Published in final edited form as:
Pediatr Blood Cancer. 2012 July 15; 59(1): 170–172. doi:10.1002/pbc.23244.

Massive Accidental Overdose of Hydroxyurea in a Young Child with Sickle Cell Anemia

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Abstract

The Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) confirmed safety and efficacy of hydroxyurea therapy for infants with sickle cell anemia. Treatment was associated with reduction in rates of pain, acute chest syndrome, hospitalizations and blood transfusions; improved hematologic values; and, perhaps, preservation of organ function. During the study, a two year-old ingested at one time an entire 35-day supply of hydroxyurea (612 mg/kg body-weight). Despite a serum level of 7,756 μM four hours post-ingestion, the only toxicity was transient mild myelosuppression. With wider usage of hydroxyurea anticipated, conservative management of future overdoses seems reasonable. (ClinicalTrials.gov NCT00006400)

Keywords

hydroxycarbamide; drug toxicity; poisoning; infant; BABY HUG

Introduction

Hydroxyurea is extremely effective in reducing complications of sickle cell anemia (SCA) in adults [1] and children. [2–4] In 1995, the double-blinded placebo-controlled Multicenter Study of Hydroxyurea (MSH) demonstrated that hydroxyurea therapy in symptomatic adults with SCA resulted in a 44 and 45 percent reduction in pain and acute chest episodes, respectively, and a 30 percent reduction in acute transfusion; [1] follow-up studies document improved survival in those who took hydroxyurea. [5,6] In 1998, hydroxyurea was approved by the FDA for use in adults with severe disease.

The Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) was a randomized, double-blinded placebo-controlled trial sponsored by the National Heart Lung and Blood Institute to determine whether hydroxyurea would, if administered to infants for two years beginning at age 9–17 months, prevent early damage to the spleen and kidneys. [7] While hydroxyurea failed to show significant impact on either primary study endpoint (^{99m}Tc

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sulfur colloid spleen scan uptake or ^{99m}Tc-DTPA renal clearance), secondary endpoints suggested a salutary effect on spleen function; very significant improvement in blood values (suggesting reduced hemolysis); and reduction in rates of pain, acute chest syndrome, hospitalizations and blood transfusions. There were no serious toxicities and markers of mutagenicity were unaffected by treatment. [8]

Off-label use of hydroxyurea, already increasing in children with SCA, [9] may further increase based on the safety and efficacy profiles documented by BABY HUG. The National Institute of Child Health and Human Development (NICHD) joined NHLBI in sponsorship of BABY HUG in 2005 to facilitate a pharmacokinetic assessment of the study's hydroxyurea liquid formulation. [10] Increased use, especially of a liquid formulation in households with young children, will likely increase accidental ingestion. A recent PubMed.gov search included no reports of hydroxyurea overdose. We here describe a massive overdose of hydroxyurea to provide guidance for management of future ingestions.

Methods

Preparation and administration of drug

Pharmacists at each institution reconstituted treatment powder (hydroxyurea or placebo) with simple syrup and water to a concentration of 100 mg/mL immediately before dispensing a 35-day supply in "child-proof" bottles. Treatment was initiated at a dose of 20 mg/kg/day and subjects were carefully monitored for toxicities. [7]

Determination of serum hydroxyurea level

Sera drawn four and 84 hours after ingestion were frozen at −80 degrees C and mailed to the laboratory of REW at St Jude Children's Research Hospital for determination of hydroxyurea concentration. Quantitation of hydroxyurea was performed as previously described [10,11] using a spectrophotometric assay with color endpoint. The standard curve for the assay ranged from 0–300 μM, so serum samples were analyzed using 1:4, 1:10, 1:25, and 1:50 dilutions and hydroxyurea levels were reported as micromolar (μM) concentrations.

Results

Case Report

A female infant with SCA enrolled in BABY HUG at age 11 months. After 22 weeks of continuous treatment her study drug dose was reduced to 17.5 mg/kg/day due to neutropenia lasting four weeks. At week 52 treatment was again stopped for two weeks because of neutropenia (ANC 0.670×10^9/L). When ANC recovered two weeks later, the child's mother received a new 35-day supply of blinded study drug (98 mL of a 100 mg/mL suspension; total dose 612 mg/kg). At 9:15 pm the subject apparently ingested the entire bottle of study medication (hour 0). Mother contacted the local Principal Investigator 15 minutes later, who suggested she try to induce vomiting and call 911. The investigator then contacted the Data Coordinating Center to request unblinding in order to possibly avoid unnecessary invasive emergency room procedures, inpatient monitoring and anxiety if she ingested placebo. The subject was receiving hydroxyurea study treatment. She arrived at the Emergency Department 1.6 hours after ingestion and was in good condition despite not having vomited. Attempts to feed her activated charcoal were unsuccessful. Blood counts were obtained (Table). The patient was observed eight hours, discharged home and monitored as an outpatient (Table). She remained asymptomatic and resumed study treatment 13 days after the ingestion.

The serum level of hydroxyurea four hours after ingestion was estimated to be 7756 μM, the average of two serum dilutions that fit onto the standard curve, each done in triplicate. Hydroxyurea was undetectable 84 hours after ingestion. There was no hepatic or renal dysfunction and only transient, mild reduction in leukocyte, neutrophil and reticulocyte counts at days three and five, with complete recovery by day 7 (Table).

Discussion

Our BABY HUG subject ingested 35 times her intended daily dose of 17.5 mg/kg (612 mg/kg (15.4 g/m^2), surpassing a reported MTD of 800 mg/m^2/dose when administered orally every four hours for 72 hours (total 14.4 g/m^2) or 3 mg/m^2/min by 24-hour continuous infusion (total 13.0 g/m^2), with myelosuppression as the dose-limiting toxicity. [12] Reported LD50 dosages after oral administration are 7330 mg/kg in mice, 5760 mg/kg in rats and greater than 2000 mg/kg in dogs (product data; Bristol-Myers Squibb). [13] Our subject's ingestion of an estimated 612 mg/kg, with a four-hour serum level of nearly 8,000 μM, was considerably above the level known to inhibit ribonucleotide reductase (~1,000 μM) and suggested as a therapeutic goal for continuous infusion therapy. [14]

The pharmacokinetics and pharmacodynamics of hydroxyurea were reviewed by Gwilt and Tracewell in 1998. [14] The drug is well absorbed orally, and the plasma half-life after a dose of 20 mg/kg is estimated to be 2–4 hrs; the actual half-life varies with age and renal function. [15–17] Our subject may have avoided severe myelosuppression in part due to rapid renal clearance. With glomerular hyperfiltration common among infants enrolled in BABY HUG, [18] the predicted hydroxyurea half-life would be only 2–3 hours, hence her measured plasma value of 7,756 μM would be expected to fall into the therapeutic range (200–500 μM) after only five half-lives, and to the limits of laboratory detection (10 μM) by 10 half-lives. Indeed, there was no detectable hydroxyurea in the serum obtained 84 hours after this overdose. Children (or adults) with diminished glomerular filtration rates might be expected to show additional toxicity. [17]

There is a paucity of readily available information regarding management and potential toxicity of hydroxyurea. A search of PubMed.gov for hydroxyurea overdose yielded no results; two modest overdoses (15 and 2.5 times the prescribed dosage) reported in the HUSOFT trial [4] resulted in only transient mild neutropenia. While ipecac therapy might be reasonable after ingestion of hydroxyurea as it does not alter the sensorium and is neither caustic nor aromatic, [19] and activated charcoal is generically useful for reducing bioavailability of ingested substances, neither are recommended for home use, and the latter requires placement of a nasogastric tube for young infants. [20] Given our patient's benign course after a single but massive oral ingestion, observation and monitoring for myelosuppression for two weeks should be adequate intervention for any overdoses that occur in most young children with SCA. Monthly monitoring of blood counts, with prescriptions limited to a month's supply of medication as done in BABY HUG, [7] provides a reasonable guide for clinicians prescribing hydroxyurea and should reduce the likelihood of any substantially larger overdoses.

Acknowledgments

We acknowledge the efforts of the BABY HUG subjects and their families, the contributions of all who participated in BABY HUG (http://www.c-tasc.com/cms/StudySites/babyhug.htm) and the support of the National Heart, Lung, and Blood Institute/National Institutes of Health Contracts N01-HB-07150 to N01-HB-07160, with partial support of the Best Pharmaceuticals for Children Act and the National Institute of Child Health and Human Development.

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Pediatr Blood Cancer. Author manuscript; available in PMC 2013 July 15.

Table

Laboratory values before and after ingestion of hydroxyurea

	At Study Entry	Day 0 Hour − 9	Day 0 Hour + 4	Day 3 Hour + 84	Day 5	Day 9	Day 13
Hemoglobin (gm/dL)	11.0	10.7	9.8	9.9	9.9	10.6	10.5
Reticulocyte %	2.4	3.0	NT	0.9	1.0	8.8	4.2
Absolute Retic ($\times 10^9$/L)	96.5	106	NT	30	34	313	140
WBC ($\times 10^9$/L)	9.6	9.3	9.9	5.4	7.2	8.3	7.1
ANC ($\times 10^9$/L)	2.5	3.2	3.2	1.6	2.1	4.3	3.1
Platelets ($\times 10^9$/L)	424	319	319	312	343	287	343
Serum ALT (U/L)	20	NT	11	12	11	10	8
Serum creatinine (mg/dL)	0.3	NT	0.3	0.3	0.3	0.3	0.3
Serum hydroxyurea (μM)			7756	0			

The time of the overdose is designated Day 0, Hour 0. NT = not tested; ANC = absolute neutrophil count; ALT = alanine aminotransferase