Clinical Case Study

Which Dose of Busulfan Is Best?

Kamisha L. Johnson-Davis, Gwendolyn A. McMillin, JoEtta M. Juenke, Clyde D. Ford, and Finn B. Petersen

CASE

A 24-year-old woman with advanced Hodgkin disease received the standard dosing protocol for busulfan/cyclophosphamide before allogeneic hematopoietic stem cell transplantation (HSCT) from a matched unrelated donor. The target area under the plasma concentration vs time curve (AUC) for busulfan was set at 950 μmol·L⁻¹·min⁻¹, near the low end of the therapeutic interval of 900–1350 μmol·L⁻¹·min⁻¹. The patient’s body mass index (BMI) was 45.5 kg/m² (height, 170.2 cm; weight, 132.0 kg), so the dose was based on the patient’s ideal body weight. The patient received 2-hour intravenous infusions of busulfan every 6 h for 4 days (16 doses total). The patient was concurrently prescribed multiple medications, including an immunosuppressant, an antiviral, an antidepressant, an anxiolytic, a β-blocker, and a muscle relaxant, as well as antibiotics, warfarin, opioids, and antiepileptic drugs.

After the first dose (51 mg Busulfex; Otsuka Pharmaceutical), timed plasma samples were collected after infusion to determine the AUC. Pharmacokinetics (PK) analysis was performed, and the AUC was determined to be 642 μmol·L⁻¹·min⁻¹. According to these results, the predicted busulfan dosage required to achieve the target AUC was 75 mg per dose for the remaining 14 scheduled doses. Because of the large change in dosage, additional PK monitoring of busulfan was performed after the fifth dose (day 2). The fifth dose was selected to allow time to reach a steady-state concentration (Css) after the dosage adjustment and to avoid challenges in interpretation due to possible circadian variation in busulfan concentrations (1). Samples for monitoring were collected at the same time of day as the first monitoring dose. The AUC after the fifth dose was 1342 μmol·L⁻¹·min⁻¹.

On the basis of the PK data from the fifth dose, dose 7 was changed from 75 mg to 53 mg, close to the original calculated dose of 51 mg. Of note is that the patient was started on an oral antifungal agent (fluconazole, 400 mg/day) after dose 6. Additional monitoring of busulfan was performed immediately after the ninth dose because of another change in dose and potential reduced clearance through busulfan interaction with fluconazole. The AUC after dose 9 was 1306 μmol·L⁻¹·min⁻¹. The busulfan dose was decreased to 39 mg for the remaining doses because the AUC was near the high end of the therapeutic range and because clearance was reduced between the fifth and ninth doses. Monitoring was performed after the 14th dose to verify the adjustment; an AUC of 871 μmol·L⁻¹·min⁻¹ was observed. No further dose adjustments were made. The busulfan half-life and elimination constant were relatively stable throughout the dosing regimen (Table 1).

DISCUSSION

Busulfan is a cytotoxic compound commonly used in preparing patients for standard myeloablative preparative regimens before hematopoietic stem cell transplantation. Busulfan PK studies have demonstrated wide intra- and interpatient variation in drug disposition, metabolism, and clearance. Individualized therapeutic drug monitoring must be performed to ensure that busulfan concentrations are optimal for treatment.

QUESTIONS TO CONSIDER

1. When is the appropriate time to measure plasma busulfan concentrations in a patient? During the distribution phase of the drug or when the patient has achieved steady-state concentration (Css)?
2. Should busulfan dose adjustments be based on first-dose PK?
3. What factors can affect drug absorption, distribution, metabolism, and excretion in patients?
4. Can the coadministration of multiple drugs during busulfan therapy affect the PK of busulfan?

1 Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, UT; 2 Intermountain Health Care, Salt Lake City, UT; 3 ARUP Laboratories, Institute of Clinical and Experimental Pathology, Salt Lake City, UT.

Received August 10, 2009; accepted January 6, 2010.

DOI: 10.1373/clinchem.2009.134940

Nonstandard abbreviations: HSCT, hematopoietic stem cell transplantation; AUC, area under the plasma concentration vs time curve; BMI, body mass index; PK, pharmacokinetics; Css, steady-state concentration; SOS, sinusoidal obstruction syndrome; Vd, volume of distribution.
and to reduce the risk for graft rejection, disease relapse, and sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease. A high first-dose AUC (>1500 μmol·L⁻¹·min⁻¹) is associated with the occurrence of SOS in 33% of adult HSCT patients (2). The incidence of SOS decreased when the busulfan distribution was assessed after the initial dose and dose adjustments were implemented by the fifth dose (3). A study by Tran et al. (4) also showed that busulfan exposure could be projected from the AUC after the first dose. In this study, two-thirds of the patients achieved the targeted AUC after the first dose, and the median values for the fifth and ninth doses were within the targeted AUC interval. This result suggests that the Css of busulfan can be calculated for most patients from the AUC after the first intravenous busulfan dose.

Busulfan PK are affected by age, weight, disease status, hepatic function, drug interactions, and sample handling. The current practice for busulfan monitoring assumes that Css are achieved after the first dose. Busulfan has a mean half-life of 2.5 h. Most drugs require at least 5 half-lives to reach a Css. Dose adjustments based on first-dose PK will underestimate plasma busulfan concentrations if the patient has not reached a Css and therefore may put the patient at risk for busulfan overdose if a dose adjustment is made. The consequence of a slowed time to aCss is a failure to accurately predict busulfan PK and dose requirements. The failure to reach a Css during the first dose in the case presented here is likely accounted for by the large BMI (45.5 kg/m²) for the patient.

Busulfan is a lipophilic drug and adjusting the dose to account for obesity has been applied in clinical practice. According to Gibbs et al. (5), 32% of obese patients had increased busulfan clearance compared with patients of typical weight. Normalizing the dose to the adjusted ideal body weight can minimize the discrepancy in clearance among underweight, typical-weight, obese, and severely obese patients. Because clearance and the volume of distribution (Vd) are related, patients who are severely obese (BMI >35 kg/m²) have a larger Vd for the drug, which may affect the time to reach a Css. Therefore, the dose predictions based on first-dose PK most likely underestimated the AUC and overestimated the required dose.

The patient in this case did not achieve a Css after the first dose. The first-dose PK analysis identified a high Vd, approximately 35% higher than that observed after the fifth dose. The AUC was 642 μmol·L⁻¹·min⁻¹, approximately 32% below the target AUC of 950 μmol·L⁻¹·min⁻¹. The predicted busulfan concentrations with the dose adjustment based on the first-dose PK data should have been therapeutic. As per the standard of care, a dose adjustment was made, and a concern was raised regarding whether the patient truly had achieved a Css. As shown in Fig. 1, however, the busulfan concentrations measured at dose 5 were approximately 30% higher than anticipated. Thus, an additional dose adjustment was made, bringing the dose close to the initial dose calculated for this patient. Most likely, the initial dose would have been appropriate for this patient without therapeutic monitoring, except for the potential impact of drug–drug interactions on the Css of busulfan. Cotherapy with the antifungal fluconazole was initiated with dose 6; therefore, subsequent monitoring was pursued with samples collected immediately after dose 9.

Busulfan is extensively metabolized via both cytochrome P450 isoenzymes (primarily CYP3A4) and conjugation with glutathione via glutathione S-transferase (6). Fluconazole is known to inhibit the drug metabolizing enzyme CYP3A4, the major route of busulfan inactivation. Slowed busulfan clearance could be anticipated with coadministration of a CYP3A4 inhibitor or a competitive substrate. There is some controversy as to whether antifungal azole medicines can affect busulfan metabolism. Studies have demonstrated that itraconazole (7) and metronidazole (8) can alter the AUC for busulfan. In addition, Eiden et al. (9) have suggested that because of the extensive metabolism of voriconazole by cytochrome P450 isoenzymes,
potential interactions between voriconazole and other drugs metabolized via this pathway could occur. Data from Nguyen et al. (10), however, suggest that fluconazole may not affect the AUC. In the present case, there is evidence of reduced busulfan clearance between doses 5 and 9 that may have been due to the coadministration of fluconazole.

In addition to fluconazole, the dosing regimen for this patient may also have been complicated by the coadministration of other drugs. The patient had been prescribed antibiotics, an immunosuppressant, and opioids, which are also substrates for the CYP3A4 enzyme. Drug–drug interactions, such as inhibiting metabolism, can occur when 2 or more drugs are metabolized by the same enzyme. Such interactions can thereby lead to delayed drug clearance. Coadministered drugs can also interact with the metabolism of busulfan by depleting glutathione or by inducing glutathione S-transferases. The patient was prescribed several medications with the potential to delay busulfan clearance. Other factors that could have altered busulfan PK include dose-administration errors and improper sample collection.

The data presented here demonstrate that first-dose PK with busulfan dosing every 6 h may not accurately predict intravenous busulfan dose requirements for patients with a large BMI and/or at high risk for drug–drug interactions. Moreover, this case supports the need for more frequent monitoring and more conservative dose adjustments, as well as for an improved definition of the optimal therapeutic targets after the first dose for high-risk patients. The current practice at our institution is to hold the dose and evaluate the PK with samples collected at dose 5 for patients who are suspected not to have achieved busulfan Css after the first dose. Failure to reach a Css after the first-dose PK analysis may be attenuated as clinical practice moves toward once-daily (every 24 h) or twice-daily dosing for busulfan.

Fig. 1. Busulfan concentrations were predicted from PK data after doses 1, 5, 9, and 14 by means of a 1-compartment model assuming an infusion with no lag time, first-order elimination kinetics, and the first-dose Vd and elimination constant. The predicted concentrations are illustrated by the solid line; open circles represent the observed concentrations. Doses are shown in the bar above the graph. The target AUC was 950 μmol·L⁻¹·min⁻¹, which corresponds to a target Css of 650 μg/L (dashed line).

POINTS TO REMEMBER

1. The therapeutic dose of intravenous busulfan is best predicted when the patient has achieved a Css. Busulfan dosing is often optimized through determination of the AUC, which is typically done after the first dose because of the intra- and interpatient variation in drug disposition, as well as the drug’s narrow therapeutic interval.

2. Individualized therapeutic drug monitoring must be performed to ensure that busulfan concentrations are optimal for treatment and to reduce the risk for SOS and graft rejection.

3. Busulfan PK are affected by age, weight, disease status, hepatic function, drug interactions, and sample handling.
Busulfan is a myeloablative agent that is used in combination with cyclophosphamide as a preparative regimen for bone marrow transplantation; high-dose busulfan can be used as a substitute for total body irradiation. The therapeutic window for busulfan is narrow, and the drug exhibits large pharmacokinetic variation (1). Overexposure to the drug produces toxic effects, including sinusoidal obstruction syndrome and gastrointestinal mucositis. Underexposure can cause relapse of the disease and/or graft rejection. This case described by Johnson-Davis et al. gives an excellent example of the role for busulfan monitoring in patient care and highlights 2 important points for therapeutic drug monitoring (TDM)—the role of TDM in individualized medicine and the importance of sample collection and handling.

Although pharmacogenomics continues to be the focus of discussions about personalized medicine, it is important to remember that nongenetic factors play a large role in drug disposition as well. In this particular case, busulfan is a substrate of cytochrome P450 3A4, and therefore its pharmacokinetics will be dependent to some degree on the genetic variation in this enzyme. This case, however, illustrates how drug–drug interactions and body composition can cause pharmacokinetic variation. These factors cannot be predicted from genetic analysis. Because of the influence of these nongenetic factors, TDM is needed for optimization (or personalization) of pharmacotherapy.

This case also illustrates the importance of sample collection and timing in TDM. When a sample is collected before the drug concentration in the patient reaches a steady state, dosage adjustments will be made with flawed information, in this case underestimating the patient’s exposure to busulfan and increasing the dose unnecessarily. Another important consideration is sample handling and the stability of the analyte. Busulfan is unstable at room temperature, and samples must be placed on ice immediately after collection and then stored at $-20^\circ$C until analysis.

Failure to follow these guidelines will produce an underestimate of patient exposure, and potential overdosing of the patient.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played a direct role in the design of the study, the choice of enrolled patients, the review and interpretation of data, and the preparation and final approval of the manuscript.

References


Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD.
* Address correspondence to the author at: Johns Hopkins Medical Institutions, 600 N. Wolfe St/Meyer B-125, Baltimore, MD 21287. E-mail wclarke1@jhmi.edu.

Received April 26, 2010; accepted April 27, 2010.
DOI: 10.1373/clinchem.2010.146183

Clinical Chemistry 56:7 (2010)