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EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

SAMUEL CHARACHE, M.D., MICHAEL L. TERRIN, M.D., RICHARD D. MOORE, M.D., GEORGE J. DOVER, M.D., FRANCA B. BARTON, M.S., SUSAN V. ECKERT, ROBERT P. MCMAHON, PH.D., DUANE R. BONDS, M.D., AND THE INVESTIGATORS OF THE MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA*

Abstract Background. In a previous open-label study of hydroxyurea therapy, the synthesis of fetal hemoglobin increased in most patients with sickle cell anemia, with only mild myelotoxicity. By inhibiting sickling, increased levels of fetal hemoglobin might decrease the frequency of painful crises.

Methods. In a double-blind, randomized clinical trial, we tested the efficacy of hydroxyurea in reducing the frequency of painful crises in adults with a history of three or more such crises per year. The trial was stopped after a mean follow-up of 21 months.

Results. Among 148 men and 151 women studied at 21 clinics, the 152 patients assigned to hydroxyurea treatment had lower annual rates of crises than the 147 patients given placebo (median, 2.5 vs. 4.5 crises per year, $P < 0.001$). The median times to the first crisis (3.0 vs. 1.5 months, $P = 0.01$) and the second crisis (8.8 vs.

4.6 months, $P < 0.001$) were longer with hydroxyurea treatment. Fewer patients assigned to hydroxyurea had chest syndrome (25 vs. 51, $P < 0.001$), and fewer underwent transfusions (48 vs. 73, $P = 0.001$). At the end of the study, the doses of hydroxyurea ranged from 0 to 35 mg per kilogram of body weight per day. Treatment with hydroxyurea did not cause any important adverse effects.

Conclusions. Hydroxyurea therapy can ameliorate the clinical course of sickle cell anemia in some adults with three or more painful crises per year. Maximal tolerated doses of hydroxyurea may not be necessary to achieve a therapeutic effect. The beneficial effects of hydroxyurea do not become manifest for several months, and its use must be carefully monitored. The long-term safety of hydroxyurea in patients with sickle cell anemia is uncertain. (N Engl J Med 1995;332:1317-22.)

SICKLING of red cells in patients with sickle cell anemia is caused by the polymerization of molecules of deoxygenated hemoglobin S ($\alpha_2\beta_2^S$) into rigid, rod-like polymers. Fetal hemoglobin ($\alpha_2\gamma_2$), which lacks β -globin chains, inhibits sickling in vitro by interfering with the polymerization of hemoglobin S. Clinical observations have suggested that increased fetal hemoglobin concentrations may have beneficial effects in sickle cell anemia.¹ Considerable interest was aroused by the discovery that the administration of 5-azacytidine to adult baboons stimulated the production of fetal hemoglobin.² Other cytotoxic agents had a similar effect,³⁻⁵ but among them, hydroxyurea appeared to be most suited for clinical trials⁶ because of its ease of administration and relative safety.

An open-label study of hydroxyurea in 32 patients

with sickle cell anemia showed that fetal-hemoglobin synthesis increased in most patients treated with doses of hydroxyurea that produced limited myelotoxicity.⁷ Fetal-hemoglobin responses were dose related, and in some patients the levels were as high as 15 to 20 percent. Laboratory studies suggested that fetal-hemoglobin levels of at least 15 to 20 percent might be required for a clinical benefit,⁸ but in a study of untreated patients, it appeared that any increase above 4 percent might be beneficial.⁹

We conducted a randomized, double-blind, placebo-controlled clinical trial to test the hypothesis that hydroxyurea could substantially reduce the frequency of painful crises (often called vaso-occlusive crises) in adults with sickle cell anemia. Because of the beneficial effects observed, the trial was stopped before the planned 24 months of treatment were completed for all patients.

METHODS

The design of the study and the methods used are described elsewhere.¹⁰ Patients were enrolled from 21 sites in the United States and Canada (see the Appendix). The study was approved by the institutional review boards of the Johns Hopkins Medical Institutions and the Maryland Medical Research Institute and at each of the clinical sites. All patients gave written consent for participation.

The original plan was to follow all patients until a uniform closing date, two years after the last patient was enrolled; however, because

From the Johns Hopkins University School of Medicine, Baltimore (S.C., R.D.M., G.J.D., S.V.E.); the Maryland Medical Research Institute, Baltimore (M.L.T., F.B.B., R.P.M.); and the National Heart, Lung, and Blood Institute, Bethesda, Md. (D.R.B.). Address reprint requests to Dr. Charache at B121 Meyer Bldg., Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-7061.

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*The institutions and investigators participating in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia are listed in the Appendix.

the study ended early, only 134 of the 299 patients enrolled had finished two years of follow-up.

Eligibility Criteria

To be eligible, the patients had to be at least 18 years old and had to have sickle cell anemia; patients known to have sickle cell- β^+ -thalassemia and sickle cell- β^0 -thalassemia were excluded, but those with sickle cell- α -thalassemia were not. If patients had received transfusions, hemolysates of their red cells could not contain more than 15 percent hemoglobin A at the time treatment was initiated. The patients had to have reported at least three crises to the study physician in the year before entry into the study; for purposes of eligibility, documentation of crises was not necessary. There was no upper limit on the number of crises per year.

Other reasons for exclusion from the study included pregnancy; known narcotic addiction or regular consumption of more than 30 oxycodone capsules (or the equivalent) every two weeks; participation in a long-term program of transfusion; concurrent treatment with another potential antisickling agent; pretreatment blood counts that could not be distinguished from levels considered to indicate marrow depression; a history of stroke during the preceding six years; prior hydroxyurea therapy; and the presence of antibody to the human immunodeficiency virus (HIV).

Titration of Treatment Dose and Laboratory Analyses

After an initial four-week run-in period, during which only folic acid tablets were dispensed, the patients were randomly assigned to a treatment group. Hydroxyurea (provided in powder form by Bristol-Myers Squibb) and placebo (Starch 1500) were encapsulated by Johns Hopkins Manufacturing Pharmacy into 200-mg and 500-mg capsules and dispensed to the clinics by the treatment distribution center. Patients assigned to hydroxyurea received an initial dose of 15 mg per kilogram of body weight per day, and the dose was increased by 5 mg per kilogram per day every 12 weeks, unless marrow depression (indicated by a neutrophil count below 2000 per cubic millimeter, a reticulocyte or platelet count below 80,000 per cubic millimeter, or a hemoglobin level below 4.5 g per deciliter) was present. If marrow depression occurred, treatment was stopped until blood counts recovered; it was then resumed at a dose that was 2.5 mg per kilogram lower than the dose associated with marrow depression, starting a new 12-week cycle. The dose of placebo was adjusted by the data coordinating center in a similar manner in order to maintain blinding. All patients were given 1 mg of folic acid per day. At each follow-up visit, the capsules were counted and patients were asked whether they had had any adverse effects.

The patients were seen every two weeks, and blood samples were shipped to Baltimore and analyzed at Johns Hopkins Hospital. Fetal hemoglobin and red cells containing fetal hemoglobin (F cells) were assayed,⁷ dense cells were counted,¹¹ and α -globin and β -globin DNA were analyzed (at the Veterans Affairs Medical Center, Jackson, Miss.) according to previously described methods.¹²

Primary Outcome

A painful crisis was defined as a visit to a medical facility that lasted more than four hours for acute sickling-related pain (hereinafter referred to as a medical contact), which was treated with a parenterally administered narcotic (except for a few facilities in which only orally administered narcotics were used); the definition is similar to that used in a previous study.⁹ The measurement of the length of the visit included all time spent after registration at the medical facility, including the time spent waiting to be seen by a physician. The occurrence of chest syndrome (chest-wall pain in association with findings of a new pulmonary infiltrate on chest x-ray films and fever), priapism, and hepatic sequestration (a sudden increase in liver size associated with pain in the right upper quadrant, a decrease in the hemoglobin concentration of at least 2 g per deciliter, and more abnormal results of liver-function tests not due to biliary tract disease) was considered a crisis; the occurrence of hematuria and exacerbations of chronic pain was not.

Ascertainment and Classification of Crises

Patients filled out daily pain diaries, recording the severity of pain, use of analgesics, and visits to medical facilities. These diaries were reviewed at each clinic visit by members of the clinic staff. The data

coordinating center cross-checked the information obtained during the clinic visits every two weeks with the information gathered during monthly telephone inquiries to patients by a coordinator in the central office who was unaware of the patients' treatment assignments, and the clinics were required to resolve discrepancies between the reports. Site visits were made to each clinic, original medical records were reviewed, and medical contacts that were not reported by the clinic staff were required to be reported to the data coordinating center.

Reports of medical contacts and all associated documents were independently reviewed by two members of a crisis review committee (composed of hematologists and general internists), who were unaware of patients' treatment assignments. If they disagreed about how to classify an event, the records were reviewed by a third committee member. With respect to the analyses on which the data safety and monitoring board based its recommendation for early termination of the study, 97.4 percent of the medical contacts were classified.

Blinding

Neither the patients nor the investigators and staff members at the clinical sites were aware of the patients' treatment assignments. Because knowledge of repeated measurements of a patient's mean corpuscular volume or fetal hemoglobin level might make the treatment assignments apparent to staff members, such measurements were made at the central laboratory. Clinic staff members agreed not to look at the results of tests requested by other clinicians at their institutions. Treatment assignments could be revealed if knowledge of the assignment would alter a patient's subsequent medical care (e.g., if a patient or a patient's partner became pregnant). In such cases, the study treatments were stopped, but we continued to follow the patients and to count their crises.

Data Safety and Monitoring Board

A board appointed by the National Heart, Lung, and Blood Institute approved the protocol, reviewed each clinic's consent form, provided advice, and oversaw patient safety and the progress of the study. The board was composed of four hematologists, two biostatisticians, an ethicist, and an educator-patient advocate. It was empowered to recommend the discontinuation of the study and did so when interim analyses showed hydroxyurea to be effective.

Statistical Analysis

All patients were included in the primary analysis according to their original treatment assignments. Treatment groups were compared on the basis of annual crisis rates. The primary end-point analysis was to be a two-sided comparison at an overall alpha level of 0.05.

Annual rates were computed by dividing the number of crises by the number of years elapsed (e.g., 6 crises in 1.9 years = 3.16 crises per year). To test the effect of treatment on the crisis rate, the patients were ranked according to the number of crises they had had per year for observed periods of up to two years. Death was considered the worst outcome, followed by a stroke (defined as a documented new neurologic deficit lasting more than 24 hours, confirmed by a neurologist) or the institution of long-term transfusion therapy (more than four months); outcomes for all other patients were ranked according to the individual crisis rate. These ranks were used to compare the two treatment groups (Van der Waerden's test).¹³ A rank statistic was planned for the primary analysis because it was expected to have more power to detect differences and to be less influenced by extreme values than a t-test of the means.

Four interim analyses were planned to be conducted every six months after enrollment began. To take into account multiple examinations of the data,¹⁴ a P value of less than 0.001 was specified for the differences between groups to reject the null hypothesis at each of the planned interim analyses, and a P value of less than 0.046 was required at the final analysis.

In secondary analyses, for discrete variables, chi-square tests were used to compare the frequency of specific characteristics.¹⁵ For continuous data, mean values were compared by analysis of variance and linear regression.¹⁶ Cumulative event rates were estimated by the product-limit (Kaplan-Meier) method,¹⁷ and the log-rank statistic was used to compare the distributions of events over time.¹⁷ An interaction term, testing whether the effect of hydroxyurea changed with time, was assessed by Cox proportional-hazards models.¹⁸ To adjust

for multiple tests of the data in secondary analyses, two-sided tests with P values between 0.01 and 0.001 were considered to provide some evidence of significant differences between groups, and tests with P values below 0.001 were considered to provide strong evidence of such differences.

This report is based on events that occurred between the start of treatment on January 28, 1992, and June 30, 1994, 10 months before the planned end of the study. The data were obtained from a file updated in December 1994; analyses were performed with SAS software.

RESULTS

Characteristics of the Patients

There were no significant differences between the two groups of patients with respect to sex, age, race or ethnic group, number of α -globin genes, or β -globin haplotype, and blood counts in the two groups were similar before treatment was begun (Table 1). After treatment had begun, one patient in the hydroxyurea group was discovered to have sickle-cell- β^+ -thalassemia (a small amount of hemoglobin A was present).

Results According to Treatment Assignment

As of June 30, 1994, 279 of the 299 patients who were enrolled (93 percent) were being seen regularly for follow-up visits at the clinics and 5034 medical contacts (occurring during two years of follow-up) had been classified. The ranks of the crisis rates differed in the two treatment groups (Table 2), with median rates of 2.5 crises per year in the hydroxyurea group and 4.5 crises per year in the placebo group — a 44 percent difference ($P < 0.001$). When only crises severe enough to cause hospitalization were considered, the median annual rates were 1.0 and 2.4, respectively ($P < 0.001$).

The incidence of death, stroke, and hepatic sequestration did not differ significantly in the two groups. By contrast, the two groups did differ with respect to the number of patients in whom chest syndrome developed (25 in the hydroxyurea group vs. 51 in the placebo group, $P < 0.001$), the number of patients who received transfusions (48 vs. 73, $P = 0.001$), and the number of units of blood transfused (336 vs. 586, $P = 0.004$ by Van der Waerden's test).

The median time to the first vaso-occlusive crisis was longer in patients treated with hydroxyurea than in those given placebo (3.0 vs. 1.5 months, $P = 0.01$), as was the time to the second crisis (8.8 vs. 4.6 months, $P < 0.001$) (Fig. 1). There was no evidence to suggest that the effect of hydroxyurea changed during two years of treatment ($P = 0.77$ for the analysis of the time to the first crisis and $P = 0.86$ for the analysis of the time to the second crisis).

After the study ended (January 1995), examination of the doses of hydroxyurea revealed that after six months of treatment, only 33 percent of the patients in the hydroxyurea group were receiving the maximal tolerated dose or had been receiving a higher dose that was subsequently reduced. By the time the study ended, 51 percent of the patients treated with hydroxyurea were receiving the maximal tolerated doses, and doses for the remainder of patients were nearly maximal. The daily doses of hydroxyurea ranged from 0 mg per kilogram in the 2 percent of patients who

Table 1. Characteristics of the Patients at Base Line, According to Treatment Group.

CHARACTERISTIC	HYDROXYUREA (N = 152)	PLACEBO (N = 147)
No. of crises in the year before study entry (% of patients)		
3–5	44	44
6–9	26	21
≥ 10	30	35
Complications of sickle cell anemia (% of patients)		
Chest syndrome	66	65
Ankle ulcer	31	33
Aseptic necrosis of bone	20	22
Hemoglobin (g/dl)	8.4	8.5
Mean corpuscular volume (μm^3)	94	93
White cells ($10^{-3}/\text{mm}^3$)	12.6	12.3
Platelets ($10^{-3}/\text{mm}^3$)	468	457
Reticulocytes ($10^{-3}/\text{mm}^3$)	327	325
Fetal hemoglobin (%)	5.0	5.2
F cells (%)	33	33
Dense cells (%)	14.3	14.0

could not tolerate hydroxyurea to 35 mg per kilogram — the maximal prescribed dose — in 21 percent of patients. Capsule counts suggested that about 75 percent of the patients took more than 80 percent of their capsules. During the dose titration, blood counts consistent with a finding of marrow depression were observed at least once in 35 percent of the patients who received placebo.

Hemoglobin levels, mean corpuscular volumes, fetal hemoglobin levels, and proportions of F cells were higher in the hydroxyurea group than in the placebo group at the time the study ended, and white-cell, platelet, reticulocyte, and dense-cell counts were lower. Differences between the groups in the mean corpuscular volume and proportion of F cells appeared within 8 weeks of the initiation of the study, reached a peak at about 40 weeks, and then declined (Fig. 2).

Safety

No deaths were related to treatment with hydroxyurea (Table 3). No neoplastic disorders developed dur-

Table 2. Annual Rates of Painful Crises According to Treatment Group.

TYPE OF CRISIS	HYDROXYUREA	PLACEBO
	<i>rate per year</i>	
All crises*		
Minimal value	0.0	0.0
25th percentile	0.6	2.0
Median value	2.5	4.5
75th percentile	7.0	10.2
90th percentile	12.7	16.3
95th percentile	16.7	24.0
Maximal value	49.5	57.0
Crises requiring hospitalization*		
Minimal value	0.0	0.0
25th percentile	0.0	0.6
Median value	1.0	2.4
75th percentile	3.5	5.0
90th percentile	7.0	10.8
95th percentile	9.5	14.9
Maximal value	17.0	52.2

* $P < 0.001$ (by Van der Waerden's two-sample test).

ing the study. Treatment was permanently stopped for medical reasons in 14 patients in the hydroxyurea group (2 because of myelotoxicity at a dose of 2.5 mg per kilogram per day) and 6 patients in the placebo group. Treatment was temporarily stopped in almost all patients in the hydroxyurea group because of marrow depression; blood counts usually recovered within two weeks.

In 12 patients who did not receive transfusions (11 in the hydroxyurea group), hemoglobin levels repeatedly exceeded 12.8 g per deciliter, a potentially adverse effect because of increased blood viscosity (if fetal hemoglobin levels in red cells were not high enough to inhibit sickling in vivo). Four patients assigned to hydroxyurea and five patients assigned to placebo had platelet counts of more than 800,000 per cubic millimeter. In no case was morbidity associated with a high hemoglobin concentration or platelet count.

Treatment was interrupted in four patients in the placebo group because of increased bilirubinemia (bilirubin, >10 mg per deciliter [$103 \mu\text{mol}$ per liter]). Hair loss, rash, fever, and gastrointestinal disturbance were

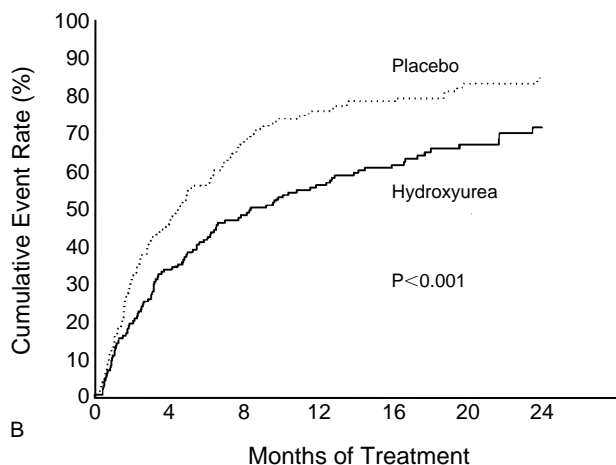
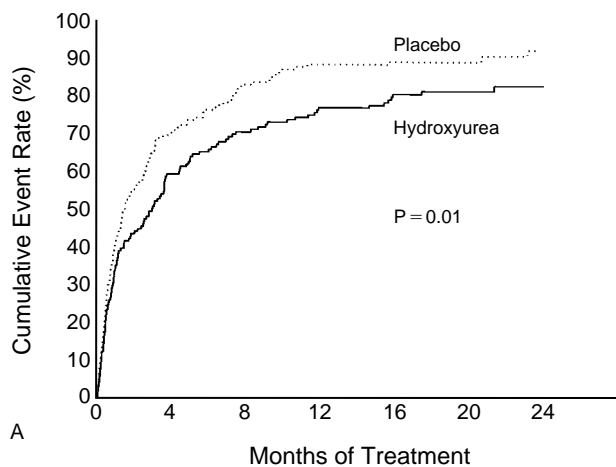
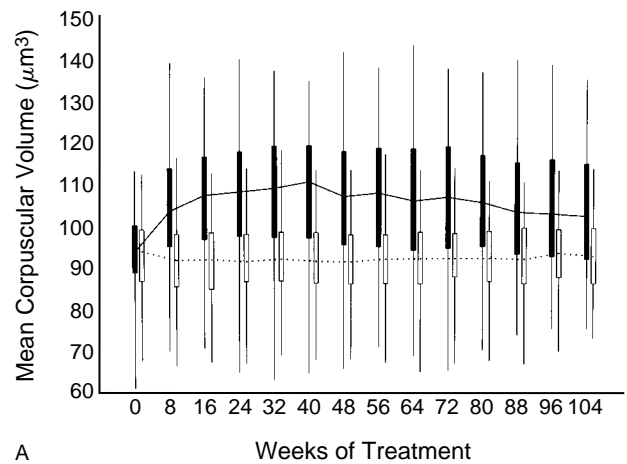
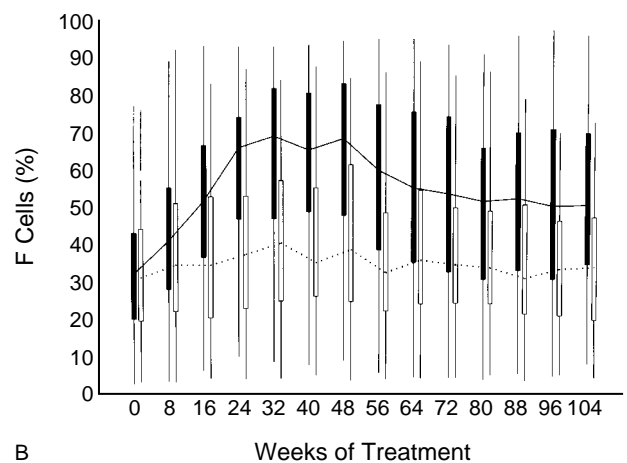


Figure 1. Median Time from the Initiation of Treatment to the First (Panel A) and Second (Panel B) Painful Crises, According to Treatment Group.

Painful crises occurred later in patients receiving hydroxyurea than in those receiving placebo, and the effect was evident in less than six months.



A



B

Figure 2. Measurements of Mean Corpuscular Volume (Panel A) and F Cells (Panel B) in Patients Who Received Hydroxyurea (Solid Bars) or Placebo (Open Bars).

At each point, the median value, the 25th and 75th percentiles (upper and lower limits of boxes), and the maximal and minimal values (vertical lines) are shown.

as common in patients receiving placebo as in those taking hydroxyurea. In six patients (one in the hydroxyurea group) parvovirus B19 infection developed during treatment; the aplastic crises caused by the virus were not prolonged, and all the patients recovered uneventfully.

Pregnancies occurred in 10 patients or their partners (Table 3). These patients were informed of their treatment assignments and counseled. Their study treatments were stopped, but they continued to be seen for follow-up. All live-born babies appeared to be normal.

DISCUSSION

In this controlled trial of the efficacy of hydroxyurea in patients with sickle cell anemia, treatment with hydroxyurea caused a 44 percent reduction in the median annual rate of painful crises. This result is both clinically meaningful and statistically significant. Reductions in the frequency of chest syndrome and the number of transfusions strengthen the conclusion that hydroxyurea is a useful agent in sickle cell anemia. We did not address the reversibility of chronic organ dam-

Table 3. Number of Deaths, Reasons for Stopping Treatment Permanently, and Pregnancies in the Two Groups of Patients as of June 30, 1994.

	HYDROXYUREA	PLACEBO
	number	
Death	2	5
Intracranial bleeding	1	0
Cardiorespiratory arrest	1	1
Acute renal failure	0	1
Pulmonary edema	0	2
Homicide	0	1
Permanent cessation of treatment	14	6
Long-term transfusion therapy	2	2
Acute renal failure	1	0
Fulminant hepatitis	1	0
Myelotoxicity at a dose of 2.5 mg of hydroxyurea/kg/day	2	—
Overdose by patient	2	0
Pregnancy		
Patients		
Normal full-term delivery	1	2
Elective termination	2	1
Partners of patients		
Normal full-term delivery	2	0
Spontaneous abortion	1	0
Still pregnant	0	1

age; it is unknown whether the inhibition of sickling could affect such preexisting lesions.¹⁹

This study was designed to measure clinical responses among patients treated with maximal tolerated doses of hydroxyurea. A difference in the frequency of painful crises between the hydroxyurea and placebo groups began to emerge within about two months of the initiation of treatment and was clearly evident at four months (Fig. 1). Since only a minority of patients (33 percent) were receiving maximal tolerated doses of hydroxyurea by six months, it might be concluded that such doses are unnecessary for all patients. Our understanding of the effect of hydroxyurea is too limited to permit such a conclusion, but evaluation of alternative dosage regimens is clearly needed.

The mechanism by which hydroxyurea reduced the frequency of vaso-occlusive crises is unclear. The proportion of F cells rose between 8 and 24 weeks (Fig. 2), and changes in the mean corpuscular volume also occurred at this time. Since the results in the hydroxyurea and placebo groups began to diverge at about eight weeks (Fig. 1), it is possible that the increase in fetal hemoglobin²⁰ is only one way in which hydroxyurea can affect sickle cell anemia. The increase in mean corpuscular volume during hydroxyurea treatment is primarily due to an increase in the hemoglobin content of the cells, but it may also reflect altered properties of red-cell membranes. Other explanations of the antisickling effect of hydroxyurea are increased water content of red cells,²¹ with secondarily increased deformability,²² and decreased adhesion of red cells to endothelium.²³

Used carefully, with frequent monitoring, hydroxyurea therapy was safe. Hematopoietic depression did occur during therapy, as anticipated, but it was short-lived. Adverse reactions were equally common in both treatment groups. In no instance could the death of a study patient be related to treatment with hydroxyurea.

Patients known to have antibodies to HIV were ex-

cluded from the study, but there is no evidence that hydroxyurea is harmful to such persons. A recent report suggests that hydroxyurea can inhibit the replication of HIV in vitro, but the clinical implications of those findings are unknown.²⁴

The safety of hydroxyurea therapy in pregnancy is unclear. In animals, very large doses (≥ 250 mg per kilogram) are teratogenic,^{25,26} possibly as a result of interference with uterine blood flow.^{27,28} The cytologic appearance of mouse sperm is altered by doses exceeding 25 mg per kilogram,²⁹ but no abnormalities have been described in the offspring of male mice treated with hydroxyurea. Normal pregnancies have been reported in five women who took hydroxyurea for chronic myelocytic leukemia,³⁰ and there have been no reports of teratogenesis or mutagenesis in humans. The children born to our patients have shown no evidence of birth defects or developmental abnormalities to date.

There is concern that long-term hydroxyurea therapy may be carcinogenic or leukemogenic, because some other antineoplastic agents have such effects. Hydroxyurea blocks the synthesis of DNA by inhibiting ribonucleotide reductase. Its cytostatic effects thus differ from those of radiation, alkylating agents, and other anticancer drugs.^{31,32} The incidence of leukemia in patients treated with hydroxyurea for polycythemia vera has been reported by the Polycythemia Vera Study Group.³³ They compared 51 hydroxyurea-treated patients who had received no prior therapy with 134 previously untreated patients who were treated by phlebotomy alone. In the most recent report,³⁴ the incidence of acute leukemia after a median follow-up of 8.6 years was 5.9 percent in the hydroxyurea group, as compared with 1.5 percent in the phlebotomy group ($P=0.18$ by the log-rank test). Reports of leukemia in smaller groups of hydroxyurea-treated patients with polycythemia vera continue to arouse concern about the leukemogenic effect of the drug.^{35,36} However, the relevance of these reports to sickle cell anemia is unclear because of the inherent tendency of myeloproliferative diseases to evolve into acute leukemia.

Perhaps more relevant to our study is the report on a group of 64 patients with erythrocytosis due to inoperable cyanotic congenital heart disease who were treated with hydroxyurea at doses comparable to those we used (9 to 21 mg per kilogram per day) for 2 to 15 years (mean, 5.65).³⁷ Cancer or leukemia did not develop in any of the patients during the period of observation. The uncertain safety of long-term hydroxyurea therapy with respect to leukemogenesis must be carefully balanced against its anticipated benefit.

Hydroxyurea is the first clinically acceptable drug shown to prevent painful crises in adults with sickle cell anemia; it has no role in the treatment of crises in progress. It is not approved by the Food and Drug Administration for the prevention of crises, and short-term and long-term use of this drug is potentially dangerous. Our data support the use of hydroxyurea therapy for the prevention of painful crises in adult patients who are able to follow directions about dosages and monitoring and can appreciate the still unclear long-term risks of such treatment.

We are indebted to the study patients and their families for their enthusiasm and cooperation.

APPENDIX

The following institutions and investigators participated in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia:

Clinical Centers (the numbers in parentheses are the numbers of patients enrolled at each center) — *University of North Carolina, Chapel Hill* (19): E. Orringer, S. Jones, and D. Strayhorn; *Duke University, Durham, N.C.* (16): W. Rosse, G. Phillips,* D. Peace, and A. Johnson-Telfair; *Medical College of Georgia, Augusta* (15): P. Milner, A. Kutlar, and A. Tracy; *Thomas Jefferson University, Philadelphia* (21): S.K. Balas, G.E. Allen, J. Moshang, and B. Scott; *University of Mississippi, Jackson* (19): M. Steinberg, A. Anderson, and V. Sabahi; *University of Miami, Miami* (12): C. Pegelow, D. Temple, E. Case, R. Harrell, and S. Childerie; *San Francisco General Hospital, San Francisco* (6): S. Embury, B. Schmidt, and D. Davies; *University of Illinois, Chicago* (57): M. Koshy, N. Talischy-Zahed, L. Dorn, G. Pendarvis, and M. McGee; *Michael Reese Hospital, Chicago* (11): M. Telfer and A. Davis; *Howard University, Washington, D.C.* (20): O. Castro, H. Finke, E. Perlin, and J. Siteman; *University of Medicine and Dentistry of New Jersey, Newark* (10): P. Gascon, P. di Paolo, and S. Gargiulo; *Emory University, Atlanta* (14): J. Eckman, J.H. Bailey, A. Platt, and L. Waller; *St. Luke's-Roosevelt Medical Center, New York* (18): G. Ramirez, V. Knors, S. Hernandez, E.M. Rodriguez, and E. Wilkes; *Children's Hospital of Oakland, Oakland, Calif.* (5): E. Vichinsky, S. Claster, A. Earles, K. Klemman, and K. McLaughlin; *Medical College of Virginia, Richmond* (19): P. Swerdlow, W. Smith, B. Maddox, L. Ustry, A. Brenner, K. Williams, R. O'Brien, and K. Genter; *Case Western Reserve University, Cleveland* (5): S. Shurin, B. Bertram, K. Chiarucci, and L. Keeverline; *Hospital for Sick Children, Toronto* (6): N. Olivieri, D. Shaw, and N. Lewis; *Brigham and Women's Hospital, Boston* (5): K. Bridges, B. Tynan, and C. Winograd; *Interfaith Medical Center, Brooklyn, N.Y.* (8): R. Bellevue, H. Dosik, M. Sheikhai, P. Ryans, and H. Souffrant; *University of Alabama, Birmingham* (8): J. Prchal, J. Braddock, and T. McArdle; and *University of Pittsburgh, Pittsburgh* (5): T. Carlos, A. Schmotzer, and D. Gardner.

Central Office Staff (Johns Hopkins University, Baltimore) — S. Charache, R. Moore, G. Dover, M. Bergner,* C. Ewart, S. Eckert, C. Lent, J. Ullrich, L. Fishpaw, G. Tirado, J. Gibson, T. Moeller, and T. Nagel.

Data Coordinating Center (Maryland Medical Research Institute, Baltimore) — M. Terrin, F.B. Barton, R.P. McMahon, C. Handy, D. Harris, M. Canner, J. Depkin, N. Meinert, M. Carroll, R. Giro, S. Karabelas, and C. Kelly.

Crisis Review Committee — *Active Members*: M. Heyman, P. Beilinson, M. Druskin, P. Ellis, W.A. Flood, S. Kravitz, S. Lanzkron, V. Loricca, A. Moliterno, A. Nahum, J.A. Nesbitt III, L. Rosenthal, W. Sharfman, M. Streiff, and M. Wachsman; *Former Members*: P. Bray, C. Van Dang, J. Casella, M. McGuire, L. Patrick, H. Schaad, and C. Steiner.

Data and Safety Monitoring Board — C. Johnson, A. Bank, G. Cutter, C.E. Davis, O. Huntley, L. Lessin, O. Platt, and M. Gray-Secundy.

Project Office (National Heart, Lung, and Blood Institute, Bethesda, Md.) — D. Bonds, C. Reid, N. Geller, and M. Waclawiw.

*Deceased.

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