INTRODUCTION: FOCUS ON HEMATOLOGY

Induction of Fetal Hemoglobin in Sickle Cell Disease

By H. Franklin Bunn

This issue of Blood features a report by Atweh et al on the induction of fetal hemoglobin (Hb F) by pulse butyrate. This study is a solid addition to the recent and gratifying momentum in the development of effective therapy for sickle cell disease. Underlying this report is a series of novel and convincing in vivo studies extending from model systems in the chicken,2 sheep,3 and baboons4-6 to observations on babies of diabetic mothers7 and on patients with metabolic disorders8 and hemoglobinopathies,9,10 all indicating that butyrates and other short chain fatty acids can cause significant increases in the levels of Hb F. Our current understanding of the molecular pathophysiology of sickle cell disease11-13 strongly indicates that patients would derive considerable benefit from pharmacological induction of Hb F.

The gold standard to which butyrate and related compounds must be compared is hydroxyurea, an agent now accepted as safe and effective therapy for sickle cell disease. Initial studies on both hydroxyurea and butyrate focused on the efficacy with which they cause upregulation of the γ-globin gene, thereby increasing the production of Hb F (α2γ2). In the earlier clinical trials, continuous administration of intravenous (IV) butyrate initially induced a significant increase in Hb F, but with further therapy, the levels tended to fall back toward baseline. As Atweh et al now report, this tachyphylaxis can be obviated by intermittent or pulse therapy. This treatment resulted in sustained and marked increases in the percentage of Hb F (Table 1). The investigators compare these impressive increases with the much more modest induction observed in the national multicenter cooperative hydroxyurea (MSH) trial.14,15 However, this is not an apt comparison, because the two studies differ markedly on issues of patient compliance and study design. The pulse butyrate protocol, involving 4-day IV infusions, necessitated full patient cooperation. In contrast, the design of the cooperative hydroxyurea study required that each participating medical center enroll a minimum number of patients. As a result, the motivation of some of these patients was suspect and, indeed, compliance was problematic.15 Moreover, because of the MSH protocol design, even among patients who were fully compliant, many were undertreated and therefore did not achieve maximal levels of Hb F. It is likely that both patient cooperation and adequacy of treatment were considerably greater in earlier studies of much smaller groups of SS patients treated with hydroxyurea.16-19 As shown in Table 1, in these smaller studies the induction of Hb F was much more impressive than what was observed in the MSH cooperative study. The responses achieved in the 15 adults who participated in these studies are comparable to the robust inductions of Hb F reported in children treated with hydroxyurea20,21 (not shown) as well as to the responses in adults treated with pulse butyrate.

Another consideration that is important in interpreting reports on pharmacological induction of Hb F is the antiscickling effect on individual red blood cells. In both normal individuals as well as in patients with sickle cell disease, Hb F is distributed in only a small proportion of cells, the so-called F cells. The remaining cells are virtually devoid of Hb F. Before drug treatment, the F cells of most SS patients contain approximately 15% Hb F. This amount is more than adequate to inhibit intracellular polymerization. As shown in Table 1, pulse butyrate results in a marked (nearly 2-fold) increase in Hb F per F cell. This increment is wasted on the already unsickleable F cell. In contrast, the increase in F per F cell is more modest in patients treated with hydroxyurea (Table 1). Thus, a given increment in Hb F resulting from hydroxyurea therapy is distributed over a larger proportion of the patient’s red blood cells and would therefore be more likely to be clinically effective.

Because hydroxyurea was developed and is widely used as an antineoplastic agent, there has been understandable fear that it may be teratogenic and/or tumorigenic. This concern is heightened by the prospect of decades of drug exposure and thus has been a major impetus in the search for other pharmacological inducers of Hb F. Although experience in the use of hydroxyurea in potentially child-bearing individuals is limited, there is no apparent increase in birth defects among infants born to mothers or fathers who were taking the drug at the time of conception. Likewise, the risk of hydroxyurea triggering neoplastic transformation appears to be very small. As the report of Atweh et al points out, sodium butyrate suppresses cell growth and, like hydroxyurea, has been used as an antineoplastic agent.22 Unlike many anticancer drugs, neither agent causes direct chemical modification of DNA and, therefore, would not be expected to be mutagenic.

In view of the inherent complexity of both sickle cell...
pathophysiology and the pharmacology of hydroxyurea and butyrate, it is critical to examine the mechanisms underlying the efficacy of each drug. In the case of hydroxyurea, there is convincing evidence that the drug not only induces a robust and sustained increase in F cells, but also has antisickling effects as assessed by a marked reduction in the fraction of irreversibly sickled cells and hyperdense cells along with an increase in cation content and deformability.17,19 These highly relevant measurements need to be made on patients before and during treatment with butyrate. Even though hydroxyurea is a myelosuppressive agent, treatment of SS patients results in a small but significant increase in hemoglobin levels, a paradox that can only be explained by the drug’s causing a marked amelioration in hemolysis. This conclusion has been documented by reductions in serum unconjugated bilirubin and LDH and by a prolongation of red blood cell life span.17,18 The 11 patients treated with pulse butyrate developed a 13% increment in hemoglobin levels, comparable to what has been observed with hydroxyurea. It will be important to learn whether pulse butyrate is as effective as hydroxyurea in lowering hemolytic rate.

A major surprise that emerged from clinical studies of SS patients treated with hydroxyurea is that induction of Hb F is not the only, and perhaps not the major, contributor to the drug’s efficacy. The benefit of hydroxyurea therapy may be due in part to its well-known ability to suppress both erythropoiesis and myelopoiesis. Reticulocytes and young (hypodense) (SS) red blood cells have particularly enhanced adherence to vascular endothelium. A marked decrease in the adhesion of patients’ red blood cells to cultured endothelial cells is observed within 2 weeks after initiation of hydroxyurea therapy, coincident with a decrease in absolute reticulocyte levels and long before there is a significant induction of Hb F.23,24 Suppression of neutrophil production may be an even greater contributor to the efficacy of hydroxyurea. A detailed multivariable analysis of data from the MSH study showed that the percentage of cells correlated inversely with rate of pain crises only during the initial 3 months of therapy.15 Thus, there was a strong correlation between neutrophil count and crisis rate throughout the 2-year study.15 Therefore, it is important to understand whether pulse butyrate therapy can be a protocol that, by design, minimizes this effect.

Considerably more inquiry at the bench and at the bedside is needed to determine whether butyrates and/or other short chain fatty acids can either replace or supplement the use of hydroxyurea. The development of safe and effective oral derivatives is essential for long-term administration in a patient group with poor IV access. One hopes that, as we enter the next millennium, academic medical centers, the pharmaceutical industry, government funding agencies, and patient volunteers all have the staying power to meet this challenge.

REFERENCES

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