

The Use of Oral Acyclovir in Otherwise Healthy Children With Varicella

Committee on Infectious Diseases

The Food and Drug Administration approved the use of oral acyclovir to treat varicella infections in otherwise healthy children in 1992. Varicella, the result of primary infection with varicella-zoster virus, is a nearly universal infection of childhood and accounts for about 3 to 4 million cases per year in the United States. While usually a self-limited disease in the otherwise healthy child, complications that may result in hospitalization include secondary bacterial skin infection (1% to 4% of cases); Reye syndrome (formerly 3 to 4 per 100 000 cases, usually in association with salicylate therapy); acute cerebellar ataxia and meningoencephalitis (approximately 1 per 4000 and 1 per 40 000 cases, respectively); and, rarely, varicella pneumonia.¹⁻⁵ Although serious complications are rare, the frequency of varicella infection results in hospitalization of more than 4500 otherwise healthy children each year. Approximately 50 to 100 deaths in otherwise healthy children occur each year in the United States with an estimated mortality rate of 1 per 50 000 cases.^{1,2,5}

Immunocompromised individuals with either primary varicella infection or recurrent infection (zoster, shingles) benefit from early therapy with intravenous acyclovir. Other groups of pediatric patients who may experience unusually severe disease or a higher rate of complications include children in the first year of life, adolescents, pregnant adolescents, and possibly patients receiving systemic steroids even for short periods of time.⁶⁻¹¹ Approximately 10% of varicella cases occur in individuals older than 14 years of age. According to many experts, varicella is more severe or may result in increased complications in those with chronic cutaneous or pulmonary disorders or those receiving chronic salicylate therapy (potentially resulting in an increased risk for Reye syndrome). However, no data currently exist that delineate benefits of oral acyclovir for these high-risk patients. Several studies have indicated that children who contract their infection at home (secondary family cases) generally have more severe diseases, including approximately 50% more skin lesions and longer duration of lesions, but the studies do not indicate increased febrile response or known complication rate.^{3,4,12}

ORAL ACYCLOVIR THERAPY FOR VARICELLA

Recommendations for the feasibility and advisability of acyclovir treatment of otherwise healthy chil-

dren with varicella involve consideration of the type and degree of potential clinical benefit, the effect of therapy on acute and long-term complications, the effect on transmission of varicella, the associated adverse effects of therapy, the potential of antiviral resistance, and the cost.

Acyclovir

Acyclovir is a nucleoside analogue. In vivo, it is phosphorylated first by viral thymidine kinase and then by host cellular kinase to form a triphosphate antiviral that inhibits herpes virus DNA polymerase and terminates DNA replication and viral production. Acyclovir administered intravenously is indicated to treat varicella-zoster virus infection in the immunocompromised patient.⁶ Oral acyclovir is 15% to 20% bioavailable.

Clinical Studies

Recent placebo-controlled, double-blind studies involving more than 900 otherwise healthy children from 2 to 16 years of age have demonstrated that early oral therapy for varicella had beneficial clinical effects.^{3,4} In the largest study involving 815 children, 5 days of acyclovir therapy (20 mg/kg orally four times a day with a maximum dose of 800 mg four times a day) initiated within the first 24 hours of onset of rash significantly reduced the mean maximum number of lesions (from 347 to 294), the percent of children with more than 500 lesions (from 38% to 21%), and the median number of late (day 28) residual lesions (from 13 to 6). By day 3, 5% of the acyclovir group continued to have new lesions compared with 20% of control children, some of whom continued to have newly formed lesions for more than 6 days.⁴ Children receiving acyclovir were less ill as determined by a constitutional illness score and had a more rapid defervescence, with the mean day of defervescence being day 1 for the treated group and day 2 for those receiving placebos. By day 3 all treated children and 75% of control children were afebrile. Children older than 12 years of age, who tend to have a more serious illness than younger children, derived similar benefits, especially if varicella was acquired from a household contact.⁷ No reduction in the occurrence of complications in otherwise healthy children could be demonstrated, but the rate of complications, 1% to 2%, in both the acyclovir and placebo groups was low, consisting of 11 cases of secondary cutaneous infection and 1 case of cerebellar ataxia in the 815 children enrolled.⁴ Rates and duration of viral shedding have not been monitored in any study to date.

The rate of transmission of varicella or the number of secondary household cases was not affected by

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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acyclovir therapy in these studies. Since varicella is most contagious during the prodromal phase, administration of acyclovir at the onset of the rash would be unlikely to affect the transmission or epidemiology of varicella. Prophylactic use of acyclovir to prevent acquisition of infection by a contact has not been adequately studied, but may result in an alteration of the incubation period and of the immune response.

Adverse Effects

In these studies adverse reactions to treatment were infrequent, and no toxicity could be attributed directly to acyclovir therapy.^{3,4,7} In adults, oral therapy with acyclovir has been associated with a low incidence of gastrointestinal tract disturbance and rash. Acyclovir has been shown to lower transiently the humoral and cellular immune responses to primary herpes simplex virus infections^{13,14} and to result in a slight increase in severity during their first herpetic recurrence in some people.¹³ If these findings were also true regarding the therapy of varicella, the potential of developing zoster could be increased. However, in studies of children receiving acyclovir for varicella, the humoral immune response 1 month to 1 year later was generally equivalent to that of placebo recipients,^{3,4,7,15} although one study revealed a lower titer of fluorescent antibody to membrane antigen in acyclovir recipients 28 days after illness.³ Acyclovir therapy had no effect on the cellular immune response as determined by the response of peripheral blood mononuclear cells to varicella antigen (Rotbart H, personal communication, 1991). No long-term data are available on the rate or severity of zoster in otherwise healthy children treated for chickenpox with acyclovir. The development of resistance to acyclovir by varicella-zoster virus is a rare event and has been reported primarily in immunocompromised patients who have received chronic or repetitive courses of acyclovir.^{16,17}

Acyclovir is not teratogenic in standard animal studies, but no controlled study of its use in pregnant women has been undertaken. While a registry of women treated with acyclovir during pregnancy could detect no increase in birth defects compared to the numbers occurring in the general population and no consistent patterns of abnormalities among acyclovir-treated children with birth defects, the number of prospective cases evaluated (312) is insufficient to detect uncommon deleterious effects.¹⁸ For this reason, acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Since maternal varicella infection is teratogenic, it could be difficult to discern whether a congenital abnormality occurring in a baby born to a mother treated with acyclovir for varicella during pregnancy was due to acyclovir or to varicella.¹⁰ No data on the effect of maternal therapy with acyclovir and possible prevention or amelioration of the congenital varicella syndrome are available.

Economic Considerations

The annual estimated cost from varicella in the United States is approximately \$400 million, with 95% of that attributed to days of work lost by parents

cares for their sick children who have been excluded from school or day care.¹⁹ The typical case of varicella in a family results in 8.7 school days and 0.5 parental workdays lost.²⁰ The Academy⁶ recommends and a recent analysis²¹ confirms that untreated children may return to school 6 days after the onset of rash (or sooner if all lesions are crusted). Current studies using acyclovir in the otherwise healthy child have not ascertained duration of viral shedding. In the absence of these data, these recommendations still apply to the acyclovir-treated child. This issue is important in cost-benefit analysis. The cost of a 5-day course of oral acyclovir therapy varies from \$50 to \$78, depending on the weight of the child and geographic location. If acyclovir were universally used for otherwise normal children with varicella, the cost of the drug would be more than \$200 million per year.

SUMMARY

Oral acyclovir therapy initiated within 24 hours of illness for otherwise healthy children with varicella typically will result in a 1-day reduction of fever and approximately a 15% to 30% reduction in the severity of cutaneous and systemic signs and symptoms. Therapy has not been shown to reduce the rate of acute complications, pruritus, spread of infection, or duration of absence from school. Its long-term effect on the rate of occurrence of zoster is unknown. To date, no significant adverse effects of oral acyclovir therapy in otherwise healthy children have been demonstrated. In adults, delay of therapy beyond the first 24 hours of illness results in loss of therapeutic effect.²² The cost-benefit ratio of therapy is currently unknown, and its determination is extremely complex.

Recommendations

1. Oral acyclovir therapy is not recommended *routinely* for the treatment of uncomplicated varicella in otherwise healthy children. This recommendation is based on the marginal therapeutic effect, the cost of the drug, feasibility of drug delivery in the first 24 hours of illness, and the currently unknown and unforeseen possible dangers of treating as many as 4 million children each year.
In individual cases, family or other circumstances may justify the modest clinical benefit expected from oral acyclovir therapy, provided it can be initiated within the first 24 hours of illness. Such a decision should be based on an informed discussion among the physician, parent, and patient.
2. For certain groups at increased risk of severe varicella or its complications, oral acyclovir therapy for varicella, if it can be initiated within the first 24 hours after the onset of rash, should be considered. These groups include the following:
 - a. Otherwise healthy, nonpregnant individuals 13 years of age or older.
 - b. Children older than 12 months with a chronic cutaneous or pulmonary disorder and those receiving long-term salicylate therapy, although in the latter instance a reduced

risk for Reye syndrome has not been shown to result from oral acyclovir therapy nor from milder illness with varicella.

- c. Children receiving short, intermittent or aerosolized courses of corticosteroids are unlikely to be significantly immunocompromised. Whether such children are at increased risk of complicated or severe varicella is unknown. However, because no data exist to confirm their immunocompetence, such children should also be considered for therapy with oral acyclovir to minimize the likelihood of severe varicella. If possible, corticosteroids should be discontinued after known exposure to varicella. If a child is immunocompromised because of administration of high-dose corticosteroids, as with other immunocompromised children, intravenous acyclovir therapy is indicated (see recommendation 4 below).
3. When given, oral acyclovir should be administered for 5 days, starting within the first 24 hours of rash onset, at a dose of 200 mg/kg four times a day, with a maximum dose of 800 mg four times a day. The patient should be maintained in a well-hydrated state by encouraging adequate fluid intake.
4. Intravenously administered acyclovir therapy continues to be recommended for treatment of primary varicella or recurrent zoster in the immunocompromised child and for virally mediated complications of varicella in the normal host. In this setting oral therapy should not be used (as indicated in the *Report of the Committee on Infectious Diseases*⁶ (p579)).
5. Oral acyclovir therapy is not recommended in the pregnant adolescent or adult with uncomplicated varicella, because the risk or benefit to the fetus currently is unknown. Intravenous acyclovir should be considered for the pregnant adolescent or adult with serious viral mediated complications of varicella.
6. Oral acyclovir therapy should not be used prophylactically in the otherwise normal child exposed to varicella in an attempt to prevent infection or illness.

Other Considerations

1. No recommendations regarding the use of oral acyclovir in infants (0 to 12 months) can be made at this time as insufficient data exist regarding the safety or efficacy of this therapy in children with varicella within the first year of life.
2. The use of acyclovir for the treatment of children who have been infected from a household contact is controversial. Some experts suggest oral acyclovir also may be considered in this situation.

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