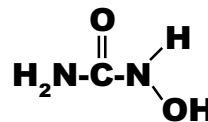


# Sickle Selections

a quarterly newsletter from the University of Rochester Sickle Cell Program

January 2000

## HYDROXYUREA



### Efficacy and Safety Trials in Children

Hydroxyurea (HU) has been shown to be an effective therapeutic drug for adults with sickle cell disease.<sup>1</sup> Several studies have examined its effect on children with sickle cell disease and have reported similar results.<sup>2,3,4</sup> The most recent trial by Koren<sup>5</sup> enrolled nineteen children and young adults with severe sickle cell anemia who received a mean dose of 21.3 mg/kg/d and were treated over a period of 20 to 68 months. They compared the incidence of vaso-occlusive crises, acute chest syndrome, hemolytic crises, splenic sequestration episodes, blood transfusions, and hospital days in the 2 years before and during HU treatment. The authors report a dramatic response with decreases in all the above parameters during treatment and no adverse effects.

A study on the safety of HU by Kinney<sup>6</sup> enrolled 84 children with sickle cell anemia over a 15 month period. HU was started at 15 mg/kg/d and escalated to 30 mg/kg/d, the maximum tolerated dose (MTD). Sixty-eight children reached MTD and 52 were treated at MTD for 1 year. Hematological changes included increases in hemoglobin concentration, MCV, MCH, and fetal hemoglobin and decreases in neutrophil, platelet and reticulocyte counts. They report no life-threatening adverse effects or growth failure in any of the children.

### HU Use at Strong

Three patients at the Sickle Cell Clinic at Strong, ages 15, 18 and 19, who have had significant vaso-occlusive crisis and many lengthy hospitalizations were chosen to receive HU. The 18 and 19 yr. olds have been on the drug for 18 mo., and the 15 yr. old for less than a year. They were started at a dose of 15 mg/kg/d. The common side effect of neutropenia is monitored by frequent blood tests and the dose adjusted accordingly. All three patients have had crises but the number of episodes and the number of hospitalizations have decreased significantly.

The beneficial effects of hydroxyurea and its availability in capsule form (currently \$1.45/500mg capsule) make it a promising future treatment for sickle disease patients who can be monitored by a pediatric hematologist. However the effects of long term use of the drug need to be evaluated.

### How Does It Work?

The studies examining the effects of HU on children with sickle cell disease report an increase in hemoglobin concentration, MCV and fetal hemoglobin and a decrease in reticulocyte count and WBC count.

- **Fetal hemoglobin** reduces the tendency of sickle hemoglobin to polymerize thereby reducing the frequency of vaso-occlusive episodes in patients.
- HU increases RBC survival but decreases RBC production. A study by Ballas<sup>7</sup> reports that the net effect of HU is a function of the **balance between RBC production and survival**. In those patients who had a beneficial response to HU, there was a preferential effect on RBC survival.
- A recent paper published by Glover<sup>8</sup> notes that the clinical benefits of HU occur in advance of increased fetal hemoglobin levels and report detectable amounts of nitrosyl hemoglobin in patients 4 hrs. after oral administration of HU. They postulate that vasodilation may in part be attributed to **HU-derived nitric oxide (NO)**<sup>9,10</sup>. NO increases the oxygen affinity of HbS while having no effect on HbA. Since sickling occurs when HbS is deoxygenated, increasing the oxygen affinity of HbS inhibits its polymerization.

<sup>1</sup> Charache S. et al., *N Engl J Med*: 332:1317,1995

<sup>2</sup> Scott JP, et al., *J Pediatr*: 128:820, 1996

<sup>3</sup> deMontalembert M., et al., *Am J Pediatr Hematol Oncol*: 19:313, 1997

<sup>4</sup> Jayabose S., et al. *J Pediatrics*: 129:559, 1996

<sup>5</sup> Koren et al. *Ped Hematology Oncology*: 16(3):221-32, 1999 May-Jun

<sup>6</sup> Kinney, T.R., *Blood*: 94(5):1550-4, 1999 Sep 1

<sup>7</sup> Ballas, S.K., *Brit J Haematology*: 105(2):491-6, 1999 May

<sup>8</sup> Glover, R.E., *Molecular Pharmacology*: 55(6):1006-1010, 1999

<sup>9</sup> Head, C.A., et al., *J Clin Invest*: 100(5):1193, 1997

<sup>10</sup> *Sickle Selections*: October 1998

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#### Regarding treatment contact:

Dr. Norma Lerner or Pat Lamarche R.N., P.N.P. Department of Pediatrics 275-2981

Dr. Karen Kaplan, Department of Medicine 275-3761

#### Regarding laboratory diagnosis, newborn screening and genetic counseling, contact:

Dr. Peter Rowley, Sandra LaBella or Starlene Loader, Division of Genetics 275-4602

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