Review Article

VALACYCLOVIR: DEVELOPMENT, TREATMENT AND PHARMACOKINETICS

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ABSTRCT: Acyclovir a specific and selective inhibitor of herpes virus has been used safely and effectively. The bioavailability of the drug is low results in poor absorption of drug. Valacyclovir is the L- valyl ester prodrug of Acyclovir. It is used in the treatment of Herpes simplex virus and Varicella zoster virus. After oral administration it is rapidly converted to acyclovir in the Gastro intestinal tract and liver, which increases the bioavailability of acyclovir three to five times that of acyclovir alone.

Keywords: Valacyclovir, Development, Treatment and Pharmacokinetics.

INTRODUCTION

Valacyclovir is L-valine 2 [(2amino 1, 6 di hydro 6-oxo-9H- purin- 9yl) methoxy]ethyl ester. After oral administration Valacyclovir is rapidly converted to acyclovir, which has demonstrated antiviral activity against Herpes simplex virus-1(HSV-1), Herpes simplex virus-2 and Varicella zoster virus [1-6]. Valacyclovir has more favourable pharmacokinetic charecteristics requiring less frequent dosing and achieving higher blood plasma levels than acyclovir. The affinity of acyclovir for herpes virus encoded thymidine kinase is approximately 200 times greater than for human thymidine kinase. After phospharilation to acyclovir monophosphate normal cellular enzymes catalyze the sequential phospharilation to acyclovir diphosphate and acyclovir tri phosphate. Acyclovir tri phosphate terminates the production of viral DNA by inhibiting DNA polymerase [7-8]. After oral administration Valacyclovir is rapidly absorbed and extensively converted to acyclovir via first pass metabolism. The plasma acyclovir concentrations approximately 3-5 times greater than those achieved with oral doses of acyclovir. The elimination half-life approximately 3hr.Acyclovir is primarily excreted unchanged in the urine [9-10].

Development of Valacyclovir

Acyclovir a synthetic purine nucleoside analogue derived from guanine is used mainly for the treatment of viral infections. Acyclovir is absorbed slowly and incompletely from the human GIT. Oral bioavailability to be between 15-30%. Several approaches initially were tried to improve after the oral bioavailability of acyclovir. Early studies focused on compounds with alterations at the 6-substituent of the purine ring. Two congeners of acyclovir with alterations in the 6-substituent of the purine ring have been extensively evaluated. The first, the 6-amino congener, is incompletely converted to acyclovir by adenosine deaminase. The second, the 6-deoxy congener, is dependent on xanthine oxidase for conversion to acyclovir. Neither compound has a chronic toxicity profile in experimental animal models as favorable as that of acyclovir itself. The toxicity of the two congeners, encountered in laboratory animal models, was hypothesized to be the result of phosphorylation of the unconverted prodrug.

Therefore to develop an effective prodrug that could not be phosphorylated before conversion to acyclovir. Amino acid esters of acyclovir were first studied by La Colla et al in 1983. Because the esters lack a free hydroxyl group, they cannot be phosphorylated, and therefore would not be expected to exhibit any antiviral activity in the absence of conversion to acyclovir. These early studies focused on the simple amino acid esters of acyclovir, such as the glycyl and alanyl esters. These compounds were water-soluble and were hydrolyzed to acyclovir in cell culture experiments. Although some antiviral activity was demonstrated *in vivo*. The complex amino acid esters of acyclovir may prove more useful as prodrugs. Eighteen amino acid esters were synthesized and tested as potential prodrugs for oral administration. After dosing by gavage in rat models, ten of the prodrugs produced greater amounts of parent compound in the urine than did dosing with unmodified acyclovir. The increased absorption appeared to be directly related to the stereochemistry of the amino acid in the prodrug ester, with a decided preference for the L-isomer. This observation suggested that a naturally occurring stereoselective transporter may be involved in the absorption of these esters [11-12].

The structure of the amino acid side chain was also a predictor of efficient prodrug absorption. Of the compounds tested, the L-valyl ester, valacyclovir, had the optimal combination of side chain length and degree of branching. This compound was chemically stable in aqueous solution, but was rapidly and extensively converted to acyclovir in vivo, with virtually undetectable prodrug present in the urine. Addition of valine moiety to acyclovir results in a substrate for active transport mechanism in the human intestine. The valine esterified compound has similar polarity and ionization at physiological pH. After oral administration of valacyclovir to humans approximately 54% dose is absorbed. Of the absorbed valacyclovir more than 99% is rapidly converted to acyclovir to give high plasma acyclovir concentration and low plasma valacyclovir concentration which became undetectable after 3hr post dose. [11]

Preclinical studies in the rat model suggested that this rapid hydrolysis of oral valacyclovir is due to first-pass intestinal and hepatic metabolism. [12]

Treatment

Valacyclovir is used in the treatment of HSV-1, HSV-2 and Varicella zoster virus.

Herpes simplex belongs to a family of eight related viruses including HSV-1& HSV-2, VZV, Epstein-Barr virus and Cytomegalo virus. All of these organisms are double stranded DNA viruses that permanently infect their target cells. These are approximately 50 million people infected with HSV in the US and an estimated one million people are newly infected each year. HSV affects the skin, mucous membrane and less frequently the esophagus and brain. HSV-1 primarily infects oropharyngeal regions and HSV-2 primarily infects genital areas [13-16].

Treatment of primary genital herpes infection

Primary genital herpes involves more systemic flu like symptoms such as fever, headache, malaise and myalgias, more severe local symptoms such as pain, itching, dysuria, vaginal and urethral discharge. The use of Valacyclovir was evaluated in a randomized, double blind trial conducted in 643 patients treated with 72 hrs. Valacyclovir 1000 mg twice daily versus acyclovir 200 mg 5 times a day for 10 days both are FDA approved regimens showed the two courses to be equally efficacious with no difference in the duration of viral shedding, pain or lesion healing. It has been proposed that valacyclovir decreased dosing frequency may improve patient compliance and thus increase clinical efficacy [17-20].

Treatment in recurrent episodes of genital herpes

Treatment of recurrent genital herpes in several placebo- or acyclovir-controlled clinical trials. A randomized, double-blind, placebo-controlled trial conducted with 987 patients who had at least 4 episodes of genital herpes per year demonstrated that valacyclovir 1 g or 500 mg twice daily for 5 days was consistently superior to placebo. The efficacy parameters were median length of recurrence, median lesion healing time, median time to termination of viral shedding, time from treatment initiation through resolution of episode in 75% of patients, and time from treatment initiation through complete healing The second study, a randomized, placebo-controlled,

parallel-group comparison with acyclovir, enrolled 1200 patients with a history of at least 4 recurrent genital herpes episodes in the last year. The patients were treated within 24 hours after onset of an episode. Valacyclovir 1 g twice daily for 5 days was as effective as acyclovir 200 mg

5 times daily, and both medications were significantly more effective than placebo in healing lesions and reducing viral shedding. By the seventh day of treatment, significantly ($p < 0.05$) more patients receiving valacyclovir or acyclovir (91%) compared with placebo (83%) reported no pain. Similar results were obtained in a 739-patient trial comparing valacyclovir 500 mg twice

daily to acyclovir 200 mg 5 times daily.18 Valacyclovir also appears effective in the episodic treatment of recurrent genital herpes with once daily dosing, but it is not approved for this schedule. In a randomized study enrolling 1199 patients with a history of at least 4 recurrences in the past year, valacyclovir 1 g once daily for 5 days was statistically and clinically equivalent to valacyclovir 500 mg twice daily for 5 days in the episodic treatment of recurrences [20, 21, 22].

Suppression of recurrent genital herpes

Recurrent genital herpes can be controlled either through episodic treatment or through suppressive therapy, in which daily treatment is used to prevent outbreaks. For patients with frequent recurrences, suppressive therapy is the best approach because it reduces the severity and frequency of episodes, reduces the occurrence of asymptomatic shedding of virus (and possibly reduces transmission of genital herpes), and reduces the psychological morbidity by enhancing

the patients' perception of control over the outbreaks. With suppressive therapy, health care providers and patients adopt a proactive approach to the management of recurrent genital herpes. Of the three guanosine nucleoside antivirals, valacyclovir is the only one shown to be effective for the suppression of genital herpes with a once-daily dosing regimen. In a 1-year study of 1479 patients with a history of at least 6 episodes of genital herpes in the past year, valacyclovir given in regimens of 1 g once daily, 500 mg once daily, 250 mg once daily, or 250 mg twice daily was significantly more effective than placebo and as effective as acyclovir 400 mg twice daily in suppressing recurrences.23 Valacyclovir 1 g once daily reduced the yearly recurrence rate by 78% relative to placebo compared with 79% in the acyclovir 400 mg twice daily group. The efficacy of valacyclovir was not enhanced by increasing the dosing frequency.

In a second study, a valacyclovir 500 mg once daily regimen was evaluated in a 16-week, randomized, double- blind trial of 382 patients with a past-year history of 8 recurrences.24 At the end of the treatment period, 69% of patients in the valacyclovir group compared with 10% of placebo patients were free of recurrences. The median time to first recurrences was more than 112 days with valacyclovir compared with 20 days with placebo. In a noncomparative study of 127 patients with recurrent genital herpes, valacyclovir showed efficacy in reducing the likelihood of recurrence. These patients were previously enrolled in a 10-year study of suppressive therapy using acyclovir 400 mg twice daily.

All subjects received valacyclovir 500 mg twice daily for 1 year. Overall, 67% were free of HSV recurrence and 80% had 0–1 recurrences.

This efficacy is higher compared with the earlier 10-year acyclovir study where 44% of patients had no recurrences after 1 year of treatment. In summary, these studies demonstrate the efficacy of valacyclovir once daily for suppressive therapy of genital herpes. Once-daily dosing is important in improving patient convenience and compliance, which will help the success of therapy [20, 23, 24].

Suppression of Recurrent Genital Herpes in Immunocompromised Patients

Immunocompromised patients, such as those infected with the human immunodeficiency virus (HIV), are frequently burdened with recurrent genital herpes. The seroprevalence for HSV in patients with HIV is high, with approximately 80% of homosexual men having infections with HSV. Similar to other infections, the frequency and severity of HSV are highly increased in immunocompromised patients compared with immunocompetent patients. A randomized, double-blind trial conducted using HIV patients compared the efficacy of valacyclovir 500mg twice daily or 1 g once daily with that of acyclovir 400 mg twice daily in the suppression of recurrent genital herpes. Both treatments were equally effective in the time to first and second recurrence or in the percentage of patients free of recurrences at the end of the 48-week treatment period [20, 25, 26].

Reduction of Asymptomatic Shedding

Asymptomatic viral shedding is thought to cause transmission of most cases of genital herpes and transmission of genital herpes may be reduced by prevention of asymptomatic viral shedding. In a double-blind crossover study conducted with 69 patients with recurrent genital herpes, valacyclovir was shown to markedly reduce asymptomatic shedding of HSV-2. Participants received valacyclovir 500 mg twice daily for 7 weeks, acyclovir 400 mg twice daily for 7 weeks, or placebo for 7 weeks. The percentage of days with viral shedding (7.5% valacyclovir vs. 40% placebo) or asymptomatic viral shedding (6.2% valacyclovir vs. 26.8% placebo) was reduced as measured by polymerase chain reaction (PCR). It was recently demonstrated that reducing asymptomatic viral shedding with valacyclovir significantly reduces transmission of genital herpes [20].

Treatment of Herpes Labialis

Twice-daily dosing of valacyclovir for one day has been approved in the United States for therapy of cold sore (herpes labialis) lesions. In this double-blind trial, patients were randomized into groups treated with placebo, valacyclovir 2 g twice daily, and valacyclovir 2 g twice daily and then 1 g twice daily. Valacyclovir reduced episodic duration by 1.3 days in the single-day dosing group and by 1.2 days in the two-day dosing group compared with the placebo group. Furthermore, valacyclovir prevented the lesions from advancing to the macular/papular stage in almost half the subjects. Single-day dosing was as effective as two-day dosing [20].

Treatment of Herpes Zoster

Herpes zoster is a physically debilitating condition caused by the reactivation of the varicella virus. Several factors are associated with persistent pain of herpes zoster. Age was the most important factor, and patients older than 50 years were significantly more likely to have prolonged zoster-associated pain than younger patients. Prodromal pain and moderate to severe pain at presentation were also strong factors. A multicenter, double-blind, randomized, placebo controlled study of valacyclovir 1 g 3 times daily for 7 days showed efficacy for herpes zoster. There were 400 immunocompetent patients enrolled in this study.

Valacyclovir was more effective than placebo in several parameters. Large clinical trials have compared the efficacy of valacyclovir, acyclovir, or famciclovir for herpes zoster. In a randomized, double-blind, comparative trial in which 1141 patients were administered valacyclovir 1 g 3 times daily for 7 or 14 days or acyclovir 800 mg 5 times daily for 7 days, valacyclovir was shown to be more efficacious than acyclovir. Compared with acyclovir, valacyclovir quickened the resolution of zoster-associated pain and post herpetic pain. The median time to cessation of zoster-associated pain was 38 days for the valacyclovir 7-day regimen and 44 days for the valacyclovir 14-day regimen compared with 51 days for the acyclovir group .Valacyclovir reduced pain cessation 34% faster compared with acyclovir. Post herpetic neuralgia, which occurred in 85%, 79%, and 80% of patients in the acyclovir, valacyclovir 7-day, and valacyclovir 14-day groups, respectively, was resolved 32% quicker by valacyclovir compared with acyclovir. Six months after complete healing of the lesions, 19% of subjects using valacyclovir had pain compared with 26% of subjects using acyclovir. Valacyclovir given in 7 and 14 day regimens had similar clinical efficacy. Although valacyclovir was more effective than acyclovir in alleviating acute and post herpetic pain.

A randomized, double-blind study conducted in 597 immunocompetent patients with herpes zoster directly compared valacyclovir 1 g 3 times daily to famciclovir 500 mg 3 times daily. Both drugs were equally safe and similarly effective in cutaneous and pain-related endpoints The resolution of zoster-associated pain was 42 days for valacyclovir compared with 49 days for famciclovir ($p = 0.84$). The resolution of post herpetic neuralgia was 36 days for valacyclovir compared with 37 days for famciclovir ($p = 0.89$). By day 7 of therapy, the rash was 100% crusted or healed in 32% of valacyclovir patients and 25% of famciclovir patients [20, 27, 28, 29].

Pharmacokinetics of Valacyclovir.

Valacyclovir is rapidly converted to acyclovir after oral administration. Maximum peak levels of valacyclovir in the serum after oral administration are 3% of corresponding acyclovir levels and AUC and urinary recovery average 1% of that seen with acyclovir. Serum levels of valacyclovir decline to undetectable within 3 hr.

Absorption

After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. The absolute bioavailability of acyclovir after administration of valacyclovir is 54.5% ± 9.1% as determined following a 1 gm oral dose of valacyclovir and a 350 mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the administration of valacyclovir is not altered by administration with food.

There is no accumulation of acyclovir after the administration of valacyclovir at the recommended dosage regimens in healthy volunteers with normal renal function.

Single and multiple dose studies in healthy volunteers have demonstrated 3-5 times fold increases in bioavailability of valacyclovir relative to acyclovir. Administration of lowest doses of valacyclovir 250mg 4 times daily resulted in C_{max} and AUC values compared to high dose oral acyclovir 800mg 5 times daily.

Distribution

The binding of valacyclovir to human plasma proteins ranged from 13.5% to 17.9%. The binding of acyclovir to human plasma proteins ranges from 9% to 33%.

Metabolism

After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract. Valacyclovir is converted to acyclovir and *L*-valine by first pass intestinal and/or hepatic metabolism. Acyclovir is converted, to a small extent, to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valacyclovir nor acyclovir is metabolized by cytochrome P450 enzymes. Plasma concentrations of unconverted valacyclovir are low and transient, generally becoming non-quantifiable by 3 hours after administration. Peak plasma valacyclovir concentrations are generally less than 0.5 mcg/ml at all doses. After single-dose administration of 1 gm of valacyclovir, average plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 mcg/ml in patients with hepatic dysfunction, renal insufficiency, and in healthy volunteers who received concomitant cimetidine and probenecid respectively.

Elimination

The pharmacokinetic disposition of acyclovir delivered by valacyclovir is consistent with previous experience from intravenous and oral acyclovir. Following the oral administration of a single 1 gm dose of radio labelled valacyclovir to 4 healthy subjects, 46% and 47% of administered radioactivity was recovered in the urine and the faeces over 96 hours, respectively. Acyclovir accounted for 88.60% of the radioactivity excreted in the urine. The plasma elimination half-life of acyclovir typically averaged 2.5 to 3.3 hours in all studies of valacyclovir in volunteers with normal renal function.

Renal Impairment

Reduction in dosage is recommended in patients with renal impairment following administration of valacyclovir to volunteers with End-stage renal disease (ESRD), the average acyclovir half-life is approximately 14 hours. During haemodialysis, the acyclovir half-life is approximately 4 hours. Reduction in dosage is recommended in patients with renal impairment.

Geriatrics

After single-dose administration of 1 gm of valacyclovir in healthy geriatric volunteers, the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 2.91 ± 0.63 hours in healthy younger adult volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of valacyclovir in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient.

Pediatrics

Acyclovir pharmacokinetics has been evaluated in a total of 98 pediatric patients (1 month to <12 years of age) following administration of the first dose of an extemporaneous oral suspension of valacyclovir. Acyclovir pharmacokinetic parameter estimates, following a 20 mg/kg dose, are provided.

Liver disease

Administration of valacyclovir to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate, but not the extent, of conversion of valacyclovir to acyclovir is reduced, and the acyclovir half- life is not affected. Dosage modification is not recommended for patients with cirrhosis.

HIV disease

In 9 patients with HIV disease and CD4+ cell counts <150 cells/mm3 who received Valacyclovir at a dosage of 1 gram 4 times daily for 30 days, the pharmacokinetics of valacyclovir and acyclovir were not different from that observed in healthy volunteers [9,30].

Pharmacokinetics of valacyclovir under fasting and fed conditions in humans.

Two separate bioavailability studies have been used, one under fasting conditions and another under fed conditions. In each study 34 healthy adult males and females have been enrolled. A 1-gram single oral dose of valacyclovir was administered in each study. Plasma concentrations of valacyclovir and acyclovir were determined by LC/MS/MS (LLOQ of 10 and 20 ng/mL for valacyclovir and acyclovir, respectively) [31].

Valacyclovir	AUC0-t (ng·h/mL)	AUC0-inf (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)
Fasting (n=34)	306.25 (28.58)	308.78 (28.48)	181.39 (31.98)	1.10 (44.00)	0.95 (19.91)
Fed (n=34)	551.77(25.50)	554.53(25.42)	350.86(37.96)	1.76 (47.25)	0.76 (25.57)

Conclusion:

Oral administration of the prodrug valacyclovir results in enhanced bioavailability and significantly greater plasma concentration of acyclovir than can be achieved with oral doses of acyclovir it self. Valacyclovir having effective antiviral activity against *Herpes simplex virus* and *Varicella zoster virus* with lower and less frequent doses.

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