Pretransplant Conditioning in Adults and Children: Dose Assurance With Intravenous Busulfan

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Purpose/Objectives: To provide clinical insights into dosing and administration of IV busulfan, a conditioning agent for hematopoietic stem cell transplantation (HSCT).

Data Sources: Review of published literature related to busulfan pretransplant conditioning using MEDLINE®. Meeting abstracts, investigational protocols, and pharmaceutical manufacturers' package inserts also were reviewed.

Data Synthesis: Busulfan is an effective myeloablative conditioning agent for HSCT. The IV formulation increases dose assurance and the ability to target a therapeutic window. Therapeutic drug monitoring ensures that targeted blood levels are achieved, especially in children, thereby preventing underdosing, which can lead to disease progression or rejection, as well as overdosing, which can cause an increased risk of toxic side effects.

Conclusions: IV busulfan is a convenient, safe, and effective conditioning agent used in HSCT that has a predictable pharmacokinetic profile.

Implications for Nursing: An understanding of the pharmacokinetic principles underlying the relationship between the therapeutic window for busulfan and optimal HSCT outcomes will facilitate proper dosing and administration of IV busulfan.

Key Points . . .

- Busulfan is a chemotherapeutic agent used in pretransplant conditioning regimens.
- IV busulfan offers significant advantages over oral busulfan.
- Adherence to dosing and administration protocols for IV busulfan, as well as the timing of laboratory draws, ensures accurate pharmacokinetic monitoring, leading to more successful outcomes.

Hematopoietic stem cell transplantation (HSCT) has become a treatment of choice for many diseases in children and adults. A conditioning or preparative regimen is an important determinant of a successful outcome. The two most common preparative regimens are cyclophosphamide in addition to total body irradiation (TBI) or busulfan plus cyclophosphamide.

Similar to TBI, busulfan works to eradicate malignant or abnormal cells in the bone marrow prior to the infusion of healthy hematopoietic cells. Regimens containing busulfan are used frequently in infants and young children to avoid or minimize late-occurring side effects associated with TBI and to eliminate the need for sedation or anesthesia at each dose (Afify, Shaw, Clavano-Harding, & Cowell, 2000).

The use of busulfan in children and infants undergoing HSCT requires special consideration because of age- and weight-dependent differences in drug metabolism and clearance. Optimal therapeutic blood levels of busulfan must be maintained, and dose-to-dose variability must be kept to a minimum to reduce organ toxicity. An understanding of the therapeutic window and pharmacokinetic parameters that can influence blood levels provides nurses with guidelines regarding proper dose administration of busulfan. This article briefly considers the goals of pretransplant conditioning for autologous and allogeneic HSCT and examines the differences between the pharmacokinetic profiles of oral busulfan and IV Busulfex® (ESP Pharma, Inc., Edison, NJ), the only form of IV busulfan approved by the U.S. Food and Drug Administration (FDA).

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Goals of Pretransplant Conditioning

Dosimetry

The goal of pretransplant conditioning is successful myeloablation with minimal toxicity. If the intensity of the conditioning regimen is too weak, the disease may be treated inadequately; conversely, if the conditioning regimen is too strong, the incidence of toxicities may be increased. With alkylating agents such as busulfan, targeting a narrow therapeutic range (window) of drug exposure is essential to positively balance dosing and outcome (Dix et al., 1996; Grochow, 1993; Grochow et al., 1989; Hassan et al., 1989; Meresse et al., 1992).

Accurate dosimetry is determination by scientific methods to correctly predict the biodistribution of the chemotherapeutic agent. When the dosimetry technique is used, a reliable assessment of the IV busulfan dose is needed for treatment planning as well as assessing clinical results. Following the distribution of the agent in the blood over time and creating an area under the plasma concentration time curve (AUC) usually accomplish this goal.

Drug Assurance

Using dosimetry as a guideline, establishing drug assurance for a myeloablative or chemotherapeutic agent is possible and is done easily with IV busulfan because of its 100% bioavailability, which results in immediate and complete systemic exposure. Because IV busulfan demonstrates predictable pharmacokinetics with low intrapatient variability from dose to dose, drug concentration is controllable within the targeted therapeutic window to achieve drug assurance (Andersson et al., 2002).

In contrast, oral busulfan has highly variable inter- and intrapatient bioavailability; therefore, systemic exposure is unpredictable and difficult to control without repeated dose adjustment. If drug exposure is too high, the incidence of treatment-related mortality increases (Andersson et al., 2002; Ljungman, Hassan, Bekassy, Ringden, & Oberg, 1997) as well as the occurrence of adverse events, particularly serious regimen-related toxicity, such as hepatic veno-occlusive disease (HVOD) (Dix et al., 1996; Grochow et al., 1989). If the systemic exposure is too low, the risk of graft failure or disease progression increases (Slattery et al., 1995).

Pretransplant Conditioning Regimens

Total Body Irradiation

The most commonly used pretransplant conditioning therapy is cyclophosphamide plus TBI, sometimes with the addition of other cytotoxic agents (Andersson et al., 2002). Although the delivery of TBI is very precise, it is associated with late complications such as cataracts, secondary tumors, growth retardation, and cognitive impairment in children (Chou et al., 1996; Cohen et al., 1996). The desired dosage of TBI can be administered in single or divided doses to minimize toxicity. Accurate dosimetry can be ensured with TBI because its administration can be precise and controlled.

Because TBI achieves persistent penetration of the central nervous system, some physicians prefer this conditioning regimen for patients with acute lymphocytic leukemia because of the increased risk of developing central nervous system involvement during the course of the disease. However, TBI may be inappropriate for patients who have received previous radiation or for small children who require sedation or anesthesia before each radiation dose. As a result of the increase in long-term survival following HSCT, delayed toxicities of TBI-based conditioning regimens are becoming evident, especially in pediatric patients, whose treatment occurs during rapid organ development (Giorgiani et al., 1995).

Busulfan

As an alternative to TBI therapy, oral busulfan plus cyclophosphamide was studied as a conditioning regimen in adult patients (Santos et al., 1983). Researchers found that busulfan plus cyclophosphamide followed by allogeneic HSCT could produce long-term remission of acute nonlymphocytic leukemia, thereby providing an effective alternative to cyclophosphamide plus TBI.

As in adults, conditioning regimens in children typically consist of myeloablative doses of radiation-based therapy or chemotherapy-only regimens (e.g., busulfan) in combination with an immunosuppressive agent (e.g., cyclophosphamide). Several busulfan-containing conditioning regimens are used prior to HSCT for various malignant and nonmalignant diseases in adults and children. Conventional myeloablative busulfan conditioning is administered with cyclophosphamide according to the dose schedules depicted in Table 1.

Rationale for Intravenous Busulfan Development

An IV busulfan formulation was developed to address the practical and clinical issues associated with oral busulfan administration such as emesis, dose assurance, proper myeloablation, and adverse events (e.g., HVOD) (Kashyap et al., 2002). Oral busulfan (Myleran®, GlaxoSmithKline, Research Triangle Park, NC), approved by the FDA in 1954 as low-dose treatment for chronic myeloid leukemia, is available only in 2 mg tablets. The busulfan dosage in the conventional oral busulfan-plus-cyclophosphamide regimen for children is one dose every six hours for four days for a

Table 1. Dose Schedules for Administration of Conventional Myeloablative Busulfan Conditioning

	Busulfan Plus Cyclophosphamide (2 Days)		Busulfan Plus Cyclophosphamide (4 Days)	
Day[a]	Drug	Dose (mg/kg)	Drug	Dose (mg/kg)
−9	–	–	Busulfan	0.8
−8	–	–	Busulfan	0.8
−7	Busulfan	0.8	Busulfan	0.8
−6	Busulfan	0.8	Busulfan	0.8
−5	Busulfan	0.8	Cyclophosphamide	50.0
−4	Busulfan	0.8	Cyclophosphamide	50.0
−3	Cyclophosphamide	60.0	Cyclophosphamide	50.0
−2	Cyclophosphamide	60.0	Cyclophosphamide	50.0
−1	Rest	–	Rest	–

[a] Hematopoietic stem cell transplantation takes place on day 0.

Note. Busulfan doses are for adults; for children ≤ 12 kg, busulfan doses are 1.1 mg/kg.

total of 16 doses of 1.0 mg/kg. Therefore, a patient weighing 50 lb (about 22 kg) must ingest eleven 2 mg tablets per dose, which equals 44 tablets per day or 176 tablets in four days. As a result, clinicians, particularly nurses, have had to be creative regarding administration of busulfan tablets to patients undergoing HSCT. The 2 mg tablets can be pulverized and added to soft foods (e.g., applesauce), gel capsules can be used to reduce the number of tablets, or a suspension can be administered via nasal gastric tube. Adding to the challenge of oral busulfan administration is the difficulty of redosing based on pill count after emesis. The variable and erratic absorption of oral busulfan into the gastrointestinal tract is one challenge associated with the oral ingestion of the drug. Absorption is compromised further by the various but necessary forms of oral administration, making clinical comparisons among patients and studies difficult.

Busulfan Pharmacokinetics

The plasma pharmacokinetic profile of a dose of busulfan was evaluated to determine the optimal therapeutic window in adults and children. See Figure 1 for definitions of clinically relevant pharmacokinetic parameters. The optimal dose reduces the odds of under- or overdosing, leading to effective engraftment while minimizing organ toxicity and adverse events caused by first-pass effects to the liver (Andersson et al., 2002). The therapeutic window is established by pharmacokinetic parameters defined as busulfan bioavailability and clearance. Plasma concentrations of busulfan are shown as AUC, expressed as μM-min, or average steady-state plasma drug concentration (Css), expressed in ng/ml (Slattery et al., 1995). The various plasma concentration measurements (i.e., minimum, maximum, average) as well as AUC characterize the systemic exposure of a drug. The AUC for oral busulfan is approximately 1.5 times greater than the Css in pediatric patients (Bolinger et al., 2001).

A clinically acceptable therapeutic window for busulfan was identified based on pharmacokinetic analyses from adult and pediatric patients undergoing HSCT who participated in clinical trials. The therapeutic window is 800–1,500 μM-min; however, some centers prefer to narrow the window to 900–1,350 μM-min. Patients whose blood concentrations fall below the lower limit of the therapeutic window (i.e., low AUC or Css) may experience disease progression or graft rejection (Slattery et al., 1995). Patients with blood concentrations above the upper limit (i.e., high AUC or Css) may experience HVOD and seizures (Dix et al., 1996; Grochow et al., 1989; Hassan et al., 1989).

In pediatric patients with malignant disease, the range of optimal busulfan exposure, or the therapeutic window, following oral administration of 0.8–1.0 mg/kg every six hours was found to be an AUC of 800–1,500 μM-min (Dupuis, Najdova, & Saunders, 2000; Grochow, Krivit, Whitley, & Blazar, 1990; Tran et al., 2000; Vassal et al., 1990). The corresponding Css range is 600–900 ng/ml (Bolinger et al., 2001; McCune et al., 2002). The oral busulfan dose should be adjusted to achieve the therapeutic plasma AUC of 800–1,500 μM-min in pediatric patients (Tran et al.).

Variability in Busulfan Pharmacokinetics

Oral busulfan: Variability in oral busulfan pharmacokinetics influences efficacy, safety, and HSCT outcomes. Oral busulfan produces erratic and unpredictable gastrointestinal

Absorption: the extent and rate at which a drug leaves a site of administration

Area under the plasma concentration time curve (AUC): a measure of plasma drug exposure in the systemic circulation; AUC describes the spectrum of plasma drug concentrations achieved over a defined time interval following administration of a specified dose of a drug.

Bioavailability: the fraction of active drug absorbed into the systemic circulation

Clearance: a measure of the body's ability to eliminate a drug; removal of a drug from the blood or plasma usually occurs via the kidneys and liver.

Coefficient of variation (CV): a statistical measure that quantifies variability for the comparison of two or more data sets; CV allows variability in a pharmacokinetic parameter obtained with one drug or during one study to be compared with others. CV usually is expressed as a percentage in parentheses following the median (e.g., 99 mm [16.7%]). A low CV indicates little variation. In statistical terms, CV is the standard deviation (SD) expressed as a percentage of the mean and is calculated by dividing SD by the mean and multiplying by 100.

Concentration: a measure of plasma drug exposure in the systemic circulation

- **Average steady-state concentration:** the average (mean) plasma drug concentration achieved during steady state
- **Maximum or peak concentration:** the maximum (peak) plasma concentration observed over a defined dosing interval; some pharmacokinetic analyses estimate the time to achieve maximum concentration.
- **Minimum or trough concentration:** the minimum (trough) plasma concentration observed following single-dose administration or over a defined dosing interval for multiple-dose administration

First-pass effect: Orally administered drugs first pass through the hepatic circulation after absorption in the gastrointestinal tract before entering the systemic circulation. This phenomenon also is called first-pass metabolism or first-pass elimination.

Half-life: the length of time necessary for a drug (usually its plasma concentration) to be reduced in the body by 50%

Pharmacokinetics (pharmacokinetic): the branch of clinical pharmacology that quantitatively describes the relationship between a drug and the body's effect on a drug over time; pharmacokinetic refers to the absorption, distribution, metabolism or biotransformation, and excretion of drugs.

Standard deviation (SD): a statistical measure of the variability of the distribution of a data set; SD is a descriptive statistic that summarizes the variability in a data set that is normally or approximately normally distributed. SD usually is expressed with the mean as ± some value (e.g., 1,224 ± 290).

Steady state: the period during which a drug's plasma concentration is relatively constant; at steady state, the rate of drug administration equals the rate of drug elimination.

Variability: the degree of variability associated with a given pharmacokinetic parameter; may be expressed quantitatively as standard deviation (typically associated with the mean or average) or as a coefficient of variation (typically associated with the median)

- **Interpatient variability:** the variability in a pharmacokinetic parameter noted between patients with comparable baseline characteristics taking a specific drug dose on a specific dose schedule under near-identical conditions; quantitatively calculated as coefficient of variation
- **Intrapatient variability:** the variability in a pharmacokinetic parameter noted between doses in the same individual; quantitatively calculated as coefficient of variation

Volume of distribution: a measure of the apparent space in the body available to contain a drug

Figure 1. Definitions of Key Pharmacokinetic Parameters

absorption, and its concentration in plasma varies between doses, causing intra- and interpatient variability (Bearman, 2001; Grochow, 1993; Grochow et al., 1989; Hassan et al., 1989; Schuler et al., 1994; Vassal et al., 1993; Vassal, Gouyette, Hartmann, Pico, & Lemerle, 1989). Clearance rates also vary widely, ranging from 0.8–20 ml/min/kg (Vassal, 1994). In children, the oral bioavailability of busulfan shows a large interpatient variation (Hassan et al., 1994).

Drug metabolism, age, weight, hepatic function, comorbidities, and concomitant drug administration also can affect busulfan pharmacokinetics in adults and children (Hassan et al., 1991; Vassal, 1994). Circadian rhythms may influence systemic drug exposures, especially in young children (Hassan et al., 1991; Vassal). The nocturnal concentration of busulfan in some young children was found to be as high as three times that observed during the day (Hassan et al., 1991). Total body clearance was significantly higher in young children (7.3 ml/min/kg) as compared to older children and adults (3.02 and 2.7 ml/min/kg, respectively) (Hassan et al., 1991).

Intravenous busulfan: Because IV busulfan enters the systemic circulation immediately when administered, its pharmacokinetic variability is much lower than that reported with oral busulfan (Grochow, 1993, 2002; Hassan et al., 1994; Wall et al., 2000). With a 0.8 mg/kg IV busulfan dose, researchers believed that the majority of adult patients would attain a beneficial therapeutic window without the need for therapeutic drug monitoring (Andersson et al., 2002). In a phase II trial of IV busulfan in adult patients with hematologic cancers, 86% of patients who received 16 doses of 0.8 mg/kg of the drug every six hours were within the target therapeutic window (800–1,500 μM-min) without requiring dose adjustment (Andersson et al.).

Variability is still a concern in special populations, such as pediatric patients (Wall et al., 2000). Interpatient variability is observed with IV busulfan in children because of ongoing organ development and the differential maturation of drug metabolizing enzymes (Wall et al.). The variability is reduced with IV busulfan, as was demonstrated in a pharmacokinetic study by the Pediatric Blood and Marrow Transplant Consortium (Wall et al.). Pharmacokinetic analyses of the data revealed that, based on the first dose, 17 of 24 subjects achieved target plasma busulfan AUC concentrations of 900–1,350 μM-min (± 5%). The remaining seven patients received dose adjustments: Five received dose increases, and two received decreases. Pharmacokinetics at doses 9 and 13 revealed that 21 of 23 patients with available data had steady-state AUC values that fell within the target range. The findings confirm that, in children as in adults, dose 1 pharmacokinetics accurately predict dose 9 and dose 13 AUC with or without dose adjustment and that dose-to-dose AUC remains within the therapeutic window. This finding provides dose assurance for the clinical effectiveness and safety of the FDA-approved dose of IV busulfan with therapeutic drug monitoring.

Therapeutic Drug Monitoring

The widespread use of therapeutic drug monitoring is based on the principle of an optimal therapeutic window for a given drug and relies on near real-time measurement of circulating drug concentrations followed by subsequent dose adjustment to achieve a predetermined target drug exposure. Therapeutic drug monitoring is important in high-dose chemotherapy administration, especially with agents such as oral busulfan that show erratic gastrointestinal absorption (Grochow, 1993). Variability in absorption and systemic exposure can lead to under- or overdosing. Targeted dosing is used to achieve optimal blood or plasma drug concentrations.

The timing of drug sampling is critical for accurately determining plasma drug concentrations. Therapeutic drug monitoring usually is recommended for oral busulfan in the pediatric and adult populations to monitor and control pharmacokinetic variability and to assist with dose adjustments (Lindley et al., 2004; McCune, Gibbs, & Slattery, 2000); however, therapeutic drug monitoring is compromised and is met with limited success with oral busulfan because as many as 25% of patients are not evaluable for pharmacokinetics (Dix et al., 1996). Targeted dosing is a valuable tool that can ensure consistency in dosing, maximum efficacy, and minimal toxicity; it also can minimize costs to patients and hospitals. Although targeted dosing is used with many drugs, the most reliable results are obtained with drugs that have a linear pharmacokinetic profile and achieve predictable blood concentrations (Russell et al., 2002). Pharmacokinetic studies of IV busulfan indicate that daily doses give predictable linear kinetics, with less variability than oral dosing (Russell et al.). Day 1 and day 4 curves are very similar, with no accumulation of the drug from one dose to the next. Transplant centers generally use dose 1 pharmacokinetic results to assess plasma busulfan concentrations and to determine dose adjustments. Some institutions administer a test dose and wait for the results before beginning a full IV busulfan schedule.

Intravenous Busulfan Dosage and Administration

Preparation

Preparation of IV busulfan by pharmacy staff is conducted according to the manufacturer's instructions and the institution's guidelines for preparing chemotherapeutic agents (see Figure 2). The recommended adult dose is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered every six hours for four days for a total of 16 doses. For obese or severely obese patients, IV busulfan should be administered based on adjusted ideal body weight. IV busulfan must be diluted prior to use with 0.9% sodium chloride injection (normal saline) or dextrose 5% in water (D_5W) injection.

Administration

IV busulfan should be administered through a central venous catheter as a two-hour infusion with a control rate pump. The same port should be used for all infusions. Once the dose and infusion flow rate are calculated, drug administration is relatively straightforward. The first dose of IV busulfan should be given in the morning because of the effect of circadian rhythms on plasma concentrations (Hassan et al., 1991). Whenever possible for pediatric patients, a syringe pump should be used to facilitate the most accurate dosing. When pharmacokinetic monitoring is performed, sampling will depend on whether the tubing is primed with the drug solution or with normal saline or D_5W.

Preparation

- IV busulfan injection is a single-use 10 ml ampoule of 6 mg/ml or 60 mg/10 ml.
- Using a filter other than the one provided is not recommended or tested.
- IV busulfan should be diluted before use with normal saline or dextrose 5% in water (D_5W).
- Add IV busulfan to the calculated volume of diluent.
- Never add diluent to IV busulfan.
- Diluent quantity should be 10 times the volume of IV busulfan.
- Do not add concentrated IV busulfan to an empty IV bag.
- Final concentration of IV busulfan should be 0.5 mg/ml.
- Stability of IV busulfan includes the two-hour infusion.
- When mixed with normal saline or D_5W, stability is for eight hours at room temperature.
- When mixed with normal saline and refrigerated at 2ºC–8ºC, stability is for 12 hours.
- Do not use polycarbonate syringes.
- Do not use solution if it is cloudy or particles are present.

Administration

- Calculate and prepare the prescribed dose based on patients' actual, ideal, or adjusted ideal weight (1.1 mg/kg for ≤ 12 kg or 0.8 mg/kg for > 12 kg).
- Use a control-rate infusion pump and infuse through a central venous catheter.
- Set the flow rate to deliver the entire IV busulfan dose over two hours.
- Bolus or rapid infusion of IV busulfan has not been tested and is not recommended.
- Do not infuse with other IV solutions.
- If the regimen contains cyclophosphamide, wait at least six hours after completion of the last busulfan dose to administer cyclophosphamide.

Administration Issues for Infusion Followed by Pharmacokinetic Sampling

- Determine the priming (hold-up) volume of the administration set being used.
- Recognize that the start time is dependent on the solution used for priming the tubing.
  - If primed with drug solution, the start time is immediate.
  - If primed with normal saline or D_5W, calculate the start time based on busulfan solution volume and tubing volume.
- Stop time is when the flush is complete.

Figure 2. Preparation and Administration of Intravenous Busulfan

Concomitant Medications

Busulfan crosses the blood-brain barrier and is known to cause seizures in some patients (Hassan, Ehrsson, & Ljungman, 1996). An antiseizure medication should be administered the day before and the day of IV busulfan dosing. Busulfan is metabolized primarily by conjugation with glutathione spontaneously and glutathione-S-transferase catalysis that then undergoes further metabolism in the liver. A number of other medications (e.g., acetaminophen) are metabolized via the same pathway and are known to decrease glutathione in the body. Acetaminophen should not be administered for 72 hours prior to or concomitant with IV busulfan infusion. Some antifungal agents also are metabolized via the same pathway and may decrease the clearance rate of busulfan, leading to higher blood concentrations. Cyclophosphamide should not be administered for at least six hours after the completion of the last busulfan dose (ESP Pharma, Inc., 2003). Commonly used antiemetics, such as ondansetron and granisetron, do not affect busulfan blood concentrations.

Pharmacokinetic Sampling and Evaluation

Pharmacokinetic sampling (see Figure 3) is conducted to determine plasma busulfan concentrations; parameters measured include busulfan peak concentration (C_{max}) and clearance, which provide an accurate measurement of AUC over time. Documentation of the timing of infusions (i.e., exact start and stop times) and sample collection is critical for accurate pharmacokinetic analysis. The timing of the sampling is calculated from the beginning of the infusion so that the two-hour sample is taken immediately after the infusion is completed. When using the central line for laboratory draws, the lumen used for drug administration should not be used for pharmacokinetic sampling because of the risk of contaminating the blood sample with the infusion drug. On completion of the infusion, blood should be drawn and collected, placed on ice, and sent to the laboratory for analysis.

In the pediatric population, a validated limited sampling strategy is recommended for pharmacokinetic sampling with IV busulfan to ensure accurate dosing. Conventional sampling strategies for determining AUC or Css after oral busulfan administration rely on a number of samples collected after a few administered doses. The limited sampling strategy for IV busulfan in pediatric patients includes three samples drawn two, four, and six hours after the start of the infusion of dose 1. Two hours is immediately postinfusion and six hours is immediately prior to the next infusion, which allow for accurate dosing and timely adjustments and also can reduce IV busulfan laboratory costs substantially compared to an unlimited sampling schema.

Pharmacokinetic Calculations

Although some commercial laboratories analyze results and provide transplant programs with raw data, AUC calculations, and descriptive statistics for all pharmacokinetic parameters, many pharmacokinetic testing laboratories only provide busulfan trough concentrations (C_{min}) and C_{max}, making the transplant team responsible for calculating AUC. Computer programs are used to assist in the calculation (e.g., WinNonLin® [Pharsight Corporation, Mountain View, CA], Adapt II [Biomedical Simulations Resource, Los Angeles, CA]).

Clinicians must recognize busulfan concentrations outside the target range that could reflect errors in infusion, collection, or processing techniques. Some laboratories report busulfan exposures as Css (ng/ml), whereas others report them as AUC (µM-min). AUC is approximately 1.5 times greater than Css. The formula for converting the busulfan dose (every six hours) Css to AUC is AUC (µM-min) = Css (ng/ml) x 360 minutes ÷ 246.3 (busulfan molecular weight) (e.g., 876 [µM-min] = 600 [ng/ml] x 360 minutes ÷ 246.4). The transplant team must recognize the difference between Css and AUC in the analysis and reports when making decisions regarding the targeted dose.

Dose Adjustment

Dose adjustments can be made as early as the third dose, depending on the availability of pharmacokinetic results. Dose adjustments for IV busulfan in the clinical trial setting typically are made between doses 5 and 7. The formula for dose adjustment is

$$\text{Adjusted dose (mg)} = \frac{\text{actual dose (mg) x target AUC (µM-min)}}{\text{Actual AUC (µM-min)}}$$

Instructions

- Know the exact start and stop times of the infusion, including the hold-up volume.
- Know the instructions for an infusion primed with the drug versus normal saline or dextrose 5% in water (D_5W) and pharmacokinetic timing. (Recorded times are different for tubing primed with the drug and tubing primed with normal saline or D_5W.)
- Know the exact timing of blood draws.
- Exact timing is critical for success: Minutes make a difference in accuracy.
- Use the same clock to ensure accuracy.
- Do not collect pharmacokinetic samples during the two-hour infusion if draws are done through the central venous catheter line because the sample will be contaminated with the drug.
- Use the morning dose for pharmacokinetics to avoid circadian rhythmicity effect.
- The critical collection time peaks at end of the two-hour infusion.

Recommended Sampling Times for Dose 1

- Timing from start of infusion
  - Two hours (immediately following infusion completion)
  - Four hours
  - Six hours (immediately before the next dose)
- Some laboratories may request additional samples.
- If sampling after dose 1, draw a baseline sample before beginning the infusion.

Critical Information for Collection Forms

- Date and exact start and stop time of the infusion
- Date and exact time of blood draws
- Total dose of IV busulfan administered
- Dose number (e.g., dose 1)
- Weight of patient (and weight used for dosing, if different)
- Target area under the plasma concentration time curve
- Age, disease, and source of graft
- Contact information for the laboratory to call a physician or designate with test results
- Individual institution's forms may require further information.

Storing Samples Before Shipment

- 1–3 ml in green-top (heparinized) tubes
- Place in wet ice.
- Complete the collection form.
- Store in a refrigerator on the unit (2°C–8°C) until the final specimen is drawn, or send to the laboratory where all of the specimens will be processed, frozen, and shipped to the pharmacokinetics testing laboratory.
- Schedule with the receiving laboratory before the patient begins therapy.

Troubleshooting

- If busulfan exposures are consistently high, low, or outside the target range, verify that sampling procedures are accurate.
- If busulfan concentrations at two hours are extremely high, the drug may have been infusing (or not cleared) at the time of the laboratory draw, contaminating the sample.
- If busulfan concentrations are consistently low, verify that the entire dose is being infused and that the time recorded is the actual stop time of the IV busulfan infusion as well as the actual blood draw time.

Figure 3. Pharmacokinetic Sampling Instructions for Intravenous Busulfan

Whenever a dose adjustment is made, pharmacokinetic sampling may be repeated. If sampling is repeated after the initial three samples, C_{min} also should be determined. Note that many centers use the same IV tubing for a number of days and the need to prime the tubing with the drug solution can be easily overlooked. Nurses should review their institutions' policies for dose 1 pharmacokinetics.

A pediatric case (see Case Study) from the prospective Pediatric Blood and Marrow Transplant Consortium allogeneic HSCT clinical trial (Wall et al., 2000) illustrates the method of dose adjustment calculations. The trial evaluated two doses of IV busulfan based on patients' ages (0.8 mg/kg for children older than four years and 1.0 mg/kg for children four years and younger). All children received IV busulfan (every six hours for 16 doses) for four days, followed by cyclophosphamide (50 mg/kg daily) for four days as conditioning before undergoing HSCT. The initial dose of IV busulfan was determined by age. All children had human leukocyte antigen tissue typing-matched sibling donors. The target busulfan AUC was 900–1,350 μM-min. The doses of patients with values outside of the range were adjusted to 1,125 μM-min, the midpoint of the range.

Further study and subsequent analyses showed that IV busulfan should be dosed according to weight (Puozzo, Fuller, Nguyen, & Lennon, 2003). An IV busulfan dose of 1.1 mg/kg was found to be more appropriate than 1.0 mg/kg for small children.

Summary and Future Considerations

Busulfan plus cyclophosphamide is used widely for myeloablative conditioning prior to HSCT. In addition to its use in conditioning regimens for patients with malignant disorders, busulfan also is used in conditioning regimens for nonmalignant disease, especially in pediatric patients. IV busulfan was developed to address the practical clinical issues of oral administration and deliver busulfan directly to the systemic circulation. The rapid and complete absorption of IV busulfan circumvents the erratic gastrointestinal absorption associated with oral busulfan and provides dose

Case Study

A one-year-old girl with juvenile myelomonocytic leukemia received IV busulfan at a dose of 1.0 mg/kg (as per Pediatric Blood and Marrow Transplant Consortium protocol). Her weight was 7.4 kg, and she was given a dose of 7.4 mg (7.4 kg x 1 mg/kg).

The busulfan concentration is 6 mg/ml, and the child's dose is 7.4 mg in 1.23 ml of undiluted drug. The ratio of diluent (normal saline or dextrose 5% in water) is 10 times the volume of the undiluted busulfan, hence 12.3 ml. The total amount of drug and diluent equaled 13.53 ml (1.23 ml undiluted busulfan and 12.3 ml diluent). The infusion volume was 13.53 ml over two hours at a rate of 6.77 ml per hour.

At 7:53 am, the tubing volume was primed with 0.7 ml of normal saline. At 8 am, the IV busulfan infusion was started at 6.77 ml per hour. At 9:53 am, a flush of 0.7 ml normal saline was attached to the tubing, and the IV busulfan infusion was completed at 10 am.

The limited sampling strategy calls for blood draws at hours two (10 am), four (12 pm), and six (2 pm). Blood samples for pharmacokinetic testing were drawn in a green-top (heparinized) tube and immediately placed on ice. The validated limited sampling strategy was applied. The blood immediately was centrifuged, frozen, and shipped to a commercial laboratory. The results were reported mid-afternoon the following day, which was close to the time for beginning dose 6. The patient's dose 1 busulfan area under the plasma concentration time curve (AUC) was 644 μM-min, which was well below the 900–1,350 μM-min target AUC range. The dose was increased to 12.9 mg/kg based on the dose adjustment formula (i.e., 7.4 mg [actual dose] x 1,125 μM-min [target AUC] ÷ 644 μM-min [actual AUC] = 12.9 mg).

assurance. In addition to its linear pharmacokinetic profile, IV busulfan also is convenient for patient administration.

Proper administration of IV busulfan should be a goal for all members of the transplant team. The nursing staff can contribute to successful HSCT outcomes and better patient care via attention to detail and due diligence in the preparation and administration of IV busulfan as well as blood collection for pharmacokinetic sampling. Any change of venue or staff during drug preparation, administration, or collection of samples introduces a potential source of error. Clear communication is important in obtaining accurate and reliable pharmacokinetic results. Proper infusion, blood collection and handling, and interpretation of pharmacokinetic results will ensure correct dosing for patients.

Ultimately, these will be helpful in determining whether a cost benefit exists for IV busulfan use compared with oral busulfan regarding patient satisfaction, reimbursement issues, and patient outcomes. Currently, no data exist regarding cost comparisons with these agents, but it is an important issue for further research.

Pretransplant conditioning for patients undergoing HSCT is evolving rapidly. More convenient dose schedules are being investigated (including once-daily IV busulfan) that certainly will lead to a higher number of patients receiving HSCT conditioning in an outpatient setting. Reduced-intensity protocols for disease states not requiring full myeloablation are of particular interest because of important patient management issues, such as reduced regimen-related toxicity, potentially shorter hospital stays, fewer transfusions following HSCT, and more rapid hematologic recovery. With the increased emphasis on outpatient treatment, understanding the reliability and pharmacokinetic properties of pretransplant conditioning agents is crucial.

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