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Performance of Busulfan Dosing Guidelines for Pediatric Hematopoietic Stem Cell Transplant Conditioning

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A B S T R A C T

Achievement of a busulfan area-under-the-concentration versus time curve (AUC) of 900 to 1500 μM·min is associated with improved hematopoietic stem cell transplant (HSCT) outcomes. Multiple pediatric busulfan dosing guidelines aim to achieve this target. The authors' objective was to describe the AUCs achieved after simulated dosing using available pediatric i.v. busulfan dosing guidelines. The health records of children who received i.v. busulfan for HSCT conditioning at The Hospital for Sick Children were reviewed. Busulfan AUCs were calculated for each patient based on plasma busulfan concentrations using either a 1-compartment model or a validated limited-sampling strategy. Published pediatric busulfan dosing guidelines were identified. Initial busulfan doses were determined for all patients using each dosing guideline and total body weight (TBW). For overweight patients (TBW-to-ideal body weight [IBW] $\geq$ 1.25), initial busulfan doses were also determined using IBW and adjusted IBW (IBW_{adj}). The resulting AUCs were simulated. The proportion of subjects (TBW/IBW $<$ 1.25, TBW/IBW $\geq$ 1.25, and infants) with an AUC within target (900 to 1500 μM·min) after dosing simulation with each guideline was compared. One hundred eleven children (mean age, 6.2 years [SD, ±5.2]) who received i.v. busulfan were included. When dosing with each of the 12 i.v. busulfan dosing guidelines identified was simulated using TBW in 97 non-overweight patients, the proportion of patients with an AUC within the target range varied from 51% to 74% and from 45% to 64% in infants. Use of IBW or IBW_{adj} to calculate initial busulfan doses in overweight children improved the performance of most guidelines. Current busulfan dosing guidelines vary in their ability to achieve AUCs within the target range. For children who are not overweight, we recommend 1 of 3 high-performing guidelines that allow individualization of the target busulfan AUC. Use of either IBW or IBW_{adj} in overweight children improves the performance of most guidelines. Regardless of the guideline used, therapeutic drug monitoring is essential to verify achievement of the target AUC.

INTRODUCTION

Busulfan is a cytotoxic alkylating agent that is widely used in pediatric hematopoietic stem cell transplantation (HSCT) conditioning regimens. The area-under-the concentration-versus-time curve (AUC) or its counterpart, the steady-state concentration (Css), best describes the relationship between the pharmacokinetic and pharmacodynamic properties of busulfan [1]. An increase in the probability of toxicity, such as hepatic veno-occlusive disease at higher AUCs coupled with concerns of engraftment failure at lower AUCs, has resulted in the general acceptance of a target AUC range of 900 to 1500 μM·min for every-6-hour dosing and 3600 to 6000 μM·min for every-24-hour dosing [2,3].

A number of pediatric dosing guidelines have been developed to assist in determining the initial dose of i.v. busulfan. However, each dosing guideline may differ in the proportion of patients who achieve the target AUC based on the doses they suggest. They may also have a tendency to produce AUCs in the upper or lower end of the target range. A

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comparative analysis of the available pediatric i.v. busulfan dosing guidelines is lacking. The primary objective of this study was to describe the performance of the published pediatric initial i.v. busulfan dosing guidelines with respect to the busulfan AUC values they achieve and their likelihood to achieve an AUC within the therapeutic target. Because it is unclear that total body weight (TBW) is appropriate for dose calculation in overweight patients, we also aimed to describe the performance of different weight descriptors to calculate the initial busulfan dose for overweight children.

METHODS

This study was developed as a Quality Improvement project and approved by the Quality and Risk Management Department at The Hospital for Sick Children.

Retrospective Chart Review

A retrospective, single-center chart review of 111 children who underwent HSCT and received i.v. busulfan from April 2003 to January 2006 and were part of a pre-existing data set [4] or from December 2010 to December 2013 at The Hospital for Sick Children in Toronto was undertaken. Children were identified through pharmacy records, and the following data were extracted from their health records: demographic information (age, gender, weight, and height on day 1 of busulfan administration), HSCT data (indication for HSCT, conditioning regimen, and seizure prophylaxis), and busulfan pharmacokinetic data (dose, time of administration, infusion duration, sampling times, and corresponding plasma concentrations). Plasma busulfan concentrations were assayed by gas chromatography with electron capture detection by The Hospital for Sick Children laboratory.

Busulfan Dosing Regimen Identification

With the assistance of a library scientist, electronic searches of OVID Medline (1980 to March 2015), EMBASE (1980 to March 2015), and PubMed (to March 22, 2015) were conducted. The systematic literature search was limited to English studies in a pediatric setting using i.v. busulfan for HSCT conditioning. The search strategy is presented in Table 1.

Busulfan Dosing and AUC Simulation

For clinical purposes, each patient's busulfan AUC was calculated using a 1-compartment model (Phoenix WinNonLin 6.3; Pharsight, St. Louis, MO) or a validated limited-sampling strategy [5]. Simulated busulfan doses were calculated using each of the identified i.v. busulfan pediatric dosing guidelines for each patient identified in the chart review.

Doses were estimated assuming an every-6-hour dosing schedule. Therefore, doses proposed by every-24-hour dosing guidelines were divided by 4. When dosing guidelines dosed busulfan according to body weight tiers (eg, 10 to 20 kg), the patient's body weight was rounded down to the lower weight category but the busulfan dose was calculated using their TBW for simulation. For example, the dosing guideline of Bartelink et al. [6] advises that patients who weigh 13 or 15 kg receive busulfan 1.3 or 1.275 mg/kg/dose, respectively. For the purposes of this study, dosing for a 14-kg patient was simulated according to the guideline for a 13-kg patient (1.3 mg/kg/dose), but the final dose (18.2 mg/dose) was calculated with the patient's TBW (14 kg). In addition, a target AUC of 1250 μM·min (equivalent to a Css of 850 μg/L) was used in dosing guidelines that required a target AUC for dose calculation with the exception of the dosing guideline of Long-Boyle et al. [7], where an AUC of 1242 μM·min was targeted because of limitations of the accompanying electronic dose calculator.

Table 1
Literature Search Strategy

Study No.	Search Strategy
1	Busulfan/ad [Administration & Dosage]
2	Busulfan/
3	Drug Dosage Calculations/
4	2 and 3
5	1 or 4
6	Limit 5 to "all child (0 to 18 years)"
7	Limit 6 to English language
8	Exp Hematopoietic Stem Cells/
9	Cord blood stem cell transplantation/or hematopoietic stem cell transplantation
10	("hematopoietic stem cell? transplant*" or "stem cell? transplant* hematopoietic" or "transplant* hematopoietic stem cell?" or "haematopoietic stem cell? transplant*" or "stem cell? Transplant* haematopoietic" or "transplant* haematopoetic stem cell?" or "placental blood stem cell? transplant*" or "cord blood stem cell? transplant*" or "haematopoietic stem cell? therap*" or "hematopoietic stem cell? therap*").tw.
12	8 or 9 or 10
13	7 and 12

Finally, busulfan dosing guidelines were assessed according to the population in whom they were developed. For example, if the busulfan dosing guideline was limited to patients ≤ 12 kg, only patients who met this criterion were included in the evaluation of the performance of that guideline. The predicted busulfan AUC achieved by simulated administration of the proposed dose was determined assuming a linear relationship between dose and AUC as follows: $AUC_{simulated} = (AUC_{observed}/Dose_{initial}) \times Dose_{proposed}$, where $Dose_{initial}$ (mg) is the first busulfan dose given to the patient, $AUC_{observed}$ (μM·min) is the busulfan AUC calculated after $Dose_{initial}$, $Dose_{proposed}$ is the dose proposed by a dosing guideline, and $AUC_{simulated}$ is the predicted AUC achieved by simulated administration of proposed dose. The results of busulfan dose simulation in infants < 1 year of age were also assessed separately.

Ideal body weight (IBW) was calculated for all patients using the following equation: $IBW\ (kg) = 2.396e^{(.01863 \times height[cm])}$ [8]. For the purposes of this study, patients with a TBW/IBW ratio ≥ 1.25 were deemed to be overweight [9]. The simulated dose proposed by each busulfan dosing guideline identified was calculated based on TBW, IBW, and adjusted IBW (IBW_{adj}) for overweight patients [9,10]. IBW_{adj} was calculated based on each patient's TBW/IBW ratio. For patients with a TBW/IBW ratio of 1.25 to 1.75, IBW_{adj} was calculated using the following equation: $IBW_{adj} = .25\ (TBW - IBW) + IBW$. For patients with a TBW/IBW ratio > 1.75, IBW_{adj} was calculated using the following equation: $IBW_{adj} = .4\ (TBW - IBW) + IBW$.

Statistical Analysis

Data were analyzed using descriptive statistics. Between-guideline comparisons of the proportion of patients achieving an AUC within the target range was performed using Pearson chi-square test (SAS Enterprise Guide 6.100; SAS Institute Inc., Cary, NC). Differences identified in this analysis were further explored using analysis of proportions [11].

RESULTS

Retrospective Chart Review

Demographic data regarding the 111 patients included in this chart review are presented in Table 2. Busulfan was given as the first conditioning agent and, with the exception of fludarabine regimens, was the only conditioning agent on each day of administration. In patients receiving conditioning with busulfan plus fludarabine, fludarabine was started on the second day of busulfan administration. The mean AUC calculated after the first busulfan dose was 1200 μM·min (95% confidence interval, 1145 to 1255). The target AUC value was achieved in 66% of patients.

Busulfan Dosing Regimen Identification

Eleven publications describing 12 busulfan dosing guidelines were identified (Table 3) [6,7,12-20]. One dosing guideline [19] was supplemented by an online dosage calculation tool (see http://holford.fmhs.auckland.ac.nz/docs/busulfan-integrated-pk.pdf) [21]. Another was supplemented by an Excel-based dose calculator tool (Dr. J. R. Long-Boyle, personal communication, March 16, 2015). Three dosing guidelines appear to have been developed using the same data [18,20,22]. The actual dosing guidelines are summarized in Appendix 1. Six guidelines [6,13-15,17,18] used body weight to determine the initial dose of busulfan; 2 guidelines [16,20] used age, 2 [7,12] used a combination of body weight and age, 1 guideline [17] used body surface area (BSA), whereas another used an equation based on busulfan clearance scaled to normal fat mass based on sex, age, and height [19]. Six dosing guidelines included the target AUC or Css as a variable [7,12,14,17,19]. Three dosing guidelines had weight restrictions: Buffery et al. [13] excluded patients with