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The Effects and Pharmacokinetics of Acyclovir in Neonates

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Abstract

Acyclovir (9-[2-hydroxyethoxymethyl] guanine) is an acyclic nucleoside analogue of guanosine which is a potent and selective antiviral agent. Acyclovir is converted to the monophosphate by thymidine kinase the virus-specific form of this enzyme and is subsequently converted to the triphosphate by the host cell kinase. Acyclovir triphosphate inhibits viral DNA-polymerase terminating the chain and is the active form. It is 30 times more potent against the herpes simplex virus enzyme than the host enzyme. Acyclovir triphosphate is fairly rapidly broken down within the host cells by cellular phosphatases. Resistance due to changes in the viral genes coding for thymidine kinase or DNA polymerase cause acyclovir-resistant herpes simplex virus and has been the cause of pneumonia, encephalitis and mucocutaneous infections.

Acyclovir can be administered orally or intravenously. When it is given orally, only 10-20% of the dose is absorbed. Acyclovir is widely distributed throughout the body, reaching concentrations in the cerebrospinal fluid which are 30 to 50% of those in the serum. In neonates, the half-life of acyclovir is about 5 hours, but it is 2.5 hours in children over 3 months old. The herpes simplex virus is transmitted vertically from infected mothers to fetuses and the administration of 400 mg acyclovir orally three times daily from 36 weeks of pregnancy until delivery has been suggested. Alternatively, a cesarean section can be performed to avoid the transmission of the herpes simplex virus to fetuses. The aim of this study is to review the effects and pharmacokinetics of acyclovir in neonates.

Key Words: Acyclovir, Effects, Herpes-Simplex-Virus, Neonates, Varicella-Zoster-Virus.

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1-INTRODUCTION

Acyclovir is an acyclic guanine nucleoside analog that lacks a 3'-hydroxyl on the side chain. Acyclovir's clinically useful antiviral spectrum is limited to herpes viruses. In vitro, acyclovir is most active against herpes simplex virus type 1 (0.02-0.9 µg/ml), approximately half as active against herpes simplex virus type 2 (0.03-2.2 µg/ml), a tenth as potent against varicella-zoster virus (0.8-4.0 µg/ml), and Epstein-Barr virus, and least active against cytomegalovirus (generally >20 µg/ml) and human herpesvirus 6 (HHV-6). Uninfected mammalian cell growth generally is unaffected by high acyclovir concentrations (>50 µg/ml). Acyclovir is converted to the monophosphate and subsequently it is converted to acyclovir triphosphate the active form. Acyclovir triphosphate inhibits viral DNA synthesis. Its selectivity of action depends on interaction with two distinct viral proteins: herpes simplex virus thymidine kinase and DNA polymerase. Cellular uptake and initial phosphorylation are facilitated by herpes simplex virus thymidine kinase. The affinity of acyclovir for herpes simplex virus thymidine kinase is about 200 times greater than for the mammalian enzyme. Cellular enzymes convert the monophosphate to acyclovir triphosphate, which is present in 40-100-fold higher concentrations in herpes simplex virus infected than in uninfected cells and competes for endogenous deoxyguanosine triphosphate (dGTP) (1).

Acyclovir is used to treat herpes simplex virus infection. It is also used, along with varicella zoster immunoglobulin, to treat those with varicella zoster (chickenpox) who are immuno-incompetent. Acyclovir, first marketed in 1957, has no effect on dormant viruses and needs to be given early to influence viral replication. Oral uptake is limited and delayed and, at high doses, progressively less complete (bioavailability 12%). Acyclovir is preferentially taken up by infected cells (limiting toxicity) and cleared by a combination of glomerular filtration and tubular secretion. Slow intravenous administration is important to prevent drug crystals precipitating in the renal tubules. Oral treatment is not recommended in the neonatal period. Signs of central nervous system toxicity, with lethargy, tremor and disorientation, will develop if poor renal function causes acyclovir to accumulate. The neonatal half-life of acyclovir is about 5 hours, but it is 2.5 hours in adults and in children over 3 months old. Acyclovir enters the cerebral system fluid and ocular fluids well. It also crosses the placenta, but there are no reports of teratogenicity (2).

Infection of herpes simplex virus can follow vaginal exposure to this virus after a variable latent period. Lesions of skin, eyes and mouth are usually the first signs, but an encephalic or a generalized illness with pneumonia and hepatitis may develop without warning even, rarely, after some weeks. The virus grows readily in cell culture, and a positive diagnosis is often possible within 2-3 days. A polymerase chain reaction test can be used to detect viral DNA in the cerebral spinal fluid in cases of suspected encephalitis. Neonates born to women with active genital infection at delivery are at significant risk of infection, the risk being very much lower (5%) with reactivated infection. Unfortunately, differentiation can be difficult, and routine cervical culture is unhelpful. Caesarian delivery can prevent the neonate becoming infected, but is of limited value if the membranes have been ruptured more than 6 hours early. Only one small trial has yet assessed whether oral acyclovir (400 mg once every 8 hours from 36 weeks' gestation until delivery) can reduce the need for cesarean delivery or risk of neonatal infection in infected mothers during pregnancy. Neonates who survive a generalized or encephalitic illness are often disabled, but long-term

oral treatment (up to 6 months) improves neurodevelopment outcomes in the survivors. A mother with recurrent facial cold sores (labial herpes) will not infect her own neonates, because both will have the same high viral antibody titer (2).

Acyclovir (9-[2-hydroxyethoxymethyl] guanine) is an acyclic nucleoside analogue of guanosine which is a potent and selective antiviral agent. It has been found to have potent in vitro antiviral activity against herpes simplex virus type 1 (50% inhibitory dose [ED_{50}] of 0.1 µM) (3-5). Subsequently, the effective dose 50 (ED50) for herpes simplex virus (types 1 and 2) and varicella-zoster virus was found to be 0.1 to 1.6 µM (3, 6, 7), respectively, while inhibiting mammalian cell growth only at very high concentrations (> 300 µM) (3, 7). This would suggest a therapeutic ratio of about 3,000 for infections with herpes simplex virus. Most strains of Cytomegalovirus appear to be relatively resistant (ED_{50} >200 µM) (7).

The selective activity of acyclovir for cells infected with herpesviruses is due to the production of 2 unique herpes-specific enzymes, an isofunctional deoxynucleoside kinase and a herpes-specific DNA polymerase. Both of these enzymes are coded for by the herpes simplex virus genome (8-11). Acyclovir is selective phosphorylated by the herpes-coded deoxynucleoside kinase to its monophosphate to di- and triphosphate (12, 13). Acyclovir triphosphate is the active antiviral compound and is a selective substrate and inhibitor of the herpesvirus DNA polymerase (12, 14, 15). Acyclovir has been found to be effective in vitro and in vivo in preclinical studies for infections caused by herpes simplex virus (3, 7, 16) varicella-zoster virus (6, 7, 17), and Epstein-Bar virus (18). In man, acyclovir has been shown to be of benefit in the prophylaxis and therapy of selected herpes simplex virus infections when used topically (19-21), orally (22), or prenatally (23-26).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; August 2016 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

Combinations of search terms from three categories ("Neonetes" keyword AND "Pharmacokinetics acyclovir neonate" and "Effects acyclovir neonate" keyword AND "Infants" keyword), were used to search for the relevant literature. In addition, the books Neonatal Formulary (2) and NEOFAX by Young and Mangum (27) were consulted.

3-RESULTS

3-1. Uses

Treatment of neonatal herpes simplex infections, varicella zoster infections with central nervous system and pulmonary involvement, and herpes simplex encephalitis (27).

3-2. Adverse effects/Precautions

Neutropenia occurs in approximately 20% of infants - decrease dose or treat with granulocyte colony stimulation factor, if absolute neutrophil count remains less than $500/mm^3$. Phlebitis may occur at intravenous site due to alkaline pH of 10. Risk of transient renal dysfunction and crystalluria is minimized by slow infusion rates and adequate infant hydration. Resistant viral strains may emerge during long-term therapy; these infants are at high risk for progressive life-threatening disease (27). Antiviral drug that is preferentially taken up by infected cells; inhibits viral DNA synthesis. Cerebral spinal fluid

concentrations are 30 to 50% of serum concentrations. Oral absorption is 15 to 30%. Most of the administered dose of acyclovir is excreted unchanged in urine primarily via glomerular filtration and tubular secretion. Protein binding and metabolism are minimal. Serum half-life is 3 to 4 hours in neonates with normal renal and hepatic functions. In neonates, the dose of acyclovir is 20 mg/kg every 8 hours administered by syringe pump over 1 hour. The dosing interval is prolonged in premature infants < 34 weeks postmenstrual age or hepatic failure. The treatment of localized herpes simplex infection should be 14 days, and disseminated or central nervous system infection should be treated for 21 days. Infusion solution should be no greater than 7 mg/ml. For chronic suppression 75 mg/kg per dose orally every 12 hours should be given (27).

3-3. Use of acyclovir in premature and term neonates

Nine infants with symptomatic infections caused by herpes simplex virus or cytomegalovirus were treated with acyclovir. Five infants had infections caused by herpes simplex virus and 4 infants were infected by cytomegalovirus. At the onset of therapy, the infants ranged in weight from 880 to 4,550 grams. Five were premature. Eight of the nine infants were less than four weeks of age at the time of enrollment in the study, the ninth infant was a premature infant who was 60 days old. Acyclovir was administered intravenously at a dosage of 5 to 15 mg/kg every eight hours for 5 to 10 days. The peak serum acyclovir levels ranged from 20 to 163 μM and the trough levels ranged from 1 to 129 μM. The doses, the peak and trough concentrations of acyclovir in neonates are summarized in **Table.1**.

The variation in peak serum acyclovir levels in different infants receiving the same dosage on a weight basis was large, but correlated with the expected renal maturity of the individual infant. Hematologic values improved during therapy. No renal toxicity was noted. All of the infants survived, including the five with herpes simplex infection (28).

3-4. Pharmacokinetics of acyclovir in the term human pregnancy and neonates

The antiviral acyclovir administration has been used effectively to suppress genital herpes simplex virus recurrences in nonpregnant adults. Its administration to pregnant women with recurrent genital herpes virus may reduce herpes simplex virus recurrences and thus may decrease the cesarean section rate among this population (29). The mothers enrolled in the study were from 27 to 39 years old (mean, 31.7 years old), mostly white, gravid 1 to 4 (mean, 2.1), and had recognized genital herpes for 1 to 10 years (mean, 4.4). During the pregnancies studied, these women had 1 to 10 (mean, 3.7) herpes simplex virus recurrences. The acyclovir courses ranged between 3 and 29 (mean, 13.7) days' duration.

Acyclovir was well tolerated by the mothers; there were no complaints of nausea, vomiting, headache, or other symptoms, and in all cases the complete blood count with differential cell count, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, blood urea nitrogen, and urinalysis (including no crystalluria) were normal on days 1, 6, and 11 or the last day of therapy. At birth, all infants appeared normal and were given Apgar ≥8.

The cord blood count with differential cell count, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, blood urea nitrogen, and urinalysis values were normal. Except for a delay in the closure of the ducts arteriosus of one infant, there were no postnatal complications, and at 6 months of age all

infants were reportedly normal. The peripartum acyclovir levels in mothers and fetuses are shown in **Table.2**.

3-5. Acyclovir pharmacokinetics in neonates with herpes virus infection

Acyclovir pharmacokinetics is accurately described by a two-compartment open model (30). The volume of distribution at steady state is about two-thirds of the body weight. The half-life of its beta phase of elimination is about three hours with normal renal function and increases to about 18 hours with anuria. Hemodialysis removes about 60 percent of the acyclovir in the body. The pharmacokinetics is independent of dose at least up to 15 mg/kg. Acyclovir is minimally (15%) protein-bound and only a small percentage (15%) of an intravenous dose is metabolized in persons with normal renal function. Acyclovir is eliminated primarily by glomerular filtration with a small addition from tubular secretion. The toxicity of acyclovir seems to be acceptably low. Local irritation with extravasation exists. Transient glomerular dysfunction is occasionally seen after bolus administration. Other side effects remain to be clearly established.

The peak acyclovir plasma levels occurred between 1.5 and 3 hours after the dose was administered orally (29). The mean $\pm$ standard deviation (SD) acyclovir plasma levels at 1.5 hours for the 200 and 400 mg doses were 1.7 ± 0.6 and 2.3 ± 1.0 µM, respectively. One infant in the 200 mg dose group appeared to absorb acyclovir unusually well. In this neonate acyclovir levels were evaluated by a statistical technique that tests extreme observation in a sample. Her 1.5-hour value rose above the 95th percentile of the sampling distribution and therefore was excluded from the data analysis. The mean acyclovir plasma levels for the 200 and 400 mg doses, respectively, were 1.4 ± 1.3 and 2.4 ± 0.9 µM, at 3 hours after the dose, and 0.5 ± 0.1 and 1.0 ± 0.5 µM at 6 hours after the dose. Plasma acyclovir trough and peak concentrations obtained on days 6 and 11 were similar. The mean $\pm$ SD plasma trough values acyclovir in the 200 and 400 mg dose groups were 0.7 ± 0.3 and 0.8 ± 0.6 µM, respectively. During steady-state, the 400 mg dose group's mean peak levels (3.3 ± 1.0 µM) increased as compared with the first-dose mean peak level (2.3 ± 1.1 µM), whereas the suggestion of acyclovir accumulation was not seen during steady-state in the 200 mg dose group with a steady-state mean acyclovir of 1.9 ± 1.0 µM and a mean first dose peak of 1.7 ± 0.6 µM. The mean ratio of the maternal/cord acyclovir plasma levels was 1.3 ± 0.3. Acyclovir concentrations in the amniotic fluid (1.87 to 15.5 µM, n=6) were found to be three to six times higher than the corresponding cord plasma levels. The mean maternal acyclovir plasma level is higher than that obtained from the newborn shortly after the last dose of acyclovir. However, the maternal mean acyclovir levels dropped more rapidly than that of the newborn, although maternal and infant were similarly low by 16 to 48 after the last dose. Acyclovir taken orally at doses of 600 to 1,200 mg/day for 3 to 29 days, was well tolerated by women late in pregnancy and did not accumulate or cause adverse effects in their newborn infants.

Hintz et al. (31) described the pharmacokinetics of acyclovir in neonates (birth to 3 months) with herpes simplex virus types 1 or 2 infections, symptomatic cytomegalovirus or progressive life-threatening acquired cytomegalovirus disease enrolled in the study. Infants were treated at 5, 10, or 15 mg/kg acyclovir per dose. Acyclovir was administered intravenously and the dose was determined by the infant's age and clinical condition at the discretion of the clinical investigator. Five mg/kg per dose were given to 5 boys and 2 girls, to 5 infants with cytomegalovirus infections and 2 infants with herpes simplex virus. Infants ranged

in age from 4 days to 2 months. Ten mg/kg per dose were given to 2 boys and 5 girls, 4 infants with cytomegalovirus infections, and 3 infants with herpes simplex virus infections; they ranged in age from 4 to 105 days. Three boys and one girl received 15 mg/kg per dose. Two had cytomegalovirus infections and 2 infants had herpes simplex virus infections; they ranged in age from 4 to 105 days. Acyclovir was administered in intravenous fluid volume and the acyclovir content was determined by the infant's age and clinical condition at the discretion of the clinical investigator, given as 60 min infusions by pump, every 8 hours. The concentration of acyclovir in the infusion fluid did not exceed 1 mg/ml. Therapy continued for 5 to 10 days in neonates with herpes simplex infections, and for 10 days in infants with cytomegalovirus infections. All infants received 10 days of acyclovir, except those receiving 10 mg/kg acyclovir per dose, whose duration of therapy ranged from 4 to 10 days. Infants were first entered at a dosage of 5 mg/kg per dose. In the absence of drug-related toxicity at this dosage, the level was raised to 10 and again to 15 mg/kg per dose. The mean plasma peak and trough acyclovir concentrations are summarized in **Table.3**.

The peak and trough acyclovir concentrations achieved varied in neonates treated at each dosage. For example, at 5 mg/kg per dose, the peak acyclovir levels ranged from 14.3 to 50.6 µM, and trough levels ranged from 1.3 to 11.6 µM. Pharmacokinetic parameters for 3 neonates at each dosage are reported in **Table.4**. The mean slow disposition half-life values ($t_{1/2\beta}$) were 4.03±1.56 hours for 5 mg/kg per dose, 4.07±1.53 hours for 10 mg/kg per dose, and 3.24±0.69 hours for 15 mg/kg, with an overall mean of 3.78±1.21 hours. The mean total body clearances were 122±51, 98±34, and 108±43 ml/min/1.73m^2, respectively, for each dosage, with an overall mean of 109±39 ml/min/1.73m^2. The mean ± SD percent urinary recovery of acyclovir administered to neonates for 5 patients at 5 mg/kg per dose was 62.2±19.9% with a range of 31.8 to 87.6%; for 6 patients at 10 mg/kg per dose, the mean was 62.1±19.4% (range, 34.3 to 103.0%); for 3 patients at 15 mg/kg/dose, the mean was 72.4±26.0% (range, 40.2 to 116.4%). The mean concentration of acyclovir excreted in urine for the 6 patients at 5 mg/kg per dose was 121±96 µg/ml (range, 37 to 356 µg/ml); for the 6 infants at 10 mg/kg per dose, the mean was 178±121 µg/ml (range, 23 to 477 µg/ml); for the 3 patients at 15 mg/kg per dose, the mean was 463±198 µg/ml (range, 138 to 816 µg/ml).

The mean plasma peak and trough acyclovir concentrations increased in a dose-depended manner: each increment in dosage produced an equivalent rise in the mean acyclovir concentration. For these neonates, as the dosage rose three-fold from 5 mg/kg dose to 15 mg/kg per dose, the mean peak acyclovir concentrations also increased three-fold from 30.0±9.9 µM to 86.1±23.5 µM. Mean trough acyclovir levels increased similarly. At each dosage, the mean trough acyclovir levels were approximately 20% of mean peak acyclovir concentrations.

At the lowest dosage, the acyclovir plasma levels achievable in neonates were approximately 200 times the 50% inhibitory dose for herpes simplex virus type 1 (0.15 µM), 20 times that for herpes simplex virus type 2 (1.62 µM), and 10 times that for varicella zoster virus (3.75 µM), but equal to or less than that for cytomegalovirus (30 to 200 µM) (32). The acyclovir half-life for neonates was dose-independent, with a mean value of 3.78±1.21 hours. This half-life is slightly higher than the mean values reported for adults, which ranged from 2.60 to 3.16 hours. Renal excretion is the major route of acyclovir elimination with most of the drug being excreted un-metabolized. At all

three dosages, the mean urinary recovery was approximately 65%, with a range of 62.2 to 72.4%. For each dosage, the acyclovir pharmacokinetic parameters, total body clearance, distribution volume at steady-state, and the elimination half-life were consistent, as has been shown for adults in single-dose studies (33, 34). The acyclovir half-life for neonates was dose-independent, with a mean value of 3.78±1.21 hours. This half-life is slightly higher than the value reported for adults, which ranged from 2.60 to 3.16 hours (33, 34). Renal excretion is the major route of elimination with most of the drug being excreted non-metabolized (35).

At all three dosages, the mean urinary recovery of acyclovir was approximately 65%, with a range of 62.2 to 72.4%. These rates are comparable to those reported from single-dose studies of adults (33, 34). In previous acyclovir pharmacokinetic studies, renal clearances have been shown to be approximately three times higher than creatinine clearances, indicating that acyclovir is excreted by both glomerular filtration and renal tubular secretion (33, 35). This excretion pattern results in the passage of large amounts of acyclovir through the renal tubular collecting system. Renal toxicity might be a problem if acyclovir urine concentration in neonatal urine exceeds the acyclovir solubility (1.3 mg/ml in bladder urine). Acyclovir is well tolerated in neonates with herpes simplex infection without signs of clinical or laboratory toxicity (31). The mean acyclovir concentration in urine did not exceed the solubility of acyclovir in bladder urine (1,300 µgrams/ml).

3-6. Pharmacokinetics of oral acyclovir in neonates and infants: a population analysis

Tod et al. (36) determined the median and the 5th and 95th percentiles of pharmacokinetic parameters (post hoc estimate) following an oral suspension of acyclovir given to children younger than 2 years of age in order to support the proposed dosing regimen (24 mg/kg of body weight three times a day for patients younger than 1 month of age or four times a day otherwise). Children younger than 2 years with herpes simplex virus or varicella-zoster virus infections were enrolled in a multicenter study. Children were treated for at least 5 days with an acyclovir oral suspension. Plasma samples were obtained at steady state, before acyclovir administration, and 2, 3, 5, and 8 h after acyclovir administration. Data for 79 children were considered in the pharmacokinetic study. Acyclovir clearance was related to the estimated glomerular filtration rate, body surface area, and serum creatinine level. The distribution volume was related to body weight. The elimination half-life decreased sharply during the first month after birth, from 10-15 hours to 2.5 hours. Bioavailability was 0.12.

The interindividual variability was less pronounced when the parameters were normalized with respect to body weight. Hence, dosage adjustment by body weight is recommended for this population. Simulations showed that the length of time that acyclovir remains above the 50% inhibitory concentration during a 24-h period was more than 12 hours for herpes simplex virus but not for varicella-zoster virus. The proposed dosing regimen seems adequate for the treatment of herpes simplex virus infections, while for the treatment of varicella-zoster virus infections, a twofold increase in the dose of acyclovir seems necessary for children older than 3 months.

The mortality rate of infants with disseminated herpes simplex virus infections remains at 57%. The mortality rate for herpes simplex encephalitis alone is 15% and approximately 54% of survivors have been found to be moderately or severely neurologically impaired at 1 year of age (34, 35). These

mortality and morbidity rates are particularly concerning, because they were determined in a series of patients who received approved treatment regimens with enteral antiviral therapy (37, 38). Neurologic impairment is not limited to those infants who have involvement of the central nervous system which is recognized during the initial infection. Fourteen percent of infants whose initial herpes simplex type-2 infection appeared to be confined to skin, eyes or mouth subsequently developed neurologic impairment characteristic of herpes simplex virus (39). These observations have strengthened earlier indications that the cause of the poor prognosis in children with herpes simplex infection may not be restricted to injuries associated with the initial infection, but rather may also be related to later activation or dissemination to the central nervous system (40-43). Because of these concerns, some children with dermal recurrences are prescribed courses of treatment with oral acyclovir in an effort to preserve neurologic well-being (37). Herpes simplex virus lesions recur in 8 to 30% of infants who receive a course of parenteral antiviral therapy for an initial infection. Long-term acyclovir is used by some clinicians to prevent recurrent herpes simplex disease (44).

Rudd et al. (44) described 9 infants who were treated with doses of oral acyclovir which were chosen to achieve 2-hour plasma concentrations of ≥ 2 μg/ml. Eight infants had herpes simplex virus encephalitis and one had multiple recurrences of dermal and ocular disease. The target plasma concentrations were chosen in order to attain acyclovir cerebral fluid distribution (≤ 50% plasma) for estimated ID_{30} of herpes simplex virus type 2 strains of 0.1 to 0.5 μg/ml. One of 9 infants developed symptomatic recurrences of the central nervous system and none of the remaining 8 infants experienced recognized dermal or neurologic recurrences of herpes simplex virus disease. Renal and neurologic status were routinely monitored and no signs of acyclovir toxicity were observed. Plasma concentration of acyclovir ≥ 2 μg/ml may be achieved with average oral doses of 1,340 mg/m^2/dose (1,000 to 1,740 mg/m^2/dose) given at 12-hours intervals.

Neonatal herpes simplex virus acquired peripartum or postnatally can be classified into three clinical conditions: skin, eye and/or mucous membrane disease, central nervous system disease and disseminated disease (45). Classification is not a discrete entity, with skin, eye and mucous membrane disease sometimes progressing to central nervous system involvement. This classification has both therapeutic and prognostic implications; with skin, eye and mucous membrane disease treated with a 14- day course of acyclovir, and concomitantly less morbidity, as compared to central nervous system and disseminated disease, treated with a minimum of a 21- day course of acyclovir (46). The use of polymerase chain reaction on cerebral spinal fluid for more accurate and rapid diagnosis and the application of high doses of acyclovir as therapy has lessened mortality from herpes simplex disease (47, 48).

It is postulated that the dismal outcomes from central nervous disease and residual mortality from disseminated disease could be aborted or lessened with earlier initiation of acyclovir. However, this is complicated by the fact that skin, eye and mucous membrane lesions are often absent with the disseminated or central nervous system disease and sometimes have an atypical appearance. Therefore, there has been increasing use of acyclovir for infants with suspected sepsis in the first 6 weeks of life. The neonatal herpes simplex virus infection is difficult to diagnose and consequently there has been a move towards using more empiric acyclovir. Vanderpluym et al. (49) reviewed the use

of acyclovir to optimize future management of neonatal herpes simplex virus infection. Charts were reviewed for infants of intravenous acyclovir up to day 43 of life. Acyclovir was started for possible (n=115) or proven (n=3) herpes simplex virus infection. Six of the infants with possible herpes simplex virus infection later had proven herpes simplex virus infection. Seizures (34%), hemodynamic instability (29%) and skin lesions (24%) were the most common indications for acyclovir treatment. Among 118 infants, 106 (90%) had cerebrospinal fluid and 82 (69%) had at least one surface swab for herpes simplex virus, but 4 (3%) had no specimens submitted for herpes simplex virus detection. Acyclovir was continued for 3.9±3.5 days in the infants with no proven herpes simplex virus disease. Possible nephrotoxicity from acyclovir was recorded in 3 of these 109 infants and in none of the infants with proven herpes simplex disease. Clinicians should primarily consider the diagnosis of neonatal herpes simplex virus infection when confronted with a neonate with seizures, hemodynamic instability or suspicious skin lesions, but need to consider the diagnosis more often if all cases are to be treated at first presentation. Often incomplete investigations to rule out neonatal herpes simplex virus infection. Adverse events from acyclovir appear to be uncommon when the drug is used for suspected neonatal herpes simplex virus disease. The infants with proven herpes simplex virus infection are reported in **Table.5**.

3-7. Preventing herpes simplex virus transmission to the neonate

Neonatal herpes simplex virus infection can have severe consequences. Skin, eye and mouth infection is rarely fatal, but disseminated or central nervous system disease has a mortality of 80% in the absence of therapy, and most surviving infants have neurological sequelae. Acyclovir therapy can improve the outcome of neonatal herpes but is often delayed due to the early non-specific symptoms of the disease (46). Even with early therapy, some infants develop disseminated infections of central nervous system complications. The virus is usually vertically transmitted to the neonate from an infected mother during delivery. As such, the optimal strategy for reducing the morbidity of neonatal herpes is to prevent the neonate from acquiring herpes simplex virus infection at delivery. The highest risk of neonatal infection occurs when the mother sheds herpes simplex virus at labour, which happens more frequently in women who acquire genital herpes in the third trimester. Therefore, one approach for reducing maternal-fetal transmissions is to prevent herpes simplex virus acquisition in late pregnancy. Definitive classification of genital herpes simplex virus infection during pregnancy as either primary, non-primary first episode or recurrent can be accomplished only when clinical evaluation is accompanied by laboratory testing, including the use of glycoprotein G (gG-1 in HSV-1 and gG-2 in HSV-2) specific serological test. The serological status of the mother's sexual partner should be considered when determining her risk of infection. The use of weekly viral cultures in pregnant women with confirmed genital herpes is not warranted, as they do not predict an infant's risk of acquisition of herpes simplex virus at delivery and are not cost-effective. High-risk susceptible women should be counseled about abstinence and reducing oral-genital contact near term.

Observational studies suggest that caesarean section can reduce transmission of neonatal herpes, and is warranted for women who shed herpes simplex virus at delivery, although different countries vary in their approach to caesarian sections and so universal recommendations are not available. If maternal antiviral therapy is

considered, the potential benefits of treatment should be balanced against potential adverse outcomes for mother and fetus, although it may be warranted when the mother has severe or life-threatening disease. Studies on the use of antiviral prophylaxis in women with known recurrences at labour are continuing. Invasive fetal monitoring can increase the risk of neonatal herpes, and should only be used in herpes simplex virus type 2 seropositive women for defined obstetrical indications.

Scott et al. (48) continued evaluation of the use of acyclovir suppression in late pregnancy after first episode genital herpes simplex virus infection, using an open-label study design. Ninety-six women diagnosed with genital herpes for the first time in the index pregnancy were prescribed suppressive acyclovir 400 mg orally three times daily from 36 weeks until delivery in an open-label fashion. Herpes cultures were obtained when patients presented for delivery. Vaginal delivery was permitted if no clinical recurrences were present; otherwise a caesarian delivery was performed.

Neonatal herpes simplex virus cultures were obtained and infants were followed clinically. Rates of clinical and asymptomatic genital herpes recurrences and caesarian delivery for genital herpes were measured, and 95% confidence intervals were calculated. In 82 patients (85%) compliant, only 1% had clinical herpes simplex virus recurrences at delivery. In an intent to treat analysis of the entire cohort, 4% had clinical recurrences (compared with 18-37% in historical controls). Asymptomatic shedding occurred in 1% of women without lesions at delivery. Two of the four clinical recurrences were herpes simplex virus-culture positive. No significant maternal or fetal side-effects were observed. In clinical practice the majority of patients are compliant with acyclovir suppression at term. The therapy appears to be effective in reducing clinical recurrences after a first episode of genital herpes complicating a pregnancy. Acyclovir therapy in late pregnancy among women with recurrent genital herpes is effective in decreasing genital lesion frequency and subclinical viral shedding rates at delivery, thereby decreasing the need for caesarian section. Despite good adherence and increased dosing schedules, breakthrough lesions and viral shedding are still observed in some women at or near delivery. Anecdotal evidence suggests that low levels of herpes simplex virus replication at delivery may result in transmission to the neonate (50). Leung et al. (50) objectives were to determine actual maternal and fetal acyclovir levels at delivery, and time since last dose. Twenty-seven patients were prescribed oral acyclovir 400 mg 3 times daily from 36 weeks' gestation until delivery. Cord blood (venous and arterial) and maternal venous blood samples were collected at delivery, and acyclovir levels were measured.

Correlations between duration of labour, and time since last acyclovir dose with acyclovir blood levels were calculated. Acyclovir levels were below the published mean steady state trough value (180 ng/ml) in 52 of venous cord samples, 55% of arterial cord samples, and 36% of maternal samples. There was a significant inverse correlation between the time since last dose and venous cord levels ($r= -0.57$, $p=0.015$), arterial cord levels ($r = -0.63$, $p<0.01$), and maternal acyclovir levels ($r= -0.69$, $p<0.03$). Oral dosing of acyclovir in women in late pregnancy may result in insufficient levels at delivery to prevent viral shedding. Alternative approaches that incorporate acyclovir dosing through labour, either through oral or intravenous administration, should be evaluated to assess effects on viral shedding.

Table-1: Peak and trough plasma concentrations of acyclovir after intravenous administration of acyclovir to neonates: relationships of dosage to neonate body weight and chronologic age, by Yeager (28)

Daily dose of acyclovir (mg/kg)	Unit dosage of acyclovir (mg/kg)	Infant	Body weight (grams)	Chronologic age (days)	Acyclovir levels (μM)	
			At onset of therapy		Peak	Trough
15 mg/kg	5 mg/kg	1	2,000	7	35-49	4-8
		2	1,650	60	20-25	1-2
30 mg/kg	10 mg/kg	3	2,609	5	60-117	21-41
		4	2,310	8	50-66	7-12
		6	2,700	4	51-93	8-7
45 mg/kg	15 mg/kg	7	2,080	6	92-152	24-37
		8	4,550	24	72-87	7-10
		9	880	25	136-163	83-129

Table-2: Concentrations of acyclovir (μM) in mothers and fetuses after 200 mg of oral acyclovir administration to mothers, by Frenkel et al. (29)

Variables	Patient No 1	Patient No 2	Patient No 3	Patient No 4	Patient No 5	Patient No 6	Patient No 7
No. of days of acyclovir	10	7	6	11	15	10	16
Maternal plasma at delivery	1.09	1.70	0.65	0.76	0.80	3.51	1.09
Cord plasma	1.08	1.23	0.59	0.46	0.67	2.23	1.02
Maternal/cord plasma	1.0	1.38	1.10	1.60	1.19	1.57	1.07
Amniotic fluid	na	3.42	1.87	6.06	na	na	na
Gastric aspirate	na	4.00	4.37	5.31	na	na	na
Placenta	1.31	6.19	1.34	1.08	na	na	na

na= not available.

Table-3: Peak and trough plasma acyclovir concentrations (μM) in neonates. Acyclovir was administered intravenously. The figures are the mean ± SD and the range, by Hintz et al. (31)

Number of neonates	Dosage mg/kg per dose	Peak		Trough	
		Mean ± SD	Range	Mean ± SD	Range
8	5	30.0±9.9	(14.3-50.6)	5.3±34	(1.3-11.6)
7	10	61.2±18.3	(38.1-116.8)	10.1±8.4	(1.8-41.0)
4	15	86.1±23.5	(51.4-151.7)	13.8±11.1	(3.4-36.5)

SD: Standard deviation.

Table-4: Pharmacokinetic parameters of acyclovir following intravenous administration of acyclovir to neonates, by Hintz et al. (31)

Dosage (mg/kg)	Patient number	Clearance[A] (ml/min/1.73m^2)	Distribution volume[B] (liter/1.73m^2)	Elimination half-life (hours)
5.0	1	169	30.0	2.57
	2	68	28.0	5.67
	3	128	31.0	3.84
Mean ± SD		122±51	30.0±2.0	4.03±1.56
10	1	62	17.8	3.59
	2	102	40.4	5.78
	3	130	28.4	2.84
Mean ± SD		98±34	28.9±113	4.07±1.53
15	1	58	17.0	3.64
	2	132	28.9	3.64
	3	134	26.3	2.44
Mean ± SD		108±43	24.1±6.3	3.24±0.69
Overall mean ± SD		109±39	27.5±70	3.78±1.21

A=Total body clearance; B=Distribution volume at steady state.

Table-5: Infants with proven herpes simplex virus infections, by Vanderpluym et al. (49)

Gestational age (weeks)	Age at treatment (days)	Time to positive HSV diagnosis from symptom onset (days)	Clinical presentation	Site of initial detection	Test	HSV classification	Outcome[A]
35	16	19	Skin lesions, maternal HSV, hemodynamic instability	CSF	PCR	CNS	Hearing and visual impairment, development delay, spastic quadriplegia
38	6	6	Skin lesions, fever, seizures, coagulopathy	Skin, eyes and throat	DEA	Disseminated	Death at day 3 of acyclovir (multi-organ failure)
40	9	3	Fever, lethargy, poor feeding	CSF	PCR	CNS	Survived-no follow-up
40	37	2	Fever, lethargy, poor feeding	Skin, mucous membranes and stool	Culture	Disseminated	Survived-no follow-up
41	13	9	Skin lesions	Skin	Culture	SEM	Recurrent HSV skin lesions
40	11	11	Hemodynamic instability, respiratory distress, coagulopathy, seizures	Skin, eyes and mucous membranes	Culture	Disseminated	Death at day 2 of acyclovir (multi-organ failure)

33	18	2	Skin lesions	Skin and mucous membranes	DFA	SEM	Well
33	9	1	Skin lesions	Skin and mucous membranes	DFA	SEM	Well
34	21	2	Skin lesion	Skin	Culture	SEM	Well

HSV=herpes simplex virus; CNS=central nervous system; DFA=direct fluorescent antibody; PCR=polymerase chain reaction; SEM=skin, eye and mucous membrane. [A]Follow-up was incomplete as only inpatient charts were available for review.

4-DISCUSSION

Acyclovir is a guanosine derivative with a high specificity for herpes simplex and varicella-zoster viruses. Herpes simplex virus is more susceptible than varicella-zoster virus to acyclovir (51). Acyclovir inhibits viral DNA synthesis. Once acyclovir penetrates the virally infected cells, it is phosphorylated into acyclovir monophosphate by herpes simplex virus thymidine kinase and subsequently into di- and triphosphate forms by cellular enzymes (12, 13). Acyclovir triphosphate is the active antiviral compound and is a selective substrate and inhibitor of the herpes simplex virus DNA polymerase (14, 15).

Acyclovir distributes widely throughout the body and enters the cerebrospinal fluid. The major route of acyclovir elimination is via glomerular filtration and tubular secretion, the mean percentage of acyclovir excreted in the urine is about 62% of the administered dose (31). Therefore, dosage adjustment is required in patients with renal dysfunction. Poor renal function causes sign of central nervous system toxicity, with lethargy, tremor and disorientation (2). Acyclovir is effective in the treatment of a number of infections caused by herpes simplex virus, including mucocutaneous, genital, and encephalitic infections, and varicella-zoster infections (2). Neonatal herpes simplex virus infection can have severe consequences. Skin, eye and mouth infection is rarely fatal, but disseminated or central nervous system disease has a mortality of 80% in the absence of therapy, and most surviving infants have neurological sequelae. Acyclovir therapy can improve the outcome of neonatal herpes simplex infection, but is often delayed due to the early non-specific symptoms of the disease (46). At each dosage, the mean trough acyclovir levels were approximately 20% of mean peak acyclovir concentrations. At the intravenous dosage of 5 mg/kg, the peak acyclovir plasma levels achievable in neonates were approximately 200 times the 50% inhibitory dose for herpes simplex virus type 1 (0.15 µM), 20 times that for herpes simplex virus type 2 (1.62 µM), and 10 times that for varicella zoster virus (3.75 µM), but equal to or less than that for cytomegalovirus (30 to 200 µM) (32).

Acyclovir can be administered intravenously or orally, when administered orally the bioavailability is 12% and oral uptake is limited and delayed. In neonates, the acyclovir half-life is 5 hours and in children over 3 months old is 2.5 hours (2). Acyclovir pharmacokinetics is accurately described by a two-compartment open model. The distribution volume at steady state is about two-thirds of the body weight. Acyclovir is 15% bound to plasma proteins. Acyclovir is concentrated in the amniotic fluid, however there is no accumulation in the fetus and the mean maternal/infant plasma ratio is 1.3 (29). Herpes simplex virus is usually vertically transmitted to the neonate from the

infected mother during delivery. The highest risk of neonatal infection occurs when the mother sheds herpes simplex virus at labour, which happens more frequently in women who acquire genital herpes simplex infection in the third trimester of pregnancy. Observational studies suggest that caesarian section can reduce transmission of neonatal herpes simplex virus, and is warranted for women who shed herpes simplex virus at delivery. Herpes cultures should be obtained when patients present for delivery. Vaginal delivery is permitted if no clinical recurrences are present; otherwise a caesarian delivery is performed (52). In clinical practice the majority of patients are compliant with acyclovir suppression at term. Women with genital herpes for the first time in the index pregnancy may be treated with acyclovir 400 mg orally three times daily from 36 weeks of pregnancy until delivery. The therapy appears to be effective in reducing clinical recurrences after a first episode of genital herpes complicating a pregnancy. Acyclovir therapy in late pregnancy among women with recurrent genital herpes is effective, thereby decreasing the need for caesarian section (49).

Owing to the ease of acyclovir administration and dosage adjustment, the oral suspension is also used in children. The recommended oral dosage in neonates is 100 mg four times a day quater in die (q.i.d.) for herpes simplex virus infections and 200 mg (q.i.d.) for varicella-zoster virus infections. In the latter case the total dose should be less than 800 mg (2). Oral acyclovir is also effective for the prevention of cutaneous recurrences after herpes simplex virus type 2 disease of the skin, eyes, and mount at a dose of 300 mg/m^2 every 8 hours (53). The bioavailability of acyclovir administered as an oral suspension is about 12%. This value is in the range of bioavailability values estimated for adults (20% for the 200-mg dose, 12% for the 800-mg dose) (53). From a practical point of view, it implies that for an oral dosing regimen, mean acyclovir concentrations are about 8 times lower than an intravenous administration to the same patients, so that doses administered by the oral route must be about 8 times higher than those administered by the intravenous route to ensure the same exposure (36).

5- CONCLUSION

In conclusion, acyclovir inhibits viral DNA synthesis. It is active against herpes simplex virus types 1 and 2 and against varicella-zoster virus infections. Acyclovir has no effect on dormant viruses and needs to be given early to influence viral replication. Acyclovir may be administered intravenously or orally. When administered orally, the bioavailability is 12%. The half-life of acyclovir is 5 hours in neonates and is 2.5 hours in children over 3 months old. Acyclovir distributes throughout the body and reaches cerebral spinal fluid concentrations 30 to 50% of serum concentrations. In neonates, the dose of acyclovir is 20 mg/kg every eight hours for 14 days given intravenously by syringe pump over one hour. The mean trough acyclovir levels were approximately 20% of mean peak acyclovir concentrations.

At the dosage of 5 mg/kg, the peak acyclovir plasma levels achievable in neonates were approximately 200 times the 50% inhibitory dose for herpes simplex virus type 1 (0.15 µM), 20 times that for herpes simplex virus type 2 (1.62 µM), and 10 times that for varicella zoster virus (3.75 µM), but equal to or less than that for cytomegalovirus (30 to 200 µM). There is a large interindividual variation in the neonate of acyclovir serum concentrations. Acyclovir binds to plasma proteins at a rate of 15%. Acyclovir is transmitted vertically from the infected pregnant women to the neonate. The highest risk of

neonatal infection occurs when the mother sheds herpes simplex virus at labour, which happens more frequently in women who acquire genital herpes in the third trimester of pregnancy. To avoid the transmission of herpes simplex virus to neonates it has been suggested administrating 400 mg acyclovir orally three times daily from 36 weeks until delivery. Alternatively, a caesarian section can be performed to avoid the infection of neonates born to mothers with genital herpes simplex virus.

6- CONFLICT OF INTERESTS

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