CASE SERIES

Safety and efficacy of hydroxyurea in children and adolescents with sickle/beta-thalassemia: two-year experience

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Abstract

Background: Hydroxyurea is a cytotoxic and myelosuppressive drug that has been used during recent years in the treatment of children with severe sickle cell disease. Nevertheless, questions remain regarding its role in young patients with no severe course, like sickle/beta-thalassemia (S/b-thal) patients often present. The aim of the present study was to evaluate the safety and efficacy of hydroxyurea in young patients with S/b-thal, which is the commonest form of the disease in Greece.
Patients-Methods: Hydroxyurea was given in thirteen children with S/b-thal for 24 months and for that period clinical and laboratory evaluation of the children was performed.
Results: A reduction in pain crises and rate of hospitalization was noted. None of the patients presented with a severe clinical event, related to the disease during the study period. A significant increase in hemoglobin, hemoglobin F, mean corpuscular volume, and mean corpuscular hemoglobin and a decrease in reticulocyte count, white blood cell and platelet count, and total bilirubin level was noted. With regards to adverse events, these were transient, short-term and dose-dependable.
Conclusions: To the best of our knowledge, this is the first study to specifically assess the effect of hydroxyurea therapy in young patients with S/b-thal and the results indicate is safe and efficacious in this patient cohort. Hippokratia 2015; 19 (2):172-175.

Keywords: Sickle cell disease, sickle/beta-thalassemia, hydroxyurea, vaso-occlusive crisis

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Introduction

Sickle cell disease (SCD) is a multisystem disease, characterized by phenotypic heterogeneity[1-3]. The phenotypic diversity of SCD is the result of multiple genetic and environmental factors, among which fetal hemoglobin (HbF) is the most thoroughly studied genetic modulator[1-3]. The main therapeutic target is restriction of red blood cell (RBC) sickling. HbF inhibits the polymerization of hemoglobin S (HbS), consequently limiting sickling and ameliorating disease severity[4,5]. Hydroxyurea is a cytotoxic, antimetabolic and myelosuppressive agent that has been used for decades in the treatment of various malignancies and other non-hematological diseases. Hydroxyurea has multiple beneficial effects in patients with SCD, mainly by inducing HbF production[6]. Additionally, hydroxyurea may be beneficial by reducing the white blood cell (WBC) count and the expression of cell adhesion molecules that contribute to the pathophysiology of vaso-occlusion in SCD[6-9].

Multicenter trials showed that hydroxyurea treatment in adults with SCD resulted in improvement of laboratory parameters, as well as in reduction of pain crises, hospitalizations, acute chest syndrome, and need for transfusions[10,11]. Due to its beneficial effects, hydroxyurea was approved in 1998 by the Food and Drug Administration (FDA) for the treatment of adult sickle cell patients[7]. Hydroxyurea has also been approved, during recent years, for the treatment of children with severe SCD (>3 vaso-occlusive crises or acute chest syndrome or persistent severe anemia)[12,13]. However, data on young patients with sickle/beta-thalassemia (S/b-thal), that is the commonest form of SCD in Greece, is limited. The aim of the present study was to evaluate the safety and efficacy of hydroxyurea treatment in children and adolescents with S/b-thal.

Patients-Methods

Thirteen children and adolescents with S/b-thal (eight girls and five boys) and a mean age of 9.4 ± 4.5 years (range: 3.5-18 years) were recruited in the study. Exclusion criteria were pregnancy, active liver disease (hepatitis B or hepatitis C infection), prior treatment with hydroxyurea, as well as unwillingness of patient to participate in the study. For each patient, data regarding laboratory parameters, frequency of vaso-occlusive crises, vascular complications (splenic sequestration, acute chest syndrome, avascular necrosis of femoral head, stroke), hospitalizations, transfusions during the two year

period prior to hydroxyurea treatment, as well as splenectomy, were recorded. Hematological and clinical parameters prior to initiating hydroxyurea therapy for the study group are shown in Tables 1, 2, and 3.

For patients to participate, informed consent from parents was obtained after full explanation regarding the benefits and possible adverse events of hydroxyurea and the general aims of the study. Each patient was clinically evaluated, prior to hydroxyurea treatment and every 8 to 12 weeks during the two-year study period. Laboratory follow-up consisted of WBC count, hemoglobin (Hb), hematocrit (Hct), red blood cell indices, reticulocyte (RETIC) count, and platelet (PLT) count twice-monthly measurements; biochemistry (urea, creatinine, transaminases) and hemolysis parameters (lactate dehydrogenase, bilirubin) monthly measurements. HbF levels were quantified using high-performance liquid chromatography (HPLC) every two to three months.

Patients received oral hydroxyurea at an initial daily dose that ranged from 10 to 15 mg/kg and for a period of 24 months. The dose was adjusted every 8 to 12 weeks according to patients' hematologic and clinical response, until the maximum tolerated dose (dose with sufficient hematologic and clinical response, without toxicity, maximum 30 mg/kg/day). Clinical course and adverse events related to hydroxyurea treatment were reported for the study period.

Hematologic toxicity of hydroxyurea was defined as a decline from baseline, more than 20% in Hb concentration or a concentration of less than 5.0 g/dl, absolute neutrophil count less than 1.0 x 10^9/l and PLT count less than 80 x 10^9/l. Hepatic toxicity was defined as an increase in transaminases greater than twice the upper limit of normal or total bilirubin concentration more than 10 mg/dl; renal toxicity was defined as serum creatinine concentration more than 1mg/dl or an increase of more than 50%. Moreover, alopecia, rash, skin hyperpigmentation, and headache were reported as drug-related toxicity. According to the protocol, in case of toxicity hydroxyurea treatment was discontinued for 4 to 7 days. In case of persistence or relapse, hydroxyurea treatment was discontinued, until the hematologic parameters returned to normal, with subsequent hydroxyurea administration to the previously tolerated dose. Finally, patients with poor adherence to hydroxyurea or follow-up visits were excluded from the study.

Statistical analysis

Statistical Package for Social Sciences for Windows version 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses. Normal distribution was evaluated using Shapiro-Wilk analysis for all dependent variables. Descriptive statistics was used to determine means and standard deviations. Student paired t-test was used for variables following a normal distribution, whereas Wilcoxon signed rank test was used to test the difference between continuous variables violating the assumption of normality at baseline and study exit. A p-value <0.05 was considered as statistically significant.

Results

Thirteen young patients with S/b-thal were recruited in the study. Twelve of the patients completed the 24-month period of hydroxyurea treatment. One patient stopped follow up after 16 months, for this reason, we report only the laboratory and clinical parameters regarding her first 12 months of therapy. In the patient cohort, the initial daily dose of hydroxyurea ranged from 10 to 15 mg/kg, with a mean of 14 mg/kg. According to patients' hematologic and clinical response to hydroxyurea treatment, administered dose at study exit ranged from 13.5 to 20.5 mg/kg, with a mean of 17.2 mg/kg.

With regards to hematological parameters, Hb concentration and HbF levels significantly increased with an average rise of 0.69 ± 0.82 g/dl (95% CI: 0.19 to 1.20; p =0.012) and 14.04 ± 7.77 % (95% CI: 9.10 to 18.98; p <0.001), respectively. Also, a significant increase in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) was detected. Furthermore, a significant decrease in the RETIC count, WBC count, PLT

Table 1: Hematologic parameters of young patients with sickle/beta-thalassemia (mean ± SD) at study entry and 12 months after hydroxyurea therapy (n: 13).

	Study entry		12 months of HU therapy		p-value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Hb (g/dl)	9.2 ± 0.7	9.3 (7.6 - 10.0)	9.7 ± 0.8	9.9 (7.9 - 10.8)	0.048
HbF (%)	9.1 ± 5.9	7.9 (2.2 - 24.2)	23.4 ± 8.9	24.5 (8.2 - 36.7)	< 0.001
MCV (fl)	66.5 ± 3.7	66.7 (60.9 - 72.0)	86.5 ± 9.5	87.0 (72.9 - 104.0)	< 0.001
MCH (pg)	21 ± 1.1	20.8 (19.3 - 22.9)	27.5 ± 2.9	27.1 (23.7 - 32.8)	< 0.001
WBC (10^9/l)	9.8 ± 3.4	9.5 (3.6 - 15.0)	7.6 ± 3.4	6.8 (4.2 – 15.8)	0.013
PLT (10^9/l)	382 ± 184	340 (137 - 669)	290 ± 135	258 (124 - 467)	0.005
RETIC (%)	9.4 ± 4.5	7.5 (2.5 - 17.5)	4.2 ± 2.3	4.5 (1.5 - 8.0)	< 0.001
Total bilirubin (mg/dl)	2.2 ± 1.4	1.8 (0.8 - 6.1)	1.3 ± 0.6	1.1 (0.6 - 2.7)	0.019
LDH (IU/l)	420 ± 158	391 (245 - 831)	464 ± 167	458 (267 - 917)	0.209

SD: standard deviation, HU: hydroxyurea, N: number of participants, Hb: hemoglobin, HbF: hemoglobin F, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cell count, PLT: platelet count, RETIC: reticulocyte count, LDH: lactate dehydrogenase.

Table 2: Hematologic parameters of young patients with sickle/beta-thalassemia at study entry and exit for patients who completed 24 months of hydroxyurea therapy (n: 12)

	Study entry		24 months of HU therapy		p-value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Hb (g/dl)	9.2 ± 0.7	9.3 (7.6 - 10.0)	9.9 ± 0.9	9.7 (7.9 - 10.9)	0.012
HbF (%)	9.5 ± 6.1	8.7 (2.2 - 24.2)	23.5 ± 9.9	22.6 (6.2 - 39.6)	< 0.001
MCV (fl)	66.6 ± 3.8	67.3 (60.9 - 72.0)	86.1 ± 10.7	85.4 (72.0 - 111.0)	< 0.001
MCH (pg)	21 ± 1.2	21.2 (19.3 - 22.9)	27.7 ± 2.7	27.7 (23.0 - 33.5)	< 0.001
WBC (10^9/l)	9.2 ± 3.3	9.1 (3.68 – 15.0)	6.6 ± 12.8	7.3 (4.7 - 8.0)	0.005
PLT (10^9/l)	359 ± 172	313 (137 - 669)	256 ± 112	273 (96 - 502)	0.008
RETIC (%)	8.7 ± 4.0	7.5 (2.5 -17.5)	5.2 ± 3.0	4.6 (1.8 - 12.0)	0.017
Total bilirubin (mg/dl)	2.3 ± 1.5	1.8 (0.8 - 6.1)	1.6 ± 0.5	1.3 (1.0 - 2.6)	0.023
LDH (IU/l)	415 ± 164	374 (245 - 831)	354 ± 129	292 (245 - 684)	0.108

SD: standard deviation, HU: hydroxyurea, N: number of participants, Hb: hemoglobin, HbF: hemoglobin F, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cell count, PLT: platelet count, RETIC: reticulocyte count, LDH: lactate dehydrogenase.

Table 3: Clinical events 24 months before and at least 24 months after hydroxyurea therapy.

	24 months pre HU		24 months after HU	
	Events	Patients	Events	Patients
Vaso-occlusive crises	34	11	12	3
Hospitalizations	23	11	5	3
Transfusions	16	4	0	0
Splenic sequestration	3	2	0	0
Acute chest syndrome	0	0	0	0
Avascular necrosis of femoral head	0	0	0	0
Stroke	0	0	0	0

HU: hydroxyurea.

count, as well as total bilirubin level was noted at 12 and 24 months of hydroxyurea therapy (Tables 1 and 2). It should be noted that at study exit, in the majority of patients (8 of 12), HbF level was more than 20%, in three it ranged from 15 to 20%, whereas in one young patient HbF level only approached 6.2% (HbF level prior to hydroxyurea therapy was 2.3%).

Concerning clinical events, a significant reduction in pain crises, as compared to the two-year period before treatment (median: 2, range 0-6 vs. median: 0, range 0-5, p =0.027), as well as of hospitalizations (median: 1, 0-4 vs. median: 0, 0-3, p =0.008) was noted. Out of a total of 12 episodes of pain crises that were noted in the study during the follow-up, only five episodes needed hospital admission. None of the study patients had any need for blood transfusion during the two-year hydroxyurea therapy. In addition, none of the patients presented with a severe clinical event (acute chest syndrome, avascular bone necrosis, stroke, splenic sequestration crisis) during the study period (Table 3).

With regards to adverse events during the two-year hydroxyurea therapy, these were transient, short-term and dose-dependable. Two patients presented with mild transaminasemia, while one had a mild elevation of serum creatinine levels. Decline in Hb concentration compared to baseline occurred in two patients: the first patient had concomitant leukopenia with mild neutropenia and the second had pancytopenia. In none of the above cases did Hb reach levels necessitating blood transfusion. Both patients presenting with hematologic toxicity discontinued hydroxyurea therapy for 4 to 7 days and subsequently continued with the previously tolerated dose. None of the subjects presented with related adverse events, such as alopecia, rash, skin hyperpigmentation or headache.

Discussion

SCD is a multisystem disease, which is characterized by phenotypic diversity due to genetic and environmental factors. Besides polymerization of HbS, various mechanisms contribute to the pathophysiology of the disease and the vaso-occlusion phenomenon, including RBC cellular rehydration, increased RBC adhesion to endothelium, increased expression of adhesion molecules and increased WBC count[1]. Hydroxyurea is an agent that interferes with the SCD pathophysiology, mainly by inducing HbF production. However, this is not its only function. Several studies have demonstrated that hydroxyurea also contributes to an increase in MCV and a decrease in WBC count, as well as ameliorating cellular adhesion to endothelium

and affecting rheological properties and hydration of RBC[7,8]. Studies, mainly in adults with sickle cell anemia, showed that hydroxyurea therapy besides been effective with regard to significant clinical parameters, is also safe even if administered for a long period[10,11].

The present study evaluated the safety and efficacy of hydroxyurea treatment in young patients with S/b-thal. The study demonstrated that hydroxyurea treatment is well tolerated in children and adolescents with S/b-thal, at least for the study period. Mild hematologic toxicity noted in a limited number of patients, was, nevertheless transient, short-term, and dose-dependable, in accordance to previous literature[10-13].

Patients, in total, presented significant improvement of the examined hematologic parameters. The improvement was already evident from the first year of hydroxyurea therapy and continued through the second year. An increase in Hb concentration and HbF level, as well as a decline in WBC count, PLT count, and serum bilirubin was noted. Studies have demonstrated that there is a correlation between increased WBC count (>15.0 x 10^9/l) and severity, and poor prognosis of SCD[1,14]. With regards to HbF levels, mean values of HbF, both at 12 and 24 months, were greater than 20%. This finding is of great value, as HbF levels over 20% seem to limit vaso-occlusion, the sickling phenomenon, and the degree of hemolysis[4,15]. Regarding the difference of HbF expression in the study group, it should be noted that this substantial variation in HbF levels in SCD patients treated with hydroxyurea has also been observed and described by other authors[16]. Etiopathogenic mechanisms of this phenotypic heterogeneity have not been elucidated so far. However, recent studies demonstrate that polymorphisms in genes regulating HbF expression, hydroxyurea metabolism, and erythroid progenitor cells, may play a crucial role in the response to hydroxyurea therapy[16,17].

With regards to clinical events, a reduction in the number of vaso-occlusion crises and the rate of hospitalizations was noted during the hydroxyurea treatment period, with no severe clinical event presentation. These findings are in agreement with data from other studies conducted in adults with sickle cell anemia[10-13]. Similar findings are also demonstrated in recent studies involving younger patients with sickle cell anemia[12,13,18-21]. It should be noted that the current study is the first that specifically evaluated young patients with S/b-thal, a group of sickle cell patients not individually studied to date.

The results of the study demonstrated that hydroxyurea treatment is safe and efficacious in young patients with S/b-thal. The study findings are quite encouraging, as hydroxyurea is, potentially, an ideal therapeutic agent for young sickle patients. It is characterized by excellent bioavailability when administered orally once per day, thereby contributing to compliance of young patients, and has limited, transient and dose-dependable adverse events. Data of ongoing multicenter studies will be able to answer pending issues, concerning both the indications of hydroxyurea administration and, also, its possible protective effect on organ dysfunction in children with SCD.

Conflict of interest

Authors declare no conflict of interest.

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