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Mini-review

Valacyclovir: a review of its antiviral activity, pharmacokinetic properties, and clinical efficacy

Karl R. Beutner *

Department of Dermatology, University of California at San Francisco, San Francisco, CA, USA

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1. Introduction

Acyclovir, a specific and selective inhibitor of the replication of herpesviruses, has been used safely and effectively for over a decade in the treatment of patients with herpes simplex and herpes zoster. Although acyclovir displays potent inhibitory activity against all herpesviruses in vitro, the individual herpesviruses vary greatly in their sensitivity to the drug. The IC_{50} values for herpes simplex virus may be as low as 0.1 μM (Collins, 1983), while for human cytomegalovirus, the least sensitive of the herpesvirus group, these values have been reported to be as high as 200 μM (Balfour, 1988). Varicella-zoster and Epstein–Barr viruses have intermediate IC_{50} values, with ranges of 1.3–20.6 μM and 0.3–25 μM, respectively, depending on the viral strain and cell lines used for testing (Biron and Elion, 1980; Balfour, 1988).

At appropriate oral doses, acyclovir has proven highly effective in the treatment of herpes simplex virus infections. The bioavailability of the drug at these doses, however, is limited to about 20%, and this value decreases with increasing doses (de Miranda and

* Fax: +1 707-643-5876.

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Blum, 1983; de Miranda and Good, 1992). As a result of this limited bioavailability, plasma levels adequate for the inhibition of the less sensitive herpesviruses have been more difficult to achieve. Multiple higher oral doses or intravenous doses of acyclovir have been necessary to attain adequate clinical results against herpes zoster and cytomegalovirus infections. In immunocompromised patients, the use of suboptimal oral doses of acyclovir to suppress herpes simplex and herpes zoster has led to the emergence of less sensitive strains of these viruses (Engel et al., 1990; Hill et al., 1991; Jacobson et al., 1990); therefore, multiple high oral dosing or intravenous dosing may be necessary for optimal treatment in these clinical settings as well.

Acyclovir is not extensively metabolized. The major metabolite, 9-carboxymethoxymethyl guanine, is pharmacologically inactive and accounts for only about 14% of an oral dose (Wagstaff et al., 1994). The limited bioavailability of orally administered acyclovir, therefore, is likely due to poor absorption of the drug. Research over the past decade has focused on the development of a prodrug of acyclovir that would retain the safety and efficacy profiles of acyclovir while greatly improving the oral bioavailability. A compound with improved absorption and bioavailability would theoretically extend the therapeutic utility of the drug. Simplified dosing regimens would increase compliance, and the higher plasma concentrations that may be attained would minimize the potential for suboptimal treatment of the less sensitive herpesviruses.

This review will focus on the most widely studied of these prodrugs: the L-valyl ester of acyclovir, valacyclovir. This compound is rapidly and extensively converted to acyclovir after oral administration; the resulting plasma levels of acyclovir are 3 to 5 times higher than those attainable with oral acyclovir itself (Blum et al., 1994; Beutner et al., 1995). The safety and efficacy profiles of valacyclovir that have now been demonstrated in several clinical studies suggest that this drug may provide significantly improved care for both immunocompetent and immunocompromised patients with herpesvirus infections.

2. Antiviral activity of acyclovir

Because the activity of valacyclovir appears to be entirely due to its conversion to acyclovir (see below), a brief overview of the antiviral mechanism of acyclovir will be presented here as an introduction to the acyclovir prodrugs. For a more thorough discussion of this topic, the reader is referred to several recent review articles (O'Brien and Campoli-Richards, 1989; Wagstaff et al., 1994).

Uptake of acyclovir is enhanced in herpesvirus-infected cells, presumably because its rapid activation to the monophosphate form, catalyzed by a herpesvirus-encoded thymidine kinase (Elion et al., 1977), creates a concentration gradient favoring uptake by infected cells. Subsequent conversion of the monophosphate to the active form, acyclovir triphosphate, is accomplished by host-cell enzymes (Elion et al., 1977; Fyfe et al., 1978).

Acyclovir triphosphate functions as a substrate for viral, but not cellular, DNA polymerase, competing with deoxyguanosine triphosphate for incorporation into the elongating chain. The DNA polymerase of herpes simplex virus has a 10- to 30-fold

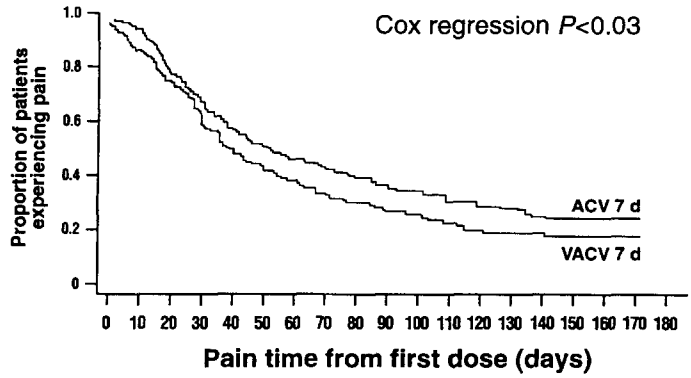

Fig. 1. Structures of acyclovir, 2'-deoxyguanosine, and valacyclovir.

greater affinity for acyclovir triphosphate than that of uninfected cells (Elion et al., 1977). The incorporation of acyclovir triphosphate into the growing chain of viral DNA results in chain termination, as acyclovir lacks the 3'-hydroxyl group necessary for subsequent elongation (Fig. 1) (structures of deoxyguanosine, acyclovir and valacyclovir).

Because the incorporation of acyclovir triphosphate results in obligate chain termination, relatively low concentrations of the drug are necessary to achieve complete inhibition. The inhibitory concentrations are readily achieved and maintained intracellularly, as demonstrated in in vitro studies by Furman et al. (1981). After removal of the drug from the culture medium, concentrations of acyclovir triphosphate reached 20–38 times the inhibitory concentration for herpes simplex virus DNA polymerase, and elevated levels persisted for 4 to 6 h. These results suggest that the attainment of adequate intracellular concentrations of active drug is a critical step in achieving optimal therapeutic outcome with acyclovir. A prodrug with increased bioavailability may well provide a means to accomplish this goal.

3. Development of valacyclovir

Numerous derivatives of acyclovir have been studied as potential prodrugs that would provide greatly increased plasma levels of acyclovir after oral dosing while maintaining safety and efficacy. Early studies focused on compounds with alterations at the 6-substituent of the purine ring (Beauchamp et al., 1992; Purifoy et al., 1993). 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 (Good et al., 1983). The second, the 6-deoxy congener, is dependent on xanthine oxidase for conversion to acyclovir (Krenitsky et al., 1984). 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, a program was initiated 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 (La Colla et al., 1983). Because the esters lack a free hydroxyl group (Fig. 1), 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 compounds showed poor stability in solution at pH 7.4, with 50% hydrolysis after 4 h.

Following the somewhat encouraging results with the simple amino acid esters, Beauchamp et al. (1992) proposed that 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.

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. Preclinical studies in the rat model suggested that this rapid hydrolysis of oral valacyclovir is due to first-pass intestinal and hepatic metabolism (Burnette and de Miranda, 1992).

In vitro tests of antiherpes activity showed greatly increased IC_{50} values for valacyclovir, as well as for the other amino acid esters tested, over that of acyclovir (Beauchamp et al., 1992). In the system used for this study, the IC_{50} value for valacyclovir against HSV-1 was 0.84 μM, while that for acyclovir was 0.1 μM. Since antiviral activity of acyclovir requires phosphorylation of a free hydroxyl group not present on valacyclovir, the observed antiviral activity of valacyclovir was attributed to acyclovir generated from partial hydrolysis of the ester. The in vitro results, coupled with the rapid and almost complete conversion of valacyclovir to acyclovir in vivo, suggest that any biological activity observed with valacyclovir is attributable to acyclovir.

4. Pharmacokinetics of valacyclovir in humans

Single- and multiple-dose studies of valacyclovir pharmacokinetics were performed in a population of healthy male volunteers ranging in age from 18 to 40 years (Weller et al., 1993). In the multiple-dose study, oral valacyclovir, administered 4 times daily for 11 days at doses of 250–2500 mg, was compared with equivalent doses of oral and intravenous acyclovir.

Table 1
Comparison of acyclovir pharmacokinetics following administration of oral valacyclovir and oral and intravenous acyclovir

Oral valacyclovir	Acyclovir	C_{max} (μg/ml)	Daily AUC [a] (h·μg/ml)
	200 mg 5×/day PO [b]	0.8	12
	800 mg 5×/day PO	1.6	24
250 mg 4×/day		3.1	23
1000 mg 4×/day		5.0	63
2000 mg 4×/day		8.5	109
	5 mg/kg q8h IV [c]	9.8	54
	10 mg/kg q8h IV	20.7	107
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Adapted with permission from Beauchamp and Krenitsky (1993).
[a] Projected daily acyclovir AUC based on data over one dosing interval.
[b] PO indicates orally.
[c] IV indicates intravenously.

The standard regimen for treatment of herpes zoster in adults is 800 mg acyclovir, 5 times daily. The daily acyclovir area under the curve (AUC) observed for this regimen was achieved with a valacyclovir regimen of 250 mg 4 times daily (Table 1). The valacyclovir dose of 1000 mg 4 times daily resulted in an acyclovir C_{max} more than 3 times that achieved with acyclovir 800 mg 5 times daily. The acyclovir AUC following a low daily oral dosing of valacyclovir could only be achieved by a high daily oral dosing of the parent compound (Table 1). The average half-life ($t_{1/2}$) of acyclovir after dosing with all dose levels of valacyclovir was 3.1 ± 0.5 h, similar to that observed for acyclovir alone.

In these studies, no accumulation of the unconverted prodrug was observed in the plasma. The highest concentration found was less than 0.87 μg/ml, immediately after the 2000-mg dose. This represented 4% of the corresponding concentration of acyclovir on a molar basis. At all dose levels of valacyclovir, acyclovir accounted for 80%–85% of total urinary recovery, with less than 1% of valacyclovir recovered unchanged.

With oral dosing of valacyclovir, it was possible to achieve close to a linear relationship between valacyclovir dose and acyclovir plasma levels. This is not the case with the parent compound alone, which levels off at a daily acyclovir AUC of approximately 24 h · μg/ml with a dose of 800 mg 5 times daily.

A formal measurement of bioavailability of valcyclovir after oral dosing was recently performed by Blum et al. (1994). After an oral dose of 1000 mg valacyclovir, the mean absolute bioavailability of acyclovir, calculated from the ratios of AUCs after adjusting for molar dose, was 54.2%. This calculation is in good agreement with previous estimates that bioavailability of acyclovir from valacyclovir is 3–5 times higher than that from oral acyclovir.

As illustrated in Fig. 2, the enhanced acyclovir levels obtained with oral valacyclovir may extend the therapeutic utility of acyclovir in infections caused by the less sensitive herpesviruses or the resistant viruses. Intravenous acyclovir has proven effective in the past for suppression of cytomegalovirus infections (Balfour, 1988; Meyers et al., 1988).

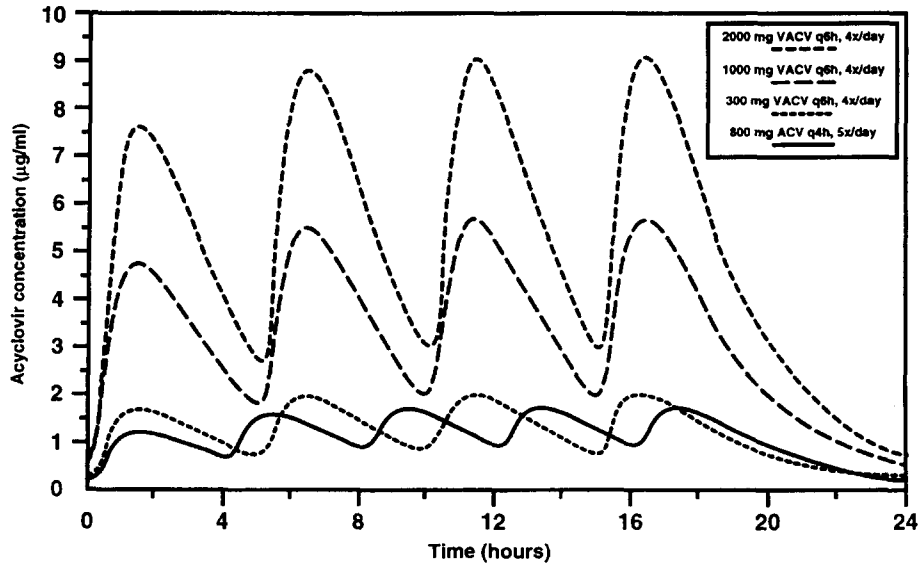

Fig. 2. The relationship between dose and plasma levels of acyclovir (ACV) and valacyclovir (VACV). Adapted with permission from Beauchamp and Krenitsky (1993).

An oral regimen of valacyclovir may be used in these settings to achieve equivalent or higher plasma levels of acyclovir.

In both the single- and multiple-dose studies carried out in healthy volunteers, the safety profile of valacyclovir was excellent (Weller et al., 1993). Adverse experiences considered associated with study medication included headaches and gastrointestinal complaints. Few changes in laboratory parameters were observed, and any abnormalities recorded were deemed clinically insignificant.

Plasma acyclovir pharmacokinetics in immunocompetent adult patients with herpes zoster was evaluated in a comparative study of oral acyclovir and valacyclovir (Beutner et al., 1995). Patients received valacyclovir 1000 mg 3 times daily for 7 or 14 days or acyclovir 800 mg 5 times daily for 7 days. Peak plasma acyclovir concentrations for valacyclovir recipients (mean, 5.73 μg/ml) were almost 3 times greater than those of patients receiving acyclovir (mean 2.23 μg/ml). Estimated mean daily AUC after valacyclovir was more than twice that following acyclovir administration (88.6 h · μg/ml vs. 40.1 h · μg/ml, respectively). The estimated bioavailability of acyclovir was approximately 4 times greater in patients receiving valacyclovir than in those receiving acyclovir.

Since acyclovir is primarily eliminated by the kidney (Laskin, 1983), age and renal function are important considerations in the evaluation of valacyclovir as a useful prodrug. To this end, Wang et al. (1993) conducted a multiple-dose trial of valacyclovir in 36 subjects age 65 to 83 years to evaluate safety, pharmacokinetics, and possible interactions with diuretics in a geriatric population. The subjects received 500 or 1000 mg valacyclovir 3 times daily for 8 days. All pharmacokinetic parameters were similar

for subjects with and without thiazide diuretics. Overall, the C_{max}, AUC, and $t_{1/2}$ values were 15%–40% higher in the geriatric subjects than in young healthy volunteers (creatine clearance > 74 ml/min); these differences were attributed to the reduced creatinine clearance in the geriatric population. Valacyclovir was well tolerated in this population, with no serious adverse events reported.

Immunocompromised hosts represent an important population for the treatment of herpesvirus infections. Patients with advanced human immunodeficiency virus (HIV) disease are at substantial risk for developing progressive or recurrent mucocutaneous herpes simplex or herpes zoster. In addition, infection with acyclovir-resistant herpesvirus isolates has become an increasing problem in this population. These patients are also at risk of developing opportunistic infections with cytomegalovirus, infections that are often sight- or life-threatening. The improved bioavailability and simplified dosing regimens achieved with valacyclovir would provide a significant improvement in treatment and prophylaxis in this population.

A phase I trial was done in volunteers with advanced HIV disease to test the bioavailability and safety of valacyclovir in this population (Feinberg et al., 1992). The 14 men and 2 women enrolled had absolute CD4 lymphocyte counts < 150 cells/μl, and were considered clinically stable. They received 1000 or 2000 mg valacyclovir 4 times daily for 30 days. All pharmacokinetic parameters examined were nearly identical to those previously obtained in healthy volunteers. In addition, despite the underlying advanced disease in these subjects, adverse events reported were not significant.

Acyclovir treatment and prophylaxis has significantly reduced the morbidity associated with herpes simplex and herpes zoster mucocutaneous disease in patients who have undergone organ transplant and aggressive chemotherapy regimens (Dorsky and Crumpacker, 1987). Valacyclovir may offer an improved oral regimen in these settings; however, pharmacokinetic parameters of the prodrug have not yet been studied in this population.

5. Clinical trials of valacyclovir

5.1. Herpes zoster

The efficacy of valacyclovir in the treatment of patients with herpes zoster was evaluated in a randomized, double-blind, multicenter study in which valacyclovir 1000 mg 3 times daily for 7 or 14 days was compared with acyclovir 800 mg 5 times daily for 7 days (Beutner et al., 1995. Patients were enrolled within 72 h of the onset of localized zoster rash and were followed for 60 days. The primary efficacy endpoints were time to complete cessation of pain, time to cessation of new lesion formation or any increase in lesion area, and time to $\geqslant$ 50% crusting/healed lesions. Secondary endpoints included time to cessation of abnormal sensations, pain intensity, and the impact of pain on daily activities. A total of 1141 patients were enrolled in the study and included in the intent-to-treat analysis.

Valacyclovir treatment for 7 or 14 days was superior to acyclovir treatment in decreasing pain duration ($P = 0.001$ and $P = 0.03$ for valacyclovir 7 and 14 days,

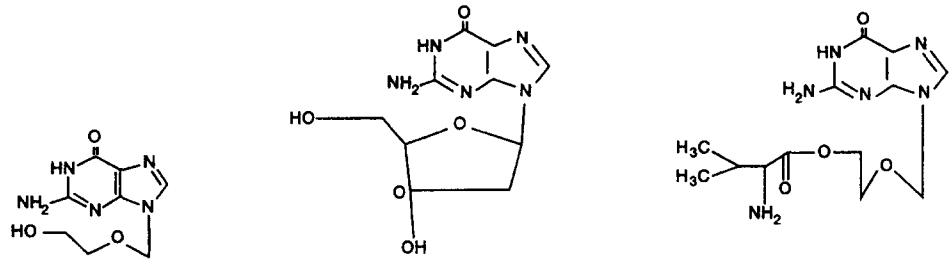

Fig. 3. Kaplan–Meier curves of the time to cessation of pain in immunocompetent adults with herpes zoster. A, Valacyclovir (VACV) 1000 mg 3 times daily for 7 days; or acyclovir (ACV) 800 mg 5 times daily for 7 days. B, VACV 1000 mg 3 times daily for 14 days; or ACV 800 mg 5 times daily for 7 days. Adapted with permission from Beutner et al. (1995).

respectively, vs. acyclovir) (Fig. 3). The median times to cessation of pain were 38 and 44 days, respectively, for valacyclovir 7 and 14 days, and 51 days for acyclovir. The median times to cessation of new lesion formation (3 days) and to $\geqslant 50\%$ crusting/healed lesions (5 days) were identical for the 3 treatment groups.

The duration of abnormal sensations was shorter for both valacyclovir treatment groups than for the acyclovir group. The median times to cessation of abnormal sensations were 45 days, 38 days, and 57 days for the 7-day valacyclovir, 14-day valacyclovir, and acyclovir groups, respectively. An additional parameter studied, the use of medication to control pain, also showed a trend in favor of the valacyclovir groups, as did differences in rates of pain resolution.

Patients with ophthalmic zoster were considered as a separate subset in this study. The relative risks for treatment differences for the three primary efficacy variables in this subset were entirely consistent with those of the overall population in the study.

The results of this study suggest that valacyclovir may offer significant advantages over the current standard regimens for the treatment of zoster. In addition to providing a more convenient regimen, which is likely to encourage patient compliance, valacyclovir offers superior reduction in pain over that of acyclovir.

5.2. Recurrent genital herpes simplex virus infection

In a multicenter, double-blind study involving 1186 otherwise healthy patients with recurrent genital herpes simplex infection, efficacy of valacyclovir was compared with that of acyclovir or placebo (The International Valacyclovir Study Group and Smiley, 1993). Patients initiated treatment within 24 h of initial signs and symptoms and continued for 5 days receiving valacyclovir 100 mg twice daily, acyclovir 200 mg 5 times daily, or placebo. Valacyclovir and acyclovir were both superior to placebo in reducing time to lesion healing and length of episode ($P = 0.0001$ for both active drugs vs. placebo). Kaplan–Meier estimates of the median time to lesion healing were 116 h, 115 h, and 144 h for the valacyclovir, acyclovir, and placebo groups, respectively.

Estimates for the median length of episode were 116 h, 114 h, and 142 h for the 3 groups, respectively.

In this study, acyclovir and valacyclovir were equally efficacious in comparison with placebo. The safety profiles were also equivalent for the two drugs, and patients may prefer the more convenient dosing schedule offered with valacyclovir.

6. Summary

Oral administration of the prodrug valacyclovir results in enhanced bioavailability and significantly greater plasma concentrations of acyclovir than can be achieved with oral doses of acyclovir itself. The results of clinical trials with valacyclovir have demonstrated significant benefits in the resolution of pain associated with herpes zoster infection. Efficacy parameters were similar for valacyclovir and acyclovir in the treatment of herpes simplex; however the results were achieved with lower and less-frequent doses of valacyclovir. The cost of a course of therapy with valacyclovir is expected to be similar to that of other antivirals.

The potential clinical benefits of valacyclovir will likely be apparent in the case of acyclovir-resistant herpesvirus infections, where high-dose intravenous treatment with acyclovir has been necessary. Most of these resistant viruses have been encountered in immunocompromised patients, and the resistance has been attributed to inadequate exposure to the drug. Because optimal levels of acyclovir are achieved with a simpler dosing regimen of valacyclovir, compliance may be improved in many patients, thus reducing the incidence of resistant virus.

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