



Pharmacokinetics of oral busulphan in children with beta thalassaemia major undergoing allogeneic bone marrow transplantation

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Summary:

The pharmacokinetics of busulphan were studied in 23 thalassaemic children undergoing BMT. Patients received busulphan at a dose of either 16 mg/kg with cyclophosphamide and ATG (Group A) or 600 mg/m² (with cyclophosphamide alone) (Group B) in 16 divided doses every 6 h over 4 days. Busulphan levels were analyzed by a modified GC-MS method. The dose of busulphan/kg for patients in group B was 64% (range 56–71%) higher than that for patients in group A. The mean AUC, Css, Cmax and MRV were significantly higher in group B as compared with group A for both doses 1 and 13. There was no significant difference in Vd/F, T1/2 and Kel between the two groups. A significant decrease in AUC and Css was found between 1st and 13th doses in group B, but not in group A. The Cl/F values in group A were significantly higher than those in group B after dose 1, but not after dose 13. No increase in toxicity due to the higher dose of busulphan was noted. We conclude that busulphan at 600 mg/m² results in much higher systemic exposure to the drug as compared to 16 mg/kg, without increase in toxicity in children with beta thalassaemia major.

Keywords: busulphan; pharmacokinetics; bone marrow transplantation; thalassaemia

a high dose. Pharmacokinetic data of busulphan in adults have shown a significant correlation between systemic exposure, particularly the area under the concentration vs time curve (AUC) and the incidence of veno-occlusive disease (VOD) of the liver.⁸ However, many studies have demonstrated that children undergoing BMT for both malignant and genetic disorders^{7,9–11} tolerate this dose well.

There are limited data on the pharmacokinetics of busulphan at 16 mg/kg in children with beta thalassaemia major, most of whom have varying degrees of chronic liver disease.^{12,13} There are no data regarding the pharmacokinetics of busulphan at 600 mg/m² in this group of patients. In this report, we describe the comparative pharmacokinetics of busulphan at these two dosages, 16 mg/kg and 600 mg/m², in conditioning therapy for BMT for heavily transfused thalassaemic children.

Patients and methods

Patients and treatment

Twenty-three consecutive children with thalassaemia major, who underwent allogeneic BMT from HLA-matched sibling donors, were included in this study. Patients were randomized to receive busulphan (Myeleran; Glaxo Wellcome, Madrid, Spain) 4 mg/kg p.o. in divided doses every 6 h daily for 4 days (total dose 16 mg/kg) on days –9 to –6 and cyclophosphamide 50 mg/kg once daily i.v. on days –5 to –2 with ATG 30 mg/kg (Lymphoglobuline, Pasteur Merieux, Paris, France) on days –4 to –2 (group A) or busulphan 600 mg/m² (total dose) p.o. in divided doses every 6 h daily for 4 days on days –9 to –6 and cyclophosphamide 50 mg/kg once daily i.v. on days –5 to –2 (group B) before BMT. All patients received 7.5 mg/kg p.o. of phenytoin in divided doses as prophylaxis against seizures, starting 1 day before and stopping 1 day after busulphan treatment. Eleven patients were in group A and 12 in group B. Informed consent was obtained from the parents of all patients. The study was approved by the institutional review board.

Sample collection

The first dose of busulphan was given at 6 am to all patients. All doses were given to patients on an empty sto-

Busulphan is widely used in conditioning regimens for patients undergoing bone marrow transplantation (BMT).^{1–6} It is most commonly used at 16 mg/kg (total dose) over 4 days. Lucarelli *et al*⁶ have used a total of 14–16 mg/kg of busulphan in thalassaemic children undergoing BMT. Rejection of the graft is a major cause of failure among them and occurs in up to 32% of class III patients.⁶ Recent studies have shown that children may need a higher dose (600 mg/m²) to achieve the same systemic exposure to the drug as adults.⁷ It is possible that this may help reduce the high incidence of graft rejection in these patients. There has been concern about the toxicities of busulphan at such

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Table 1 Details of patients and individual dosage of busulphan

No.	Age	Weight (kg)	BSA (m ²)	Risk category ^a	Bu dose (mg/kg)	% Excess
<i>Group A: Busulphan 16 mg/kg with cyclophosphamide 200 mg/kg and ATG</i>						
1	6	19	0.75	III	16	
2	8.5	21	0.84	III	16	
3	11	25	1.0	II	16	
4	11	31	1.1	III	16	
5	7.5	20	0.84	III	16	
6	9	22	0.84	III	16	
7	5.5	15	0.67	II	16	
8	5	19	0.73	III	16	
9	8	20	0.67	III	16	
10	4	15	0.67	II	16	
11	13	35	1.24	III	16	
Mean	8.05	22	0.85		16	
<i>Group B: Busulphan 600 mg/m² with cyclophosphamide 200 mg/kg</i>						
1	2.5	13	0.54	II	20	64
2	7	21	0.85	III	32	66
3	4	17	0.65	II	24	71
4	2.5	13.5	0.57	II	21	64
5	10	23	0.9	III	34	68
6	5	20.5	0.65	II	24	68
7	8	20.5	0.83	II	31	68
8	6	19	0.8	III	30	62
9	6	15.5	0.66	III	25	56
10	12	22	0.87	III	33	56
11	4	13.5	0.65	III	24	67
12	11	25.5	0.95	III	36	62
Mean	6.5	19	0.74		27.8	64

^aAs per Lucarelli *et al.*²⁹

mach. Blood samples (3–5 ml) were taken from a central venous catheter into glass tubes containing 150 IU heparin. They were collected immediately before starting the drug and at 0.5, 1, 1.5, 2, 4 and 6 h after the first, second and 13th doses. Samples were immediately refrigerated and centrifuged within 1.5–3 h of collection and stored at –80°C until analysis. Busulphan in plasma samples was found to be stable for up to 2 years at –80°C. Samples analysed after 6 months, 1 year and 2 years of storage after collection showed good correlation ($r = 0.89$, $P < 0.001$) (unpublished data).

Busulphan assay

Samples were analysed by a modified GC-MS method¹⁴ as previously reported. Briefly, busulphan in plasma was mixed with 100 μ l internal standard-d8-busulphan (1,4-butanediol-1,1,2,2,3,3,4,4,-d8) and extracted with ethyl acetate for 10 min. The organic layer was separated and allowed to evaporate at 60°C under nitrogen gas. The residue was subjected to derivatization by adding 1 μ l 2,3,5,6, tetrafluorothiophenol and 1 μ l sodium hydroxide and heated at 70°C for 2 h. It was then mixed with ethyl acetate and 1 μ l sodium hydroxide, for extraction of the derivatized compound. The organic phase was dried under nitrogen gas and the residue dissolved in 100 μ l of ethyl acetate. An aliquot of 1 μ l was injected into the GC-MS system. The gas chromatographic system was a Hewlett Packard (California, USA) model 5890 equipped with a CP sil5CB WCOT fused

silica capillary column (25 m \times 0.25 mm ID) with a film thickness of 0.12 μ m (Chrompack, Middleburg, The Netherlands). Helium was used as the carrier gas at a flow rate of 1.9 ml/min. The oven temperature was initially kept at 60°C for 1 min then increased with a first gradient of 35°C/min to 170°C and maintained for 3 min, a second gradient of 4°C/min to 200°C and a third 35°C/min to 250°C. The injector was in the splitless mode and heated at 250°C. The autosampler tray was refrigerated at 4°C. Detection was performed with a Hewlett Packard mass spectrometer model 5971A equipped with an electron impact source (tuned to m/z 237 and 245 for derivatized busulphan and derivatized-d8 busulphan, respectively). For the mass spectral identification of busulphan and busulphan-d8, a chemical ionization (CI) source was employed with methane as the reagent gas. The two sources were heated at 175°C.

Pharmacokinetic analysis

Pharmacokinetic analysis was done using the 'TOPFIT' program.¹⁵ Parameters including elimination half-life (T_{1/2}), elimination rate constant (K_{el}), AUC were estimated directly from the data using non-compartmental analysis. T_{1/2} was determined from the linear portions of the log plasma AUC curves. All the other parameters were derived.

The mean concentration at steady state (C_{ss}) was calculated from the following formulae: expected C_{ss} = AUC₀₋

Table 2A Intergroup comparison of busulphan pharmacokinetic parameters of doses 1 and 13

Parameter (units)	Dose 1			Dose 13		
	Group A, 16 mg/kg (mean \pm s.d.)	Group B, 600 mg/m ² (mean \pm s.d.)	P value	Group A, 16 mg/kg (mean \pm s.d.)	Group B, 600 mg/m ² (mean \pm s.d.)	P value
Age (years)	8 \pm 2.8	6.1 \pm 3	NS			
Number	11	12	NS			
Dose (mg/kg)	16	27.8 \pm 5.4				0.0092
Cmax	949 \pm 278	1579 \pm 400	0.0015	1147 \pm 355	1645 \pm 316	NS
Tmax	1.4 \pm 0.6	1.85 \pm 1.58	NS	1.5 \pm 1.0	1.1 \pm 0.57	0.006
AUC (ng*h/ml)	3167 \pm 878	6287 \pm 1194	0.0002	3485 \pm 1210	5083 \pm 1039	
(range)	(1971–4590)	(4888–8659)		(2244–6322)	(3859–6717)	
Cl/F (ml/min/kg)	5.66 \pm 1.688	4.15 \pm 1.06	0.037	5.24 \pm 1.5	5.11 \pm 1.04	NS
(range)	(3.6–8.5)	(2.66–6.03)		(2.67–7.41)	(3.4–6.58)	
Vd/F (l/kg)	0.94 \pm 0.3	0.79 \pm 0.2	NS	0.91 \pm 0.3	1.05 \pm 0.64	NS
T1/2 (h)	1.92 \pm 0.42	2.17 \pm 0.55	NS	2.14 \pm 0.9	2.29 \pm 1.1	NS
Kel	0.38 \pm 0.077	0.34 \pm 0.12	0.0815	0.37 \pm 0.1	0.35 \pm 0.12	NS
Css (ng/ml)	528 \pm 146	1048 \pm 199	0.0025	581 \pm 202	847 \pm 173	NS
MRV (ng/ml)	202 \pm 78	420 \pm 145	0.0012	***	***	***

AUC = area under the concentration curve (ng*h/ml); Cmax = maximum concentration (ng/ml); Tmax = time for maximum concentration (h); T1/2 = elimination half-life (h); Kel = elimination rate constant; Cl/F = clearance (ml/min/kg); Vd/F = volume of distribution (l/kg); Css = steady-state concentration (ng/ml); MRV = mean residual value (ng/ml); NS = not significant.

Table 2B Intra-group comparison of busulphan pharmacokinetic parameters of doses 1 and 13

	1st dose (mean \pm s.d.)	13th dose (mean \pm s.d.)	P value
<i>Group A (16 mg/kg)</i>			
Cmax	949 \pm 278	1147 \pm 355	NS
Tmax	1.4 \pm 0.6	1.1 \pm 0.57	NS
AUC (ng.h/ml)	3167 \pm 878	3485 \pm 1210	NS
Cl/F (ml/min/kg)	5.66 \pm 1.688	5.24 \pm 1.25	NS
Vd/F (l/kg)	0.94 \pm 0.3	0.91 \pm 0.3	NS
T1/2 (h)	1.92 \pm 0.42	2.14 \pm 0.9	NS
Kel (per h)	0.38 \pm 0.077	0.37 \pm 0.1	NS
Css (ng/ml)	528 \pm 146	581 \pm 202	NS
<i>Group B (600 mg/m²)</i>			
Cmax	1579 \pm 400	1645 \pm 316	NS
Tmax	1.85 \pm 1.58	1.1 \pm 0.57	NS
AUC (ng.h/ml)	6287 \pm 1194	5083 \pm 1039	0.03
Cl/F (ml/min/kg)	4.15 \pm 1.06	5.11 \pm 1.04	0.06
Vd/F (l/kg)	0.79 \pm 0.2	1.05 \pm 0.64	NS
T1/2 (h)	2.17 \pm 0.55	2.29 \pm 1.1	NS
Kel (per h)	0.34 \pm 0.12	0.35 \pm 0.12	NS
Css (ng/ml)	1048 \pm 199	847 \pm 173	0.05

Abbreviations as in Table 2A.

α of 1st dose/dosing interval, ie 6 h; observed Css = AUC_{0–6 h} of the 13th dose/dosing interval. Clearance (Cl/F) was calculated as the ratio of dose to AUC. Vd/F (in L/kg) was calculated as the ratio of Cl/F to Kel. Mean residual value (MRV) was calculated as the mean of all trough levels from dose 2 to dose 16. Maximum concentration (Cmax) was the peak value of busulphan after the first and 13th doses.

Analysis of outcome

Regimen-related toxicities were documented according to the grading system of Bearman *et al.*¹⁶ VOD was defined

by the presence of hepatomegaly, ascites and hyperbilirubinemia as previously described by Jones *et al.*¹⁷ and McDonald *et al.*¹⁸ Idiopathic interstitial pneumonia was diagnosed on the basis of clinical and radiological features after infectious agents were excluded.

Statistical analysis

Mean and standard deviations were calculated for all pharmacokinetic parameters. These parameters were compared by the Mann–Whitney *U* test and Wilcoxon rank sum test. The difference in busulphan AUC and Css values between those who developed VOD and those who did not was analyzed by the two-tailed Student's *t*-test. The differences in the incidence of VOD in the two groups were analyzed by Fisher's exact probability test.

Results

Patients and protocols

The patients' age, sex, body weight, body surface area (BSA), status at BMT, busulphan dose and the excess dose received by children in group B are given in Table 1. The mean age, weight, BSA and pre-BMT bilirubin, transaminases and serum ferritin in both these groups were comparable. A total of 39 curves from 23 patients was available for analysis, because sample collection was stopped in two patients after the 1st dose and started in four patients after the 1st dose. In one patient, after the 1st dose, the busulphan plasma concentration continued to increase until 6 h, and so it was not possible to calculate T1/2 and other kinetic parameters. Patients receiving the 600 mg/m² dose of busulphan, received a mean of 64% (range 56–71%) higher dose by weight as compared to the 16 mg group.

Table 3 Comparison of busulphan kinetic parameters in patients with and without VOD by Jones's criteria

Parameter	VOD (Jones) ¹⁷		No VOD		P value	
	1st dose	13th dose	1st dose	13th dose	1st dose	13th dose
Cmax ^a (mean ± s.d.)	960 ± 373	1442 ± 544	1009 ± 258	1066 ± 196	0.84	0.35
AUC ^a (mean ± s.d.)	3242 ± 316	4449 ± 2050	3736 ± 1128	3268 ± 619	0.16	0.42
Css ^a (mean ± s.d.)	540 ± 52	742 ± 342	623 ± 188	545 ± 103	0.16	0.42

^aAll values have been corrected to busulphan dose in mg/kg.

Table 4 Comparison of pharmacokinetic parameters of busulphan at 600 mg/m² with previous studies

Parameters	Vassal ⁷	Yeager ¹¹	Shaw ^{10a}	Present study
No. of patients	27	7	12	12
Dose	37.5 mg/m ² /dose	40 mg/m ² /dose	150 mg/m ² /day	37.5 mg/m ² /dose
Age (years)	2–14	1.1–5.7	5.5	2.5–12
Cmax (ng/ml)	1258		4953 ± 1114	1579
AUC (ng·h/ml)	6404 ± 2378	4530 ± 1918	29388 ± 8295	6287 ± 1194
(range)	(3566–13129)	(3280–8528)	—	(4888–8659)
Cl/F (ml/min/kg)	4.5 ± 1.4	—	3.44 ± 1.13	4.15 ± 1
Half life (h)	2.94	—	2.48 ± 0.5	2.17
Vd/F (l/kg)	1.04 ± 0.38	—	0.7 ± 0.10	0.79 ± 0.2

^aBusulphan administered as a single daily dose. In all the other studies, busulphan was administered in four divided doses every day.

Pharmacokinetic analysis

Pharmacokinetic parameters calculated by non-compartmental analysis are given in Tables 2A and B.

Intergroup variation: AUC, Cmax, Css and MRV of doses 1 and 13 were significantly higher in group B than in group A. Cl/F values, corrected to body weight, were significantly higher in group A than in group B after the 1st dose ($P = 0.037$) but not after the 13th dose. There was no significant difference in other parameters such as T1/2, Tmax, Kel and Vd/F between the two groups (Table 2A).

Intra- and inter-individual variations: Within group B, there was a significant decrease in AUC ($P = 0.037$) and a trend for significant increase in Cl/F values ($P = 0.06$) between dose 1 and 13. All other parameters showed no significant difference between doses. Expected and observed Css were not significantly different in group A but there was a significant decrease in observed Css of group B ($P = 0.05$) (Table 2B). Within the same group, there was a two- to 12-fold inter-individual variation in parameters such as Cl/F, Cmax, T1/2, AUC and MRV. Some patients who received 16 mg/kg busulphan achieved a Cmax similar to those seen in patients receiving the higher dose of 600 mg/m².

Busulphan toxicity

There was no correlation between busulphan AUC, Cmax and Css and the incidence of hepatic toxicity. Regimen-related hepatic toxicity as graded by the system of Bearman *et al*¹⁶ was as follows: group A: 8/11 (grade I – one, grade II – six and grade III – one); group B: 7/12 (grade II –

seven). Patients who developed VOD did not have a higher AUC as compared to those who did not have VOD (Table 3). In fact, the mean of first dose AUC was higher in those who did not develop VOD. Only three children, all of whom were in group A, had VOD according to Jones's criteria.¹⁷ By McDonald's criteria,¹⁸ 9/11 patients in group A and 7/12 patients in group B had VOD. However, these differences were not statistically significant. None of these patients had seizures or interstitial pneumonia.

Discussion

This is the first randomized prospective study comparing the pharmacokinetics of two different dosages of busulphan in a uniform group of patients – children with thalassaemia major. Although the evaluation of busulphan kinetics started with the development of a GC-MS method for its assay by Ehrsson *et al*¹⁹ in 1983, most clinical studies have involved heterogeneous patient populations. In 1997, Pawłowska *et al*¹³ reported the kinetics of busulphan in the dose range of 14–16 mg/kg and correlated it with the outcome of BMT in 64 children and young adults with thalassaemia major. However, the kinetics of a higher dose of 600 mg/m² has not been evaluated in a homogeneous population.

Earlier studies^{7,11} have reported that a higher dose of busulphan, based on body surface area, would be required in young children to produce systemic exposure similar to adults and overcome age-dependent variation in kinetics. This would provide a greater antitumour, myeloablative and immunosuppressive effect²⁰ than the usual 16 mg/kg dose. Our data show that by administering busulphan at 600 mg/m², patients received a 64% higher dose of busul-

phan than would have been the case had they received 16 mg/kg. This resulted in a much higher AUC in these patients ($P < 0.0002$) (Figure 1). In fact, children treated with the 600 mg/m² dose in our study achieved AUCs similar to those of adults treated with 16 mg/kg in another study²¹ (6287 ± 1194 vs 6520 ± 1845 , $P = 0.71$). Other busulphan kinetic parameters such as Cmax, Cl/F, Vd/F and T1/2 in children receiving the higher dose of busulphan in our study are similar to previous reports (Table 4).^{7,10,11} Shaw *et al*¹⁰ did not find any significant difference in busulphan Cl/F values between those given 16 mg/kg and 600 mg/m² in patients with malignant disorders receiving busulphan as a single daily dose. This difference may be attributed to the frequency of administration of busulphan. By a single daily dose, steady state can be attained at a faster rate and the steady-state trough plasma levels are lower than when the drug is administered once in 6 h.¹⁰ This results in a shorter T1/2 and Cl/F even though the AUC and Cmax values are five and three times higher, respectively, than we observed. Similar to the report of Shaw *et al*,¹⁰ we did not observe any significant difference in the other pharmacokinetic parameters including Vd/F, Kel, T1/2 and Tmax between the two groups, suggesting that these parameters are not dose dependent.

There are conflicting reports about the intraindividual variability in busulphan kinetics. Among patients receiving 16 mg/kg, there was a correlation between the expected (calculated from the extrapolated 1st dose AUC) and observed Css and AUC values ($r = 0.6$, $P < 0.01$), showing that there is no accumulation of the drug, and busulphan pharmacokinetics are linear in children with thalassaemia undergoing BMT. This observation was similar to recent studies in thalassaemic children¹² and in children with malignant disorders,²² in which kinetic analysis of first and last dose using AUC, Cmax and Cmin were comparable and showed no sign of accumulation or decline in busulphan plasma levels over time. Therefore, the AUC after the first dose can be a good predictor of AUC at steady state

for this dose of busulphan. Hassan *et al*²¹ have found a 25–50% lower trough concentration after the last dose than the 1st dose in infants and older children receiving 16 mg/kg. Other studies have also reported insignificant increases and decreases^{11,23} but there was no significant change in trough concentrations in our study.

Previous studies in children treated with 600 mg/m² busulphan did not show any significant intra-individual variability.^{7,10,11} Our data show that in children receiving 600 mg/m², there is a significant decrease in AUC, Css, and a significant increase in Cl/F of the 13th dose when compared to the 1st dose. Therefore, in these patients, 1st dose AUC may not be predictive of AUC at steady state. In studies on children with malignant disorders, Vassal *et al*⁷ and Yeager *et al*¹¹ have shown no alteration between 1st dose and steady-state AUCs, when busulphan dose was based on body surface area. It is difficult to explain this difference between these studies. The present study included only children with beta thalassaemia major. Influence of underlying disease process on busulphan kinetics has been reported earlier.^{9,24}

Wide inter-individual variations have been reported on the same dose of busulphan in various pharmacokinetic parameters. We observed two- to 12-fold inter-individual variations. Other studies in children^{10,12,24} have shown a six- to 20-fold variation in Cl/F, Vd/F and AUC. This suggests that individual variables such as busulphan bio-availability and metabolism affect plasma levels of the drug. The rate of metabolism of the absorbed drug could also vary, resulting in widely varying systemic exposure. Hassan *et al*,²¹ in their pharmacokinetic studies in children with malignant disorders, suggested that the wide inter-individual variation in busulphan kinetics may be attributed to the differences in the levels of glutathione or GST in the liver. However, this has not yet been documented in any study. If clear correlation can be established between busulphan pharmacokinetics and outcome of BMT, then these data emphasize the need for individual dose adjustment for

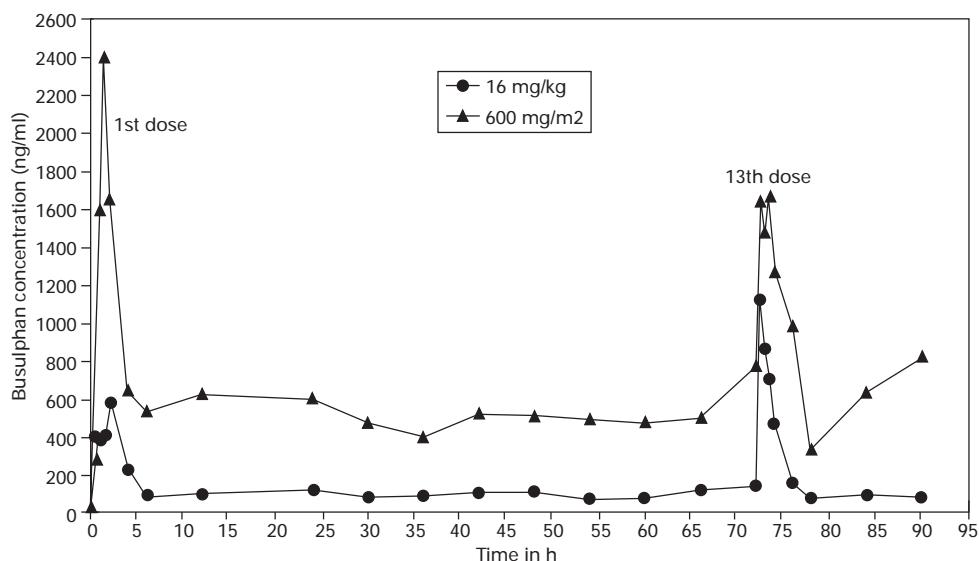


Figure 1 Representative busulphan concentration-time curve for a child receiving 16 mg/kg and another receiving 600 mg/m². The points between doses 1 and 13 are the trough levels before each dose.

patients undergoing BMT to reduce the effect of inter-individual variability and systemic exposure to busulphan.

Hepatic enzyme inducers such as phenytoin or phenobarbital, given as prophylaxis against seizures to patients receiving busulphan therapy for BMT have been shown to influence its kinetics.^{25,26} Hassan *et al*²¹ reported a decrease in plasma busulphan levels over time in about 40% of adults and children and postulated that busulphan may induce its own metabolism. Subsequently, they attributed this decrease to the concomitant administration of phenytoin.²⁶ In this study comparing busulphan at 16 mg/kg and 600 mg/m², both groups received phenytoin but only children receiving the higher dose of busulphan showed decreased AUC, Css and enhanced Cl/F of the drug at steady state. This could suggest that busulphan may induce its own metabolism at higher dosage by putatively switching on GST enzymes. However, the role of phenytoin in the occurrence of this dose-dependent alteration of busulphan pharmacokinetics between the 1st and 13th doses cannot be totally excluded.

Previous studies in children with malignant disorders^{9,27} have shown that by giving a dose of 600 mg/m², there was an increased incidence of hepatic VOD.²⁸ In this study, no significant difference in the incidence of VOD between children receiving 16 mg/kg and 600 mg/m² was noted. There was no correlation between the busulphan AUC, Css and Cmax with the occurrence of VOD. In fact, the 1st dose AUC values are higher in those who did not develop VOD. However, since the numbers of patients evaluated in each group in our study are small, this observation needs to be carefully interpreted. Our results are similar to a previous study in thalassaemic children receiving standard 16 mg/kg dose of busulphan where there was no association between AUC and the incidence of VOD and other toxicities associated with busulphan conditioning.¹³ None of these patients developed seizures or interstitial pneumonia.

We conclude that much higher systemic exposure to busulphan is achieved by children with thalassaemia major who receive 600 mg/m² of the drug compared with those receiving 16 mg/kg as shown by the high Cmax, AUC, MRV and Css. It is well tolerated by these patients, as evidenced by no increase in regimen-related toxicity. The two- to 12-fold inter-individual variations in pharmacokinetics and the differences in clearance values among the two groups may be due to variations in busulphan bio-availability or the levels of GST in the liver. This is presently being evaluated in these patients. Whether this increase in systemic exposure to busulphan in children receiving the 600 mg/m² dose will result in reduced rejection and relapse of thalassaemia will be apparent when this ongoing study is completed and adequate follow-up data are available on larger numbers of patients. Therapeutic drug monitoring and individual dose adjustment of busulphan might reduce this inter-individual variation and improve transplant outcome.

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