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Acyclovir for Neonatal and Pediatric Viral Infections Marcia L. Buck, Pharm.D., FCCP

Since its introduction in the United States in 1984, acyclovir has become the drug of choice for the prophylaxis and treatment of herpes simplex infections in neonatal and pediatric patients. It has been shown to be both effective and safe in even the youngest patients. Recently, a new high-dose intravenous (IV) acyclovir regimen has been adopted for the treatment of herpes simplex infections in neonates which appears to further reduce the morbidity and mortality associated with this disease.¹ At the same time, reports of acyclovir resistance in viral isolates from neonates have raised questions about the drug's long-term efficacy. This issue of the newsletter will address the recent literature on acyclovir and provide a general review of its use in infants and children.

Mechanism of Action

Acyclovir is a synthetic purine nucleoside analog, with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and varicella-zoster virus. Because of its affinity for thymidine kinase (TK), acyclovir is taken up into infected cells and converted to the active triphosphate form, which interferes with viral DNA polymerase and inhibits replication.^{2,3}

Indications

Parenteral acyclovir is approved by the Food and Drug Administration (FDA) for the treatment of herpes simplex encephalitis, initial and recurrent HSV-1 and HSV-2 and herpes zoster (shingles) in immunocompromised patients, and severe initial episodes of genital herpes in immunocompetent patients. Oral acyclovir is indicated for the acute treatment of herpes zoster and varicella, as well as the treatment of initial and recurrent episodes of genital herpes.³

Neonatal HSV Infections

The incidence of neonatal HSV infection is estimated at 1 in 20,000 to 30,000 births.⁴ Symptoms may develop at any time during the

first month of life. Neonatal HSV encephalitis carries a high rate of morbidity and mortality, with central nervous system (CNS) sequelae and/or recurrent skin lesions in many surviving infants. Early initiation of acyclovir has been shown to significantly improve the outcome of neonatal HSV infections.^{5,6}

The original studies of acyclovir in neonatal HSV infections used a dosing regimen of 30 mg/kg/day.⁶ This regimen was found to be effective and well tolerated and quickly became the standard. Despite the widespread adoption of this regimen, the morbidity and mortality associated with neonatal HSV infections remained high. In 2001, the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group published the results of a trial using a high-dose acyclovir regimen in an attempt to improve outcomes.⁷ In this open-label multicenter trial, the first 16 neonates enrolled received an intermediate-dose regimen of 45 mg/kg/day and the next 72 patients received a high-dose regimen of 60 mg/kg/day. In both groups, acyclovir was administered IV in three divided doses for 21 days. The groups were compared to each other and to the results of an earlier study of standard acyclovir (30 mg/kg/day) conducted by the same investigators.

Survival rates for neonates with disseminated disease were significantly better for the high-dose regimen than with standard dosing (odds ratio 3.3 with 95% CI 1.4-7.9). Intermediate dosing was no different than standard. In patients with CNS disease, there was no difference among groups. When stratified for extent of disease, and after controlling for confounding variables, the authors found a significant benefit from the high-dose regimen both in overall survival and reduction in morbidity. Patients treated with high-dose acyclovir were 6.6 times as likely to be developmentally normal at 12 months as those treated with standard dosing.

Viral Resistance

Reports of viral resistance have also caused concern with standard dosing. Viral resistance to acyclovir may result from quantitative or functional changes in either the TK gene or viral DNA polymerase. Mutation of the TK gene may produce TK-deficient viral strains or strains with partial or altered TK function.³ Acyclovir resistance has been estimated to occur in 0.1 to 0.6% of immunocompetent adults and up to 5% of immunocompromised patients.⁸

Although the initial reports involved adults, there have been several recent case reports of acyclovir-resistant HSV strains isolated in neonatal patients.^{9,10} In 2000, Oram and colleagues reported mutation of the TK gene in an HSV-2 strain isolated from a 708 gram, 26 week gestation baby with skin and CNS disease.⁹ Despite treatment for 21 days with acyclovir (30 mg/kg/day), HSV was still detectable in the cerebrospinal fluid (CSF) at the end of treatment. Reinstitution of therapy following the reappearance of symptoms did not clear the infection until day 53. The patient expired on day 65 of disseminated HSV and a concomitant candidal infection.

Another case of resistance was reported last year by Levin and coworkers in *The Pediatric Infectious Disease Journal*.¹⁰ This patient, a 1,200 gram baby born at 27 weeks gestation, was placed on acyclovir (30 mg/kg/day) on day 4 of life following the diagnosis of maternal disseminated HSV infection. A CSF sample was positive for HSV by polymerase chain reaction. On day 9, the patient developed increasing cardiovascular and respiratory instability, progressing to hepatic dysfunction and disseminated intravascular coagulation. Foscarnet was initiated (33 mg/kg IV every 8 hrs), but did not alter the patient's course. Support was withdrawn on day 14. Analysis of the HSV isolate taken after 7 days of acyclovir revealed a mutation in the TK gene.

Pharmacokinetics

Oral acyclovir is slowly and incompletely absorbed from the gastrointestinal (GI) tract. Peak serum concentrations are reached 1.5 to 2 hours after a dose. Bioavailability is low, at 10 to 20%, and decreases with increasing doses. Absorption is unaffected by the presence of food. Acyclovir is widely distributed into tissues and body fluids, with minor protein binding (9-33%). Acyclovir concentrations in the CNS are approximately 50% of serum concentrations. Renal excretion of unchanged drug accounts for 62-91% of an acyclovir dose. The remainder is

eliminated as the 9-[(carboxymethoxy)-methyl]guanine metabolite.^{2,3}

Elimination half-life and total body clearance are dependent on renal function. The average half-life in adults with normal renal function is 2.5 to 3.3 hours. As creatinine clearance falls, half-life lengthens. Anuric patients may have a half-life greater than 19 hours. Acyclovir is removed by hemodialysis, with approximately 60% of a dose removed after 6 hours. Preliminary research suggests that acyclovir is also removed by continuous venovenous hemodialysis, and to a lesser extent, by continuous arteriovenous hemodialysis (CAVHD) and CAVHD with hemofiltration. Peritoneal dialysis removes only minimal amounts of acyclovir. Despite the method used, all patients requiring dialysis should be monitored for drug accumulation.^{11,12}

The pharmacokinetics of acyclovir in children and adolescents are similar to those of adults.¹³⁻¹⁵ In a preliminary study of 47 children (neonates to 17 years of age) receiving either 250 or 500 mg/m² doses, the average half-life was 2.52±1.04 hours.¹³ When divided into subgroups (0-3 months, 3 months-1 yr, 1-2 yrs, 2-7 years, 7-12 years, and 12-17 years), the patients < 3 months of age had the longest half-life, with an average of 4.05±1.22 hours. This finding has recently been reproduced in the high-dose IV study⁶ and a study of oral acyclovir in 79 children less than 2 years of age.¹⁵ Elimination half-life in the oral study was found to decline sharply during the first month of life, from 10-15 hours at birth down to 2.5 hours at one month.

Drug Interactions

Acyclovir has relatively few drug interactions. When given with probenecid, renal clearance of acyclovir is reduced, producing increased serum concentrations and a longer elimination half-life. When acyclovir is administered with zidovudine, some patients have experienced severe drowsiness and lethargy. Because of its ability to precipitate in renal tubules, acyclovir should be used with caution in patients receiving other nephrotoxic agents.^{2,3}

Adverse Effects

Acyclovir is generally well tolerated. Following oral administration, the most common adverse effects associated with acyclovir in children and adults are nausea and/or vomiting (in 2-8% of patients), diarrhea (0.3-4%), headache or malaise (0.6-12% of patients), asthenia or paresthesia (0.8-2%), and skin rash (0.3-2%). In patients given IV acyclovir, additional adverse effect include: inflammation or phlebitis (in 9% of patients), transient neutropenia (3%), elevations

in serum creatinine or BUN (5-10%), and elevation of hepatic transaminases (1-2%).^{2,3}

Encephalopathic changes, such as obtundation, tremors, confusion, agitation, hallucinations, and seizures, have been reported in approximately 1% of patients receiving acyclovir. A causal relationship with acyclovir may be difficult to establish, as these symptoms may be associated with the patient's underlying viral infection. Other rare, serious adverse effects include hyperbilirubinemia, hepatitis, renal dysfunction, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS). TTP/HUS has been fatal in immunocompromised patients receiving acyclovir.

Dosing Recommendations

Acyclovir (Zovirax[®]; GlaxoSmithKline or generic) is available in 200 mg capsules, 400 and 800 mg tablets, and a 200 mg per 5 ml suspension. Acyclovir for injection is available in a 50 mg/ml concentration.³

Parenteral Dosing

The acyclovir regimen for neonatal HSV in the *2000 Red Book* is 60 mg/kg/day for 14 to 21 days. In older infants and children with HSV encephalitis, the recommended dose is 30 mg/kg/day for 14 to 21 days. For the treatment of HSV in immunocompromised patients, whether localized, progressive, or disseminated, the dose of acyclovir is 15-30 mg/kg/day for 7 to 14 days. For the treatment of varicella in an immunocompromised patient or zoster infections, a dose of 30 mg/kg/day for 7 to 10 days (or 1,500 mg/m²) is recommended. For genital HSV infection, the first episode may be treated with IV acyclovir 15 mg/kg/day for 5 to 7 days.¹⁶

All regimens are given as 3 divided doses in patients with normal renal function. In premature infants with HSV infection, the dosing interval may be extended to 12 hours to account for reduced renal clearance. Acyclovir should be infused over at least one hour, to avoid crystalluria and renal tubule damage, as well as irritation at the injection site. In patients with renal dysfunction, the dose and dosing interval should be adjusted based on the creatinine clearance (CrCL) as described below:

CrCL (ml/min/1.73m ²)	% of Normal Dose	Interval (hrs)
> 50	100	8
25-50	100	12
10-25	100	24
0-10	50	24

Oral Dosing

Oral administration of acyclovir must account for its poor bioavailability. In children treated for varicella infection, a dose of 20 mg/kg/dose given 4 times daily (80 mg/kg/day) is recommended for a period of 5 days. Adults and children over 40 kg should be treated with 800 mg 4 times daily for 5 days. For genital HSV infections, 40-80 mg/kg/day divided in 3 or 4 doses is recommended for 5 to 10 days. In older patients with HSV infections, the dose is 1,000 to 1,200 mg/day divided in 3-5 doses for 5 to 14 days. As with IV administration, oral doses should be adjusted for renal dysfunction by extending the dosing interval.¹⁶

Valacyclovir and famciclovir

Although only limited information is available in children, valacyclovir and famciclovir may become useful alternatives to acyclovir in the future.^{17,18} Valacyclovir is a prodrug which is converted to acyclovir in the GI tract and liver. Unlike acyclovir, valacyclovir is rapidly absorbed after an oral dose and has a bioavailability approaching 50%. In some studies, serum acyclovir concentrations following valacyclovir administration matched those achieved with IV acyclovir dosing. Famciclovir is an oral prodrug of penciclovir, another guanine analog. Like acyclovir, penciclovir is phosphorylated by viral TK to its active form. Famciclovir has a bioavailability of 75%.

The primary advantage of these agents is their longer duration. In adults, valacyclovir is dosed twice daily (500 mg to 1 gram twice daily) for genital herpes infections in adults and once daily for suppression of infection. For herpes zoster, the dose is 1 gram three times daily for 7 days. Valacyclovir can be made into a liquid for patients unable to swallow tablets.¹⁹ The recommended dose of famciclovir for the treatment of genital herpes in adults is 125 mg twice daily. The dose for herpes zoster is 500 mg every 8 hours for 7 days.³ There are only case reports on the use of valacyclovir and famciclovir in children at this time. More work is needed to define the optimal pediatric dose.

Summary

Acyclovir has been used in the United States for nearly 20 years, yet there is still new information being accumulated about its role in treating viral infections in infants and children. Recent studies suggest that larger doses may be more effective in treating neonatal infections. The adoption of a new high-dose regimen, as well as the potential addition of valacyclovir and famciclovir to the options for long-term therapy, may mark the

beginning of significant changes in the use of antiviral therapies in pediatric patients.

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Pharmacology Literature Review

Cognitive effects of anticonvulsants

Based on their assessment of the current literature, the authors of this review suggest that the newer anticonvulsants (oxcarbazepine, vigabatrin, lamotrigine, gabapentin, tiagabine, topiramate, levetiracetam, and zonisamide) have fewer adverse effects on cognition than the traditional agents (phenobarbital, phenytoin, carbamazepine, and valproic acid). While most of the research cited involves adults, the results from these trials are likely to be of interest to pediatric practitioners considering the impact of these therapies on academic performance. Brunbeck L, Sabers A. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: a comparative review of newer versus older agents. ***Drugs* 2002;62:593-604.**

Immunosuppressive therapy review

The pharmacokinetic profiles of immunosuppressive agents in children is the focus of this extensive review. The studies are organized by drug (cyclosporin, tacrolimus, mycophenolate, and others) and further classified by type of transplant. The authors also provide a very useful introduction, highlighting the difficulties in performing pharmacokinetic studies in children, and a summary section with suggestions for future study design. de Gatta M, Santos-Buelga D, Dominguez-Gil A, et al. Immunosuppressive therapy for paediatric transplant patients: pharmacokinetic considerations. ***Clin Pharmacokinet* 2002;41:115-35.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/24/02:

1. The results of the enoxaparin medication utilization review (MUE) in adults were presented. For more information, contact the Drug Information Center at 4-8034.

Contributing Editor: Marcia L. Buck, Pharm.D.

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Michelle W. McCarthy, Pharm.D.

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