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Side Effects of Hydroxyurea in Patients with Sickle Cell Anemia

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Abstract

Background: Hemoglobin S arises is the result of a point mutation (A-T) in the sixth codon on the β-globin gene on chromosome 11 causing sickle cell anemia. The presence of fetal hemoglobin in infancy plays a relatively protective role for vaso-occlusive symptoms that are the major contributor for the morbidity and mortality among patients with sickle cell anemia. hydroxyurea, an s-phase-specific and non-DNA-hypomethylating chemotherapeutic agent is capable of inducing HbF synthesis.

Materials and Methods: We reviewed the records of 28 sickle cell anemia patients, aged 4-52 years, treated with hydroxyurea to study the drug's side effects.

Results: In our study, the most common adverse effect was dermatologic complication which occurred in 15 patients (53.5%). The gastrointestinal side effects were nausea, vomiting, abdominal pain and anorexia occurring in 3 patients 10.7%. The neurologic adverse effects were uncommon and occurred in 4 patients (14.3%).

Conclusion: Side effects of hydroxyurea were common but mild to moderate, benign and transient. Starting a low dose of hydroxyurea (10 mg/kg per day) and increasing the dose slowly in pediatric and adult patients with sickle cell anemia can be tolerated well, without serious side effects.

Keywords: Side effect, hydroxyurea, sickle cell, anemia.

Introduction

Sickle hemoglobin is the most common abnormal hemoglobin found in the United States. Hemoglobin S arises is the result of a point mutation (A-T) in the sixth codon on the β-globin gene on chromosome 11, which causes a single amino acid substitution (glutamic acid to valin at the position 6 of the β-globin chain). In patients with sickle cell anemia (SCA), the presence of fetal hemoglobin (HbF) in infancy plays a relatively protective role since HbF interferes with hemoglobin S polymerization, reducing the vaso-occlusive symptoms that are the major contributor for the morbidity and mortality patients with sickle cell anemia [2].

Hydroxyurea has multiple beneficial effects that may contribute to its efficacy in SCD. The effects include the induction of HbF production. a concomitant increase in the total hemoglobin, and a decrease in hemolysis and the release of free hemoglobin (a contributor to endothelial dysfunction)[3,4]. hydroxyurea may also be beneficial by reducing the white blood cell count and the expression of cell-adhesion molecules that contribute to vaso-oclusion [5]. The national heart, lung and blood institute issued recommendations in 2002 supporting the use of hydroxyurea for the treatment of children with SCD [6].

Materials and Methods

tWe reviewed the records of 28 sickle cell anemia patients, aged 4-52 years. All patients were treated at in research center for thalassemia and hemoglobinopathies, Shafa hospital, Jondishapour University of Medical Sciences.

The initial dosage for hydroxyurea was 10 mg/kg per day with the daily dosage being increased to 5 mg/kg every 4-6 weeks until toxicity or achieving the desired clinical response.

Results

Seventeen male and eleven female patients

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were included in our study. The mean age of diagnosis was 2.5±8.3 years, the mean starting age for hydroxyurea treatment was 14.25±8.3 years, and the mean dose of hydroxyurea was 8.5±20 mg/kg/day.

Twenty-two patients had a history of transfusion. Twenty six patients were Arab and 2 patients had Persian ethnicity.

The adverse effects of hydroxyurea were seen in 17 patients (60.7%). The most common side effect was hair loss which occurred in 11 patients (39.3%). Other side effects were headache in 2 patients (7.1%), hyper pigmentation in 2 patients (7.1%), nausea and vomiting in 1 patient (3.6%), dizziness in 1 patient (3.6%), abdominal pain in 1 patient (3.6%), anorexia in 1 patient (3.6%), somnolence in 1 patient (3.6%), weight gain in 1 patient (3.6%), nail pigmentation in 1 patient (3.6%), maculopapular rash in 1 patient (3.6%), and seizure in 1 patient (3.6%).

Laboratory adverse effects were neutropenia (ANC<1500) in 2 patients (7.1%), decrease in Hb level in 2 patients (7.1%), increase in AST and ALT in 2 patients (7.1%), and decrease in PLT in 1 patient (3.6%). Statistical analysis did not show any significant correlation between ethnicity, age, gender, history of transfusion and side effects.

Discussion

Hydroxyurea has been established as an efficacious treatment to decrease the incidence of vaso-occlusive crises in adults with sickle cell anemia (SCA) [7].

In the 1992-1995 multi center trial of hydroxyurea, 75% of patients met basic compliance criteria, i.e, taking the drugs 80% of the time. The mean treatment period was 21 months. There were no serious side effects, although this did not eliminate concerns about drug safety [7]. Another study showed that the common adverse events were reversible mild to moderate neutropenia, mild thrombocytopenia, severe anemia, rash or nail changes (10%), and headache (5%) [8]. Young et al. has reported a patient who developed widespread skin changes including hydroxyurea dermopathy, during long term treatment with hydroxyurea for polycythemia vera [9].

In our study, the most common adverse effect was dermatologic complications which occurred in 15 patients (53.5%). The gastrointestinal side effects were nausea, vomiting, abdominal pain and anorexia occurring in 3 patients (10.7%).

The neurologic adverse effects were uncommon and occurred in 4 patients (14.3%) including headache, dizziness and seizure. We also found an increase in hepatic enzymes in 2 patients (7.1%). All of these complications were mild to moderate.

In 3 patients with neutropenia and seizure, we decided to discontinue the treatment and in two other patients with increased hepatic enzymes we decreased the dose of hepatic enzymes.

Conclusion

Side effects of hydroxyurea were common but mild to moderate, benign and transient. Starting a low dose of hydroxyurea (10 mg/kg per day) and increasing the dose slowly in pediatric and adult patients with sickle cell anemia can be tolerated well, without serious side effects.

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