

Optimal Once-Daily Busulfan Administration in Pediatric Patients: A Simulation-Based Investigation of Intravenous Infusion Times

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Purpose: Pediatric patients receiving hematopoietic stem cell transplantation undergo regular administration of intravenous busulfan as a conditioning regimen. Once-daily regimen of busulfan has been proposed as a more convenient alternative to the traditional regimen, but it may increase the risk of toxicity such as veno-occlusive disease (VOD). The study aims to evaluate the pharmacokinetics (PKs) of once-daily regimens and investigate appropriate intravenous infusion times to reduce the risk of toxicity.

Patients and methods: Once-daily busulfan dosing regimens for pediatric patient were reviewed and selected including EMA- and FDA-based once-daily dosing regimens. We generated busulfan PK data of virtual pediatric patients using a previously developed population PK model. PK profiles and proportion of patients achieving the referenced maximum concentration (C_{max}) and exposure to busulfan were used to evaluate the appropriateness of both infusion time and dosing regimens.

Results: Predicted PK profiles and exposure of busulfan showed relatively similar distributions for all once-daily dosing regimens. Most patients exceeded the referenced C_{max} possibly associated with a high risk of VOD with all once-daily regimens when applied with 3 hours of infusion.

Conclusion: While intravenous infusion of once-daily busulfan is typically administered over 3 hours, our findings emphasize the necessity of considering sufficient infusion times to ensure safe drug utilization and prevent toxicity, which will aid in optimal busulfan use in pediatric oncology.

Keywords: busulfan, pediatrics, population pharmacokinetics, once-daily dosing regimen, infusion times

Introduction

Pediatric patients receiving allogeneic hematopoietic stem cell transplants (HSCT) frequently receive intravenous busulfan as part of their myeloablative conditioning regimens.¹ The clinical use of busulfan can be challenging due to its narrow therapeutic index and significant inter- and intra-individual pharmacokinetic (PK) variability, especially in young patients.^{2,3} For example, underexposure of busulfan is linked to graft failure and disease recurrence, and overexposure is linked to toxicity such as acute graft versus-host disease. Therefore, determining the ideal busulfan exposure remains a challenge.⁴ On the other hand, busulfan exhibits highly variable PK profiles among patients, and it has been reported that busulfan clearance per day varies among busulfan dosing days even within the same patient.⁵ These factors suggest that intravenous busulfan in combination with dose targeting based on therapeutic drug monitoring (TDM) may be preferable to dosing without dose targeting in patients.

Traditionally, Busulfan has been given to pediatric patients either intravenously or orally four times per day for four consecutive days. The optimal dosing regimens for Busulfan have been recommended by the FDA and EMA. According to the FDA label, pediatric patients weighing ≤ 12 kg should receive a 2-hour infusion of 1.1 mg/kg, while those weighing > 12 kg should receive 0.8 mg/kg.⁶ In contrast, the EMA label recommends a 2-hour infusion of 1.0 mg/kg for patients weighing < 9 kg, 1.2 mg/kg for those weighing 9–16 kg, 1.1 mg/kg for 16–23 kg, 0.95 mg/kg for 23–34 kg, and 0.80 mg/kg for patients

weighing >34 kg.⁷ However these dosing regimens require frequent preparations and an uncomfortable administration at night.⁶ To address these limitations, studies have reported that both once-daily and four-times-daily regimens have similar PK and clinical outcomes in both adults and children. Once-daily regimen has been found to be more convenient and practical.^{8–12} Several studies have been conducted to develop a once-daily regimen of busulfan suitable for pediatric patients, and several regimens have been proposed.^{13–19} For those studies, in general, a 3-hour infusion was applied when busulfan was administered once a day, and the appropriateness of the regimen was evaluated based on daily area under the concentration time curve (AUC) or 4-day total AUC. However, the optimal once-daily busulfan regimen has not been determined and is still being investigated.

One of the primary side effects of busulfan is veno-occlusive disease (VOD), commonly known as sinusoidal obstruction syndrome (SOS), which is a fatal vascular disease of the liver.²⁰ It is well-known that certain clinical outcomes are correlated with systemic exposure to busulfan, as determined by the average steady-state concentration (C_{ss}) or AUC.⁴ A greater prevalence of VOD/SOS in children has been associated with maximum concentration of busulfan (C_{max}) and 4-day cumulative AUC.^{3,21} Additionally, even in patients whose plasma busulfan AUC is within the standard goal range, the incidence of VOD is still considerable, indicating that busulfan AUC may not be the only predictor of VOD.^{22,23} In other words, once daily administration of intravenous busulfan may increase the risk of toxicity such as VOD, due to high instantaneous busulfan concentration compared to 4-times-daily regimen.

The busulfan C_{max} after once-daily regimen can be about 3-fold higher than that observed with 4-times-daily regimen. That is, the administered dose of busulfan per hour on the once-daily regimen with 3-hour infusion would be about 2.7 times greater than when busulfan was given with 4-times-daily regimen with 2-hour infusion. Since high C_{max} is usually associated with drug toxicity,^{21,24} changes in dose as well as infusion rate of busulfan, may lead to changes in drug effects, especially in terms of safety. Despite a possible association between C_{max} and VOD, previous studies did not consider infusion time (ie, duration of infusion) to reduce the potential risk of toxicity when suggesting once-daily regimen of busulfan. Moreover, there has been no consensus on the appropriate infusion time for once-daily busulfan dosing. Based on these understanding, we performed a simulation study to 1) evaluate the PKs of once-daily busulfan dosing regimens and 2) provide information on the level and profile of busulfan concentration according to various infusion times for guiding appropriate once-daily busulfan dosing in pediatric patients.

Methods

Review of Once-Daily Busulfan Regimens

To investigate the status of once-daily intravenous busulfan regimen for pediatric patients, a thorough search of the published literature was performed for studies conducted up to December 2022, using the terms including “Busulfan”, “Once daily”, “Pediatric”, and “Pharmacokinetics”. The literature search was restricted to English research in pediatric settings employing intravenous busulfan for HSCT conditioning. Among the searched busulfan regimens for pediatric patients, the regimens proposed in the study that evaluated the adequacy of clinical results or PK exposure after once-daily administration of busulfan to pediatric patients were selected as the regimens to be evaluated in this study. In addition, EMA- and FDA-based once-daily dosing regimens (ie, 4-fold dose at one time compared to the original regimens) were also evaluated with varying infusion times.

Generation of Busulfan PK Data

The virtual dosing regimens in this study were simulated using the same dataset as our prior paper (n = 137), with the covariate profile of the virtual patient population derived from the demographic and clinical information of the previously developed model’s patient population. The busulfan PK data (ie, concentrations over time following busulfan administration) for each patient in the virtual population were generated and replicated 100 times by simulation using a previously developed population PK model of intravenously administered busulfan.¹⁷ The model was a one-compartment linear model with proportional residual variability, which incorporated several significant covariates. For instance, the effects of age, aspartate transaminase, and dosing day were reflected on clearance (CL), while the effects of body surface area (BSA) were reflected in both volume of distribution and CL. Moreover, the model included inter-occasional variability to describe daily changes in

busulfan CL, which may reflect the impact of physiological changes and other patient-specific factors on busulfan elimination over time.

The PK simulation for data generation was performed using a non-linear mixed effects modeling software package NONMEM version 7.3 (ICON Development Solutions, MD, United States), and Pirana 2.9.6 as the modeling interface. RStudio 1.2.1335 (RStudio Inc. Boston, MA, United States) and R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for data management, statistics, and visualization.

Evaluation of Infusion Time

Busulfan concentration-time profiles were predicted and compared for various infusion times ranging from 2 to 7 hours, for each of EMA- and FDA- based once-daily dosing regimens as well as other once-daily dosing regimens reported in the literature. Moreover, PK parameters, including daily C_{max}, C_{max}, all (ie, the highest concentration over four dosing days), daily AUC, and total AUC (ie, the sum of the daily AUC values over four dosing days), were calculated in order to assess the PK appropriateness of both the infusion time and dosing regimens.

The distribution of daily and total AUC was compared among different dosing regimen, and their attainment with previously known therapeutic target was evaluated. The therapeutic AUC targets were defined as both wide and narrow ranges, with a wide therapeutic target ranging from 59,200 to 98,400 µg·h/L,²⁵ and a narrow target ranging from 70,800 to 87,400 µg·h/L.¹⁴ The infusion time was assessed by comparing the PK profiles and the proportion of patients whose C_{max} values fell within previously reported reference values. The reference values for C_{max} were set at two levels: <1880 µg/L, which has been suggested as a cut-off value for VOD risk, and <3348 µg/L, taking into account the upper limit of the C_{max} range for patients who did not develop VOD.²¹

Results

Busulfan Once-Daily Dosing Regimens

Summary and description of intravenous busulfan once-daily dosing regimens studied in pediatric patients are listed in [Table 1](#). As well as traditional EMA- and FDA-approved dosing regimens, six intravenous dosing regimens including EMA- and FDA-based once-daily dosing regimens were reviewed and selected for PK simulation.^{13–19} Four dosing regimens, including EMA- and FDA-based once-daily dosing regimen, used body weight as the primary determinant of busulfan dosage. On the other hand, two other regimens used both age and BSA to determine the busulfan dose, one of which further suggested different doses according to dosing days.

Comparison of Dosing Regimens

To evaluate the appropriateness of once-daily busulfan dosing regimens, the simulated PK profiles ([Figure 1](#) and [Supplementary Figure S1](#)), and the distribution of daily and total AUC were compared. In terms of busulfan exposure, the FDA-based dosing resulted in lower exposure levels compared to the EMA-based dosing ([Figures 1](#) and [2](#)). When predicting daily and total AUCs of busulfan during four dosing days for various dosing regimens, Lee, et al's regimen¹⁴ showed relatively high AUCs, while Yin, et al's regimen¹⁶ had relatively low AUCs. When considering a wide therapeutic AUC range, the median of daily and total AUCs from all regimens fell within the target range. Additionally, the total AUCs from EMA-based, Buffery, et al's and Rhee, et al's regimens showed a similar distribution and median values within the narrow target range ([Figure 2](#)). Overall, predicted AUCs showed relatively similar distributions with only slight differences around the target range for all regimens.

Busulfan PK According to Infusion Time

To investigate the pharmacokinetic profile based on infusion time for once-daily intravenous busulfan dosing in pediatric patients, we calculated and compared the percentage of patients achieving the C_{max} reference values across various intravenous infusion durations, ranging from 2 to 7 hours. As a result, for the EMA-based once-daily regimen, most patients (87.9%) exceeded the C_{max} cut-off (ie, 1880 µg/L) associated with a high risk of VOD,²¹ even if the infusion time was increased to 7 hours ([Figure 1](#) and [Supplementary Table S1](#)). As far as we know, most of the once-daily dosing regimens have been studied using the 3-hour infusion time, but in that case, only small percentage (ie, 0.3% and 1.8%) of

Table 1 Summary and Description of Intravenous Busulfan Once-Daily Dosing Regimens Studied in Pediatric Patients

| Regimen | Description of Dosing | Dosing Parameter | Demography of Study Population | | | | Reference |
|-----------------------------|--|--------------------------|----------------------------------|-----------------|-----------------|------------------|-----------|
| | | | Number of Subjects (Male/Female) | Age | Body Weight | BSA | |
| EMA | 2-hour infusion of 1.0 mg/kg for a body weight of <9 kg, 1.2 mg/kg for 9–16 kg, 1.1 mg/kg for 16–23 kg, 0.95 mg/kg for 23–34 kg, and 0.80 mg/kg for > 34 kg, repeat every 6 h for 4 days | Body weight | 24 (12/12) | 6.0 (0.45–16.7) | 22.9 (7.1–62.6) | 0.8 (0.37–1.67) | [7,18] |
| EMA based once-daily dosing | 4.0 mg/kg for a body weight of < 9 kg, 4.8 mg/kg for 9–16 kg, 4.4 mg/kg for 16–23 kg, 3.8 mg/kg for 23–34 kg, and 3.2 mg/kg for > 34 kg | Body weight | 54(34/20) | 21.7 (0.3–53.5) | 44.1 (4.1–82.7) | NR | [13] |
| FDA | 2-hour infusion of 1.1 mg/kg for a body weight of ≤ 12 kg, and 0.8 mg/kg for > 12kg, repeat every 6 hours for 4 days | Body weight | 24 (12/12) | 6.3 (0.25–16.7) | 23.8 (7.1–62.6) | 0.8 (0.37–1.7) | [6,19] |
| FDA based once-daily dosing | 4.4 mg/kg for a body weight of ≤ 12 kg, and 3.2 mg/kg for > 12 kg | Body weight | NR | NR | NR | NR | NR |
| Lee, et al | 3-hour infusion of 80 mg/m ² for < 1 year of age, and 120mg/m ² for ≥ 1 years old | Age and BSA | 24 (11/13) | 9.3 (0.9–18.1) | NR | 1.07 (0.48–1.89) | [14] |
| Buffery, et al | 2-hour infusion of 4.8 mg/kg for a body weight of 10–16 kg, 4.4 mg/kg for 17–18 kg, 4.0 mg/kg for 19–22 kg, 3.6 mg/kg for 23–25 kg, and 3.2 mg/kg for >26 kg | Body weight | 144 (NR) | 12.5 (0.5–58) | 53 (6–122) | NR | [15] |
| Yin, et al | 3-hour infusion of 3.2mg/kg | Body weight | 25 (21/4) | 31 (13–61) | NR | NR | [16] |
| Rhee, et al | 3-hour infusion of BSA-based doses by 9 age categories, according to dosing day | Age, BSA, and dosing day | 137 (70/67) | 8.9 (0.6–22.2) | 32.8 (7.4–76.2) | 1.06 (0.37–1.92) | [17] |

Note: Demographic data are presented as mean (range) except for number of subjects.

Abbreviations: BSA, body surface area; NR, not reported.

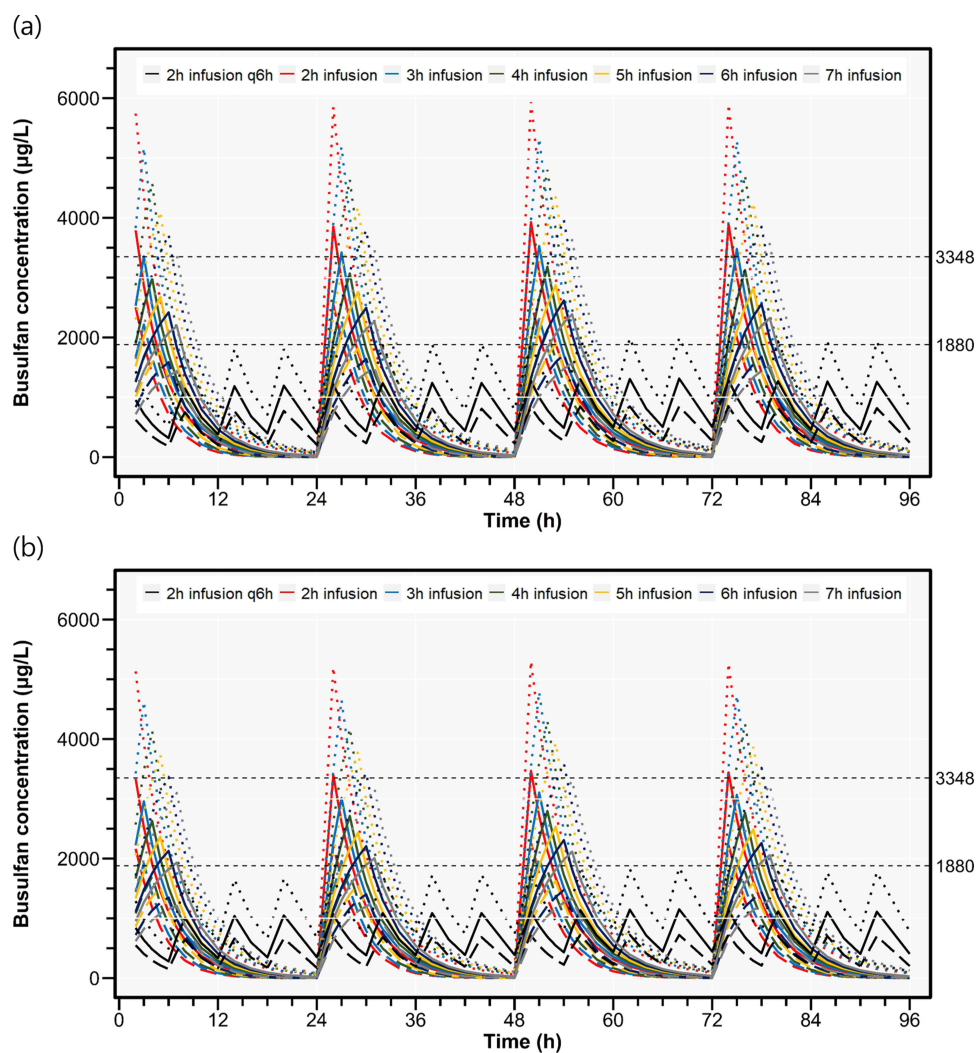


Figure 1 Simulated concentration-time profiles of busulfan after intravenous administration of (a) EMA based^{7,18} and (b) FDA based^{6,19} once-daily dosing regimens with various infusion times. Dashed and dotted lines represent the 5th and 95th percentiles, respectively, and solid lines represent the median of the simulated concentration data. Horizontal dashed lines represent the reference values for maximum concentration.²¹

C_{max} simulated from the EMA- and FDA-based regimens, respectively, were predicted not to exceed the C_{max} cut-off (Figure 3 and Supplementary Table S1).

When evaluating based on the upper C_{max} reference level (ie, <3348 µg/L), the FDA-based once daily regimen was expected to provide the attainment of upper C_{max} reference value in about 60% of patients when applied over 3 hours of infusion. On the other hand, the EMA- based once-daily regimen required an infusion time longer than 4 hours to achieve similar proportion (Figure 3 and Supplementary Table S1). An infusion time of 3 hours was sufficient to achieve the upper C_{max} reference of 60% in the once-daily dosing regimen studied by Yin, et al,¹⁶ whereas in the regimen predicted by Lee, et al,¹⁴ longer than 5 hours were required for similar attainment (Figure 3, Supplementary Figure S2, and Supplementary Table S1). Summarizing these results, except for one regimen (ie, by Lee et al), when once-daily intravenous busulfan dosing is used in pediatric patients, a sufficient infusion time of longer than 3 hours would be necessary to achieve C_{max} of about 50% or more of patients within the upper reference value.

Discussion

The PK simulations from a population PK model using busulfan PK data from pediatric patients have provided valuable insights into the optimal infusion time with various once daily busulfan regimens. While the AUC remains a pivotal

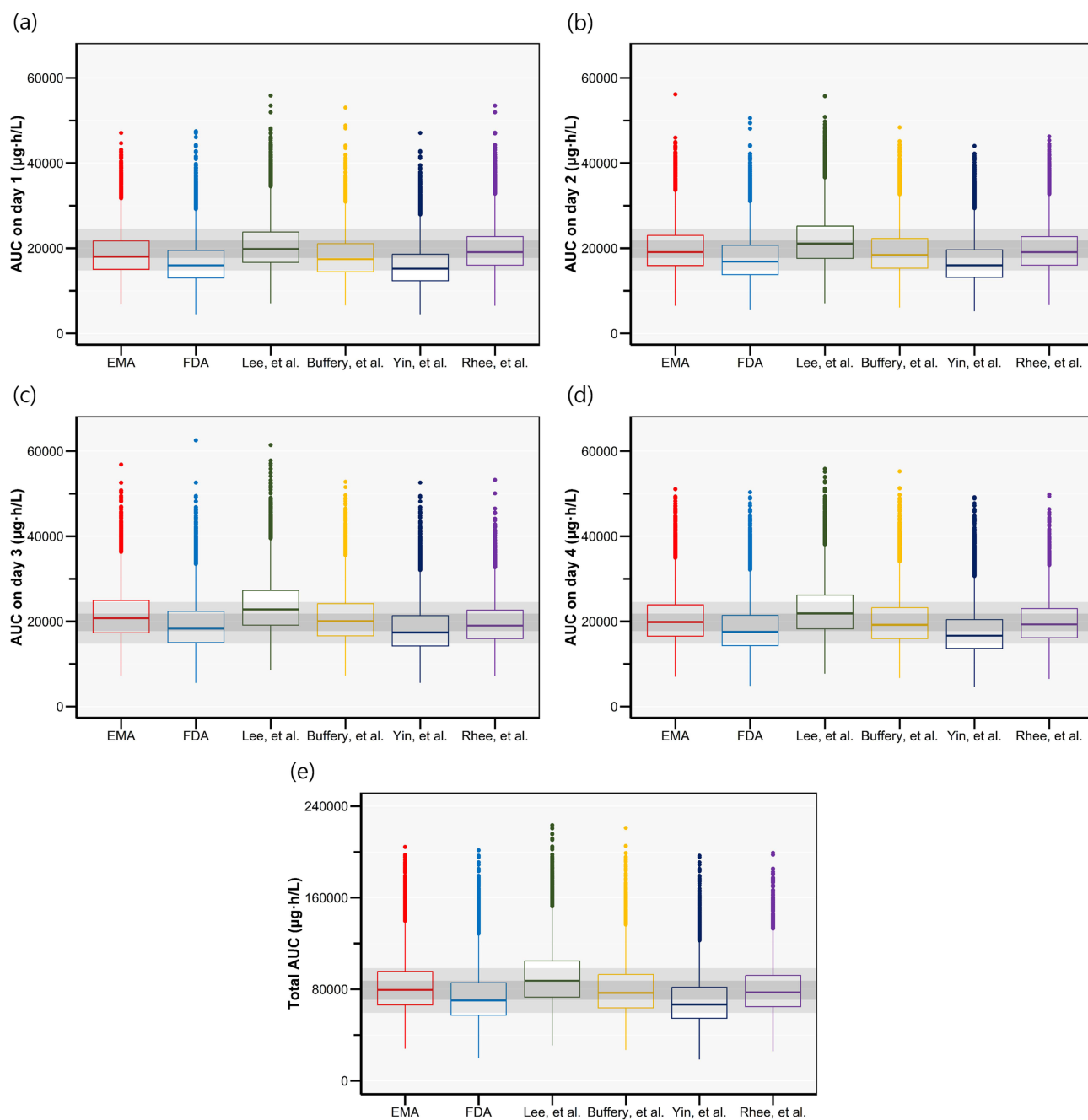


Figure 2 Predictions of (a–d) daily and (e) total AUCs of busulfan during 4 dosing days according to various busulfan dosing regimens. The regimens were derived from EMA,^{7,18} FDA,^{6,19} Lee et al,¹⁴ Buffery et al,¹⁵ Yin et al,¹⁶ and Rhee et al.¹⁷ Shaded areas represent the therapeutic AUC ranges; on the total AUC plot, the wide range is 59,200–98,400 $\mu\text{g h/L}$ ²⁵ and the narrow range is 70,800–87,400 $\mu\text{g h/L}$.¹⁴ The shaded ranges on the daily AUC plots are one quarter of the ranges on the total AUC plot (ie, 14,800–24,600 and 17,700–21,850 for wide and narrow range, respectively).

metric for clinical assessment of busulfan, there remains an unmet need in accurately predicting the occurrence of toxicity.²⁶ Our findings emphasize the significance of considering infusion time, particularly in the context of altering dosing intervals, such as with once-daily dosing. The data presented herein offers valuable insights into determining a pragmatic infusion time, allowing for the modulation of instantaneous concentration levels and thereby mitigating the risk of reaching potentially toxic levels while maintaining therapeutic efficacy. These results are significant because they provide evidence-based guidance for clinicians regarding the safe and effective administration of busulfan in a pediatric population.

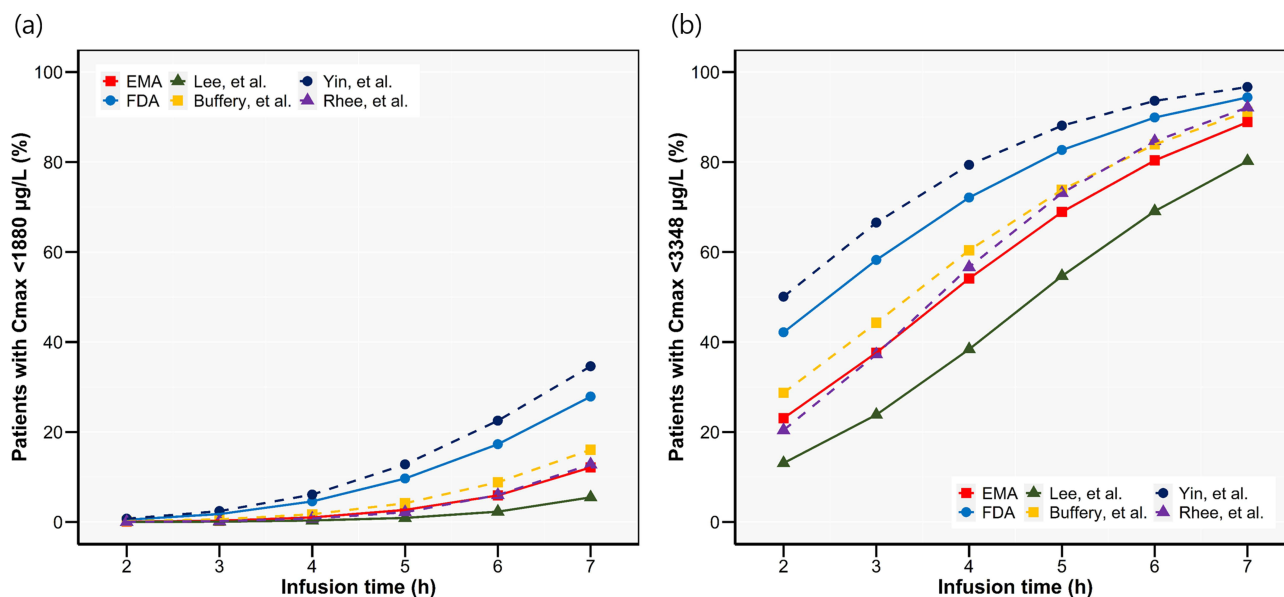


Figure 3 Percentages of patients achieving C_{max}, all within reference values of (a) 1880 µg/L and (b) 3348 µg/L²¹ according to various infusion times. The dosing regimens were derived from EMA,^{7,18} FDA,^{6,19} Lee et al.,¹⁴ Buffery et al.,¹⁵ Yin et al.,¹⁶ and Rhee et al.¹⁷ C_{max}, all, maximum concentration of busulfan during 4 dosing days.

The once-daily dosing regimen for busulfan offers several advantages including allowing for drug metabolizing enzymes recovery in between doses, preventing the accumulation of busulfan.^{8,10,12,27} It is also more practical for both patients and caregivers, as it places less burden on patients, is simpler for nursing staff, and has a lower risk of administration errors. Additionally, a shorter exposure time to busulfan in a once-daily regimen may be associated with reduced toxicity.¹¹ Furthermore, TDM can be easier to perform with a once-daily regimen since busulfan exposure is anticipated to be more consistent. However, there is a concern that busulfan C_{max} can be higher with once-daily dosing compared to four times daily dosing, which may increase the incidence of concentration-dependent toxicity. Therefore, when using the once-daily regimen, sufficient time should be applied as the infusion time at a feasible and realistic level to lower the instantaneous maximum concentration.

The six once-daily regimens evaluated in this study were investigated with only fixed infusion time of either 2 or 3 hours, and no studies have investigated the impact of varying infusion times on dosing regimen (Table 1). Although VOD is generally manageable, the higher incidence of VOD (37% of children) with once-daily dosing regimens remains a significant safety concern.²⁸ Additionally, a study has indicated that the greater peak levels achieved with once-daily dosing may contribute to a higher risk of toxicity, even with equivalent total AUCs.²¹ This underscores the importance of considering not only exposure over time (ie, AUC) but also instantaneous or peak levels of busulfan when implementing once-daily dosing. Adjusting the infusion time can thus play a crucial role in managing these peak levels and mitigating potential toxicity risks.

As of now, the relationship between C_{max} of busulfan and the risk of VOD is controversial. One study reported that 81.8% of patients (9 out of 11 children) who received busulfan once or twice a day experienced VOD, with a median C_{max} of 3300 µg/L.²¹ In addition, children in a different study experienced VOD much more frequently when receiving intravenous once-daily dosing (11 out of 30) than when receiving oral four-times daily dosing (4 out of 30), with an odds ratio of 3.76 and a p-value of 0.044.²⁸ In contrast, another study reported no discernible difference in VOD incidence between once-daily intravenous busulfan and four-times daily dosing (5 vs 3 cases, respectively).¹² However, drawing a consensus is difficult due to limited research, varying designs and patient populations. Moreover, the only cut-off value previously proposed for VOD risk was derived from PK data primarily obtained after administering busulfan four times a day. Thus, it is challenging to evaluate whether it is an appropriate cut-off for a high level of C_{max} with once-daily dosing regimen. Indeed, our study's simulation results suggest that achieving the reported cut-off value for VOD risk with once-daily dosing is challenging for the majority of patients, even with extended infusion times. Additionally, given the current lack of clear clinical significance regarding the importance of C_{max}, the likelihood of causing significant issues in real-world clinical settings due to the failure

to achieve this cut-off is low. Therefore, the observed maximal C_{max} in the patient group where VOD did not occur was set as an additional reference value and used to investigate an appropriate infusion time. To fully understand the relationship between high busulfan concentration and VOD, further research is needed to evaluate the safety of once-daily dosing regimens in both children and adults, and to assess the impact of varying infusion times on PKs and VOD risk.

There are some limitations in this study. First of all, although our study suggests an appropriate infusion time according to previously reported once-daily dosing regimens, which can be convenient and practical for caregivers and patients, further research is necessary to determine the optimal intravenous infusion time with support from a PK model linked to clinical outcomes. The inherent constraint of this approach lies in its inability to directly demonstrate the relationship between the investigated regimens and the subsequent transplant outcomes and associated toxicity. Additionally, it is important to confirm that changes in infusion time do not cause additional variability in the PKs of busulfan, as daily CL can have a variability of around 10%.¹⁷ Real-world clinical trials and empirical observations remain imperative to validate and extend the findings presented here, bridging the gap between simulated predictions and actual patient outcomes. This will aid in ensuring the safe use of the drug, preventing toxicity-related complications, and ultimately enhancing treatment outcomes for pediatric patients undergoing hematopoietic stem cell transplantation. Second, there is no definitive reason to believe that the model chosen for this study is the most robust. Nevertheless, the model utilized in this study reflects the commonly known pharmacokinetic properties and influencing factors of busulfan, which identified covariates including patient's BSA, age, and dosing day. In particular, we believe that the model captures the daily variation in CL during four consecutive doses of busulfan, and thus differentially accounts for the variability in busulfan pharmacokinetics compared to other previously reported models.

Conclusion

In conclusion, this study demonstrates that the optimal infusion time for once-daily intravenous busulfan dosing in pediatric patients should be reconsidered, based on the population PK model simulation. This information can serve as a foundation for establishing optimal dosing regimen, facilitating adequacy-based utilization of various once-daily dosing regimens and informing the setting of infusion times. Such insights can be crucial for enhancing the safety of drug administration and mitigating the risk of toxicity-related complications in pediatric patients undergoing hematopoietic stem cell transplantation. Ultimately, these efforts will improve treatment outcomes and promote the development of personalized medicine in pediatric oncology.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors have no conflicts of interest to disclose in this work.

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