Hydroxyurea in sickle cell disease patients from Eastern Saudi Arabia

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ABSTRACT

Objectives: To assess the efficiency and safety of hydroxyurea in patients with sickle cell disease from the Eastern Province, Kingdom of Saudi Arabia.

Methods: The study was an open-label and uncontrolled trial. Patients older than 10 years of age with sickle cell disease who suffered 4 or more episodes of painful vaso-occlusive crises requiring admissions per year were included, 36 patients (23 males and 13 females) were included between June 1994 and June 1998. Patients were started on hydroxyurea at a dose of 8-10mg/kg per day and the dose was escalated to a maximum tolerated dose or a dose of 35 mg/kg per day. Blood count, renal and liver functions, and hemoglobin F levels were monitored regulary. Clinical response was assessed by record of number of vaso-occlusive crises, requirement for hospital admission and self scoring at the end of each year of treatment.

Results: Thirty-six patients were enrolled in the study until the time of analysis of the data. The data of the first 27 patients (18 males and 9 females) who completed 12 months of therapy were analyzed and presented. There was significant reduction in leukocyte, platelet counts and rise in total hemoglobin and hemoglobin F. Hemoglobin F rose by 1.2-13 folds, from the baseline. Seventy-four percent of patients had at least 2 fold rise of maximum hemoglobin F. The mean maximum tolerated dose of hydroxyurea was 16.4 mg/kg. There was significant reduction in hospital admissions and hospital stay. No major side effects had occured.

Conclusion: Hydroxyurea seems to be effective in decreasing the frequency of vasooclusive crises in patient with sickle cell disease from Eastern Saudi Arabia. In this preliminary analysis no major side effects were observed. Long term side effects need to be monitored.

Keywords: Hydroxyurea, sickle cell disease, vaso-occlusive crises.

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Sickle cell disease (SCD) is one of the most common hereditary disorders worldwide. In the Arabian Peninsula, SCD is an important public health problem, especially in the Eastern Province and South West of the Kingdom of Saudi Arabia (KSA). Although, the disease in the Eastern part of the country is considered milder than that in the South West,[1,2] all manifestations of SCD except leg ulcers have been described in this population.[3-7] Painful bony crises are the most common presenting complaint.[3,8] This occurs despite the generally higher levels of hemoglobin F (HbF) in patients from the Eastern Province compared to those from South West of KSA or Africa.[8] Hydroxyurea (HU) was shown in controlled trials to be effective in ameliorating the manifestation of SCD in adults[9] and children.[10-12] Hydroxyurea trials were started in 3 centers in KSA, first at King Saud University, Riyadh (Central

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Province) and in Dhahran Health Center (Saudi Aramco) and Qatif Central Hospital (both in Eastern Province). The beneficial effects of HU are probably not confined to stimulation of HbF synthesis. We hypothesized that it may be effective in ameliorating the disease in patients from Eastern KSA who, despite relatively high HbF levels, have severe disease manifestations. Therefore, we embarked on an open-label, uncontrolled trial to test the efficacy and safety of HU in treating SCD patients from Eastern KSA. We report here on patients who completed one year of therapy and were compliant to their medication.

Methods. This was an open-label, uncontrolled study. Enrollment of patients was started in Muharram 1415H, (June 1994). Inclusion criteria were: confirmed diagnosis of SCD, sickle cell anemia (SCA), or sickle cell beta thalassemia (Sß thal) age of 5 years or more, frequent painful vaso-occlusive crises (VOC) defined as 4 or more VOCs requiring hospital admission in the preceding year and stable personality. Exclusion criteria included: Pregnancy, lactation, the unwillingness to use a reliable contraceptive method by patient or spouse, significant renal impairment defined as creatinine of >1.8mg/dl, significant impairment of liver functions defined as alanine transaminase (ALT) more than 150U/L or albumin less than 3gm/dl, narcotic addiction, the use of theophyllines, androgens, estrogens, progesterones (other than those in oral contraceptive pills) and viral infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). Once the patient was found fit for the study and the consent was obtained, a baseline clinical and the laboratory evaluation was carried out including detailed history, physical examination, complete blood count (CBC), differential leukocyte count (DLC), reticulocyte (retic) count (percentage and absolute), liver function tests (LFT), electrolytes, blood urea nitrogen (BUN), creatinine, iron, total iron binding capacity (TIBC), serum Ferritin and baseline Hb electrophoresis. Complete blood count was carried out by a coulter counter. Differential leukocyte count and retic count were carried out manually by conventional laboratory methods. Hemoglobin electrophoresis was carried out on cellulose acetate gel at an alkaline pH (Helena laboratories). The patient was started on HU at a dose of 500mg/day for patients weighing more than 50 kg. Patients weighing less than 50kg were started on 500mg every other day as no other HU preparation was available. The patient was seen at weekly intervals during the first month then monthly unless otherwise indicated by the blood tests. At each visit complete blood count and retic count, DLC, LFT and creatinine were carried out. Hemoglobin electrophoresis was carried out every 2 months. The dose was increased by 500mg at monthly intervals until the maximum tolerated dose or a dose of 35mg/kg/day were reached. Maximum tolerated dose was defined as the dose at which the patient was having mild bone marrow suppression but not reaching the levels of toxicity. Toxicity was considered to be present if any of the following occurred: neutrophil count $<1500x10^9$/L, platelet count $<80x10^9$/L, absolute retic count $<80x10^9$/L, hemoglobin <6gm/dl in the absence of an obvious cause, 50% increase in serum creatinine or absolute increase of 0.4mg/dl, doubling of ALT, significant gastrointestinal disturbance, skin rash, or development of hair loss. If toxicity occurred, the drug was stopped until signs of toxicity resolved and then the drug was resumed at the same dose. If toxicity recurred after resumption of the drug, it was stopped until toxicity resolved then the drug was resumed at the dose preceding the toxic dose. If toxicity recurred again, the drug was stopped until the blood tests returned to the pre-treatment levels and then the drug was resumed at a previously tolerated dose. The drug was withdrawn altogether if it was considered that the toxicity precluded continuation. Each patient was given a diary to register the disease episodes, the severity of pain on a scale of one to 10 (one the minimum pain and 10 the maximum pain ever experienced), the action taken and the side effects of the drug. The patients were asked to report to our hospital as much as possible for management of the disease episodes. If admission occurred in another hospital, a discharge summary was obtained for that admission. The compliance was assessed by inquiry regarding the unused pill count at each visit. At the end of one year, the patients or their legal guardian (for young children), were asked to assess themselves regarding the response to therapy, on a scale of 0-3 (0=no response, 1=minimal response, 2=moderate response and 3=maximum response). Statistical analyses were carried out by Epistat, a statistical software package by Dr. Tracy L. Gustafson of no. 1705, Gattis School Road, Round Rock, Texas, 78664. Unpaired t-test was used to compare the means of the samples, and chi-square to compare the proportions. The correlation coefficient was used to examine the association between the dose of HU, the initial HbF and the HbF after treatment.

Results. From June 1994 to June 1998, 36 patients were enrolled in the study. They were 23 males and 13 females. Their age ranged between 10 and 36 years, with a mean and median age of 22.3 and 21.5 years. At the time of analysis of this data (June 1998), 14 patients had withdrawn from the study. **Table 1** shows the reasons and time of withdrawal. One female patient had withdrawn

Table 1 - Reasons for withdrawal from the study.

Reasons	N
Failure of response	2 males *
Side effects	1 male *
Non-availability of drug	2 females
Difficult assessment of response**	2 females*
Desire for conception	2 males
Pregnancy on Rx	1 female
Moved to another area	1 male
Did not show-up	1 male
Rest from Rx	1 male

N - number, *withdrawn by investigators,
**due to possible psychogenic instability, Rx - treatment.

before starting the therapy for the fear of potentially carcinogenic treatment. The median time of withdrawal was 23 months, with a range of 12-37 months. We analyzed the data of 27 patients who completed 12 months of therapy as representative of the response of the group. The 27 patients were 18 males and 9 females. Their age ranged between 10 and 36 years, with a mean of 21.3 years. They were followed up for up to 49 months with a mean of 29.3 months, and median of 30 months .

Hematological response. **Table 2** shows the hematological parameters at baseline, 3 months, 6 months and one year of therapy. The leukocyte count and platelets were significantly lower than baseline values at 3 months, 6 months and one year. The total hemoglobin, the mean corpuscular volume (MCV) and the HbF levels were significantly higher than baseline values at 3 months, 6 months and one year of therapy. The HbF had risen in all patients. By 6 months, the rise ranged from one to an 8 fold rise. By one year HbF had increased 1.2-13 fold. At

Table 2 - Hematologic parameters.

Parameter	Mean ± SD				Median			
	Baseline	3 Months	6 Months	1 Year	Baseline	3 Months	6 Months	1 Year
WBC	8.99 ± 3.48	6.3 ± 2.2*	6.14 ± 2.17*	6.26 ± 2.58*	7.80	5.8	5.30	5.6
Hb	9.71 ± 1.2	10.5 ± 1.5*	10.95 ± 1.42*	10.74 ± 1.44*	9.50	10.7	10.80	10.6
MCV	71.93 ±11.10	84.3 ± 14.0*	86.45 ± 15.95*	85.59 ± 14.69*	71.20	80.9	84.80	83.9
HbF	12.57 ± 5.41	18.5 ± 10.6*	23.72 ± 9.05*	25.77 ± 7.32*	12.60	19.3	25.10	25.2
Platelets	360 ± 190	205 ± 119*	229 ± 129*	229 ± 118*	352.00	163.0	193.00	190.0

*P=<0.05 from unpaired t - test comparing pretreatment values with values at 3 months, 6 months, and one year.
WBC - white blood cell, Hb - hemoglobin, MCV - mean corpuscular volume,
HbF - hemoglobin F, SD - standard deviation.

Table 3 - Hemolysis parameters.

Parameter	Mean ± SD			Median		
	Baseline	6 Months	1 Year	Baseline	6 Months	1 Year
Retics	10.1 ± 5.5	6.8 ± 4.4*	6.2 ± 1.9*	9.10	5.30	6.2
LDH	315.1 ± 104.5	246.5 ± 99.5*	223.9 ± 72.7*	282.00	221.50	205.0
Tot bili	1.86 ± 0.9	1.6 ± 1	1.6 ± 0.8	1.65	1.25	1.4

*P=<0.05 from unpaired t - test, comparing pre-treatment values with values at 6 months and 1 year,
LDH - lactic dehydrogenase, Tot bili - total bilirubin, SD - standard deviation, retics - reticulocytes.

Table 4 - Hospital admission and duration of hospital stay.

Variable	Pre-treatment		Post-treatment		P - value*
	Median	Mean±SD	Median	Mean±SD	
Admissions per year	6	6.5 ± 2.8	0	0.93 ± 2.2	<0.000001
Duration of stay (days per year)	26	33.9 ± 26.1	0	5.1 ± 13.5	<0.0006

*students t -test (unpaired), SD - standard deviation.

maximum HbF level attained (Fmax) the rise ranged from 1.3-18 fold. Twenty patients (74%) had at least a 2 fold rise at Fmax. The absolute HbF at Fmax ranged between 16.7% and 40.6% with a mean of 31% and standard deviation (SD) of ± 6.5. The time taken to reach Fmax was variable among patients ranging from 3 months to 23 months with a median of 9 months. The maximum tolerated dose (MTD) of HU ranged between 8.5mg/kg and 30.3mg/kg with a mean of 16.9 mg./kg. The dose at Fmax ranged between 9.1 and 34 mg./kg with a mean of 14.5mg/kg. There was no correlation between the initial HbF (Fini) and Fmax (r=0.167), but Fmax was positively correlated to the dose of HU at Fmax, (r=0.57, P value = 0.0018).

Hemolysis indicators. **Table 3** shows the comparison between baseline lactic dehydrogenase (LDH), total bilirubin and retic count and their values at 6 months and one year. The difference was significant at 6 months and one year for both LDH and retic count but not for total bilirubin.

Clinical response. Improvement in clinical condition of patients was reflected by a decrease in the frequency of painful episodes. There were fewer admissions and fewer days spent in the hospital by the patients compared to the mean number of admissions and hospital days for 2 to 3 years prior to treatment with HU. **Table 4** shows the number of admissions and hospital stays pre-treatment and post-treatment with HU. There was a highly significant reduction in these 2 parameters. For self-assessment at 12 months of treatment 22 patients (81.5%) scored 3, 5 patients (18.5%) scored 2, while none scored 0 or one. All admissions were for painful episodes. None was for acute chest syndrome and one patient received blood transfusion for bone marrow suppression with symptomatic anemia (Hb 5.5g/dl).

Discussion. Since the report on the multicenter, placebo-controlled trial on HU in adult sickle cell patients,[9] this chemotherapeutic agent has been accepted as an effective therapy for SCD. It was approved by the United States of America Food and Drug Administration for use in adults who suffer from frequent vaso-occlusive crises (VOC) (3 or more per year).[14] We report our experience with HU in the so-called "benign" SCD of East Saudi Arabia. In this sickle cell population, painful episodes are still the most common presenting complaint and the most common cause of emergency visits and hospital admissions.[3] There was significant reduction in the number of VOCs as reflected by the marked decrease in the number of hospital admissions and duration of hospital stay in the group. This result is consistent with a beneficial effect of HU observed in other trials that included adults and children.[9-11] The improvement in the general well being of the patients can be detected from the score of self-assessment of the benefit obtained from HU at the end of one year. Most of the patients scored maximum benefit. Of interest are some comments heard from the patients or their close relatives about the drug, describing it as a magic drug. One patient felt so strongly that it encouraged him to participate in a course of Scuba diving, which he finished successfully without any mishaps. Because of the open label design for the study, we cannot completely exclude a placebo effect on decreasing the frequency of crises and improved feeling of well being. High HbF level has long thought to be a major ameliorating factor of sickle cell related complications, as seen in SCD in Eastern Saudi Arabia.[8,15] In vitro studies have shown that the extent of hemoglobin S (HbS) polymer formation is inversely proportional to the concentration of HbF.[16] Clinically, the high rates of pain were associated with low HbF levels.[17] It is of interest to note that the mean HbF level of our study group was 12.5%, which is below the mean HbF level of sickle cell population of the Eastern Province of KSA (22.4% for adult men and 26.8% for adult women).[8] This suggests that the study of population represents a sub-group of patients with a relatively more severe disease. At baseline, they suffered from frequent painful crises of 3-4 episodes per year, requiring hospital admission. Most of our patients showed a significant rise in HbF, a finding that is consistent with the previous studies. The rise in HbF level is probably not the only mechanism of beneficial effect of HU. Other mechanisms are likely to contribute to the clinical benefits of HU. These include an increase in MCV, increase in deformability, and decrease in adhesion of red cells.[10] The adhesion of sickle red cells to the vascular endothelium is considered an important mechanism of vaso-occlusion.[18] Activation of platelets and leukocytes is also proposed to contribute to the mechanism of vaso-occlusion.[19,20] Granulocytosis typically accompanies episodes of painful crises and acute chest syndrome.[21] The reduction of leukocyte count by HU was proposed to

be the reason for the control of an episode of pain in a sickle cell patient in whom total leukocyte count rose suddenly after the experimental use of recombinant glanulocyte colony-stimulating factor (G-CSF).[21] In our study there was a significant reduction of white blood cells (WBC), and platelets at 3, 6 and 12 months of treatment. This may contribute to the beneficial effects of HU. The reduction of reticulocytes during HU therapy may be beneficial. Hydroxyurea was postulated to modulate adhesion receptors on reticulocytes, which could contribute to its clinical benefit.[22] The increase in total Hb and hematocrit was found to be deleterious in patients with SCD, and was associated with high rates of pain.[17] In our study as in other studies, total Hb increased during HU treatment. The increase was proposed to be due to the increase in HbF.[10] It may be related to decrease in rate of hemolysis as we found. Therefore, the increase in total Hb may not be detrimental and may be contributing to the improvement of the patients general well being. More studies are needed to measure this benefit more objectively. There were no major side effects of the drug during this study. The most frequent were varying degrees of reversible bone marrow suppression, which was managed by dose adjustment or temporary witholding of the drug. We cannot comment on the long-term side effects in this preliminary report.

In conclusion, HU seems to be effective in decreasing the frequency of VOC in sickle cell disease patients of Eastern Saudi Arabia. Due to the unknown long-term side effects, it is probably advisable to restrict its use to the more severely affected patients. Long-term follow-up is recommended to ascertain the long term unwanted adverse events such as leukemogenesis.

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References

1. Serjeant GR. The challenge of sickle cell disease in Saudi Arabia. *Annals of Saudi Medicine* 1990; 10: 443-448.
2. Padmos MA, Roberts GT, Sackey K, Kulozik A, Bail S, Morris JS, et al. Two different forms of homozygous sickle cell disease occur in Saudi Arabia. *Br J Haematol* 1991; 79: 93-98.
3. Al Dabbons IA, Abusrair HA, Al Fariss. Pattern of admissions of children with sickle cell disease in Qatif Central Hospital Saudi Arabia. *Bahrain Medical Bulletin* 1994; 16: 3-6.
4. Al Jama AH, Al Dabbous IA, Abdullah E, Al Jishi N. Avascular necrosis of the femoral and humeral heads in sickle cell disease: Experience at Qatif Central Hospital, Saudi Arabia. *Saudi Med J* 1995; 16: 252–256.
5. Al Dabbons IA, Al Jama AH. Priapism in sickle cell disease in Qatif Central Hospital. *Saudi Med J* 1993; 14; 440-442.
6. Al Salem AH, Jaber A, Abusrair H, Al Jama A, Al Jish N. Cholelithiasis in Saudi patients with sickle cell Anemia. *Annals of Saudi Medicine* 1992; 12: 387-390.
7. Al Salem AH, Ahmed HA, Qaisarnddin S, Al Jama A, El Bashier A, Al Dabbous I. Osteomyelitis and septic arthritis in sickle cell disease in Eastern province of Saudi Arabia. *International Orthopedics* 1992; 16: 398-402.
8. Perrine RP, Pembrey ME, John P, Perrine S, Shoup F. Natural history of sickle cell anemia in Saudi Arabs, A study of 270 Subjects. *Ann Intern Med* 1978; 88: 1-6.
9. Characache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV et al. The investigators of the multy center study on Hydroxyurea in sickle cell aneamia, effect of Hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; 332: 1317-1322.
10. Jayabose S, Tugal O, Sandoval C, Patel P, Puder D, Lin T et al. Clinical and hematologic effects of Hydroxyurea in childern with sickle cell anemia. *J Pediatrics* 1996; 129: 559-565.
11. Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ. Hydroxurea therapy in children severely affected with sickle cell disease. *J Pediatrics* 1996; 128: 820-828.
12. Maier-Redelsperger M, De Montalembert M, Flahault A, Neonato MG, Ducrocq R, Masson M et al. Fetal hemoglobin and F-Cell responses to long term Hydroxyurea treatment in young sickle cell patienst. *Blood* 1998; 91: 4472-4479.
13. Ault A. US FDA approves first drug for sickle all anemia. *Lancet* 1998; 351: 809.
14. Perrine RP, Brown MJ, Clegg JB, Weatherall DJ, May A. Benign sickle cell anemia. *Lancet* 1972; 1163-1167.
15. Poilin WN, Kim BC, Rodgers GP, Noguchi CT, Schechter AN. Sparing effect of HbF and HbA^2 at physiologic ligand saturations. *Proc Natl Acad Sci USA* 1993; 1990: 5039.
16. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E et al. Pain in sickle cell disease rates and risk factors. *N Engl J Med* 1991; 325: 11-16.
17. Barabino GA, Liu XD, Ewenstein BM, Kaul DK. Anionic polysaccharides inhibit adhesion of sickle erythrocytes to the vascular endothelium and result in improved hemodynamic behavior. *Blood* 1999; 93: 1422-1429.
18. Barabino GA, Wise RJ, Woodbury VA, Zhang B, Briges KA, Hebbel RP et al. Inhibition of sickle erythrocyte adhesion to immobilized thrombospondin by Von Willebrand Factor Under Dynamic Flow Conditions. *Blood* 1997; 89: 2560-2567.
19. Kasschau MR, Barabino GA, Bridges KR, Golan DE. Adhesion of sickle neutrophils and erythrocytes to fibronectin. *Blood* 1996; 87: 771-780.
20. Abboud M, Laver J, Blau CA. Granulocytosis causing sickle cell crisis. *Lancet* 1998; 351: 959.
21. Styles LA, Lubin B, Vichinsky E, Lawrence S, Hua M, Test S et al. Decrease of very late activation antigen-4 and CD36 on reticulocytes in sickle cell patients treated with Hydroxyurea. *Blood* 1997; 89: 2554-2559.