, Autmizguine J, Hornik CP, Clark RH, Benjamin DK Jr, et al. Safety of High-dose Acyclovir in Infants With Suspected and Confirmed Neonatal Herpes Simplex Virus Infections. Pediatr Infect Dis J. 2017; 36: 369-373.
6. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber, WC, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics. 2001; 108: 230-238.
7. Tyring SK, Baker D, Snowden W. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. J Infect Dis. 2002; 186: S40-S46.
8. Szenborn L, Kraszewska-Głomba B, Jackowska T, Duszczyk E, Majda-Stanisławska E, Marczyńska M, et al. Polish consensus guidelines on the use of acyclovir in the treatment and prevention of VZV and HSV infections. J Infect Chemother. 2016; 22: 65-71.
9. Tiffany KF, Benjamin DK Jr, Palasanthiran P, O'Donnell K, Gutman LT. Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. J Perinatol. 2005; 25: 156-161.
10. Kneen R, Jakka S, Mithyantha R, Riordan A, Solomon T. The management of infants and children treated with aciclovir for suspected viral encephalitis. Arch Dis Child. 2010; 95: 100-106.
11. Memon IA, Jamal A, Memon H. An experience of oral acyclovir in treating children with varicella infection. Pak J Med Sci. 2008; 24: 590-594.
12. Helldén A, Odar-Cederlöf I, Diener P, Barkholt L, Medin C, Svensson J-O, et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. Nephrol Dial Transplant. 2003; 18: 1135-1141.
13. Amir J, Harel L, Smetana Z, Varsano I. Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study. BMJ. 1997; 314: 1800-1803.
14. Balfour HH Jr 1, Kelly JM, Suarez CS, Heussner RC, Englund JA, Crane, DD, et al. Acyclovir treatment of varicella in otherwise healthy children. J Pediatr. 1990; 116: 633-639.
15. 15. Sampson MR, Bloom BT, Lenfestey RW, Harper B, Kashuba AD, Anand R, et al. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. Pediatr Infect Dis J. 2014; 33: 42-49.
16. Tod M, Lokiec F, Bidault R, De Bony F, Petitjean O, Aujard Y. Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. Antimicrob Agents Chemother. 2001; 45: 150-157.
17. Sullender WM, Arvin AM, Diaz PS, Connor JD, Straube R, Dankner W, et al. Pharmacokinetics of acyclovir suspension in infants and children. Antimicrob Agents Chemother. 1987; 31: 1722–1726.
18. Bomgaars L, Thompson P, Berg S, Serabe B, Aleksic A, Blaney S. Valacyclovir and acyclovir pharmacokinetics in immunocompromised children. Pediatr Blood Cancer. 2008; 51: 504-508.
19. Smith JP, Weller S, Johnson B, Nicotera J, Luther JM, Haas DW.

Pharmacokinetics of Acyclovir and Its Metabolites in Cerebrospinal Fluid and Systemic Circulation after Administration of High-Dose Valacyclovir in Subjects with Normal and Impaired Renal Function. Antimicrob Agents Chemother. 2010; 54: 1146–1151.

20. de Miranda P, Good SS, Krasny HC, Connor JD, Laskin OL, Lietman PS. Metabolic fate of radioactive acyclovir in humans. Am J Med. 1982; 73: 215-220.

21. Gimenez F, Foeillet E, Bourdon O, Weller S, Garret C, Bidault R, et al. Evaluation of pharmacokinetic interactions after oral administration of mycophenolate mofetil and valaciclovir or aciclovir to healthy subjects. Clin Pharmacokinet. 2004; 43: 685-692.

22. Yue Z, Shi J, Li H, Li H. Association between Concomitant Use of Acyclovir or Valacyclovir with NSAIDs and an Increased Risk of Acute Kidney Injury: Data Mining of FDA Adverse Event Reporting System. Biol Pharm Bull. 2018; 41: 158-162.

23. De Bony F, Tod M, Bidault R, On NT, Posner J, Rolan P. Multiple interactions of cimetidine and probenecid with valaciclovir and its metabolite acyclovir. Antimicrob Agents Chemother. 2002; 46: 458-463.

24. Maeda Y, Konishi T, Omoda K, Takeda Y, Fukuhara S, Fukuzawa M, et al. Inhibition of theophylline metabolism by aciclovir. Biol Pharm Bull. 1996; 19: 1591-1595.

25. Downes KJ, Boge CLK, Baro E, Wharton GT, Liston KM, Haltzman BL, et al. Acute Kidney Injury During Treatment with Intravenous Acyclovir for Suspected or Confirmed Neonatal Herpes Simplex Virus Infection. J Pediatr. 2020; 219: 126-132.

26. Rao S, Abzug MJ, Carosone-Link P, Peterson T, Child J, Siparksy G, et al. Intravenous acyclovir and renal dysfunction in children: a matched case control study. J Pediatr. 2015; 166: 1462-1468.

27. Rudd C, Rivadeneira ED, Gutman LT. Dosing considerations for oral acyclovir following neonatal herpes disease. Acta Paediatr. 1994; 83: 1237-1243.

28. Feder HM Jr 1, Goyal RK, Krause PJ. Acyclovir-induced neutropenia in an infant with herpes simplex encephalitis: case report. Clin Infect Dis. 1995; 20: 1557-1559.

29. Kimberlin DW, Whitley RJ, Wan W, Powell DA, Storch G, Ahmed A, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med. 2011; 365: 1284-1292.

30. Karli A, Şensoy G, Tekin E, Sofuoğlu AI, MC, Özyürek H. Prolonged acyclovir treatment in a child with opercular syndrome related to herpes simplex encephalitis. J Infect Public Health. 2017; 10: 232-234.

31. Klassen TP, Belseck EM, Wiebe N, Hartling L. Acyclovir for treating varicella in otherwise healthy children and adolescents: a systematic review of randomised controlled trials. BMC Pediatr. 2002; 2: 9.

32. Kneen R, Jakka S, Mithyantha R, Riordan A, Solomon T. The management of infants and children treated with aciclovir for suspected viral encephalitis. Arch Dis Child. 2010; 95: 100-106.

33. Arvin AM. Varicella-zoster virus. Clin Microbiol Rev. 1996; 9: 361-381.

34. Amir J, Harel L, Smetana Z, Varsano I. Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study. BMJ. 1997; 314: 1800-1803.

35. Kesson AM, Grimwood K, Ferson MJ. Gilbert GK, Hogg G. et al. Acyclovir for the prevention and treatment of varicella zoster in children, adolescents and pregnancy. J Paediatr Child Health. 1996; 32: 211-217.

36. Huang YC, Lin TY, Lin YJ, Lien RI, Chou YH. Prophylaxis of intravenous immunoglobulin and acyclovir in perinatal varicella. Eur J Pediatr. 2001; 160: 91-94.

37. Serna-Ojeda JC. Management of Herpes Simplex Virus Keratitis in the Pediatric Population. Pediatr Infect Dis J. 2019; 38: e164.

38. Lin TY, Huang YC, Ning HC, Hsueh C. Oral acyclovir prophylaxis of varicella after intimate contact. Pediatr Infect Dis J. 1997; 16(12): 1162-1165.

39. Asano Y, Yoshikawa T, Suga S, Kobayashi I, Nakashima T, Yazaki T, et al. Postexposure prophylaxis of varicella in family contact by oral acyclovir. Pediatrics. 1993; 92: 219-222.

40. Lindström J, Helldén A, Lycke J, Grahn A, Studahl M. An unexpectedly high occurrence of aciclovir-induced neuropsychiatric symptoms in patients treated for herpesvirus CNS infection: a prospective observational study. J Antimicrob Chemother. 2019; 74: 3565-3572.

41. Pouplin T, Pouplin JN, Toi PV, Lindegardh N, van Doorn HR, Hien TT, et al. Valacyclovir for herpes simplex encephalitis. Antimicrob Agents Chemother. 2011; 55(7): 3624-3626.

42. Lycke J, Malmeström C, Ståhle L. Acyclovir levels in serum and cerebrospinal fluid after oral administration of valacyclovir. Antimicrob Agents Chemother. 2003; 47: 2438-2441.

43. Mejías A, Bustos R, Ardura MI, Ramírez C, Sánchez PJ. Persistence of herpes simplex virus DNA in cerebrospinal fluid of neonates with herpes simplex virus encephalitis. J Perinatol. 2009; 29: 290-296.

44. Hagen A, Eichinger A, Meyer-Buehn M, Schober T, Huebner J. Comparison of antibiotic and acyclovir usage before and after the implementation of an on-site FilmArray meningitis/encephalitis panel in an academic tertiary pediatric hospital: a retrospective observational study. BMC Pediatr. 2020; 20: 56.

45. Lee SK, Kim DJ, Lee UH, Kim MS, Choi JH. Herpes zoster with meningitis in a vaccinated, immunocompetent child. J Dermatol. 2017; 44: 1419-1420.

46. Gilstrap LC, Bawdon RE, Roberts SW, Sobhi S. The transfer of the nucleoside analog ganciclovir across the perfused human placenta. Am J Obstet Gynecol. 1994; 170: 967-972.

47. Henderson GI, Hu ZQ, Johnson RF, Perez AB,Yang Y, Schenker S. Acyclovir transport by the human placenta. J Lab Clin Med. 1992; 120: 885-892.

48. Drake AL, Roxby A, Kiarie J, Richardson BA, Wald A, John-Stewart G, et al. Infant safety during and after maternal valacyclovir therapy in conjunction with antiretroviral HIV-1 prophylaxis in a randomized clinical trial. PLoS One. 2012; 7: e34635.

49. Sheffield JS, Fish DN, Hollier LM, Cadematori S, Nobles BJ, Wendel GD Jr. Acyclovir concentrations in human breast-milk after valaciclovir administration. Am J Obstet Gynecol. 2002; 186: 100-102.

50. Taddio A, Klein J, Koren G. Acyclovir excretion in human breast milk. Ann Pharmacother. 1994; 28: 585-587.

51. Meyer LJ, de Miranda P, Sheth N, Spruance S. Acyclovir in human breast milk. Am J Obstet Gynecol. 1988; 158: 586-588.

52. Lau RJ, Emery MG, Galinsky RE. Unexpected accumulation of acyclovir in breast-milk with estimation of infant Exposure. Obstetrics and **Gynecology**. 1987; 69: 468-471.

Cite this article

Pacifici GM (2021) Clinical Pharmacology of Aciclovir in Infants and Children. J Drug Des Res 8(1): 1081.