Side Effects of Hydroxyurea in Patients with Sickle Cell Anemia

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Submitted: 20-12-2010, Accepted: 18-03-2011

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. 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). Hydroxyurea may also be beneficial by reducing the white blood cell count and the expression of cell-adhesion molecules that contribute to vaso-occlusion. The national heart, lung and blood institute issued recommendations in 2002 supporting the use of hydroxyurea for the treatment of children with SCD.

Materials and Methods

We 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
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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