Hydroxyurea can increase fetal hemoglobin (HbF) and improve the clinical course of sickle cell disease (SCD) patients. However, several issues of hydroxyurea therapy remain unresolved, including differences in patients' drug clearance, predictability of drug response, reversibility of sickle cell disease-related organ damage by hydroxyurea, and the efficacy of elevated HbF. We treated two patients with hydroxyurea for periods of 1 to 4 years, monitoring clinical course and laboratory parameters at regular intervals. The first patient (patient A) had a history of chronic pain and extensive hospitalizations. The second patient (patient B) had a history of stroke and refused to continue with chronic transfusion therapy and chelation. Both patients showed a fivefold to tenfold increase in HbF (5% to 25%, 3% to 31%). However, patient A developed an acute chest syndrome, despite an HbF level of 20%. After red blood cell transfusions for hypoxia, the HbF level decreased to 5%. When hydroxyurea dosage was increased, pancytopenia developed and was not resolved until 2 months after hydroxyurea was discontinued. Patient B developed a cerebral hemorrhage on hydroxyurea; he died shortly thereafter. His HbF level was 21% before death. We noted an increase in HbF and a general improvement in the two patients. However, both experienced major SCD-related complications despite HbF levels over 20%. Our findings also suggest that the progressive vascular changes associated with SCD are unlikely to be dramatically affected by increased HbF levels. Because neither the efficacy nor the toxicity of hydroxyurea have been thoroughly investigated, physicians should be cautious in prescribing hydroxyurea for patients with SCD before completion of the National Clinical Trial.

CASE REPORTS

Patient A, a 26-year-old woman with a diagnosis of homozygous sickle cell anemia, had a history of severe, chronic pain. Approval for experimental treatment with hydroxyurea on a compassionate basis was obtained from the Institutional Review Board. Informed consent was obtained from the patient before initiation of the therapy. Results of baseline hematologic parameters and the range of values for an extended period before therapy are shown in Table I. Initial laboratory assessment included a bone marrow (BM) biopsy that showed a hypercellular marrow and increased erythroid activity consistent with a hemolytic anemia. Maturation of all cell lines was normal. The creatinine clearance was 119 mL/min/1.73 m² (0.0198 L/s/m²) and the echocardiogram, chemistry profile, and chest x-ray were normal. During the 104-week period before hydroxyurea therapy, the patient required hospitalization for 238 days to manage severe sickle cell-related pain.

The starting dose of hydroxyurea was 3 mg/kg/d, 7 days a week (weight, 58 kg), and the dose was increased by 5 mg/kg every 8 to 12 weeks to a maximum dose of 30 mg/kg at 87 weeks. Toxicity requiring modification of drug dosage was defined as absolute neutrophil counts less than 2.5 × 10⁹/L, platelet counts less than 100,000/mm³, and a decrease in Hb concentration of 20% or more. The Hb concentration, mean corpuscular volume (MCV) and HbF level increased and the absolute neutrophil count and reticulocyte count decreased in comparison with values before hydroxyurea (Table I). The patient was hospitalized for 43 days during this 87-week interval. She felt well, gained 2.1 kg, graduated from high school, and obtained a full-time job.

At week 88, an episode of severe pain required hospitalization for 14 days. Laboratory findings at admission (Table I) were Hb 4.6 g/dL (46 g/L), MCV 130 fL, HbF 30%, reticulocyte count 0.5%, and neutrophil count of 2.17 × 10⁹/L. Because of the drop in Hb value, hydroxyurea was immediately discontinued. The blood counts returned to normal without transfusion over the next 2 weeks, but the HbF level decreased to 9.4%. During weeks 92 to 126, the dose of hydroxyurea was slowly increased to 21 mg/kg/d to increase the HbF level. The values shown in Table I are the maximal responses
noted at week 126. The Hb rose to 9.4 g/dL (94 g/L) and the HbF to 21%. The patient was in good health and did not require hospitalization for this period of time.

At week 127, respiratory distress was noted and an acute chest syndrome was diagnosed, similar to presentations in three previous acute chest syndrome episodes. Despite this history, steady-state blood gases were normal. Oxygen therapy and RBC transfusions were required. On admission, hematologic values were Hb 8.6 g/dL (86 g/L), MCV 124 fL, HbF 21%, reticulocyte count 6%, and absolute neutrophil count 3.84 × 10^9/L (Table 1). Over a period of 9 weeks after recovery from the acute chest syndrome, the total Hb concentration was 7.6% and the HbF level fell to 4.8% by week 135. This prompted an increase in the dose of hydroxyurea to 27 mg/kg/d.

After an exchange transfusion, he had complete resolution of the blood counts. By week 153, rather than improve, the patient developed severe pancytopenia with a Hb of 4.7 g/dL (47 g/L). Over the next several days, the absolute neutrophil count decreased to 0, the reticulocyte count to 0, and the platelet count to less than 10,000/mm^3. BM biopsy showed complete aplasia without any erythroid precursors. Erythroid colony cultures did not show serum inhibition. Serial IgM and IgG titers by Western blot for parvovirus were negative. A search for other etiologies of BM aplasia, including serology and viral cultures for parvovirus, hepatitis A, B, and C, Epstein-Barr virus, cytomegalic virus, human immunodeficiency virus, and CMV, was negative. The patient was believed to be compliant with both hydroxyurea and folic acid therapy, and folic acid deficiency was excluded (folate level was 6.4 mg/mL; normal range is 3 to 21 mg/mL).

Treatment with erythropoietin, 1,000 U/kg/d subcutaneously, was not successful. Because of the requirement for multiple RBC and platelet transfusions, the patient developed several new RBC and platelet alloantibodies, making it extremely difficult to transfuse further. Before the onset of aplasia, anti-Kell and anti-E antibodies were present; after transfusion, Fy^a, Jk^a, Cw, and I antibodies developed. In addition, the patient's platelet-associated IgG and IgM antibodies were elevated. Hospitalization was required for 4 weeks. By week 169, 14 weeks later, the blood counts returned to baseline values. In view of the hematopoietic toxicity, the patient was not considered to be a candidate for further therapy with hydroxyurea.

In the 28-week observation period after hydroxyurea therapy, the patient had recurrent vaso-occlusive episodes and required hospitalization for 164 days. The mean and range of laboratory values were similar to those before hydroxyurea therapy.

Patient B, born in 1972, had homozygous sickle cell anemia. At age 6 he developed a tonic clonic seizure, from which he completely recovered. Two months later he developed right-sided hemiplegia. After an exchange transfusion, he had complete resolution of the hemiparesis. He was subsequently placed on a chronic transfusion program.

In 1982, although asymptomatic, a cerebral arteriogram was performed to determine his central nervous system vascular status before discontinuing transfusion therapy. The results showed complete occlusion of the right and left anterior cerebral arteries and extensive collateral circulation in the posterior cerebral and leptomeningeal vessels. Marked moyo-moya changes were shown. As a consequence of these findings, transfusion therapy was continued. During the next 8-year period, serial vascular and radiographic studies showed no significant change and he experienced no overt neurologic problems. However, progressive hemosiderosis, with a mean serum ferritin of 6,500 mg/mL (6.5 mg/dL), and anti-Kell, E, and C alloantibodies developed.

In 1991, despite strong medical advice, he elected to stop transfusion therapy. Experimental therapy with hydroxyurea was accepted as an alternative to no therapy. He was started on 10 mg/kg/d increasing by 5 mg/kg every 8 to 12 weeks and showed a dramatic hematologic response (Fig 1). Baseline data showed a Hb of 9 g/dL (90 g/L), reticulocyte count of 27%, MCV of 104 fl, and HBF of 6%. Within 4 months the Hbf level increased to 20%. For the next 6 months the patient was asymptomatic, gained 1.8 kg, and maintained a mean Hb of 10.3 g/dL (103 g/L) and a mean HBF of 21%.

On September 28, 1992, he awoke with sudden headache and numbness on his right side. He rapidly became comatose and was rushed to the hospital. A CAT scan showed a large intracerebral hemorrhage approximately 3 × 8 × 5 cm involving the parietal, basal ganglion, and periventricular area. The concomitant arte-
transfusion in continual decrease in HbF levels over several weeks after the onset of toxicity. Although dilutional effects exist, the investigators speculated that toxicity to erythroid progenitors was cumulative. This study, as well as the present report, suggest that a significant lag phase may occur before the onset of toxicity. Although dilutional effects exist, the continual decrease in HBF levels over several weeks after transfusion in our patient as well as in a reported patient suggests that hemodilution is not the primary mechanism. As a consequence, it is possible to inappropriately increase the dose of hydroxyurea during the period of early BM suppression.

There appears to be marked variation in the ability of patients to tolerate hydroxyurea. Although limited data are available, toxicity appears to relate to individual variation in drug metabolism. Metabolic studies in animals show that hydroxyurea is converted to urea in the liver and then excreted in the urine, and that impaired liver function alters drug metabolism. In humans, hydroxyurea is mainly cleared from the plasma by the kidney. Change in renal function could impair hydroxyurea clearance and alter sensitivity to hematopoietic toxicity. Modification of dose based on renal function has been recommended. However, measurement of creatinine clearance and hydroxyurea plasma turnover have not proven to be useful in predicting toxicity.

Recent reports suggest that myelotoxicity may be prevented by treating patients with recombinant erythropoietin and oral iron. Cycles of hydroxyurea and erythropoietin may reduce the total dose of hydroxyurea required to increase HBF, perhaps by enhancing the population of erythroid progenitors programmed to synthesize HBF. It is possible that other combinations, such as hydroxyurea and butyric acid, would minimize the risk of hematopoietic toxicity, because the mechanism of action of butyric acid appears to be quite different from that of hydroxyurea. The identification of new drugs that block adherence of sickle RBCs to endothelial cells could also be included in combined therapy.

The mechanism by which hydroxyurea works is unknown. One hypothesis is that hydroxyurea increases HBF by killing a population of rapidly cycling, mature erythroid progenitors. As a consequence, immature progenitors capable of high HBF synthesis are recruited into the erythroid lineage.28 It is possible that other combinations, such as hydroxyurea and butyric acid, would minimize the risk of hematopoietic toxicity, because the mechanism of action of butyric acid appears to be quite different from that of hydroxyurea.28 The identification of new drugs that block adherence of sickle RBCs to endothelial cells could also be included in combined therapy.

Fig 1. Hematologic response to hydroxyurea therapy in patient experiencing fetal hemorrhagic infarct. Hb (a) and HBF (C) response to hydroxyurea in patient B is shown. The arrow indicates the time of the hemorrhagic infarct. At the time of the CNS event, the HBF concentration increased from a baseline of 5% g/dL to 21%. At autopsy, a marked increase in the number of vascular attachments were noted over the dural surface of the brain. An 8 x 8 x 5 cm clot was present in the left temporal region. Sectioning of the brain in the area of the clot showed increased numbers of serpiginous vessels in the walls surrounding the region of the clot. Adherence of sickle cells to the endothelium was noted. The internal elastic lamina of the vessels was irregularly thick and fragmented. Dilated capillary sinusoids were very prominent throughout the white matter in the area of the basal ganglia adjacent to the clot. Perivascular hemorrhage of these dilated capillary sinusoids was striking in portions of the cerebrum.

DISCUSSION

Guidelines for establishing a therapeutic dose of hydroxyurea are generally based on determination of the dose that will give the maximum HBF response without inducing marrow toxicity. If myelosuppression is noted, therapy is either discontinued or the dose of hydroxyurea is reduced. Myelosuppression is generally reversed when the drug is stopped. Patient A represents an exception to this reversal.

Charache et al9,10 observed marked anemia in two patients at the end of a 3-month trial of hydroxyurea. The dose of hydroxyurea was not changed before the onset of toxicity. The investigators speculated that toxicity to erythroid progenitors was cumulative. This study, as well as the present report, suggest that a significant lag phase may occur before the onset of toxicity. Although dilutional effects exist, the continual decrease in HBF levels over several weeks after transfusion in our patient as well as in a reported patient suggests that hemodilution is not the primary mechanism. As a consequence, it is possible to inappropriately increase the dose of hydroxyurea during the period of early BM suppression.

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The mechanism by which hydroxyurea works is unknown. One hypothesis is that hydroxyurea increases HBF by killing a population of rapidly cycling, mature erythroid progenitors. As a consequence, immature progenitors capable of high HBF synthesis are recruited into the erythroid lineage. It is possible that these two pools also have different sensitivity to hydroxyurea and that transfusion suppresses the pool most resistant to hydroxyurea. Patient A showed a dramatic decrease in HBF (21% to 4% in 4 weeks) after a transfusion of packed RBCs. This occurred despite maintenance of hydroxyurea at a dose of 20 mg/kg/d. Others have also noted that RBC transfusions may decrease the HBF response induced by hydroxyurea. If this effect is not appreciated, the dose of hydroxyurea may be inappropriately increased and BM toxicity may occur.

The central nervous system complication observed in patient B illustrates an additional factor that should be considered when evaluating the efficacy of hydroxyurea therapy. Hydroxyurea trials have focused on older patients because of the potential long-term risks to children. However, in adulthood, the pathologic endothelial changes that occur as a result of long-standing cerebral vascular ischemia are unlikely to be ameliorated by an increase in HBF. Staging
with magnetic resonance imaging may help to detect vascular pathology before initiation of therapy.

These two cases illustrate several important points concerning the use of hydroxyurea in patients with sickle cell anemia. The HbF levels increased, hematologic parameters improved and both patients felt subjectively better while on therapy. Yet, both patients had major complications. Patient A developed an acute chest syndrome despite a HbF level of 20%. She subsequently developed aplastic anemia that was life-threatening. Patient B died of a cerebral hemorrhage despite having a HbF of 30%. Although hydroxyurea did not contribute to his death, his course suggests that progressive vascular changes are not reversed, and that to be effective in SCD, a drug that increases HbF should ideally be administered to children before the development of vascular changes. Physicians should not assume that hydroxyurea therapy is benign in SCD and are encouraged to await completion of the National Clinical Trial before using this drug to treat complicated patients.

ACKNOWLEDGMENT

We are indebted to Dr Susan Cluster, Sarah Bodner, and Ann Earles for their clinical assistance, and to Klara Kleman, Jolene Edwards, and Rachel Lewis for their assistance in the preparation of the manuscript.

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A cautionary note regarding hydroxyurea in sickle cell disease

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