

Cidofovir: a new drug to combat CMV retinitis in patients with AIDS

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Abstract

Cidofovir is an analogue of monophosphate nucleotide which is phosphorylated by cellular enzymes into its active diphosphate form. This active form inhibits viral DNA polymerase.¹ Cidofovir is active against human cytomegalo virus (CMV) and is indicated for the treatment of CMV retinitis in patients with AIDS. Cidofovir is also being investigated for its therapeutic role in other viral diseases like herpes simplex, adenovirus, varicella zoster and human papilloma virus.

At present, in the United States it is being used for the management of AIDS while in European Union it is under regulatory review.

Keywords: Cidofovir; CMV retinitis; AIDS

Cidofovir undergoes cellular phosphorylation to produce diphosphate form which inhibits viral DNA polymerase.¹ It competitively inhibits the incorporation of deoxycytosine-5' - triphosphate by viral DNA polymerase into viral DNA.² After incorporation, it slows down DNA synthesis and causes destabilization of viral DNA.²

Pharmacodynamic studies

Antiviral Activity

In Vitro studies:

- Antiviral activity of cidofovir was seen in plaque reduction assay against human clinical isolates and laboratory strain (AD-169) of CMV in human embryonic lung fibroblasts (HEL).
3 IC₅₀ of cidofovir against AD169 was 0.017 mg/L.

Drugs	IC ₅₀ *
Cidofovir	0.069 mg/L
Ganciclovir	20.4 mg/L
Foscarnet	0.58 mg/L

* Drug concentration needed to produce 50% viral inhibition.

- Selective index (50% toxic concentration / IC₅₀) of cidofovir for CMV clinical isolates was 8 to 150 fold greater than those of ganciclovir and foscarnet respectively.³
- Cidofovir exhibited cytoprotective effect, when added up to 48 hours after infection of human embryonic lung fibroblasts with human CMV laboratory strain.⁴

- Synergistic inhibition on several strains of human CMV was seen with combination of cidofovir with foscarnet, ganciclovir, zidovudine or aciclovir. Zidovudine in combination with foscarnet, ganciclovir or aciclovir was more toxic to human HEL fibroblasts than the combination of cidofovir and zidovudine.⁵

In-vivo Studies

Animal Studies:

- In genetically immune suppressed mice, murine CMV is generally fatal and when these infected mice with murine CMV were treated with cidofovir (1 to 10 mg/day X 10 days), it increased the mean survival time by 15 to 30 days as compared to placebo, while treatment with ganciclovir (12.5 to 50 mg/kg/day X 10 days) was less effective (the mean survival time was increased by only 2 to 8 days).⁶

Human Studies:

- In a clinical study, 31 AIDS patients (mean CD 4 + count 61 cells/ μ l) suffering with concurrent CMV infection were given 39 courses of i.v. cidofovir (0.5 to 10 mg/kg/week). Recipients of cidofovir (>3.0 mg/kg/week) showed greater reduction of CMV titres in semen and urine ($P < 0.005$) than those given lower dosage.⁷ In 14 out of 19 and 20 out of 22 patients who received >3.0 mg/kg/week of cidofovir a >100 fold reduction in CMV titres was seen in semen while the urine samples changed from CMV negative to positive.
- 21 patients with (median CD4+ count of 39 cells/ μ l) who underwent cidofovir intravenous therapy (1.0 to 5.0 mg/kg/week), two out of 8 patients (administered <3.0 mg/kg/week) were found CMV negative on urine examination whereas 11 out of 13 on higher dosage became CMV negative.⁸

Viral Resistance

The resistance to cidofovir is theoretically unlikely because it is converted to its active form by cellular kinases⁹ and unlike ganciclovir, mutations of viral phosphorylases cannot confer resistance to cidofovir. However, a laboratory strain of CMV (AD-169) when cultured in human foreskin fibroblast with gradual addition of increasing doses of cidofovir for 10 months, resulted in loss of sensitivity of cidofovir and ganciclovir by 20 and 10 fold respectively. Also the same CMV strain in presence of ganciclovir became 26 and 67 fold less sensitive to cidofovir and ganciclovir respectively. However, both strains remained sensitive to foscarnet.¹⁰ Clinical isolates taken from 22 patients before and after treatment with cidofovir for 2-38 weeks (mean 8 weeks) showed no reduction in sensitivity to cidofovir. The IC₅₀ values were <0.5 to 1.85 μ mol/L for pre-treatment isolates and <0.5 to 2.0 μ mol/L for post treatment isolates.¹¹

Toxicity

Cidofovir was associated with mammary adenocarcinomas in female rats¹² but the same was not observed when cidofovir was administered in cynomolgus monkeys for 52 weeks.¹³ In Cidofovir recipients, till date, no patient has developed a non-AIDS related malignancy.^{14,15,16,17} In those who had AIDS related malignancies the incidence was consistent with the previous existing illness.

Cidofovir is nephrotoxic in monkeys, rats, guinea pig and humans¹⁸ and this limits the dose of this drug.¹⁸ This ADR is effectively reduced by coadministration of probenecid and fluids. Bone marrow toxicity of zidovudine (given at low concentration 3.74 μ mol/L) is reduced when cidofovir or ganciclovir is given in combination with zidovudine. However, at higher concentrations of zidovudine (74.9 μ mol/L), ganciclovir increased the myelotoxicity of zidovudine while cidofovir had no such effects.¹⁹

Pharmacokinetics

- To 5 mg/kg of cidofovir in patients with AIDS (with or without CMV infection) peak plasma concentration ranged between 7.3-11.5 mg/L. Over 80% of the drug was excreted unchanged in urine within 24 hours of administration. The pharmacokinetics of cidofovir did not change by repeated weekly administration of cidofovir at the dose rate of 3 mg/kg.^{7,20}
- The pharmacokinetics of cidofovir did not alter on concurrent administration of probenecid (1 gm 3 hours before and 0.5 g 2 and 8 hours after cidofovir infusion) with or without hydration with 1 litre saline. However, there was a two fold increase in serum concentration of cidofovir when dose of probenecid was doubled in conjunction with saline. This occurred because probenecid blocked the active tubular secretion of cidofovir.²⁰
- In monkeys' kidney cells, cidofovir diphosphate showed a biphasic metabolism with first and second phase intracellular elimination half lives of 24 and 65 hours respectively.²¹
- Cidofovir phosphate choline, another metabolite of cidofovir, has a intracellular half life of about 87 hours and it may act as reservoir for cidofovir diphosphate.^{1,21}

Pharmacokinetic parameters of Cidofovir:

	Doses	
	3 mg/kg	5 mg/kg
C _{max} (mg/L)	7.3	11.3
Elimination t _{1/2} hour	2.4	3.2

Drug Interaction

Cidofovir may have a significant pharmacokinetic interaction with cotrimoxazole, didanosine, fluconazole and aminoglycoside antibiotics.²²

Clinical Trials

One hundred patients with AIDS (median CD4 + count 6 cells/ μ l) and CMV retinitis intolerant to ganciclovir and foscarnet were given cidofovir either 5 or 3 mg/kg followed by the same dose given on alternative weeks.¹⁷ Concomitantly probenecid 4 g and 2 L of saline (for hydration) were given to prevent the cidofovir associated nephrotoxicity. Significantly longer median time to CMV retinitis was observed in patients on high dose of cidofovir (5 mg/kg) than those in low dose (3 mg/kg), 115 vs 49 days ($p=0.0017$).¹⁶ Progression of retinitis was assessed by retinal photograph as appearance of a new lesion or the advancement of existing lesion.¹²

Clinical data on Cidofovir

<i>n</i>	<i>Nature of disease</i>	<i>Dose of cidofovir</i>	<i>Any other medication</i>	<i>Median time to CMV retinitis progression</i>
100	AIDS (median CD4+count 6 cells/ μ l) along with CMV retinitis	5 mg/kg week for 2 weeks followed by 5 mg/kg every alt week.	Probenecid 4Gm Saline-2L	115 days
		5 mg/kg week for 2 weeks followed by 3 mg/kg every alt week.	Probenecid 4Gm Saline-2L	49 days

- In another study, patients with CMV retinitis were randomised into two groups either deferred (CD4 + counts of 9 cells/ μ l) or immediate (CD4 + counts of 6 cells/ μ l). Therapy with i.v. cidofovir 5 mg/kg/week for 2 weeks followed by 5 mg/kg every alternative week and probenecid 4g with 1L

of saline hydration was given concomitantly in both the groups. The median time to CMV retinitis progression was 120 and 22 days in immediate and deferred groups respectively ($P < 0.0001$).¹⁵

Tolerability

The dose limiting adverse effect of cidofovir in clinical trials has been nephrotoxicity.^{7,8} In 1 out of 10 patients proteinuria was observed (< 3.0 mg/kg of cidofovir alone). Glucosuria and abnormal serum creatinine levels were also observed in these patients.⁷ Probenecid and hydration reduced the incidence of severity of nephrotoxicity in patients administered cidofovir. Probenecid per se caused mild to moderate adverse reactions which included nausea, vomiting, headache, fever and flushing.⁷

Current Status

Current pharmacological intervention for treatment of CMV retinitis include ganciclovir and foscarnet. The drawback of these drugs is that these drugs must be administered 2 or 3 times a day during initiation of therapy and once daily for maintenance. In addition, administration of these drugs requires placement of indwelling catheter.^{23,24} However, cidofovir overcomes these problems. Unlike ganciclovir, chances of development of resistance with this drug are remote, as cidofovir is phosphorylated to its active form by cellular rather than viral enzymes and any alterations in phosphorylation activity due to viral mutation does not result in resistance to cidofovir. Cidofovir effectively delays development of retinitis as assessed by retinal photography (dosage regimen once weekly for 2 weeks followed by once every alternative week), which makes treatment cost effective and less cumbersome. Although nephrotoxicity caused by cidofovir is a serious adverse effect, concurrent administration of probenecid and saline hydration reduces the incidence and severity of this adverse effect.

Anti CMV activity of cidofovir along with its long intracellular half life is a promising alternative to currently available agents for prophylaxis and management of CMV retinitis.

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