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Busulfan Bioavailability

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Busulfan is widely used as a component of the myeloablative therapy in bone marrow transplantation. Recent studies have shown that the drug disposition is altered in children and is associated with less therapeutic effectiveness, lower toxicities, and higher rates of engraftment failure. We have evaluated the bioavailability of the drug in two groups of patients: eight children between 1.5 and 6 years of age and eight older children and adults between 13 and 60 years. Oral bioavailability showed a large interindividual variation. In children, the bioavailability ranged from 0.22 to 1.20, and for adults, it was within the range 0.47 to 1.03. The elimination half-life after intravenous administration in children (2.46 ± 0.27 hours; mean ± SD) did not differ from that obtained for adults (2.61 ± 0.62 hours). However, busulfan clearance normalized to body weight was significantly higher in children (3.62 ± 0.78 mL·min^{-1}·kg^{-1}) than that in adults (2.49 + 0.52 mL·min^{-1}·kg^{-1}). Also, the distribution volume normalized for body weight was significantly higher in children (0.74 ± 0.10 L·kg^{-1}) compared with 0.56 ± 0.10 L·kg^{-1} in adults. The difference in clearance between children and adults was not statistically significant when normalized to body surface area, which most probably shows that busulfan dosage should be calculated on the basis of surface area rather than body weight. However, to avoid drug-related toxicities, drug monitoring and an individual dose adjustment should be considered because of the variability in busulfan bioavailability.

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BONE MARROW transplantation (BMT) using busulfan and cyclophosphamide (BUCY) as myeloablative regimen has become a widespread treatment in hematologic malignancies[1-4] and nonmalignant disorders such as immunodeficiencies, thalassemia, and osteopetrosis.[5-7] Busulfan has been introduced as an alternative for total body irradiation (TBI). The therapeutic efficacy for BUCY is considered to be equivalent if not superior to cyclophosphamide and TBI[8] and the busulfan dose was established to 1 mg/kg every 6 hours for 16 doses. However, a randomized French study in patients with acute myeloid leukemia showed a survival advantage for patients treated with TBI[9] and a Nordic multicenter trial found an increased transplant-related mortality associated with busulfan treatment.[10]

Busulfan's pharmacokinetics has been extensively studied during the last years in both adults and children.[11-15] In children, lower plasma levels of busulfan, minimal toxicity and higher rates of failure to achieve engraftment have been reported.[16-19]

These studies showed an alteration in busulfan disposition in children compared with adults. Despite the long clinical use of busulfan, and because of the fact that there is no parenteral drug available, the influence of bioavaliability on the blood level could not be studied. We conducted this investigation to study the bioavailability of busulfan in children and adult patients.

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Submitted October 4, 1993; accepted June 2, 1994.

Supported by Grant No. 2805-B91-02XAA from the Swedish Cancer Society.

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0006-4971/94/8407-0019$3.00/0

MATERIALS AND METHODS

Patients. Eight children with median age of 1.5 years and eight adults (seven adults and one older child with median age 43 years) undergoing BMT took part in the study (Table 1). Patients were hospitalized 2 days before their high-dose therapy. All patients had a normal liver function immediately before entering the study and none of the patients were given other medications during the period of the study. The first day, 1.0 mL was given as a bolus injection (0.5 minutes) of about 2 mg busulfan (Table 1). The injection solution was prepared by dissolving busulfan powder, for human use (Wellcome Foundation Ltd, Beckenham, UK) in 2 mL (propylene glycol, ethanol, dimethyl sulfoxide (DMSO): 0.8, 0.50, and 0.70 mL, respectively). The solution was passed through a Millex filter (0.22 μm, Millipore GV, Bedford, MA) and was examined and found to be pyrogen free and sterile. Busulfan solution was prepared, analyzed for each individual, and kept at 4°C for no more than 12 hours before administration because of the poor stability of busulfan in this formulation ($t_{1/2}$ = 114 hours at 20°C). On the second day, a 2-mg tablet (Wellcome) was administered. All the patients received their oral dose from the same batch, where the tablets were assayed for busulfan concentration (2.00 ± 0.04 mg/tablet, n = 5). The drug was administered at 8 AM, on both first and second day, to minimize the risk of chronopharmacologic variation described previously.[12,13] High-dose therapy with busulfan was started (1 mg/kg every 6 hours for 16 doses) on the third day. The study was designed according to the recommendations of the ethics committee at the Karolinska Institute and was approved by the Swedish Medical Products Agency. The adult patients and the parents for the younger patients were informed and asked for their consent.

Samples. Whole blood samples (1 to 2 mL for children and 3 to 5 mL for adults) were obtained from indwelling venous catheters before the drug administration and at 2.5, 5, 10, 20, 30, 60, 75, 90, 120, 180, 240, 300, 360, 480, and 600 minutes after the dose. Blood samples were also obtained from the patients during high-dose therapy immediately before each dosage interval to determine the mean minimum concentrations of the drug, except for three adult patients (LM, LA, and BN) because they have been conditioned with TBI/CY. Plasma was separated and frozen at −20°C until assay.

Drug analysis. Busulfan concentrations in plasma were measured using gas chromatography with electron capture detection as described previously.[20]

Pharmacokinetics. Individual pharmacokinetic parameters for oral administration curves were evaluated and fit by a one-compartment model with first-order absorption. The intravenous administration curves were evaluated using a two-compartment model. Parameter estimation using nonlinear least squares analysis was performed

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Table 1. Clinical Data for All Patients

Patient	Sex	Weight (kg)	Length (cm)	Age (yr)	Diagnosis	SA (m^2)	Dose (mg)
LS	F	10.4	86	1 5/12	ALL	0.52	3.03
MH	M	10.5	78	2	Hurler	0.49	1.97
JJ	F	12.8	97.5	3 4/12	AML	0.61	1.94
EO	M	19.0	103	3 7/12	AA	0.77	2.00
CH	F	20.0	100	3 6/12	FHL	0.78	1.92
DM	M	14.5	98	5	B-DA	0.65	2.10
MW	F	18.5	113	6	AML	0.78	1.84
MS	F	20	116	6	AML	0.83	1.72
MM	M	38.4	154	13	AML	1.30	1.91
LM	M	68	179	20	AML	1.84	2.00
YN	F	55	174	34	AML	1.64	2.13
SO	M	70	184	43	AML	1.89	1.54
LA	M	74	173	49	CML	1.88	2.00
BN	F	69	176	50	ALL	1.84	2.00
RS	M	95	176	60	AML	2.13	1.64
UA	M	99	185	48	Myeloma	2.23	1.97

Dose values represent the exact dose injected intravenously into each patient.

Abbreviations: AML, acute myelocytic leukemia; AA, aplastic anemia; FHL, familial erythrophagocytic lymphohistiocytosis; B-DA, Blackfan-Diamond anemia.

using PCNONLIN (Statistical Consultants, Lexington, KY) and the estimation curves to high-dose concentration data were performed using SIPHAR (Smid, Paris, France).

Kinetic parameters estimated using PCNONLIN are absorption constant (ka), elimination constant (ke), distribution volume at steady-state level (Vdss), lag time, and area under the curve (AUC).

The differences in pharmacokinetic parameters between the groups were compared using the Student's *t*-test. The correlation between the pharmacokinetic parameters and age was established using a linear regression method.

The absolute bioavailability was obtained by comparing AUCs for intravenous and oral administration for each individual.

RESULTS

The plasma concentration curves for two patients (LS and EO) after oral and intravenous administration of busulfan are given in Figs 1 and 2.

Table 2 shows the calculated pharmacokinetic parameters for both adults and children after intravenous administration of the drug. Clearance normalized for body weight was significantly ($P = .004$) higher in children with a value of 3.62 ± 0.78 $mL \cdot min^{-1} \cdot kg^{-1}$ (mean ± SD) compared with adult patients (2.49 ± 0.52 $mL \cdot min^{-1} \cdot kg^{-1}$). An age-related clearance was shown (Fig 3) by a regression analysis ($P = .02$). However, this difference was not significant when clearance was normalized to surface area (Table 2).

The distribution half-lives (α) in both children and adults were similar (0.059 and 0.051 hours, respectively). Also, the elimination half-lives (β) for children (2.46 ± 0.27 hours) did not differ from those for adults (2.61 ± 0.62 hours). The estimated Vdss was 0.74 ± 0.10 $L \cdot kg^{-1}$ for the children, which was significantly higher ($P < .005$) than that estimated for the adult patients (0.56 ± 0.10 $L \cdot kg^{-1}$). The AUCs for children ranged from 309 to 1,510 $ng \cdot hr \cdot mL^{-1}$, whereas for adults, the values were within the range 103 to 270 $ng \cdot h \cdot$

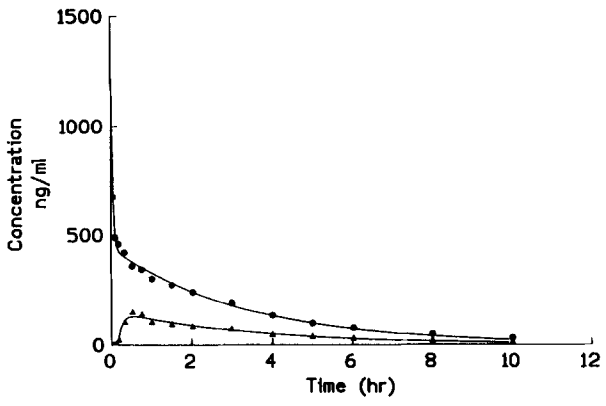

Fig 1. Plasma time-concentration curve after 3.03 mg intravenous (●) and 2 mg oral administration (▲) of busulfan (patient LS with bioavailability of 52%).

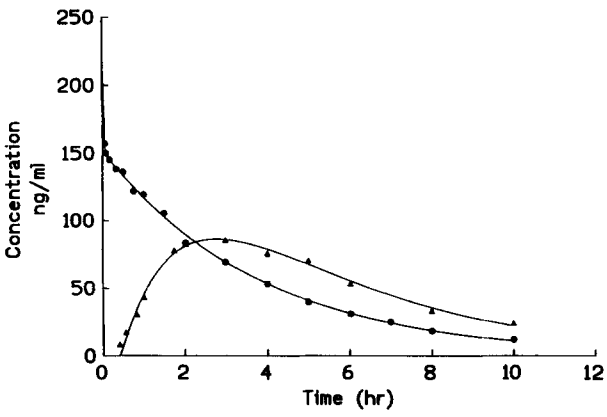

Fig 2. Plasma time-concentration curve after 2 mg intravenous (●) and 2 mg oral administration (▲) of busulfan (patient EO with 100% bioavailability).

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Table 2. Pharmacokinetic Parameters for Intravenous Administration

Patient	α (h)	β (h)	Vdss ($L \cdot kg^{-1}$)	C_{max} ($ng \cdot mL^{-1}$)	AUC ($ng \cdot h \cdot min^{-1}$)	Clearance ($mL \cdot min^{-1}/m^2$)	Clearance ($mL \cdot min^{-1}/kg$)
LS	0.027	2.32	0.63	1,308	1,510	64.31	3.22
MH	0.055	2.60	0.87	503	823	81.42	3.99
JJ	0.063	2.66	0.74	439	769	68.93	3.28
EO	0.015	2.65	0.72	294	581	74.51	3.02
CH	0.012	2.61	0.68	753	523	78.44	3.06
DM	0.170	2.71	0.76	296	733	73.46	3.30
MW	0.027	2.05	0.87	751	309	127.24	5.36
MS	0.101	2.06	0.62	292	387	89.25	3.71
MM	0.044	1.98	0.54	458	239	102.46	2.46
LM	0.041	3.08	0.71	121	196	92.43	2.50
YN	0.021	1.88	0.53	750	250	86.59	2.58
SO	0.048	2.16	0.59	139	110	123.28	3.33
LA	0.071	3.73	0.51	179	270	65.67	1.67
BN	0.032	2.81	0.64	104	181	100.08	2.67
RS	0.078	2.70	0.60	77	103	83.66	2.79
UA	0.071	2.52	0.39	161	176	83.66	1.88
Mean for children (±SD)	0.059 (0.054)	2.46 (0.27)	0.74 (0.10)	577 (349)	704 (373)	82.20 (19.73)	3.62 (0.78)
Mean for adults (±SD)	0.051 (0.021)	2.61 (0.62)	0.56 (0.10)	249 (235)	191 (62)	97.35 (19.93)	2.49 (0.52)

Abbreviations: α, distribution half-life; β, elimination half-life; AUC, area under plasma concentration curve; C_{max}, maximum plasma concentration; Vdss, distribution volume at steady-state.

mL^{-1}. Both the distribution volume and clearance were correlated to age with correlation coefficients of 0.65 and 0.57, respectively (Figs 3 and 4).

The pharmacokinetic parameters, the drug bioavailability after oral administration of 2 mg busulfan and the mean minimum concentrations during high-dose therapy calculated from dose 4 to dose 16 (corrected for 1 mg/kg) are listed in Table 3. The simulated mean minimum concentrations using the obtained parameters (ka, ke, and the bioavailabilty) are also listed in Table 3.

The kinetics of oral busulfan in all patients were fitted to a one-compartment open model with first-order absorption. A large variability was seen in the absorption half-life. In children, the absorption half-life was 0.37 ± 0.41 hours, whereas in adults, it was 0.21 ± 0.21 hours. No difference in the elimination half-life between children and adults was seen (2.80 and 2.68 hours, respectively). An interindividual variability in the time to reach peak plasma concentration and the area under the concentration time curve was seen. Maximum plasma concentration appeared between 0.29 and 2.78 hours in children and between 0.48 and 2.32 hours in adults. Comparison of AUCs after oral and intravenous administration showed an oral availability of 0.68 ± 0.31 in children and 0.80 ± 0.19 in adults.

DISCUSSION

Busulfan pharmacokinetics has been extensively studied in both adults and children during the last few years.[11-15]

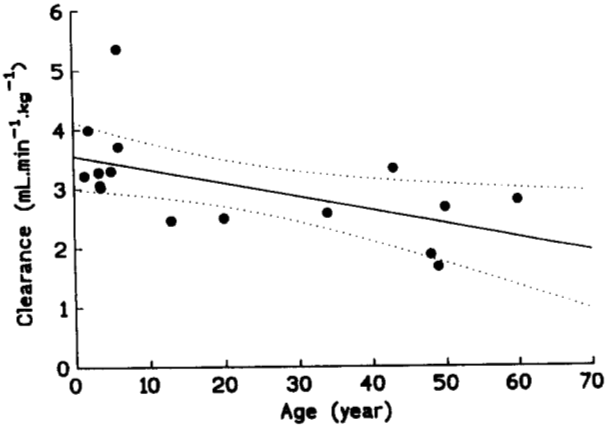

Fig 3. The relation between clearance corrected for body-weight and age. The solid line is the regression line and the dotted lines are the 95% confidence interval. Slope = −0.023 ± 0.008, $r = -.57$, $P = .02$.

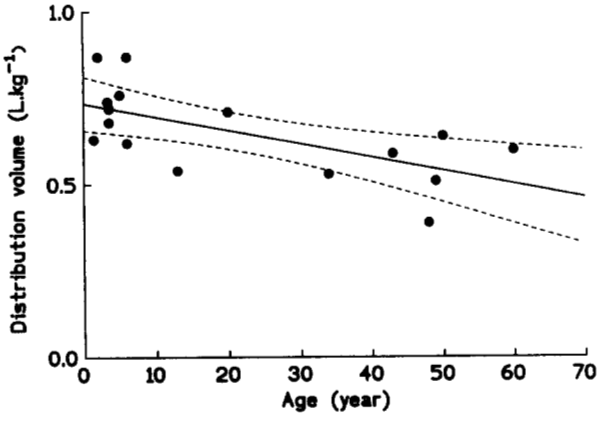

Fig 4. The relation between distribution volume normalized for body-weight and age. The solid line is the regression line and the dashed lines are the 95% confidence interval. Slope = −0.004 ± 0.001, $r = -.65$, $P = .006$.

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Table 3. Pharmacokinetic Parameters for Per Os Administration

Patient	ka (h)	ke (h)	T-lag (h)	T_{max} (h)	C_{max} (ng·mL^{-1})	AUC (ng·h·mL^{-1})	Bioavailability (%)	High Dose (1 mg/kg) Mean Concentration Found (ng·mL^{-1})	High Dose (1 mg/kg) Mean Concentration Simulated (ng·mL^{-1})
LS	0.08	2.47	0.14	0.54	130	516	52	330 ± 91	297
MH	0.12	3.22	0.02	0.61	28	183	22	160 ± 82	139
JJ	0.08	3.51	0.09	0.54	142	955	120	890 ± 550	810
EO	1.07	2.74	0.42	2.78	86	600	103	583 ± 106	560
CH	0.68	5.03	—	2.38	34	302	55	166 ± 56	176
MW	0.80	1.39	0.70	2.08	53	205	61	319 ± 89	322
DM	0.06	2.32	0.14	0.45	113	414	59	319 ± 69	318
MS	0.05	1.75	0.04	0.29	115	322	72	360 ± 102	365
MM	0.06	2.52	0.18	0.48	66	216	86	300 ± 111	318
LM	0.69	2.41	0.44	2.18	28	159	81	—	
YN	0.06	1.91	0.43	0.71	41	110	47	310 ± 72	305
SO	0.06	2.01	0.30	0.60	28	89	62	280 ± 60	286
LA	0.31	4.98	0.72	1.50	34	278	103	—	
BN	0.18	2.73	0.72	2.11	32	180	99	—	
RS	0.22	2.56	1.46	2.32	19	89	71	677 ± 216	624
UA	0.10	2.35	0.29	0.73	44	168	94	714 ± 86	691
Mean for children (+SD)	0.37 (0.41)	2.80 (1.14)	0.22 (0.25)	1.21 (1.02)	88 (44)	437 (254)	68 (31)		
Mean for adults (+SD)	0.21 (0.21)	2.68 (0.97)	0.56 (0.41)	1.33 (0.79)	37 (14)	161 (66)	80 (19)		

Abbreviations: ka, absorption half-life; C_{max}, plasma maximum concentration; T-lag, lag-time; T_{max}, time to reach C_{max}; ke, elimination half-life.

Those studies have shown differences in drug disposition in children compared with adults.

The bioavailability of busulfan was investigated here in eight children and eight adults for the first time since the introduction of the drug in the 1950s.[21] The patients studied showed a high variability in bioavailability of about sixfold in children and twofold in adults. The distribution volumes and the clearance values calculated after an oral dose of 2 mg (with the assumption of complete bioavailability) were in agreement with the previously published data on high-dose therapy (Table 4).

Despite the low administered dose of intravenous busulfan and with respect to its bioavailability, the levels of busulfan (expressed as a mean minimum concentration) measured during high-dose therapy were in good agreement with those simulated using the pharmacokinetic parameters obtained after oral (2 mg) administration (Table 3). This indicates that our results may also be valid at therapeutic levels and most probably confirms the linear pharmacokinetics of busulfan.

All data from patients receiving oral doses were fitted to a one-compartment open model with first-order absorption.

The younger children showed a slightly, but not significant, slower absorption rate than the adults. This is probably

Table 4. Busulfan Disposition According to Age and Route of Administration

Reference	n	Age (yr)	t½ (h)	Clearance (mL/min/kg) (mean ± SD)	Vd (L/kg) (mean ± SD)
Grochow[15]	28	>18	2.33	2.9 (1.7)	0.59 (0.44)
Hassan[12]	16	>18	2.59	2.64 (0.56)	—
Grochow[16]	14	0.2-3.6	1.54	8.4 (4.3)	1.42 (0.83)
Vassal[14]	11	4-14	2.33	4.4 (2.2)	1.06 (0.44)
Vassal[39]	25	2-14	2.94	4.5 (1.4)	1.04 (0.38)
Hassan[12]	9	1.3-14	2.43	4.9 (2.2)	—
Vassal[41]	33	0.2-2.75	2.83	6.8 (3.0)	1.69 (1.29)
Present study					
Oral dose (2 mg)*	7†	1.8-6	2.74	5.2 (2.1)	1.15 (0.52)
Oral dose (2 mg)*	8	>13	2.68	3.6 (1.3)	0.64 (0.12)
Intravenous	8	1.8-6	2.46	3.62 (0.78)	0.74 (0.10)
Intravenous	8	>13	2.61	2.49 (0.52)	0.56 (0.10)

* Clearance and distribution volume are calculated with assumption of f = 1 to simplify comparison with published results.

† Patient MH was excluded because of the extreme values of cl (17.3 mL/min/kg) and Vd (11.8 L/kg), which most probably was because of his diagnosis.[41]

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caused by differences between adults and children in transit time in the gastric region. In high-dose therapy, the variation can be of a higher magnitude because crushed tablets in combination with gastric tube,[12] in gelatine capsules,[14] and in apple sauce[16] are usually used for younger children. The elimination half-lives were within the range of the average obtained in adults. Only one child showed an extremely long elimination half-life.

According to the venous equilibrium or sinusoidal model,[22] the hepatic clearance of a drug may be increased because of (1) higher metabolic activity as a function of the hepatic mass; (2) decreased plasma protein binding and/or (3) increased hepatic blood flow. On the other hand, the distribution volume may be influenced by body composition, protein binding, and tissue binding of the drug. This study showed potentially important differences between children and adults in the disposition of busulfan. After an intravenous administration of busulfan, both clearance normalized to body weight and distribution volume adjusted to body weight appear to be age dependent (Fig 3 and Fig 4). Clearance and distribution volumes were significantly higher in children than in adult patients (45% and 34%, respectively). No difference in the elimination rate constant was observed. The present results using intravenous busulfan confirm the results reported by several investigators after oral administration of the drug[12-16] regarding busulfan disposition in relation to age (Table 4).

Busulfan protein binding does not explain these differences between adults and children because it was shown that its binding is very low in both high and low doses.[11,23]

In our investigation it was shown that the distribution volume was higher in children than adults. The values obtained after intravenous administration were in agreement with those previously published using oral doses of busulfan[14,16] when the variability in bioavailability was considered. Surprisingly, the values for distribution volumes obtained after intraveous administration corresponded directly to total body water, and the difference between adults and children was equal to that reported for body water.[24,25] This might indicate that despite the lipophilicity of busulfan,[26] it is still distributed to body water. In this respect, busulfan might be like caffeine, which is also a rather lipophilic compound and has a distribution volume equal to body water.[27,28]

The differences in clearance could be explained if the liver blood flow or hepatic mass is different in children compared with adults when normalized to body weight, but not to body surface area. Grygiel et al[29] and Rylance et al[30] showed in two independent studies in children that the liver volume examined by ultrasound scans averaged 30 to 35 mL/kg, whereas in two adult studies,[29,31] the liver volume was 19.5 to 22 mL/kg. Recently, Evans et al[32] showed a clear decrease in liver volume to body weight (mL/kg) with increasing age, but no significant age-related decrease in liver volume was found when correlated with body surface area (mL/m^2).

Recently, we have shown that [^{11}C-busulfan] is highly distributed into the liver of the monkey using positron emission tomography.[33] Grochow et al[16] have suggested the first-pass elimination to explain the high clearance found in children below 4 years of age. Also, it has already been shown that busulfan is highly metabolized in the liver through enzymatic conjugation with glutathione.[11,34,35] However, to our knowledge, no age-related differences in either glutathione or its transferase in humans have been reported, but it is known that there are a variety of ways in which drug handling in young children may differ from adults,[36,37] and that their metabolic capacity is higher than in adults. It seems clear that children below 6 years of age have a higher hepatic clearance than adults if the adjustment is based on body weight, whereas there is no difference when the surface area is considered.

The elimination half-life for intravenously administered busulfan in young children was longer than that reported previously by Grochow et al and by us using high doses of oral busulfan. However, the elimination values were in better agreement with those reported by Vassal et al.[14] This is most likely a result of an interaction between busulfan and phenytoin used as anticonvulsants in our previous studies.[11,12] Recently, we reported[38] a possible interaction between busulfan and phenytoin, expressed as a lower AUC and faster elimination after the last dose compared with the first dose during high-dose therapy. This interaction or liver activation can be more pronounced in children,[36,37] resulting in a higher hepatic clearance than in adults.

Several investigators have expressed their concern about busulfan dosage in children because of the higher failure rates to achieve engraftment.[16-18] Recently, Vassal et al[39] have recommended a dose of 600 mg/m^2 for young children, whereas Yeager et al[40] have suggested 640 mg/m^2. In a very recent study, Vassal et al[41] have described a dose of 749 mg/m^2 for children below 3 years of age. The new recommended dosages[39-41] provide systemic drug exposure closer to that obtained in adults. Also, the present results show that a dosage based on the body surface area will be more accurate, might achieve higher therapeutic effectiveness, and will hopefully lower relapse rates in young children. However, Vassal et al[39] reported a higher rate of neurotoxicity using the new dosage, whereas increased incidence of mucositis was reported by Yeager et al.[40] The wide range of AUC observed in both studies can most likely be explained by the variation in bioavailability shown in the present study.

Patient MH in the children's group has shown extremely low bioavailability after oral administration of busulfan (0.22). Vassal et al[41] have recently shown higher clearance and distribution volumes in children with lysosomal storage disease than other children, and a great variation in drug disposition was observed. In fact, this might be caused by low bioavailability of busulfan in children with metabolic disorders disease as observed in the above-mentioned child. Other studies investigating the bioavailability in children with metabolic disorders are urgently warranted.

It has also been shown that some young individuals have very high initial concentrations when busulfan is given as a bolus injection in a dose as low as 3 mg. Indeed, an intravenous formulation is warranted, but not as a bolus form because of the neurotoxicity reported[39,42] and our results showing that at least 20% of the injected dose enters the human brain[33] during the first 5 minutes after administration. Moreover, lack of information about the combined toxicity of

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busulfan and DMSO, poor stability of busulfan in the present formulation, and low solubility of busulfan make the injection of higher doses or larger volumes unadvisable.

Our study shows a variability in busulfan bioavailability by fivefold in young children and by twofold in adults. It was also shown that children have significantly higher clearance and distribution volumes compared with adults.

In addition, a dosage regimen based on body surface area might enhance drug efficacy in children,[39,40] but considering the variability in the bioavailabilty and the correlation between a high systemic exposure to busulfan and both its neurotoxicity[42] and the occurrence of veno-occlusive disease (VOD),[15] therapeutic monitoring of busulfan concentrations and individualized adjustment of its dosage have to be considered to optimize drug exposure and avoid both neurotoxicity and VOD.

ACKNOWLEDGMENT

We thank Susanna Kumlien and Victoria Lieu-Wang for invaluable assistance in conducting the present study.

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