Resident's Page

Acyclovir versus valacyclovir

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Antiviral drugs have been developed at an extraordinary pace during the past two decades.[1] To date, there are almost 30 FDA approved systemic antiviral drugs for the treatment of infections due to human herpes viruses (HHV) and human immunodeficiency virus (HIV).[2]

ACYCLOVIR (ACV)

Acyclovir, 9- [(2-hydroxy ethoxy) methyl] guanine is a guanosine analogue, was the first specific antiviral drug,[3] to become widely used in the treatment of herpes simplex virus (HSV) and herpes zoster virus (HZV) infections.[1,2]

Dr. Gertrude Elion, for her work in the discovery and development of ACV, received the Nobel Prize for Physiology and Medicine in 1988.[4]

Pharmacokinetics

ACV is available as oral, intravenous and topical formulations. After oral administration, bioavailability is as low as 15-30% [Table 1]. It is widely disseminated in the body fluids-cerebrospinal fluid, vesicle fluids, vaginal secretions and is excreted mainly through the kidneys, 85% in unmetabolized form. ACV crosses the placenta at all stages of pregnancy and is secreted into breast milk.[1,2]

Topical administration results in detectable drug concentrations in the lesions, but little systemic absorption if any. However, penetration of stratum corneum is low resulting in low efficacy.[1] Intravenous ACV is reserved for severe illnesses and in immunocompromised patients.[2]

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Mechanism of action[2-4]

ACV is a potent and selective inhibitor of herpes virus DNA replication. ACV is initially phosphorylated into ACV monophosphate by viral thymidine kinase, and not by the thymidine kinase of uninfected cells. ACV monophosphate is converted into ACV triphosphate by cellular (human) guanosine monophosphate (GMP) kinases and other kinases. Therefore, the amount of ACV triphosphate formed in the virally infected cells is 40 to 100 times greater than that in normal uninfected cells. ACV triphosphate competes with normal deoxy adenosine triphosphate and functions as a substrate for the enzyme viral DNA polymerase and produces:

1. Complete and irreversible inhibition of herpes virus DNA polymerase.
2. Viral DNA chain termination

Pharmacologic basis for selective inhibition of herpes virus DNA replication[4]

1. Selective accumulation (trapping) in viral infected cells due to phosphorylation by HSV thymidine kinases.
2. Preferential affinity of ACV triphosphate for the viral rather than cellular DNA polymerases.

FDA -approved indications[1]

- Herpes simplex infections (HSV 1 and 2)
  - Primary episodes
  - Recurrent episodes
  - Suppressive therapy
- Varicella zoster infections
  - Chicken pox
  - Herpes zoster
- Herpes simplex or varicella zoster infections in immunocompromised patients (HIV)

Other dermatological uses[2,5,6]

- Other subsets of HSV infections-Primary

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Table 1: Key pharmacologic concepts

	Acyclovir	Valacyclovir
Peak levels (h)	1.5 – 2.0	Uncertain
Bioavailability (%)	15 – 30	54.50
Protein binding (%)	9 – 33	13.5 – 17.9
Half-life (h)	1.3 – 1.5	2.5 – 3.3
Metabolism	No hepatic microsomal metabolism	No hepatic microsomal metabolism; conversion to acyclovir occurs
Excretion	Roughly equal urine and fecal	Roughly equal urine and fecal

gingivostomatitis, recurrent herpes labialis, herpes gladiatorum, eczema herpeticum, herpetic whitlow, herpetic keratoconjunctivitis, prophylaxis before facial resurfacing, recurrent erythema multiforme (presumed or proven to be due to HSV) and Stevens-Johnson syndrome, and Bell's palsy (with prednisolone)
- Postexposure prophylaxis and treatment for herpes simiae after monkey bite.
- Epstein Barr virus related oral hairy leukoplakia (may improve with ACV).
- Prophylaxis against varicella in susceptible contacts.
- Recurrent erythema multiforme (presumed or proven to be due to HSV) and Stevens Johnson syndrome.

Initiation of therapy[1,6,7]

In general, therapy for mucocutaneous HSV disease should begin as soon as possible after the lesions are seen [Tables 2 and 3]. Treatment for episodic recurrent disease should begin during the prodromal period. Treatment for varicella should begin within 24 h of the onset of the rash. Treatment for herpes zoster in the immunocompetent host is of benefit only if started within three days of the onset of the rash.

Intravenous ACV[2,6] is reserved for immunocompromised patients and patients with severe illness because of greater bioavailability.

Indications for intravenous use include[2]
- Disseminated HSV infection
- Complicated primary infection
- Neonatal herpes
- Eczema herpeticum
- Herpes encephalitis
- HSV that fails to oral therapy
- Varicella zoster in a pregnant female with any evidence of pneumonia
- Herpes zoster in severe trigeminal nerve distribution
- Herpes zoster in immunocompromised patients.

Indications of topical ACV include[8]
- Genital herpes simplex infections- ACV 5%

Table 2: Clinical regimen for human herpes virus infections in immunocompetent patients

Clinical scenario	Acyclovir	Valacyclovir
Herpes simplex-primary	400 mg TID for 10 days	1000 mg BID for 10 days
Herpes simplex-recurrence	400 mg TID for 5 days	500 mg BID for 3 days
Herpes simplex-suppression	400 mg BID	500 mg OD
Herpes zoster-acute treatment	800 mg 5 times a day for 7-10 days	1000 mg TID for 7-10 days
Primary varicella-children	20 mg/kg QID up to 800 mg/dose for 5-7 days	Not well evaluated

Table 3: Clinical regimen for human herpes virus infections in immunocompromised patients

Clinical scenario	Acyclovir	Valacyclovir
Herpes simplex-primary	200-400 mg 5X/day for 10 days or 5 mg/kg IV q 8 h for 7-10 days	No studies reported
Herpes simplex-recurrent	At least 400 mg TID for 7-10 days	500 mg BID for 7 days
Herpes simplex-suppression	At least 400 mg BID	500 mg BID for 7 days
Herpes zoster-adults	800 mg 5X/day for 7-10 days	I g TID for 7-10 days
Primary varicella-children	10 mg/kg IV q8h for 7-10 days	20 mg/kg for 7-10 days

ointment is FDA approved for the management of initial genital herpes infections and limited non-life threatening mucocutaneous infections in immunocompromised patients.
- Herpes labialis- ACV 5% ointment is FDA approved for use in limited non- life threatening mucocutaneous HSV infection in immunocompromised patients.
- Herpes zoster, especially in immunocompromised patients[9,10]

ACV minimally affects the symptoms or viral shedding in recurrent herpes labialis and is not generally used for this disease. However in a dose of 400 mg twice daily, it is effective in preventing recurrent herpes labialis in those with frequent relapses and in preventing photo exposure-induced relapse.[5,6]

In a meta analysis evaluating the clinical efficacy of high dose ACV in patients with HIV infection, results showed that ACV offered a modest survival benefit. Although the mechanism is unclear, since ACV has no antiretroviral activity, suppression of bursts of HIV replication during active HHV infections may contribute to prolonged survival.[2] In herpes zoster and varicella, ACV decreases the pain, accelerates the healing and prevents dissemination of viruses in immunocompromised patients. But, it has no effect on the establishment of latency, frequency of recurrence and incidence of post herpetic neuralgia.[5] Prophylactic intravenous/ oral ACV is effective in preventing CMV disease in some transplant settings (renal, perhaps bone marrow), but not in others.[5]

Topical ACV ointment can shorten the period of pain and viral shedding in HSV mucocutaneous lesions in immunosuppressed patients, but not in patients with normal immunity.[5,8] In contrast, ACV cream appears to reduce the duration of pain and viral shedding by one day in immunocompetent patients.[5]

Adverse effects[1,3,11,12]

- Potentially life threatening effects: none has been reported.
- Severe or irreversible adverse effects: crystallization in renal tubules leading to obstructive nephropathy and interstitial nephritis, can occur in 5% of patients on intravenous ACV. Very rarely acute renal failure can occur.
- Symptomatic adverse effects:
  i. Infusion site reactions: phlebitis and severe local inflammation at the intravenous infusion site due to extravasation of the drug
  ii. Central nervous system (in 1% of patients on intravenous ACV): lethargy, obtundation, tremors, confusion, hallucinations, agitation, extrapyramidal symptoms and seizures or coma.
  iii. Cutaneous: skin rashes, recall dermatitis, contact dermatitis, fixed drug eruption
  iv. Gastrointestinal: nausea, vomiting, diarrhoea (most frequent after oral dosing)
  v. Malaise, headache, giddiness, marked drowsiness and sleep
- Other effects:
  i. Raised blood urea and/or creatinine
  ii. Increase in liver related enzymes
  iii. Decrease in hematological indices- neutropenia
- Topical:[8,12] Mild pain, burning, stinging. Rash, pruritus, and vulvitis with the ointment and dry or cracked lips and desquamation with the cream have also been reported.

Precautions[1,3,5]

Crystalline nephropathy due to ACV has been reported with high dosage, dehydration or rapid intravenous administration. Central nervous system toxicity has been associated with high plasma levels of ACV, and with underlying disease involving the CNS. Dosages of ACV must be adjusted for patients with a creatinine clearance level of less than 50 ml per min (ml/min). Dosage of oral preparations of ACV for HSV and VZV infections should be reduced to 200 mg in every 12 h or 800 mg in every 12 h respectively, in patients with severe renal impairment (creatinine clearance of less than 10 ml/min). If the creatinine clearance is above this value, normal doses may be given for genital herpes infections. For VZV infections, 800 mg in every 8 h should be used in patients with a creatinine clearance of 10- 25 ml/min. Intravenous dosage of ACV should be calculated as shown in Table 4. Since hemodialysis reduces the serum levels significantly, the daily dose should be given after hemodialysis.

Drug interactions[2]

Since ACV is not metabolized by hepatic microsomal enzyme CyP450, there is a relative paucity of important drug interactions.

Contraindications[2]

Hypersensitivity to ACV/ to any component of the formulation

Table 4: Intravenous dosage of ACV calculated according to creatinine clearance

Creatinine clearance (ml/min)	Herpes simplex	Varicella zoster
	Dose (mg/kg) Time interval (h)	Dose (mg/kg) Time interval (h)
25- 50	5 mg/kg Q 12 h	10 mg/kg Q 12 h
10-25	5 mg/kg Q 24 h	10 mg/kg Q 24 h
0-10	2.5 mg/kg Q 24 h	5 mg/kg Q 24 h

VALACYCLOVIR (VACV)

Valacyclovir, 2-[2-amino-1, 6-dihydro-6-oxo-9H-purin-9-yl-methoxy] ethyl valinate hydrochloride, is the L-valine ester of ACV. It was developed to provide increased oral bioavailability of ACV.[1] VACV is better absorbed than ACV due to an active stereoselective transporter in intestinal brush border membrane.[13] VACV is converted rapidly and virtually to ACV after oral administration in healthy adults by intestinal and hepatic first pass metabolism through hydrolysis.[14] Thus, the mechanism of action and spectrum of activity of VACV are the same as that of ACV. After a 1 g oral dose of VACV, peak plasma concentration of ACV of 5.7 μg /ml is achieved in 1.75 h, with area-under-the-curve concentration that are similar to those achieved with 5 mg/kg of ACV given intravenously.[1] Unlike ACV, VACV is a substrate for intestinal and renal peptide transporters. Therefore, the relative bioavailability of ACV increases 3-5 fold to approximately 70% following VACV administration.[14] The better oral bioavailability of VACV contributes to the need for less frequent administration. Apart from the differences in bioavailability, the mechanism, clinical spectrum and adverse effects are similar [Table 1].

FDA-Approved indications of VACV[2]

1. Herpes simplex infections
   - Primary episodes
   - Recurrent episodes
   - Suppressive therapy
2. Varicella zoster infections
   - Herpes zoster
3. Herpes simplex and varicella zoster infections in immunocompromised patients (HIV)

Other dermatological uses[2,5,6,15,16]

Recurrent erythema multiforme (presumed/proven due to HSV)-not responding to ACV. Other subsets of HSV infections-primary herpetic gingivostomatitis, recurrent herpes labialis, herpes gladiatorum, eczema herpeticum, herpetic whitlow, herpetic keratoconjunctivitis, prophylaxis against orofacial herpes prior to laser cutaneous resurfacing and prophylaxis of cytomegalovirus infection in solid organ or bone marrow transplantation.

Initiation of therapy[1]

As with its parent compound, ACV, VACV therapy is initiated as soon as possible after the appearance of an HSV or VZV rash, within 72 h of onset of rash [Tables 3 and 4].

Adverse effects[1,2]

Same as those that would be expected with ACV. However, severe and even fatal cases of thrombotic thrombocytopenic purpura / hemolytic uremic syndrome (TTP/HUS) have been reported in AIDS and transplant recipients taking high doses of VACV. The basis for and causal relationship to VACV of these occurrences have not been established, and TTP/HUS has not been reported in patients taking conventional low dosages up to 3 g/day of VACV. Symmetrical drug related intertriginous and flexural exanthem has been reported.[17]

Drug interactions[1,2]

Cimetidine and probenecid decrease the rate of conversion of VACV to ACV, but not the overall extent of conversion.

VACV versus ACV

There have been several recent advances in the nucleoside analogues used in the treatment of HSV infections. VACV is indicated for the treatment of both genital and orofacial herpes infections.[1,2,18] VACV is the best prophylaxis for herpes infections reducing the frequency and severity of outbreaks.[18] When given during the prodromal stage, VACV 2 g twice daily for 1 day is beneficial.[2] Two randomized, double-blind, placebo-controlled studies found oral VACV administered more conveniently as 500 mg once a day over four months among patients with a history of four or more recurrences in the previous year, effectively suppresses recurrent herpes labialis outbreaks. Recurrence was reduced from 68 to 40%.[19]

For first episode genital herpes, VACV 1 g twice daily for 10 days is recommended. Ten day courses of ACV five times daily and VACV twice daily are equally effective in accelerating the resolution of first episode genital herpes. Moreover, the twice daily regimen of VACV is also more convenient for patients to take, which leads to potentially greater compliance. For

episodic treatment of recurrent genital herpes, VACV is dosed at 500 mg twice daily for three days.[2]

Continuous therapy with VACV 500 mg daily for suppression of recurrent genital herpes is approved for people with nine or fewer episodes each year. Alternatively, patients with 10 or more episodes yearly may require 1g daily or 500 mg twice daily. Daily use of VACV also reduces HSV transmission by decreasing asymptomatic HSV shedding. During the eight-month study, HSV-2 transmission was decreased by 50% among susceptible partners.[2] VACV 500 mg daily decreases the rate of viral shedding and transmission of HSV in discordant monogamous couples.[4] Such, once daily regimens of either ACV or famciclovir were not considered sufficiently effective and cannot be recommended for routine clinical use.[20-22]

An additional benefit was recently described for VACV. In genital HSV, VACV 500 mg twice daily was associated with 44% likelihood of lesions aborting i.e., they did not progress beyond the papule in genital herpes. Analysis of aborted lesion rate in relation to time of treatment initiation shows that chance of genital herpes lesion aborting increases almost two fold when treatment commences within 6 h of symptom onset compared with that after 6 h. This benefit has not been described with ACV or famciclovir.[22] The cost of antiviral therapy for genital herpes should not be seen as a barrier. In the United States, analysis of cost of VACV, ACV and famciclovir prescribed for one-year period clearly indicate the economic advantage of 500 mg once daily regimen of VACV.[23]

VACV is approved for use in HIV seropositive patients with recurrent genital herpes.[24-28] In a double-blind control trial, 1062 patients infected with HIV with a history of recurrent anogenital herpes were randomized to receive VACV 500 mg twice daily, VACV 1g daily or ACV 400 mg twice daily for one year. While there was no significant difference between VACV 1 g daily and ACV 400 mg daily, patients treated with VACV 500 mg twice daily had significantly less recurrent episodes of genital herpes. VACV significantly reduces the rectal and plasma HIV-1 levels in HIV-1/HSV-2 coinfected men. HSV suppression may provide clinical benefits to persons not receiving highly active anti retroviral therapy (HAART) as well as public health benefit.[24-28]

In herpes zoster, both ACV and VACV significantly shorten the periods of acute pain, virus shedding, rash, acute onset and late onset anterior segment complications. VACV has been shown to be as effective as ACV in its effect on the appearance of new lesions, time to crusting and time to 50% healing, but VACV significantly decreases the incidence and severity of post herpetic neuralgia. VACV recipients had a mean duration of 40 days of pain after lesion resolution compared to 60 days of pain after lesion resolution for ACV recipients. In terms of zoster related discomfort overall, it is estimated that VACV provides a 25% benefit over ACV. The more convenient dosing schedule as well as quicker cessation of pain makes VACV more efficacious than ACV in treating acute herpes zoster.[2]

Gilbert and Mc Burney, in an uncontrolled study, found that prophylactic VACV 500 mg twice daily started either the day before or on the day of facial resurfacing and continued for 14 days thereafter almost eliminated the risk of HSV recurrence following this procedure.[16]

Recurrent cases of erythema multiforme have been prevented with continuous ACV. Patients who have no response to ACV may have a response to VACV (500 to 1000 mg/day) or famciclovir (125 to 250 mg/day), which have greater oral bioavailability and more convenient dosing. The dosage of the antiviral may be reduced once the patient is recurrence free for four months, and eventually the drug may be discontinued.[25] In erythema multiforme and in Stevens Johnson syndrome, although ACV is effective, the greater bioavailability of VACV offers more convenient dosing and better control of HSV reactivation.[17]

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