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Valaciclovir (BW256U87): The L-Valyl Ester of Acyclovir

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Valaciclovir (BW256U87) is an L-valyl ester of acyclovir, which is extensively and almost completely converted to acyclovir. In healthy human volunteers, single valaciclovir doses of 100–1000 mg resulted in dose-proportional increases in acyclovir area under the curve (AUC). The 1,000 mg dose produced an acyclovir peak plasma concentration (Cmax) of 5–6 μg/ml, AUC_6 of 19 hr . μg/ml, time to maximum plasma concentration (Tmax) of 1–2 hr, and half-life ($T_{1/2}$) of 2.8 hr. Plasma valaciclovir peak levels were <0.3 μg/ml, and the prodrug was undetectable after 3 hr. Multiple valaciclovir doses of 250–2,000 mg given four times daily for 10 days resulted in dose-proportional increases in acyclovir Cmax. There were less than proportional increases in the AUCs. No serious or unexpected adverse events or laboratory abnormalities were reported. In volunteers with advanced human immunodeficiency virus (HIV) disease (absolute CD4 lymphocyte count <150 cells/μl), acyclovir and valaciclovir pharmacokinetic results were nearly identical to those in healthy volunteers. At the 2 g dose administered four times daily, steady-state acyclovir Cmax = 8.4 μg/ml, Tmax = 2.0 hr, AUC_6 = 30.5 hr . ug/ml, and $T_{1/2}$ = 3.3 hr. Nausea, vomiting, diarrhoea, and abdominal pain were commonly reported; however, only one adverse event (diarrhoea) was causally linked to valaciclovir exposure. There were no renal or neurologic adverse events. Valaciclovir is well absorbed and is rapidly converted to acyclovir, resulting in three- to fourfold higher acyclovir levels than can be achieved with oral acyclovir, even in patients with advanced HIV disease. The safety profile is generally favourable, with no evidence of nephrotoxicity or neurotoxicity.

KEY WORDS: HIV, HSV, CMV, AIDS

PHASE 1 EVALUATION OF VALACICLOVIR

2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-ethyl L-valinate hydrochloride, or valaciclovir, is an L-valyl ester of acyclovir with a molecular weight of 324.34 [Beauchamp et al., 1992]. This agent is rapidly converted to acyclovir after oral administration to rats, primates, and humans [Burnette and de Miranda, 1992; de Miranda and Burnette, 1992; Blum et al., 1991]. Preclinical animal studies suggest that the rapid hydrolysis of orally administered valaciclovir to acyclovir is due to first-pass intestinal and hepatic metabolism [Burnette and de Miranda, 1992]. Thus valaciclovir is essentially an acyclovir prodrug, metabolised in vivo rapidly and nearly completely to acyclovir, with the potential for substantially increasing acyclovir bioavailability compared to currently available acyclovir oral formulations.

Preclinical animal data suggest that valaciclovir has a safety profile similar to acyclovir. Doses up to 1 g/kg of valaciclovir have been tolerated well in rats and mice, with only moderate ataxia observed (Burroughs Wellcome Company, unpublished data). Single 2–5 g/kg doses caused lethal nephrotoxicity, and multiple 150–300 mg/kg doses in rats and 400–600 mg/kg doses in monkeys caused reversible obstructive nephropathy and mild anaemia (Burroughs Wellcome Company, unpublished data). Valaciclovir doses of up to 3g/kg did not cause chromosomal damage.

To test the bioavailability of acyclovir from oral valaciclovir administration, single-dose and multiple-dose escalation studies were conducted first in healthy male volunteers [Blum et al., 1991; Weller et al., 1991]. Single doses ranging from 100 to 1,000 mg resulted in dose-proportional increases in acyclovir Cmax levels from 0.8 ± 0.1 to 5.6 ± 2.4 μg/ml and in acyclovir AUCs from 2.3 ± 0.4 to 18.9 ± 6.1 hr μg/ml. Mean acyclovir half-life was approximately 2.8 hr at all doses. In the multiple-dose study, steady-state acyclovir Cmax and AUC values were nearly identical to the single-dose results, suggesting that bioavailability does not decrease over the dose range studied. Even at the highest doses administered, plasma valaciclovir peak levels were <0.3 μg/ml, and valaciclovir was undetectable after 3 hr, while urinary recoveries of valaciclovir and

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TABLE I. Acyclovir Peak Plasma Concentrations (Cmax) and Area Under the Curve (AUC) Resulting From Various Dosing Regimens of Oral and Intravenous Acyclovir and Valaciclovir

Oral valaciclovir	Acyclovir	Cmax (μg/ml)	Daily proj. AUC (hr. μg/ml)
	Oral		
	200 mg 5 × daily	0.8	12
	800 mg 5 × daily	1.6	24
250 mg qid		2.1	23
500 mg qid		3.7	41
1,000 mg qid		5.0	68
1,500 mg qid		6.4	92
2,000 mg qid		8.5	112
	Intravenous		
	5 mg/kg q 8 hr	9.8	54
	10 mg/kg q 8 hr	22.9	107

TABLE II. Steady State (%CV) Acyclovir Pharmacokinetic Parameters Resulting From Valaciclovir Administration to Patients With Advanced HIV Disease

Dose (mg) 4 × daily	Cmax (μg/ml)	Tmax (hr)	AUC_6 (hr μg/ml)	$T_{1/2}$ (hr)
1,000	5.5 (29)	2.0 (52)	17.8 (23)	3.1 (15)
2,000	8.4 (24)	2.0 (38)	30.5 (25)	3.3 (8)

acyclovir were 0.5% and 50%, respectively. No serious or unexpected adverse events or laboratory abnormalities occurred. Subsequent analysis of a 2,000 mg dose of valaciclovir administered four times daily to normal volunteers has revealed further increases in acyclovir Cmax and AUC [Weller et al., 1991] (Table I).

To test the acyclovir bioavailability and the safety of valaciclovir in patients with advanced human immunodeficiency virus (HIV) disease, we conducted an additional Phase 1 trial of valaciclovir in two cohorts of eight volunteers who were each administered valaciclovir at a dose of 1,000 or 2,000 mg four times daily for 30 days [Feinberg et al., 1992]. In this trial, 14 men and two women, 27–51 years old, were enrolled. All had an absolute CD4 lymphocyte counts <150 cell/μl. All were clinically stable, without any changes in medications for management of their HIV disease for ≥6 weeks prior to entry, and had a baseline haemoglobin >9 g/dl, absolute neutrophil count >750 cells/μl, serum creatinine <2 mg/dl, and serum alanine transferase less than three times the upper limit of normal. In this trial, acyclovir and valaciclovir pharmacokinetic results were nearly identical to those previously obtained in healthy volunteers (Table II). As in the previous trials, plasma valaciclovir levels were <0.5 μg/ml and undetectable after 3 hr. Nausea, vomiting, diarrhoea, and abdominal pain were the most frequently reported adverse events, and each was reported in 31% of patients. The adverse events must be interpreted with caution in that all patients had underlying advanced HIV disease and the trial was not placebo-controlled. Of note was that only one adverse event (diarrhoea) was casually linked to valaciclovir exposure. In addition, four patients developed neutropenia (two at each dose level), which did not result in fever or opportunistic bacterial or fungal infection. There were no renal, hepatic, or neurologic adverse events.

In summary, Phase 1 evaluations of valaciclovir have revealed that this agent is well absorbed and is rapidly converted to acyclovir, resulting in three- to fourfold greater acyclovir levels than can be achieved with oral acyclovir, even in patients with advanced HIV disease (Tables I, II). The safety profile has generally been favourable, without evidence of renal toxicity or neurotoxicity, which can occur with high dose intravenous acyclovir.

POTENTIAL APPLICATIONS OF VALACICLOVIR IN THE THERAPY OF HUMAN HERPESVIRUS INFECTIONS

With a new orally administered agent that could achieve substantially higher plasma levels of acyclovir than has been possible with currently available oral acyclovir formulations, a number of potential applications would be appropriate for investigation. For immunocompetent patients with mucocutaneous herpes simplex virus (HSV) infection, oral acyclovir has been quite effective, both in acute treatment and in suppression [Dorsky and Crumpacker, 1987]. However, because of pharmacokinetic considerations, multiple daily dosing of oral acyclovir has been required. It is possible, given the substantially higher acyclovir Cmax achievable with valaciclovir, that less frequent dosing with valaciclovir might be equally effective. It is also plausible that, with similar dosing frequency, healing might occur substantially faster with valaciclovir than with oral acyclovir. Clinical trials are underway to test these hypotheses.

The efficacy of oral acyclovir in treating varicella zoster virus (VZV) disease in immunocompetent individuals has been less dramatic, in part because of the higher ED50 of acyclovir for VZV than for HSV [Huff et al., 1988, Morton and Thomas, 1989: Wood et al., 1988; Dunkle et al., 1991]. Several large clinical trials are ongoing to compare valaciclovir, with high-dose oral acyclovir for treatment of VZV infection.

In immunocompromised hosts, acyclovir treatment and prophylaxis of HSV and VZV mucocutaneous disease have been effective and have significantly reduced the morbidity associated with these infections in patients who have undergone organ transplantation and aggressive chemotherapy regimens for haematologic and lymphoproliferative malignancies [Dorsky and Crumpacker, 1987]. It would be reasonable to compare valaciclovir to standard oral acyclovir regimens for these indications. In addition, patients with advanced HIV disease and low absolute CD4 lymphocyte counts are at high risk for developing progressive or recurrent mucocutaneous HSV or VZV disease, and the develop-

ment of progressive mucocutaneous disease caused by acyclovir-resistant HSV and VZV isolates has become a problem of increasing clinical importance [Ehrlich et al., 1989; Jacobson et al., 1990]. Many of these acyclovir-resistant cases have developed in patients receiving chronic oral acyclovir regimens [Ehrlich et al., 1989; Jacobson et al., 1990]. The effect of valaciclovir in prevention of the emergence of clinically significant acyclovir-resistant HSV or VZV strains is being studied in suppression trials in immunosuppressed patients.

Finally, valaciclovir is particularly of interest for its potential in preventing opportunistic cytomegalovirus (CMV) disease. Among bone marrow transplant patients who received intravenous acyclovir, 500 mg/m^2 administered three times daily, and recipients of renal allografts who received oral acyclovir, 800–3,200 mg/day according to estimated renal function, acyclovir significantly reduced the rate of posttransplant CMV infection and disease compared to placebo [Meyers et al., 1988; Balfour et al., 1989; Fletcher et al., 1991]. In spite of the fact that the ED50 for CMV clinical isolates in these studies generally exceeded 10 μg/ml, acyclovir prophylaxis at doses which achieved maximum plasma levels lower than the in vitro ED_{50} still had an antiviral and beneficial clinical effect in preventing opportunistic CMV disease [Fletcher et al., 1991]. Intravenous acyclovir at 500 mg/m^2 three times daily administered to patients with normal renal function achieves a mean acyclovir Cmax of ~20 μg/ml and AUC over 24 hr of ~110 hr . μg/ml [de Miranda et al., 1979; Laskin et al., 1982]. Although maximum oral acyclovir dosing (800 mg 5 times per day) achieves a mean Cmax of only 1.6 μg/ml and AUC over 24 hours of only 24 hr . μg/ml in patients with normal renal function [Van Dyke et al., 1982], mean acyclovir Cmax in the renal transplant study ranged from 2.5 to 4.2 μg/ml with projected 24 hr AUC in the range of 44–85 hr . μg/ml [Fletcher et al., 1991]. The acyclovir pharmacokinetic parameters following oral administration of valaciclovir compare quite favourably with these values (Tables I, II). Thus valaciclovir trials for prophylaxis of CMV disease in renal or bone marrow transplant patients are ongoing or planned.

Patients with advanced HIV disease are also at substantial risk for developing opportunistic CMV end-organ disease; 7–30% of patients with acquired immunodeficiency syndrome (AIDS) will develop sight or life-threatening CMV disease [Jacobson et al., 1988; Jabs et al., 1989]. The risk of developing opportunistic CMV disease is limited almost exclusively to individuals with <100 CD4 lymphocytes/μl [Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group, 1992]. Acyclovir prophylaxis in transplant patients has resulted in a 40–70% reduction in serious opportunistic CMV disease [Meyers, 1988, Balfour, 1989]. A similar reduction in AIDS-related CMV disease might be expected to provide a major impact on the natural history of HIV disease and the morbidity of its complications.

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