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ADHERENCE TO HYDROXYUREA IN CHILDREN WITH SICKLE CELL ANEMIA

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Abstract

Objective(s)—To assess adherence to hydroxyurea in children with sickle cell anemia (SCA), to evaluate the association between adherence and hematologic profile, and to identify barriers and facilitators of adherence.

Study design—Seventy-five children with SCA on hydroxyurea were recruited for a single-institution cross-sectional study. The primary outcome was association between treatment adherence and percent fetal hemoglobin (HbF).

Results—Good adherence was estimated at 82% by visual analog scale; 84% by Morisky score; 85% by medical provider report; 77% by clinic visits; and 49% based on pharmacy refills. Increase in HbF was moderately associated with good adherence as measured by the parent/proxy Morisky score ($r = -0.39$; 95% CI = $-0.58, -0.17$; $p < 0.01$) and prescription refills ($r = 0.39$; 95% CI = $0.16, 0.57$; $p < 0.01$). The number of pharmacy refills and the Morisky score explained 23% of the variation in HbF response.

Conclusions—Adherence was 75% by 4 out of 5 measures. Pharmacy refills and Modified Morisky Scale may be used to identify: children at high risk for poor response due to non-adherence and children with good adherence with poor response due to individual pharmacodynamics. Future research should prospectively compare adherence measures and evaluate methods to improve treatment adherence.

Keywords

hemoglobinopathy; anti-sickling agent; compliance

BACKGROUND

Based on prospective, non-randomized studies hydroxyurea appears safe and efficacious for reducing the number of pain crises and episodes of acute chest syndrome in children with sickle cell anemia (SCA) (1, 2). The National Institutes of Health (NIH) Consensus Development Statement on Hydroxyurea Treatment for SCA identified multiple barriers to assuring that children benefit from hydroxyurea (3). One of the key barriers is lack of adherence.

Adherence with penicillin, desferoxamine, and pain medication is challenging for patients with SCA (4-7). There are limited data regarding adherence with hydroxyurea in clinical trials. Oliveri reported 4% nonadherence in a series of 17 patients starting hydroxyurea (8). However, in two larger clinical studies, 10-20% of children stopped hydroxyurea due to nonadherence (1, 9). Higher rates of non-adherence are expected outside of a clinical trial. In clinical practice, adherence with hydroxyurea is particularly challenging because benefits may not be apparent until after 3 to 6 months of treatment (10), treatment requires frequent monitoring, and some formulations of the drug are not available at all pharmacies. Adherence is difficult to measure; there is not a gold standard for measuring adherence or monitoring drug levels, nor is there a single measure for measuring or defining response to therapy.

We report a single-institution cross-sectional study of treatment adherence for children with SCA taking hydroxyurea. The specific aims of the study were to assess adherence to hydroxyurea, to evaluate the association between adherence and percent fetal hemoglobin (HbF) response, and to identify barriers and facilitators of adherence which may inform a future investigational intervention to improve adherence and health outcomes among children with SCA.

METHODS

Patient Selection. Between 2006 and 2008 children (<18 years) with SCA on hydroxyurea for 5 months were enrolled in an IRB-approved study of treatment adherence at Duke University Medical Center (DUMC). Patients were enrolled sequentially.

Measurements of Adherence. We used a multi-modal assessment of adherence. Adherence with clinic visits was determined by comparing actual clinic visits with recommended visit schedule. Patients on hydroxyurea in our clinic are initially followed monthly until maximum tolerated dose (MTD) is reached and then every 2-3 months. Good adherence was defined as a scheduled visit within 1 week for subjects with visits scheduled monthly, 2 weeks for subjects with visits scheduled every 2 months, and 3 weeks for subjects with visits scheduled every 3 months of recommended time frame. Caregiver reports were obtained with both the Modified Morisky Scale (11) and a visual analog scale (VAS). The Modified Morisky Scale includes the following yes/no questions: Do you ever forget to take your medications? Are you careless at times about taking your medications? When you feel better, do you sometimes stop taking your medications? Sometimes, if you feel worse when you take your medications, do you stop taking them? We adapted the scale for completion by caregivers. The adapted scale included the following questions: Do you ever forget to give your child his/her medications?; Are you careless at times about giving your child his/her medications?; When your child feels better, do you sometimes stop giving your child his/her medications?; Sometimes, if your child feels worse when he/she takes medications, do you stop giving them? Each "yes" answer is scored with 1 point and each "no" answer is scored with 0 points. The answers are summed to give a score (range 0-4); 1 indicating good adherence). The VAS was adapted to this research. Caregivers marked an "X" on a line from 0-100 indicating percentage of doses taken within the last 3-4 weeks (>75% of doses indicating good adherence). Physicians or physician extenders seeing the patient in clinic provided an estimate of adherence (estimates of "often" or "always" adherent in the last 3-4 weeks indicating good adherence). Pharmacy prescription refill data were obtained (5 month-supply refills in the six months prior to enrollment indicating good adherence).

Barriers to Adherence. Caregivers completed a written questionnaire regarding factors that may affect adherence such as prior SCA complications, reason(s) for starting hydroxyurea, and family structure. The questionnaire was designed by the authors based on the Health

Belief Model (12). This questionnaire was not a validated measure but was designed for hypothesis generation.

Hematologic Outcomes. Data were abstracted from written and electronic medical records for pertinent clinical and laboratory data. Baseline hematologic values were those immediately preceding hydroxyurea initiation but at least 4 weeks after an acute vaso-occlusive event (VOE) and 8 weeks after a red blood cell transfusion. If patients were switched from chronic blood transfusions to hydroxyurea, baseline values were those prior to the initiation of chronic blood transfusions. Study enrollment values were those on the day of enrollment. If subjects were enrolled within 4 weeks of an acute VOE or within 8 weeks of a red blood transfusion, the study enrollment values were those at steady state prior to the event.

Statistical analyses. Descriptive statistics were summarized by means and standard deviations for continuous variables and percent and numbers for categorical variables. Differences in hematologic measures were compared using a paired Student t-test. Association between pre and post HbF was assessed by the Pearson correlation. Similarly the association between adherence and HbF response was measured by Pearson partial correlation analyses in order to adjust for known confounders (dose, age at enrollment and length of treatment). Relative importance for linear regressions was used to determine effect of adherence measures on HbF response. Analysis and figures were performed with R Version 2.9.0 (13).

RESULTS

Seventy-five children with SCA and their caregivers enrolled in the study (Table 1). Four subjects read the consent but declined participation. Twenty-eight (37%) children started hydroxyurea as part of a clinical trial (14-18), but none were participating in a clinical trial at time of this study. Reasons for starting hydroxyurea which were documented in the medical record included: pain (n=31; 41%), acute chest syndrome (ACS) (n=26; 35%), and primary or secondary stroke prevention as part of prior research studies (n=21; 28%). Caregivers noted the following reasons for initiation of hydroxyurea: to prevent pain (n=66; 90%); prevent ACS (n=56; 78%); prevent stroke (n=60; 85%); and prevent transfusions (n=62; 85%).

Hydroxyurea was dose-escalated as previously described trying to achieve an increase in HbF and hemoglobin and myelosuppression with an absolute neutrophil count (ANC) $2000-4000 \times 10^9/L$ (1). The mean dose at the time of the study was 24.4 mg/kg/dose (range 16.6-31.6). Fifty (67%) children took a pill form of hydroxyurea; the remainder took liquid hydroxyurea formulated by the pharmacy at DUMC (19). Thirty-eight (50%) obtained prescriptions from the DUMC out-patient pharmacy, 36 (48%) obtained prescriptions from their local pharmacy and 1 obtained prescriptions via mail order. Sixty-eight (91%) children had follow-up scheduled every three months; 3 (4%) children had follow-up scheduled every two months; and four (5%) children had scheduled monthly visits.

Six children had previously discontinued hydroxyurea: 1 because the parent was wary of “prophylactic therapy”; 1 due to splenomegaly and myelosuppression; 2 due to lapse in insurance; 1 due to lack of transportation; and 2 due to lack of adherence with clinic visits. All children subsequently restarted hydroxyurea therapy. Overall, good adherence was estimated at 77-85% by self-report, medical provider report and clinic visits (Table 2).

Adherence was substantially lower based on pharmacy refills (Table 2). There were significant increases in HbF (mean change 8.0%; 95% CI= 6.2, 9.8; $p<0.0001$), hemoglobin (mean change 1.3 g/dL; 95% CI=1.0, 1.5; $p<0.0001$) and mean corpuscular hemoglobin

volume (MCV) (mean change 13 fL; 95% CI 10, 17; $p < 0.0001$). There was a significant decrease in absolute neutrophil count (mean change -1699 cells/mm³; 95% CI = -2513 , -885 ; $p < 0.0001$) indicating effective myelosuppression.

Increase in HbF was moderately associated with good adherence as measured by the parent/proxy Morisky score ($r = -0.39$; 95% CI = -0.58 , -0.17 ; $p < 0.01$) [Figure 1A] and prescription refills ($r = 0.39$; 95% CI = 0.16 , 0.57 ; $p < 0.01$) [Figure 1B] when adjusting for confounding factors (dose, age at enrollment and length of treatment). The number of pharmacy refills and the Morisky score explained approximately 23% of the variation in HbF response. HbF response was not predicted by age at enrollment, dose or length of treatment.

Eighty-eight percent of parents rated hydroxyurea as very valuable, 93% of parents agreed that hydroxyurea helps prevent pain, and 95% of parents agreed that hydroxyurea helps their child be more active, lead a more normal life and go to school. Fifteen to twenty percent of families identified the following barriers to hydroxyurea administration: other responsibilities; dealing with sickle cell disease on a regular basis; obtaining refills from local pharmacy; and coming to clinic. Most families identified the following facilitators of hydroxyurea administration: support from family and friends; understanding the benefits of hydroxyurea; and feeling better.

A variety of methods were used by caregivers to facilitate hydroxyurea administration. At least two caregivers specifically stated that giving hydroxyurea to their child is a duty. Thirty-three (44%) caregivers associated giving hydroxyurea with another daily activity such as dinner. Forty-six (61%) reported that the child remembers to take the medication. Families identified further discussion about hydroxyurea ($n = 46$; 61%) and educational materials ($n = 53$; 72%) as ways to improve adherence with hydroxyurea. Fewer families felt that more frequent follow-up by phone ($n = 29$; 40%) or in clinic ($n = 20$; 28%) would improve adherence.

DISCUSSION

In this study, most families valued hydroxyurea and believed that hydroxyurea provides significant benefits. The proportion of subjects with good adherence was 75% by 4 out of 5 measures. Although there was significant increase in HbF% there was variability in response which was partially explained by lack of adherence based on pharmacy prescription refills and Modified Morisky Score. We expected that HbF might be predicted by age with adolescents being less adherent, and by length of treatment with adherence decreasing over time. However, HbF was not predicted by age or length of treatment. In addition, we expected that higher dose would be associated with higher HbF. However, dose did not predict HbF. The lack of association between change in HbF and length of treatment or dose may be explained by the fact that the majority of patients had reached the MTD prior to study enrollment. Future studies should evaluate pharmacodynamic factors the variation in MTD between individual children.

In this study, the primary barriers included coming to clinic and obtaining refills. Efforts should be made to help family with transportation and ensure that local pharmacies can provide hydroxyurea; patients on stable dose hydroxyurea may benefit from mail order pharmacies that provide a ninety-day supply. Sixty-one percent of parents reported that the child remembers to take the medication. Treadwell *et al.* previously showed that joint parent and child responsibility for chelation therapy was associated with improved adherence (7). This suggests that interventions to improve adherence should be targeted at both the child and the parent.

Previous interventions to overcome barriers to adherence with SCA management include a day camp to promote education about desferoxamine (20), multi-phase educational programs to improve adherence with prophylactic penicillin (5, 21) and structured telephone calls using nonmedical personnel to improve adherence with comprehensive SCA care (22). Based on our study, families would prefer more discussion with the Sickle Cell Center and educational materials. Discussion and educational materials should be targeted at both adults and children, particularly adolescents. We developed the Duke Sickle Cell Transition Program for adolescents 13-18 years of age and plan to incorporate more education about hydroxyurea. Families may benefit from a specific educational strategy using the peripheral blood smear as an educational tool to improve adherence (10). One way to improve adherence could be to increase the frequency of clinic visits. However, in our study only 28% of families identified this as a way to improve adherence. This finding may be influenced by the significant distance that many of our families travel to attend clinic and the established protocol of quarterly visits once MTD is reached.

The study is a single institution study, and individual center practices may affect adherence, thus affecting the generalizability of the study. For example, our center follows patients every three months once MTD is reached compared to every 4-6 weeks at some centers. In addition, the study is limited by the lack of gold standard for measuring treatment adherence. We utilized a multi-modal approach to assess hydroxyurea adherence; each measurement has its limitations. Measures were not directly compared; each measure was evaluated to determine its correlation with change in HbF. Estimates of adherence ranged from 49-85% depending on the method used. The lowest estimate of adherence was based on pharmacy refills. When similar methods were utilized in prior study of penicillin adherence, there was similar discrepancy between pharmacy refills and self-report (4, 23). Pharmacy refills may underestimate adherence due to family filling prescriptions at a pharmacy other than the pharmacy indicated at the time of enrollment or due to extra stock of drug at home, reduction in dose or sibling supply. The prescription refills may have been affected by drug dispensed during hospitalization. However, only 2 patients had significant hospitalizations that may have affected prescription refills. Pharmacy refills may overestimate adherence if prescriptions are filled but medication is not taken. Alternatively, there may be a true discrepancy between adherence measurements if patients don't fill prescriptions even though they attend clinic visits and report adherence.

In conclusion, hydroxyurea provided a significant biologic effect in a non-clinical trial setting. There is variation in hematologic response, partially explained by adherence. Although there is no perfect measure of adherence, pharmacy refills and Modified Morisky Scale may be used to identify children at high risk for poor response due to non-adherence and children with good adherence with poor response due to biologic factors such as pharmacodynamics. Further hydroxyurea effectiveness research is indicated to prospectively compare the predictive value of these adherence measures and to investigate interventions to improve adherence.

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ABBREVIATIONS

SCA	Sickle cell anemia
NIH	National Institutes of Health
HbF	percent fetal hemoglobin
DUMC	Duke University Medical Center
MTD	maximum tolerated dose
VAS	visual analog scale
VOE	vaso-occlusive event
ACS	acute chest syndrome
ANC	absolute neutrophil count
MCV	mean corpuscular hemoglobin volume

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Figure 1.

Scatterplot of Change HbF(%) with Morisky score (Panel A) and Number of Refills (Panel B) adjusted for (dose, age at enrollment and length of treatment). The solid black line represents the best linear fit corresponding to a correlation of -0.39 for the Morisky sum and 0.39 for the number of refills.

Table 1**Demographics**

	N (%)
Subjects	75
Male	40 (53.0)
Female	35 (47.0)
Race	
African or African American	74 (98.7)
American Indian	1 (1.3)
Age	11.2 years (range 3.5-17.8 years)
Diagnosis	
HbSS	75 (100.0)
Family history	
Parent with SCD	2 (2.7)
Sibling with SCD	21 (28)
Concurrent medical condition	
Any	51 (68)
Post-splenectomy state	17 (22.7)
Asthma	17 (22.6)
Chronic pain	1 (1.3)
Duration of hydroxyurea therapy	4.6 years (range 0.4 to 11.3 years)

Table 2

Adherence with hydroxyurea

Adherence measure	Good adherence n (%)
	N=75
Clinic visits *	59 (77)
VAS,	
75% doses in the last 3-4 weeks	58 ** (82)
Modified Morisky Score,	
Score 1	62 *** (84)
Medical provider estimate,	
“always” or “often” adherent	64 (85)
Pharmacy refills,	
5 (1 month) refills in six month period	37 (49)
4 (1 month) refills in six month period	44 (59)
3 (1 month) refills in six month period	63 (84)

* Every 3 months schedule, 3 weeks from scheduled visit; Every 2 months schedule, 2 weeks from scheduled visit; Monthly schedule, 1 weeks from scheduled visit.

** For VAS N=71.

*** For modified Morisky Score N=74.