ASBMT
American Society for Blood and Marrow Transplantation

Busulfan Dosing in Children with BMIs ≥85% Undergoing HSCT: A New Optimal Strategy

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Childhood obesity has more than tripled in the past 30 years. The prevalence of overweight and obese children has also increased in the pediatric cancer setting, causing substantial concern over proper chemotherapeutic dosing in this population. The purpose of this study was to determine if children with an increased body mass index (BMI) have an alteration in busulfan pharmacokinetics during hematopoietic stem cell transplant (HSCT) conditioning. We retrospectively reviewed data on busulfan pharmacokinetics (PK) on HSCT subjects (subjects were part of a prospective study previously reported by our group at Children's Memorial Hospital) to determine appropriateness of dosing. Subjects were divided into appropriate BMI categories (<25th percentile, 25th-85th percentile, ≥85th percentile) and busulfan PK dosing was analyzed (test dose, regimen dose, area under the curve [AUC], and clearance). The dosing based on PK test dose data of children with BMI ≥85% was compared against the package insert dosing recommendations of using adjusted ideal body weight (AIBW) in obese patients to determine which dosing schema was most accurate. Children with high BMIs had higher AUCs when dosing on actual weight then their normal or low BMI counterparts. This indicates that children with a high BMI require less drug (2.9 mg/kg using actual body weight) to achieve the same AUC as children with normal BMI (4.0 mg/kg) or low BMI (3.6 mg/kg). Using the recommended AIBW dosing schema, 53% of the patients with high BMIs would have had regimen dose AUCs ≥20% over/under the target; whereas with the PK test dose method, only 16% of the patients with high BMIs had regimen dose AUCs ≥20% over/under the target. PK testing continues to be the gold standard for busulfan dosing in children. Particular vigilance should be paid to PK monitoring in high BMI categories because of the potential risk of imprecise dosing when using the AIBW schema.

Biol Blood Marrow Transplant 17: 1383-1388 (2011) © 2011 American Society for Blood and Marrow Transplantation

KEY WORDS: Busulfan, BI, Pharmacokinetics, Pediatrics

INTRODUCTION

The rate of obesity in children is a continually growing problem in the United States and Western world. The rate of childhood obesity has more than tripled in the past 30 years. The prevalence of pediatric obesity, age 6 to 11 years, has increased from 6.5% in 1980 to 19.6% in 2008. The prevalence of obesity among adolescents age 12 to 19 years increased from 5% to 18.1% during that same time period [1,2]. A total of 9.5% of infants and toddlers are >95th percentile on weight-for-length growth charts, indicating nearly 10% of this population is obese. A total of 31.7 % of children aged 2 to 19 years are greater than the 85th percentile on standard body mass index (BMI) growth charts, which indicates over 30% of the pediatric population is overweight or obese [3].

The effect of obesity on pharmacokinetics of drug absorption, distribution, metabolism, and elimination (ADME) has been studied in adults. It has been observed that drug absorption is rarely affected by obesity. Alternatively, drug distribution is variable depending on tissue size and permeability, plasma protein binding, and drug affinity for the tissue compartment, all of which are affected to some degree by obesity. Obesity can cause development of fatty liver infiltrates, alterations in liver and cardiac blood flow, and shifts in overall substrate metabolism, which in turn, affects the metabolism of drugs. In addition, obesity may cause an increase in renal tubular secretion

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Financial disclosure: See Acknowledgments on page 1388.

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Received July 22, 2010; accepted January 20, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.01.013

and a decrease in tubular reabsorption, both of which alter the elimination of drug compounds [4].

Therapeutic drug monitoring (TDM) has been used for multiple compounds in the adult and pediatric cancer setting. TDM has been shown to improve overall survival (OS), event-free survival (EFS), and in the case of busulfan (BU), sinusoidal obstruction syndrome–free survival [5-7].

Gibbs et al. [8] observed oral BU clearance (mL/min) was increased 16.2% in adult obese patients versus their normal-weighted counterparts. However, most studies on TDM have been done in adult populations. There is very little information on drug clearance in overweight/obese pediatric patients, and what does exist is compound specific, and the results are difficult to generalize.

The purpose of this investigation was to determine if children with high BMIs have an alteration in Bu pharmacokinetics (measured by altered area under the curve [AUC]) compared to children who have normal or low BMIs.

METHODS

To determine the appropriate dosing for BU in children with high BMIs, a retrospective chart review of 68 pediatric patients from Children's Memorial Hospital (CMH) was undertaken. These children were a subset of a prospective study of reduced-intensity conditioning (RIC) for hematopoietic stem cell transplant (HSCT) carried out between July 2003 and May 2008, which included a test dose of Bu in children with malignant and nonmalignant disorders [9]. Signed informed consent (and adolescent assent when applicable) was obtained for record review at the time of transplantation in compliance with the hospital's institutional review board policy.

In the RIC study, the actual body weight (ABW) was used to determine the BU test does (TD), and then the BU regimen dose (RD) was adjusted depending on the pharmacokinetic (PK) results from the TD. The TD was administered prior to the RD, allowing for PK analysis to determine the targeted single daily dose of BU. The following is the procedure used for the administration of the TD and the RD of BU.

Test Dose

Subjects received a TD of BU infused intravenously (i.v.) over 3 hours at 0.8 mg/kg, 5 to 7 days before beginning their regimen dose. The expected AUC for the TD was 1000 μmol/min. Whole-blood samples were drawn from a separate i.v. catheter than the catheter used for infusing BU at the following time points: 3, 3.5, 5, and 7 hours from the start of the infusion. Plasma was separated by centrifugation at 2500 rpm for 10 minutes at 4°C. The processed plasma was split into cryovials and stored at −20°C. Samples were shipped to Seattle Cancer Care Alliance Clinical Pharmacokinetics Laboratory, Seattle, Washington, for analysis. The AUC and clearance information from the TD were provided to the SCT team. The AUC of the TD was used to calculate the RD of BU for the conditioning therapy by the clinical care team at CMH. The predicted target AUC from the standard TD of 0.8 mg/kg was 800 to 1200 μMol/min.

Calculation of the AUC, Clearance, and Dose Modification Criteria

Clearance and bioavailability was calculated from the first dose by fitting a biexponential equation with the RSTRIP program (MicroMath, Salt Lake City, UT) to the data. AUC was calculated by trapezoidal approximation and extrapolation based on computer-generated parameters from 0 to infinity. The clearance was calculated using the dose given divided by the weight and then divided by the AUC. On the basis of these parameters of the test dose, the dose was modified to achieve an optimal AUC for the single daily dose administration [10].

Regimen Dose

The RD was given on day −5, −4 of the SCT conditioning regimen that included either fludarabine (Flu) 30 mg/m^2 from day −10 to day −5 and rabbit antithymocyte globulin 2 mg/kg on days −4 to −1 or extracorporeal photopheresis (ECP) on day −15 to day −14 and Flu 30 mg/m from day −6 to day −2. The BU was infused i.v. over 3 hours. The target AUC for the RD was 4000 μm/min (n = 51) or 5000 μm/min (n = 17) ± 800 μm/min. Whole-blood samples were drawn at the following time points for pharmacokinetic testing: 3, 3.5, 5, 8, and 24 hours from the start of the infusion on the first day of the regimen dose. Samples were processed in the same manner as the TD and sent to Seattle Cancer Care Alliance Clinical Pharmacokinetics Laboratory, Seattle, Washington, for analysis. Because of the time for transport and analysis by Seattle, it was not possible to use the information obtained from the RD PKs for further dose adjustment. Therefore, only 1 day of RD PK sampling was done.

In addition to the AUC, drug clearance, actual doses given for the BU TD and RD, the following parameters were collected from the medical record: date of birth, sex, date of SCT, height, weight, liver function tests (AST/ALT), and administration of concomitant medications (phenytoin, acetaminophen, cyclophosphamide, fluconazole, or voriconazole).

BMI Categories

BMI {wt (kg)/[height (m)]^2} for children 2 to 19 years of age or weight-for-length percentile for children 0 to 2 years of age was determined from the recorded height and weight at the time of test dose. The children's BMI or weight for length was graphed on a standard Centers for Disease Control (CDC)