ACYCLOVIR

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Acyclovir is a synthetic purine nucleoside analogue with *in vitro* antiviral activity against the herpes group of DNA viruses(1). This drug has provided significant therapeutic benefits in the treatment of infections due to *Herpes simplex* and varicella viruses.

The mechanism of antiviral action of this drug is complex, and not yet completely understood. The viral thymidine kinase enzyme converts acyclovir intracellularly to its active triphosphate form, which then inhibits the DNA polymerase enzyme in the herpes virus, preventing viral DNA synthesis(2). Further replication of the virus is thus arrested. The presence of thymidine kinase appears to be vital in the action of this drug, and the insensitivity of cytomegalovirus to acyclovir is thought to be due to a lack of this enzyme. However, since the Epstein barr virus does show susceptibility to acyclovir without containing thymidine kinase, it is clear that other mechanisms must also be active(3).

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Antiviral Spectrum

Acyclovir is active against *Herpes simplex* virus 1 and 2, *Varicella zoster* virus and *Epstein barr* virus(1). The cytomegalovirus is relatively insensitive to this drug *in vitro*(2). No action has been demonstrated against other viruses. Acyclovir is more efficacious than vidarabine, cytarabine, and idoxuridine against *Herpes simplex* virus. This drug has no activity against latent viruses, though it can prevent them from becoming active and establishing infections(3).

Resistance to this drug is a theoretical possibility but has not yet emerged as a clinical problem(4), perhaps due to the low incidence of mutants deficient in thymidine kinase. Long term use of acyclovir for 1-2 years has not been associated with the development of resistant strains(5).

Pharmacokinetics

Given orally, the drug is poorly absorbed and only 20% reaches the systemic circulation. Systemic absorption following topical administration is minimal. On intravenous administration in 8 hourly dosage ranging from 5 mg/kg to 15 mg/kg/dose, steady state plasma concentrations between 6.7 and 20.6 μg/ml are attained, which are directly dose related(6). The elimination half life is between 2.0 and 2.9 hours. Both the plasma concentration and the half life are increased by the concurrent administration of probenecid, which competes for the excretory pathways. In neonates, who have relatively underdeveloped renal function, the half life is in-

creased to approximately 4 hours, and total body clearance reduced by two-thirds(7,8). The presence of severe renal function impairment also alters the pharmacokinetics, elevating plasma mean peak concentrations up to two fold, and delaying half life up to 20 hours(2).

The drug has a low protein binding (9-33%), and is thus widely distributed in the body. Though sufficient data are lacking, acyclovir concentrations in CSF, skin vesicle, saliva and tears are reported to be 50, 100, 13 and 18%, respectively of the simultaneous of plasma concentration(9). Good intraocular penetration has been reported from topical application or subconjuctival injection(10).

The excretion is mainly via the kidneys, 80% being excreted unchanged, by both glomerular filtration and tubular secretion. Only 2% is excreted in stools. Adjustments in both dosage and interval are required in renal impairment, as shown in *Table 1.*

TABLE I–*Dose Adjustment in Renal Failure*

Creatinine Clearance (per ml/min/1.73 m^2)	Acyclovir dosage (mg/kg/dose)	Internal (h)
25–50	5	12
10–25	5	24
<10	2.5	24

Acyclovir crosses the placenta, and is also found in breast milk(11). Meyer *et al.*(11) reported that the concentration of acyclovir in breast milk was three times the simultaneous plasma concentration. It did not appear, however, to have any adverse effect on the neonate as the total load was very small.

Adverse Effects

The oral preparation in therapeutic dosage is generally well tolerated, with an occasional incidence of skin rash or gastrointestinal effects like nausea and vomiting. The topical preparation may rarely cause local burning and erythema. The opthalmic ointment may be associated with stinging, and rarely superficial punctate keratopathy(12). Side effects of intravenous administration are mainly local and include pain, inflammation and phlebitis at the site of the injection. Extravasation of the drug may lead to ulceration, and must be avoided.

Two important though infrequent adverse effects with acyclovir include renal impairment and neurological dysfunction. Rapid intravenous administration can lead to a rapid rise in blood urea and creatinine levels, and acyclovir crystals may precipitate in the renal tubules, leading to acute tubular necrosis and acute renal failure(3). Slow infusion over 1 hour at a concentration not greater than 7 mg/ml, minimises the incidence of this complication. Should renal impairment occur, adequate hydration, along with dose reduction or withdrawal, is usually sufficient(1). If necessary, hemodialysis can be used to eliminate acyclovir. Neurologic manifestations may occur in the form of lethargy, tremors, confusion, hallucinations and seizures, by either intravenous or oral route(13). Other rare systemic manifestations include a mild elevation of hepatic enzymes and megaloblastic anemia.

In general, the incidence of side effects is low and most are of minor nature. Mertz *et al.* found a drug induced complication rate of less than 5% when using acyclovir for long term suppression of frequent herpes infection, over a period of 1-2 years(5).

Preparations(14)

Acyclovir is available as an intravenous preparation, tablets, topical cream or ointment, and an opthalmic ointment. The intravenous preparation (Zovirax-Burroughs Wellcome) contains 250 mg acyclovir as the lyophilized sodium salt in a 10 ml vial, costing approximately Rs. 450 per vial in India. Tablets [Zovirax 200 mg (Burroughs Wellcome)] cost Rs. 25 each. Topical preparations are available as a 5% cream (50 mg/g acyclovir in propylene glycol base) or 5% ointment (in polythylene glycol); the former is considered superior. This is available as Herpex cream [Torrent (Rs. 45 for 5 g)]. Topical ointment is not available in India. Ocuvir opticaps [FDC (Rs. 9.75 for 3 opticaps)] containing 3% acyclovir are available for ocular use.

Dosage of acyclovir in different conditions are shown in *Table II.*

TABLE II–*Dosage of Acyclovir in Patients with Normal Renal Function*

Indication	Route	Dosage (mg/kg/dose or mg/m^2 dose)	Interval (h)	Duration (days)
HSV or VZV (immunocompetent)	Intravenous	250 mg/m^2 or 5 mg/kg	8	5
HSV or VZV (immunocompromised)		500 mg/m^2 or 10 mg/kg	8	7
Herpes encephalitis		500 mg/m^2	8	10
Mucocutaneous HSV	Oral			
>2 yrs		200 mg	5 times daily	5
<2 yrs		100 mg	5 times daily	5
Herpes zoster		600-800 mg	5 times daily	5-7
Prophylaxis HSV				
>2 yrs		200 mg	4 times daily	
<2 yrs		100 mg	4 times daily	
Mucocutaneous HSV	Topical cream	As needed	5 times daily	5
Mucocutaneous HSV	Topical ointment	As needed	6 times daily	7
HSV Keratitis	Ophthalmic ointment	As needed	5 times daily	≥ 3 after healing

HSV - Herpes simplex virus; VZV = Varicella zoster virus.

Therapeutic Uses

Acyclovir is recommended in the treatment of various infections caused by *Herpes simplex* virus types 1 and 2, and *Varicella zoster* virus, both in immunocompetent and immunosuppressed individuals. Its efficacy remains to be proven, in infections with *Epstein barr* virus and cytomegalovirus.

Herpes simplex Infections

Infections with this virus can be local, *e.g.,* herpes labialis, genital herpes, herpes keratitis, or generalized as in herpes encephalitis. Large collaborative studies comparing intravenous treatment using acyclovir and vidarabine have established acyclovir to be the treatment of choice for biopsy proven herpes encephalitis(15). It is particularly beneficial in improving the overall survival rate and reducing the incidence of serious sequelae. Acyclovir is beneficial in neonatal herpes as well(16), where its efficacy is comparable with vidarabine. In mothers with disseminated *Herpes simplex* infections near term, case reports have shown that the use of acyclovir was followed by survival, without complications, in both mothers and infants(17).

Double blind, placebo controlled studies in immunocompetent patients have shown that therapy with intravenous or oral acyclovir, initiated within 4 days of the first appearance of signs and symptoms, produces significant reduction in the duration of viral shedding and time to complete healing in patients with severe mucocutaneous lesions(18). Topical therapy with 5% cream or ointment is less effective, especially in the relief of pain or dysuria, though healing time may be shortened.

Acyclovir 3% ophthalmic ointment applied 5 times daily is highly effective in curing herpetic corneal ulcers and keratitis, and may produce cure rates in 95-100% within 5 days(2).

Prophylaxis for recurrent herpes infection with acyclovir has also been effective. Oral acyclovir therapy during the prodromal stage of recurrent genital herpes inhibits new lesion formation and viral shedding, and reduces episode durations by 1-2 days(19). The long term use of this drug for 1-2 years, has led to complete suppression of recurrences of genital herpes in 60-90% of patients(5). Unfortunately, the recurrence rates returned to pretreatment levels after discontinuation of acyclovir. Topical acyclovir cream has been effective as prophylaxis in recurrent orofacial herpes. In general, the best results are obtained when the drug is introduced in the early stage of the disease, in order to control the replicating virus. Latent viruses are not affected, though this drug prevents the onset of established infection.

Double blind placebo controlled studies conducted in immunocompromised patients have shown that parenteral acyclovir leads to dramatic reductions in viral shedding and healing time(2). Oral acyclovir has shown similar results in bone marrrow transplant recipients with herpes simplex infections(20). Since the lesions in immunocompromised patients may prolong or disseminate, acyclovir is recommended at any stage of infection in these patients.

Herpes zoster Infections

Intravenous acyclovir significantly reduces the development of rash and pain, and protects against eye involvement, in patients with acute *Herpes zoster.* Oral therapy provides similar benefits, though the dose required is higher than used for *Herpes simplex infections*(1). The drug does not, however, reduce the intensity of post herpetic neuralgia, and withdrawal of the

drug may cause recurrence of pain. Ocular sequelae are less when acyclovir is used in treating zoster of the trigeminal nerve(21).

Varicella Infections

Immunocompromised patients who develop acute varicella infection benefit with the use of intravenous acyclovir which protects against progression and dissemination of the infection(22). Comparison with vidarabine has shown this drug to be superior in promoting pain relief and cutaneous healing, in addition to better protection against dissemination. Its use in otherwise normal children with chicken pox is controversial. Balfour *et al.*(23) reported no significant improvement in normal children, though a later study by them has found significant improvements in defervescence times and complication rates in normal adolescents(24). This difference is probably due to the more severe disease present in adolescents.

Congenital varicella infection in neonates has also been treated successfully with acyclovir, in conjunction with immunoglobulin therapy(25).

Intravenous acyclovir produces marginal but insignificant benefit in severe infectious mononucleosis, and CMV infections. Acyclovir has also been used in chronic active hepatitis B with unsatisfactory results(1).

Current Role of Acyclovir

Therapy with acyclovir is established in the treatment of acute localized or disseminated *Herpes simplex* infections, irrespective of immune status. The drug is life saving in herpes encephalitis. It is also effective in preventing recurrences of herpetic infections. It is at least as effective as alternate antiviral therapy in varicella zoster infections. Though not practical for routine use in normal children with chicken pox, in immunocompromised patients and adolescents it is of significant therapeutic value. Maximal benefit is obtained in all the above situations when the drug is started early. In the recommended dosage, the adverse effects are generally mild and the drug is well tolerated.

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