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Safety of Short-Term Valacyclovir as an Anti-Sickling Agent in Sickle-Cell Anemia

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Abstract

To assess safety and tolerability, we administered valacyclovir, an oral anti-viral medication that inhibits erythrocyte sickling in vitro, to 14 subjects with sickle-cell anemia for 1 week at a standard dose of 1,000mg every 8 hr. No clinically significant adverse effects occurred. In 11 subjects in steady state, the mean hemoglobin concentration was almost constant while the absolute reticulocyte count decreased in eight ($P = 0.1$) and the overall mean fell slightly although not significantly (10%, $P = 0.2$). These results suggest that valacyclovir is safe and well tolerated in patients with sickle-cell anemia and that a longer duration of therapy merits investigation.

Keywords

anti-sickling agent; sickle-cell anemia; valacyclovir

INTRODUCTION

Valacyclovir is a widely used anti-viral medication that has been shown to inhibit erythrocyte sickling in vitro [1]. A screening study of drugs known to be safe and effective for other indications found that the guanine-based compounds valacyclovir, acyclovir, and ganciclovir inhibit aggregation of deoxygenated hemoglobin S in solution and prevent sickling of intact erythrocytes under near anaerobic conditions. Valacyclovir is a pro-drug that is quickly and completely converted to acyclovir after oral administration. Acyclovir enters human erythrocytes rapidly via the same purine nucleobase carrier that transports guanine, adenine, and hypoxanthine [2]. Within the red blood cell, acyclovir is not metabolized, and no route for efflux has been identified. Valacyclovir has a bioavailability three to five times greater than acyclovir and has been shown to be safe in a variety of patient populations [3–8], but its use in patients with sickle-cell disease has not been specifically examined. We conducted a prospective, open-label Phase 1 study to investigate the safety and tolerability of short-term oral valacyclovir as a potential anti-sickling agent in sickle-cell anemia.

METHODS

The Institutional Review Board of Columbia University Medical Center approved this study for human subjects. We recruited adults and adolescents with sickle-cell anemia (homozygous for the β^S gene) to take 1 week of valacyclovir at the standard dosing schedule for herpes zoster infection, 1,000 mg orally three times daily. Subjects were at least 12-years-old and were studied at steady state. Exclusion criteria included acute vaso-occlusive crisis or other acute illness, chronic transfusion therapy or red blood cell transfusion in the previous 2 months, change in hydroxyurea dose in the previous 6 weeks, abnormal creatinine, pregnancy, and known allergy to acyclovir or valacyclovir. Patients with acute illnesses were excluded to permit examination of the effects of valacyclovir under steady-state conditions. Laboratory studies were obtained prior to initiation of valacyclovir and then on days 1, 2, 3, and 9, and included complete blood count, reticulocyte count, basic metabolic panel, hepatic panel, lactate dehydrogenase, haptoglobin, and urinalysis. Subjects were observed as inpatients for the first 2½ days of study medication and were taught to keep a medication diary of compliance and symptoms. The paired *t*-test was used to compare laboratory parameters before and after 1 week of valacyclovir administration.

RESULTS

Between December 2007 and July 2009, we enrolled subjects with sickle-cell anemia from the pediatric and adult hematology clinics in the Departments of Pediatrics and Medicine, Columbia University College of Physicians and Surgeons. Nineteen patients signed informed consent, but five were unable to participate because they persistently met exclusion criteria or had scheduling conflicts. The 14 subjects who did participate included five females (36%) and nine males (64%) who were 14- to 37-years-old (mean 21.4 years). Five subjects were taking hydroxyurea (at a stable dose for at least 6 weeks). Three subjects were excluded because they developed acute illnesses while on study medication, including two febrile upper respiratory infections and one vaso-occlusive crisis. The remaining 11 subjects in steady state all completed 1 week of study medication and had laboratory tests drawn on the study days 0 and 9 for analysis. Mean compliance rate based on medication diaries and pill count was 96% (range 83–100%).

No adverse effects occurred except for mild, transient headaches in four subjects. No new laboratory abnormalities developed except for one episode of transient, asymptomatic hyperbilirubinemia on day 9 which resolved by day 16. Figure 1 shows individual and Table I lists mean hemoglobin concentrations and absolute reticulocyte counts before and after 1 week of valacyclovir for subjects who were ($N = 5$) or were not ($N = 6$) being treated with hydroxyurea. The mean hemoglobin concentrations did not differ significantly between the two groups, either before or after administration of valacyclovir. The absolute reticulocyte count decreased in 8 of the 11 subjects with an overall decline of about 10% (from 271 ± 42 to 243 ± 35 , $P = 0.2$). In the group receiving chronic hydroxyurea therapy, the mean absolute reticulocyte count was almost constant with no significant change in mean indirect bilirubin (from 2.6 ± 0.8 to 3.2 ± 1.7 mg/dl, $P = 0.6$). By contrast, in the group not treated with hydroxyurea, valacyclovir therapy was associated with a decrease, not statistically significant, in the mean absolute reticulocyte count of about 15% (from 367 ± 47 to 314 ± 42 , $P = 0.2$) along with a small but significant decrease in mean indirect bilirubin (from 3.7 ± 1.0 to 3.4 ± 0.9 mg/dl; $P = 0.03$). Lactate dehydrogenase (LDH) did not change significantly in either group ($P = 0.59$ with hydroxyurea and $P = 0.37$ without).

DISCUSSION

This Phase 1 clinical trial provides evidence that 1 week of oral valacyclovir is safe and well tolerated in patients with sickle-cell anemia. Because valacyclovir administration had not previously been examined in patients with sickle-cell disease, the use of a well-studied dosing schedule for initial assessment seemed prudent. We chose the standard regimen for treatment of herpes zoster infection, 1,000 mg every 8 hr for 1 week. With an average red blood cell lifespan of 35 days in patients with sickle-cell anemia [9], longer durations of treatment would almost certainly be needed to detect evidence of inhibition of sickling in vivo. Hydroxyurea, the only agent currently approved for the treatment of sickle-cell disease, has no significant effect on hemoglobin concentration after 2 weeks. In the large number of patients enrolled in the Multicenter Study of Hydroxyurea in Sickle-Cell Anemia, an increase in mean hemoglobin concentration was observed only after 6 weeks of therapy, and improvement of clinical status, as measured by rate of painful crises, after 3 months [10]. In our patients treated with valacyclovir in steady state, the mean hemoglobin concentration was constant over the 1-week period of observation.

The mechanism of inhibition of sickling by valacyclovir in vitro is not known. We hypothesize that acyclovir directly interferes with hemoglobin S polymerization by altering the interaction between adjacent hemoglobin S tetramers. The observation that acyclovir, ganciclovir, and valacyclovir all inhibit sickling while penciclovir does not [1] suggests that the effect is stereospecific. Each of the three active compounds has an oxygen in an ether linkage in the acyclic side chain attached to the N9 of the guanine; penciclovir does not. Acyclovir, ganciclovir, and valacyclovir may inhibit the polymerization of sickle hemoglobin by specifically interacting with either the β^S -sickle valine or the corresponding hydrophobic pocket in the adjacent tetramer. In their screening study, DeBellis et al. [1] found that under conditions of complete deoxygenation, acyclovir, ganciclovir, and valacyclovir substantially inhibited sickling at concentrations of 0.9–1.3mM and virtually abolished sickling at a concentration of 1.8 mM. For perspective, the concentration of hemoglobin within the erythrocyte is about 5.3 mM. In patients with sickle-cell disease, the average venous pO_2 is about 46 Torr, and the fraction of sickle hemoglobin polymerized in vivo is less than 20%, corresponding roughly to a concentration of 1mM hemoglobin [11]. Acyclovir enters human erythrocytes rapidly via a purine nucleobase carrier [2] and is not metabolized within the red blood cell. No route for acyclovir efflux has been reported. In normal (hemoglobin A) erythrocytes, acyclovir influx proceeds until reaching an equilibrium in which the intraerythrocytic concentration of acyclovir is approximately equal to the extracellular concentration [2]. After oral administration of valacyclovir, 1,000 mg, mean maximum plasma concentrations of acyclovir are about 0.02mM in healthy volunteers [12]. Influx into sickle erythrocytes has not been examined, but even modest reductions in the concentration of deoxy hemoglobin S that is able to polymerize within the erythrocyte could have meaningful clinical benefits [11]. For example, reductions in the concentration of deoxy hemoglobin S participating in polymerization of 0.2–0.6mM have been estimated to reduce the severity of sickle-cell anemia to that of the much milder syndrome of sickle-beta-(+)-thalassemia [13]. Whatever the mechanism of inhibition of sickling, we conclude, based on the evidence presented here for safety and tolerability, that longer duration of therapy with valacyclovir in patients with sickle-cell anemia merits investigation.

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Fig. 1. Hemoglobin concentration and reticulocyte count before and after 1 week of oral valacyclovir for subjects who were (N = 5) or were not (N = 6) being treated with hydroxyurea. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

TABLE I

Mean ($\pm$ SEM) Hemoglobin Concentrations and Absolute Reticulocyte Counts Before and After 1 Week of Valacyclovir for Subjects who Were (N = 5) or Were Not (N = 6) Being Treated With Hydroxyurea (HU)

	Day 0	Day 9	P
Hemoglobin (g/dl)			
All subjects	8.9 ($\pm$ 0.3)	8.8 ($\pm$ 0.3)	0.7
Not treated with HU	8.6 ($\pm$ 0.5)	8.5 ($\pm$ 0.4)	0.6
Treated with HU	9.2 ($\pm$ 0.4)	9.2 ($\pm$ 0.5)	1
Reticulocytes ($\times 10^9$ /L)			
All subjects	271 ($\pm$ 42)	243 ($\pm$ 35)	0.2
Not treated with HU	367 ($\pm$ 47)	314 ($\pm$ 42)	0.2
Treated with HU	156 ($\pm$ 25)	158 ($\pm$ 24)	0.9