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Pharmacokinetic Disposition and Clinical Outcomes in Infants and Children Receiving Intravenous Busulfan for Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

We conducted a retrospective pharmacokinetic analysis of i.v. busulfan in children undergoing hematopoietic stem cell transplantation (HSCT) and describe its relation to transplantation outcomes. Forty-five children (median age, 3 yr) underwent HSCT at The Hospital for Sick Children from April 2003 through January 2006 and received i.v. busulfan every 6 h as part of their conditioning regimen. Initial busulfan doses were based on actual patient weight: <9 kg, 0.95 mg/kg per dose; 9-16 kg, 1.2 mg/kg per dose; 16-23 kg, 1.1 mg/kg per dose; 24-34 kg, 0.95 mg/kg per dose; >34 kg, 0.8 mg/kg per dose. Plasma busulfan concentrations were obtained after the first dose. The fourth and subsequent busulfan doses were adjusted to achieve an area under the concentration versus time curve (AUC) of 900-1500 μM · min. Development of hepatic venous occlusive disease (HVOD; modified Baltimore criteria) and engraftment (absolute neutrophil count ≥0.5 × 10^9/L) were evaluated. Busulfan pharmacokinetic parameters were calculated using 1-compartment methods. Mean busulfan pharmacokinetic parameters were maximum concentration (C_{max}; 4.7 ± 0.75 μM), volume of distribution at steady state (0.68 ± 0.17 L/kg), elimination rate constant (0.0051 ± 0.0010 min^{-1}), total body clearance (3.5 ± 1.23 mL/[min · kg]), and AUC (1271 ± 280 μM · min). Mean volume of distribution at steady state was larger in children <1 yr of age (0.77 ± 0.24 vs 0.64 ± 0.11 L/kg; $P = .040$) and children <4 yr of age (0.73 ± 0.18 vs 0.60 ± 0.11 L/kg; $P = .001$) than in older children. Compared with older children, mean weight-adjusted total body clearance was higher in children <4 yr of age (3.8 ± 1.40 versus 3.0 ± 0.76 mL/[min · kg]). HVOD was diagnosed in 8 children (18%), including 4 children <1 yr of age. Children who developed HVOD achieved a lower C_{max} than did those without HVOD (4.2 ± 0.68 versus 4.8 ± 0.73 μM; $P = .035$). Other than C_{max}, no association was observed between busulfan disposition and development of HVOD in children for whom i.v. busulfan doses were adjusted to achieve a target AUC. The influence of factors other than busulfan disposition on transplantation outcomes, such as genetic polymorphisms, should be evaluated.

KEY WORDS

Hematopoietic stem cell transplantation • Children • Busulfan • Infants • Pharmacokinetics

INTRODUCTION

High-dose busulfan is widely used in pediatric hematopoietic stem cell transplantation (HSCT) preparative regimens. In adults, a relation has been described between systemic exposure to busulfan, as measured by the area under the busulfan plasma concentration versus time curve (AUC) or steady state

concentration (Css), and certain transplantation outcomes. Low systemic exposure has been associated with engraftment failure in some settings, whereas high systemic exposure has been associated with hepatic veno-occlusive disease (HVOD) [1-3], more recently termed "sinusoidal obstruction syndrome" [4]. These relations are influenced by factors such as underlying diagnosis because adults with chronic myelogenous leukemia (CML) have tolerated high systemic exposure to busulfan without an increased risk of HVOD [5].

Acknowledging the large interpatient variability in apparent busulfan clearance [6], especially in younger children, individualization of busulfan doses has been recommended to obtain optimal dose intensity to achieve engraftment and avoid relapse and toxicity [7]. Characterization of busulfan pharmacokinetic disposition after oral administration is complicated by its delayed and erratic absorption [8]. Moreover, emesis and the subsequent replacement of vomited tablets often result in difficulty in estimating AUC, even if numerous samples are available.

Disposition of busulfan is more predictable after i.v. administration because the variability resulting from absorption and the first-pass effect is eliminated. I.V. busulfan also offers the practical advantages of not requiring the use of nasogastric tubes to administer the drug to uncooperative patients, particularly children, and obviates replacement of vomited doses. Further, HVOD has been shown to occur less frequently in adult patients who received i.v. busulfan administration compared with those receiving oral therapy [9].

The primary objective of this study was to describe the pharmacokinetic disposition of busulfan after i.v. administration to infants and children before HSCT. We also evaluated the relations between busulfan pharmacokinetic parameters and transplantation outcomes, specifically HVOD, engraftment failure, and overall survival, in this group of patients.

METHODS

This study was approved by our institution's research ethics board. Children ≤18 yr of age who underwent HSCT from April 1, 2003 to January 30, 2006 at The Hospital for Sick Children (Toronto, Ontario, Canada) and received i.v. busulfan as part of their conditioning regimen were studied. Data were collected from patients' health records and/or pharmacy records including demographic information, receipt of previous antineoplastic treatment, HSCT date, type of conditioning regimen, busulfan first dose, plasma busulfan concentrations, busulfan dose adjustment (if any), time of neutrophil engraftment, diagnosis of HVOD, and survival at day +100 after transplantation. Hepatic function was considered to be impaired if transaminase values were >3 times the upper limit of normal for age and serum bilirubin values were above the upper limit of normal for age.

Table 1. *Initial i.v. Busulfan Dosage**

Child's Actual Weight (kg)	Initial Busulfan Dose (mg/kg per dose)	No. of Children
<9	1	9
9 to <16	1.2	5
16 to <23	1.1	2
23 to <34	0.95	4
≥34	0.8	4

*Busulfan was given i.v. over 2 h every 6 h for 16 doses. The fourth and subsequent doses were adjusted if necessary to achieve a target AUC of 900-1500 μM · min.

Busulfan Dose and Dose Adjustment

Intravenous busulfan was dosed based on actual body weight as outlined in Table 1. The first dose was administered as a 2-h infusion, including the line flush, using an i.v. infusion pump on day −9 at 0300 h. Serum busulfan levels were obtained at 0, 15, 30, 60, 120, 180, and 240 min after infusion of the first dose. Serum busulfan concentrations were assayed by gas chromatography with electron capture detection [10,11]. The coefficient of variation of the assay is 3.8%-6.0%. For clinical purposes, busulfan AUC was calculated for each patient using the trapezoidal rule [12]. Because the relation between busulfan dose and AUC is linear, the following equation was used to determine an adjusted dose: adjusted dose = (test dose × target AUC)/test dose AUC. The intended acceptable AUC range was 900-1500 μM · min [13,14]; the clinical team aimed for AUC values at the high or low end of this range at their discretion. The adjusted busulfan dose was given from the fourth dose on such that patients generally received 3 nonadjusted doses followed by 13 adjusted doses. The busulfan AUC determination was repeated after dose adjustment and the dose was readjusted at the discretion of the clinical team.

For the purpose of this study, busulfan pharmacokinetic parameters were calculated using a 1-compartment, first-order model (WinNonLin 4.1, Pharsight Corp, Mountainview, Calif). The cumulative AUC was calculated by multiplying the number of doses administered by the AUC each busulfan dose produced or was predicted to produce.

Hepatic Veno-occlusive Disease

The diagnosis of HVOD was determined by the clinical team and retrospectively confirmed by a study investigator (TS) using the modified Baltimore diagnostic criteria [15]. For the purposes of this study, only patients who met diagnostic criteria were deemed

to have HVOD. Severe HVOD was defined as HVOD that did not resolve before day +100 and/or was fatal [16]. HVOD was considered to be moderate if it required treatment and/or patients developed adverse effects from liver disease; mild HVOD was self-limited and required no treatment.

Neutrophil Engraftment

Neutrophil engraftment was defined as the first of 3 consecutive days on which the absolute neutrophil count was $\geq 0.5 \times 10^9$/L.

Transplant-related Mortality

Death during the first 100 d after HSCT was documented as early mortality.

Statistical Analysis

Descriptive statistics were used to calculate mean pharmacokinetic parameters. Differences between subgroups were evaluated by nonparametric tests. Comparisons of the incidence of HVOD between groups were made using the Fisher exact test. The a priori level of significance for all statistical tests was .05. Statistical analysis was performed with SPSS 13.0.1. (SPSS, Inc, Chicago, Ill).

RESULTS

A total of 47 children who underwent HSCT during the study period received i.v. busulfan as part of their conditioning regimen. Two children were excluded from analysis because a low busulfan dose was given as part of a reduced intensity conditioning protocol. Demographic data for the remaining 45 patients, including 13 infants, are presented in Table 2. Four patients had impaired liver function at time of HSCT. Abnormalities observed in these patients were elevations in alanine aminotransferase (2 patients), in unconjugated bilirubin (1 patient), and in alanine and aspartate aminotransferases (1 patient). Immediately before HSCT, 2 patients who underwent transplantation for beta-thalassemia had hepatic function test and hepatic iron stores values within the normal range for age. The third patient with beta-thalassemia had high liver iron stores (>3 mg/g liver, dry weight) and high serum ferritin concentrations (1969 μg/L) 6 wk before HSCT.

Forty-three patients received 16 doses of busulfan given every 6 h for 4 d. Inadvertent breakage of the central venous catheter of 2 patients necessitated oral administration of busulfan until the catheter was repaired. These patients received a total of 12 and 11 i.v. busulfan doses and 4 and 5 oral busulfan doses, respectively.

In 42 patients, busulfan was followed by cyclophosphamide. On average, the first cyclophosphamide dose was given 13.7 h (range, 11.8-16.3 h) after the initiation of the last busulfan dose. No HVOD prophylaxis was given. To prevent busulfan-induced seizures, all patients received phenytoin. A loading phenytoin dose of 20 mg/kg (maximum, 1 g/dose) was given by mouth or i.v. 24 h before the first busulfan dose was due. Maintenance phenytoin dosing was initiated 8 h after the loading dose and continued until 24 h after the last busulfan dose. No patient demonstrated seizures during or within 24 h of busulfan administration.

Table 2. *Demographic Data for 45 Children Who Received i.v. Busulfan during the Study Period*

Patient age (yr), mean/median/range	**5.1/3.0/0.25-16.2**
Patient weight (kg), mean/median/range	**23.4/13.7/4.8-108.7**
Male:female	**26:19**
Diagnosis (no. of patients)	
AML	**10**
Immune deficiency syndrome	**8**
Histiocytosis	**4**
CML	**4**
Hurler syndrome	**4**
Beta-thalassemia	**3**
Medulloblastoma	**3**
Osteopetrosis	**2**
Wiskott-Aldrich syndrome	**2**
Other	**5**
Donor type (no. of patients)	
Matched related	**15**
Mismatched related	**3**
Matched unrelated	**15**
Mismatched unrelated	**2**
Matched cord	**3**
Mismatched cord	**3**
Autologous	**3**
Haploidentical	**1**
Conditioning regimen (no. of patients)	
Bu, Cy	**26**
Bu, Cy, ATG	**11**
Bu, Cy, Eto	**4**
Bu, thiotepa	**3**
Bu, Cy, ATG, melphalan	**1**
GVHD prophylaxis (no. of patients)	
Cyclosporine and methotrexate	**26**
Cyclosporine and methylprednisolone	**13**
Cyclosporine alone	**3**
None (autologous transplants)	**3**

Bu indicates i.v. busulfan; Cy, cyclophosphamide; Eto, etoposide.

Busulfan Dose and Pharmacokinetics

Twenty-five children (56%), including 7 infants, achieved an AUC within the target range after administration of the initial busulfan dose (median, 1209 μM · min; range, 924-1474 μM · min). Dose elevations of 25%-51% (median, 27%) were made in 7 patients, including 3 infants. The initial AUC values of these patients were 772-1014 μM · min (median, 901 μM · min). An initial AUC >1500 or 1350 μM · min was achieved in 9 and 14 children, respectively. Dose reductions of 10%-26% (median, 15%)

were made in 12 patients, including 3 infants. The initial AUC values of these patients were 1301-1932 μM · min (median, 1629 μM · min). The first busulfan dose administered to 1 patient was higher than intended. This patient's adjusted busulfan dose was higher than the initial dose originally prescribed. One patient underwent 2 AUC determinations.

Mean busulfan pharmacokinetic parameters (AUC, maximum plasma concentration [C_{max}], total body clearance [TBC], and volume of distribution at steady state [Vss]) calculated after each patient's first busulfan dose are presented in Table 3. Children <1 yr of age were found to have higher mean Vss values when corrected for body weight compared with older children (0.77 versus 0.64 L/kg; $P = .040$). This difference was also seen in children <4 yr of age compared with older children (0.73 versus 0.60 L/kg; $P = .001$). Weight-adjusted TBC was significantly higher in children <4 yr of age compared with older children (3.8 versus 3.0 mL/[min · kg]; $P = .029$). However, TBC adjusted for body surface area was significantly lower in children <1 yr of age (76 versus 99 mL/[min · m^2]; $P = .028$) and <4 yr of age (84 versus 103 mL/[min · m^2]; $P = .009$) compared with older children.

Hepatic Veno-occlusive Disease

Eight patients (18%) developed HVOD (mean age, 7.5 yr; age range, 0.5-16.2 yr). Six patients (2 infants) had moderate HVOD and 2 infants had severe HVOD. Neither infants (4 of 13 versus 4 of 32; $P = .20$) nor children <4 yr of age (4 of 26 versus 4 of 19; $P = .70$) were more likely to develop HVOD than were older children. None of the children with impaired liver function at the start of conditioning and neither of the 2 children who had received several oral busulfan doses during conditioning because of malfunction of their central venous catheter developed HVOD. The child with beta-thalassemia and high liver iron and serum ferritin concentrations before HSCT did not develop HVOD. Diagnoses before HSCT for the 8 patients with HVOD were beta-thalassemia (2 children), hemophagocytic lymphohistiocytosis (1 infant and 1 child), Hurler syndrome (2 infants), myelodysplastic syndrome (1 child), and severe combined immunodeficiency (1 infant). All patients with HVOD were conditioned with a regimen containing cyclophosphamide. Patients presented with abdominal pain, hyperbilirubinemia, and weight gain (2 patients), hepatomegaly (2 patients), or increased abdominal girth (4 patients). All patients received supportive treatment of HVOD including fluid restriction and furosemide. Ursodiol, defibrotide, and *N*-acetylcysteine were also given to 6, 7, and 1 patients, respectively. Two patients with severe HVOD died on days +35 and +55 from multiorgan failure despite aggressive intensive care.

Table 3. *Mean ± SD Busulfan Pharmacokinetic Data in 45 Children Receiving i.v. Busulfan*

Pharmacokinetic Parameter	All Patients (n = 45)	Patients <1 yr Old (n = 13)	Patients ≥1 yr Old (n = 32)	Patients <4 yr Old (n = 26)	Patients ≥4 yr Old (n = 19)	Patients with HVOD (n = 8)	Patients without HVOD (n = 37)
C_{max} (μM)	4.7 ± 0.75	4.6 ± 0.77	4.8 ± 0.74	4.9 ± 0.80†	4.5 ± 0.66†	4.2 ± 0.68‖	4.8 ± 0.73‖
ke (min^{-1})	0.0051 ± 0.00100	0.0050 ± 0.00133	0.0052 ± 0.00085	0.0052 ± 0.00113	0.0051 ± 0.00080	0.0050 ± 0.00158	0.0052 ± 0.00090
Half-life (h)	2.3 ± 0.49	2.4 ± 0.65	2.3 ± 0.41	2.3 ± 0.53	2.3 ± 0.43	2.5 ± 0.79	2.3 ± 0.41
Vss (L/kg)	0.68 ± 0.167	0.77 ± 0.239*	0.64 ± 0.111*	0.73 ± 0.176‡	0.60 ± 0.109‡	0.67 ± 0.137	0.68 ± 0.174
TBC (mL/[min · kg])	3.5 ± 1.23	3.9 ± 1.84	3.4 ± 0.86	3.8 ± 1.40§	3.0 ± 0.76§	3.3 ± 0.97	3.5 ± 1.28
TBC (mL/[min · m^2])	92 ± 52.1	76 ± 33.1¶	99 ± 57.3¶	84 ± 52.8#	103 ± 50.4#	107 ± 83.5	89 ± 43.7
AUC (μM · min)	1271 ± 280	1268 ± 339	1272 ± 259	1317 ± 308	1209 ± 230	1202 ± 380	1286 ± 258

C_{max} indicates maximum plasma busulfan concentration; ke, elimination rate constant; Vss, volume of distribution at steady state; TBC, total body clearance; AUC, area under the plasma busulfan concentration versus time curve.
*$P = .040$; †$P = .054$; ‡$P = .001$; §$P = .029$; ‖$P = .035$; ¶$P = .028$; #$P = .009$.

Children who developed HVOD achieved a lower C_{max} than did those who did not develop HVOD (4.2 versus 4.8 μM; $P = .035$). No other statistically significant differences in busulfan disposition parameters (elimination rate constant, Vss, TBC, weight-adjusted TBC, body surface area-adjusted TBC, AUC, or cumulative AUC) were observed between children who developed HVOD and those who did not. The interval between the last busulfan dose and the first cyclophosphamide dose was also similar in children who did and did not develop HVOD (13.8 vs 13.6 h; $P = .65$).

Engraftment and Survival

All patients demonstrated engraftment. Median time to neutrophil engraftment was 17 d (median, 16 d; range, 8-36 d).

Overall survival at day +100 was 91% (41 of 45). Two children died as a result of HVOD and 2 because of multiorgan failure.

DISCUSSION

We have described the pharmacokinetic disposition of busulfan after i.v. administration to 45 children, including 13 infants, undergoing HSCT. We observed no relation between development of HVOD and busulfan TBC or AUC in children receiving individualized i.v. busulfan doses. However, children who developed HVOD had a significantly lower busulfan C_{max} than did children who did not develop HVOD.

Our observations regarding busulfan disposition in children are consistent with the findings of other investigators [17-22] (Table 4). Age-related differences in busulfan disposition were first identified after oral administration of the drug [23]; however, variability in absorption likely obscured some of this effect. Examination of values reported in the literature after oral busulfan administration indicates that weight-adjusted TBC and Vss are lower and half-life is longer in adults than in children [24-28]. Children have been shown to conjugate busulfan more efficiently than adults; thus, after oral administration to children, a larger proportion of the busulfan dose may undergo glutathione conjugation during passage through the intestinal wall and in the liver [29,30]. Appreciation of age-related differences in busulfan disposition after i.v. administration within the pediatric age group has been hampered by the limited number of very young children studied. However, existing data indicate that busulfan TBC is higher in young children than in adolescents. Tran et al [31] included 1 infant in their study sample; these investigators identified higher mean weight-adjusted busulfan TBC in children <6 yr compared with children ≥6 yr of age.

Table 4. *Summary of Published Studies of Pharmacokinetic Disposition of Busulfan after i.v. Administration to Children*

Study	No. of Patients (Age Range)	Conditioning Regimen (No. of Patients)	Seizure Prophylaxis	Mean TBC (mL/[min · kg])	Mean Vd (L/kg)	Mean $t_{1/2}$ (h)
Zwaveling et al [17]	31 (0.25-14 yr)	BU/CY (11), BU/MEL/CY (15), BU/CY/etoposide (2), BU/CY/FLU (3)	Clonazepam for high-risk patients only	<4 yr old, 5 ± 1.3; ≥4 yr old, 4 ± 1.0	<4 yr old, 0.73 ± 0.12; ≥4 yr old, 0.77 ± 0.22	<4 yr old, 2.1 ± 0.4; ≥4 yr old, 2.3 ± 0.7
Oechtering et al [18]	17 (0.9-17.3 yr)	Unspecified	Unspecified	3.5	0.72	2.35
Tran et al [19]	20 (0.8-14.9 yr)	Thiotepa/BU/CY (17), BU/CY/ATG (3)	Lorazepam	4.0 (range, 2.3-7.5)	1.5 (range, 0.21-5.83)	1.98 (range, 1.2-3.64)
Dalle et al [20]	14 (0.06-1 yr)	BU/CY (7), BU/FLU (3), BU/MEL (4)	Midazolam or phenytoin	3.6 ± 0.63	Not provided	Not provided
Cremers et al [21]	6 (1.5-14 yr)	BU/CY (6)	Unspecified	4.8	0.84	2.0
Kletzel et al [22]	26 (0.1-16 yr)	BU/FLU/ATG (26)	Phenytoin	3.6 ± 1.2	Not provided	Not provided

TBC indicates total body busulfan clearance; Vd, busulfan volume of distribution; $t_{1/2}$, busulfan elimination half-life; BU, busulfan; CY, cyclophosphamide; FLU, fludarabine; MEL, melphalan.

Similarly, Zwaveling et al [17] observed a higher mean weight-adjusted TBC in children <4 yr of age compared with children ≥4 yr of age. A close examination of the data provided by Dalle et al [20] indicates that the mean weight-adjusted busulfan TBC was significantly higher in infants ≤6 mo of age compared with infants >6 mo of age. Recently, Kletzel et al [22] described busulfan pharmacokinetic disposition after i.v. administration to 26 children. No assessment of age-related differences in disposition was made.

In our study, we observed significant differences in busulfan Vss between younger (<1 yr and <4 yr) and older (>1 yr and >4 yr) children. However, these differences did not translate into differences in busulfan weight-adjusted TBC between infants and older children, although significant differences in TBC were observed between children <4 yr of age and older children. Other investigators have observed a relatively larger liver volume normalized to body weight in younger children [31]. This may explain the need for higher doses of drugs that are primarily cleared by the liver, such as busulfan, when expressed as milligrams per kilogram in children. Interestingly, we found body surface area-adjusted TBC to be lower in younger than in older children.

Values of busulfan pharmacokinetic parameters may differ among studies depending on the type of seizure prophylaxis administered. In cohorts such as ours in which phenytoin, an enzyme inducer, is administered, one might expect higher values for busulfan TBC and lower values for half-life. However, Nguyen et al [32] observed no evidence of enzyme induction in 120 adults receiving i.v. busulfan. That is, no change in busulfan clearance from busulfan dose 1 to dose 13 was observed. The contribution of phenytoin to the interpatient variability in busulfan disposition is therefore unlikely to be significant, at least when busulfan is given i.v.

The incidence of HVOD in our patients was 18%. This is in agreement with our institution's and others' previous experience with oral busulfan in children [33-35]. Several risk factors for the development of HVOD after HSCT have been identified including genetic polymorphisms and mutations; iron overload; pre-existing liver damage; history of pancreatitis; prior HSCT; underlying malignant disease; donor type; conditioning with busulfan, cyclophosphamide, or dacarbazine; and GVHD prophylaxis with cyclosporine and methotrexate [36-39]. Children who developed HVOD in our study all received i.v. busulfan followed by cyclophosphamide. Interestingly, only 1 of our patients with HVOD had received antineoplastic or radiation therapy before HSCT. This patient had myelodysplastic syndrome and had been treated with cytarabine for 5 d. Myelodysplastic syndrome has been identified as a risk factor for developing HVOD [9]. We therefore speculate that the underlying diagnosis may have increased this patient's risk of developing HVOD. Two of 3 patients with beta-thalassemia developed HVOD. The degree of siderosis on liver biopsy and serum ferritin concentrations, which reflect severity of disease, have been reported to be associated with the occurrence of HVOD [40]. However, the patients in our cohort who developed HVOD did not have signs of significant liver involvement immediately before HSCT.

The association between high busulfan dose intensity as measured by Css or AUC and HVOD is well accepted, at least in adults given oral busulfan [3,6]. The existence of this association in children is controversial, although generally accepted [13,33,40,41]. Vassal et al [42] observed a trend toward an increased incidence of HVOD in 57 children who achieved a higher AUC after oral busulfan administration. Of the 24 children who developed HVOD, 12 achieved an AUC >1500 μM · h. Bolinger et al [43] also observed a trend toward a relation between increasing Css and an increased incidence of regimen-related toxicity after oral administration of busulfan. The relation between busulfan pharmacokinetics parameters and HVOD was not specifically addressed in this study. Seven of the 32 children studied achieved a Css >900 ng/mL (AUC >1300 μM · h). Conversely, McCune et al [14] did not observe an association between high Css and regimen-related toxicity in 53 children receiving oral busulfan. Only 1 of 10 children who achieved a Css >900 ng/mL had severe regimen-related toxicity. HVOD was not specifically addressed.

We observed an inverse relation between busulfan C_{max} and development of HVOD. That is, children who developed HVOD achieved a lower C_{max} than did children who did not develop HVOD. This difference, although of statistical significance, may be of marginal clinical value. Recent explorations of clinical outcomes after administration of once-daily i.v. busulfan to adults [26,27,44] and children [22] undergoing HSCT have shown no detrimental effect associated with the high peak plasma busulfan concentrations achieved as a result of this dosing regimen.

Intravenous busulfan administration to adults has been reported to reduce the incidence of HVOD to as low as 8% compared with that seen after conditioning that includes oral busulfan [9,45]. However, neither comparative study to date adjusted busulfan doses to achieve a target AUC or Css and in 1 study the AUCs achieved were low. Patients who have high busulfan TBC and presumably high intrahepatic busulfan concentrations may be at increased risk of HVOD regardless of the route of administration. Srivastava et al [40] reported a significantly higher incidence of HVOD in children who had a weight-adjusted apparent oral busulfan TBC >6.2 mL/(min · kg) and/or the glutathione S-transferase (GST) M1-null genotype. No infants were included in this study; all patients re-

ceived phenytoin for seizure prophylaxis. The weight-adjusted busulfan TBC was >6.2 mL/(min · kg) in only 1 of our patients (9.3 mL/[min · kg]), an infant who did not develop HVOD. Infants generally have higher weight-adjusted busulfan clearances than do older children. They, like patients with the GST null genotype, may be at higher risk of developing HVOD because they may have higher intrahepatic busulfan concentrations. The lack of a statistically significant difference in the number of infants who developed HVOD compared with older children may result from the small overall sample or the small number of infants included in our study compared with the number of older children. A larger number of infants must be studied to fully evaluate age-related differences in busulfan clearance and the incidence of HVOD.

Current data regarding the incidence of HVOD after administration of i.v. busulfan to children are conflicting. Some studies in children have reported that i.v. busulfan is well tolerated by children, without any documented cases of HVOD [18,19]. Busulfan doses were individualized in 1 of these studies [19] and a significant proportion of children in the second failed to achieve a busulfan AUC in the target range. Our findings compare with those of Zwaveling et al [17] who observed an incidence of HVOD of 8 of 31 (26%) in children after administration of individualized i.v. busulfan doses. Neither we nor other investigators have identified a relation between busulfan disposition parameters and transplantation outcomes including HVOD in children after i.v. busulfan administration. However, it must be acknowledged that the ability to identify such relations may be blunted by busulfan dose adjustment and/or administration of low doses that ensure that the busulfan AUC remains <1500 μM · min. In addition, evaluation of GST M1 genotype in our patients was beyond the scope of this work and therefore we cannot determine its effect on our present findings.

In summary, our data suggest that the prevalence of HVOD in children is lower after i.v. administration of busulfan than that seen after oral administration of the drug, but not dramatically so. Children with HVOD had a lower C_{max} than did children without HVOD. We did not observe a relation between any other busulfan pharmacokinetic parameter and HVOD. Although the hypothesis that infants may be at higher risk of busulfan-induced HVOD than older children should be explored further, the influence of factors other than busulfan disposition on transplantation outcomes, such as genetic polymorphisms, should also be evaluated.

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