Acyclovir

Class:
Acyclovir is an acyclic analogue of 2'-deoxyguanosine.

Antiviral Activity:
Acyclovir has activity against herpesviruses.

Mechanism of Action:
Acyclovir is converted to its triphosphate form, acyclovir triphosphate (ACV-TP), which competitively inhibits viral DNA polymerase, incorporates into and terminates the growing viral DNA chain, and inactivates the viral DNA polymerase.

Mechanism of Resistance:
The primary mechanism of resistance to acyclovir is related to viral thymidine kinase (TK) and DNA polymerase mutations.

Pharmacodynamics:
No relationship has been established between the effective *in vitro* and *in vivo* concentrations of acyclovir, although there is a significant correlation between the ID_{50} of acyclovir for the virus and the clinical response.

Pharmacokinetics:
Acyclovir is slowly and poorly absorbed from the gastrointestinal tract and bioavailability decreases with increasing dose. Acyclovir is widely distributed into tissues and body fluids. Plasma protein binding is relatively low at 9 to 24%. Renal excretion is the major route of elimination of acyclovir.

Adverse Effects:
Most common with oral acyclovir are lightheadedness, headache, diarrhea, nausea, vomiting and abdominal pain. The most common effects associated with parenteral acyclovir are lightheadedness and anorexia. The most common adverse effects associated with topical acyclovir are mild pain, burning and stinging.

Dosage:
Capsule 200mg
Cream 5%
Ointment 5%
Oral Suspension 25mg/ml, 50mg/ml, 200mg/5ml
Powder for Injection 500mg
Tablet 400mg, 800mg

HSV infections of skin and mucous membranes including initial and recurrent genital herpes

Adult: 200 mg po 5 x daily for 5 days
400 mg po 5 x daily or 5 mg/kg IV q8h for 5 days in severely infected or immunocompromised patients

Initial genital: 400 mg po tid x 7 – 10 days or 200 mg po 5 x daily x 7 – 10 days
Recurrent genital: 400 mg po tid x 5 days or 200 mg po 5 x daily x 5 days or 800 mg po bid x 5 days

Pediatric: Age = 2 years = adult dose
Age < 2 years = half adult dose
Neonates and infants = 20 mg/kg IV q8h for 14 days (21 days for disseminated or CNS infection)

Episodic HSV treatment in HIV-infected patients
Adult: 400 mg po tid x 5 – 10 days or 200 mg 5 times daily for 5 – 10 days
Pediatric: No data

Suppression of recurrent HSV in immunocompetent patients
Adult: 400 mg bid
Pediatric: No data

Prophylaxis of HSV in immunocompromised patients
Adult: 400 – 800 mg po 2 or 3 times daily
5 mg/kg IV q8h in severely immunocompromised (i.e. bone marrow transplant) patients or those with impaired absorption from gut
Pediatric: Age = 2 years = adult dose
Age < 2 years = half adult dose

Herpes encephalitis
Adult: 10 mg/kg IV q8h
Pediatric: 500 mg/m^2 IV q8h

VZV infections including varicella (chicken pox) and herpes zoster (shingles)
Adult: 800 mg po 5 x daily for 7 days
10 mg/kg IV q8h in severely immunocompromised patients or those with impaired absorption from gut (treat for 2 – 7 days or until clinical improvement, followed by po therapy to complete 10 days of total treatment)
Pediatric: Varicella infections:
Age > 6 years = 800 mg po 4 x daily
Age 2 – 5 years = 400 mg po 4 x daily
Age < 2 years = 200 mg po 4 x daily
Continue treatment for 5 days
Alternatively: calculate dosing at 20 mg/kg po (max 800 mg) 4 x daily
IV dose = 250 mg/m^2 q8h
Immunocompromised children = 500 mg/m^2 IV q8h
No data on treatment of herpes zoster in immunocompetent children

Disease state based dosing:

Renal Impairment: Oral tablets for Herpes simplex (HSV) or Varicella Zoster (VZV):
CrCl 10-29ml/min (VZV only) give 800mg PO q8h
CrCl < 10ml/min (VZV) give 800mg PO q12h

CrCl < 10ml/min (HSV) give 200mg PO q12h
Intravenous dosing for HSV: CrCl 25-50ml/min give 5mg/kg IV q12h
CrCl: 10-25ml/min 5mg/kg IV q24h
CrCl: < 10ml/min 2.5mg/kg IV q24h
Intravenous dosing for VZV: CrCl 25-50ml/min give 10mg/kg IV q12h
CrCl: 10-25ml/min 10mg/kg IV q24h
CrCl: < 10ml/min 5mg/kg IV q24h

Hepatic Impairment:
No dose adjustment is necessary

Dosing during Continuous Renal Replacement Therapy
CVVH (Continuous venovenous hemofiltration): 5-7.5mg/kg q24h
CVVHD (Continuous venovenous hemodialysis): 5-7.5mg/kg q24h
CVVHDF (Continuous venovenous hemodiafiltration) 5-7.5mg/kg q24h
Note: CVVH is mainly for fluid removal alone. Many institutions will employ more CVVHD or CVVHDF which combine dialysis with fluid removal.

Drug Interactions:
Use caution when combining acyclovir with potentially nephrotoxic agents.

Pregnancy:
Category B: No evidence of risk in humans but studies inadequate.

Monitoring Requirements:
Baseline serum creatinine/BUN

Brand names/Manufacturer:
Zovirax®/Glaxo Wellcome Inc, Glaxo Wellcome Division Smithkline Beecham Corp, Biovail Pharmaceuticals Inc
Acyclovir/STADA Pharmaceuticals Inc, Akyma Pharmaceuticals, Ranbaxy Pharmaceuticals Inc, Genpharm Inc, Mova Pharmaceuticals Corp, Par Pharmaceutical Inc, Apotheca Inc, Watson Pharmaceuticals Inc, Mylan Pharmaceuticals Inc, Purepac Pharmaceutical Co, Goldline Laboratories Inc/IVAX Pharmaceuticals, Ivax Corporation, Ivax Pharmaceuticals Inc, Teva Pharmaceuticals USA Inc, American Pharmaceutical Partners Inc (APP), Mayne Pharma (USA) Inc, Meridian Medical Technologies Inc, Bedford Laboratories, Alpharma USPD Inc, Stason Pharmaceuticals Inc.