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ORIGINAL ARTICLE

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Population pharmacokinetics of oral busulfan in children

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Abstract *Purpose*: To characterize the population pharmacokinetics of oral busulfan in 48 children including pooled data from three transplantation centres with the aim of estimating the variability in the kinetics of busulfan and to identify covariates that could be used for dose calculation. *Methods*: A total of 508 plasma samples from 250 administrations (mean 9 samples per patient over 4 days of treatment) were collected from 48 children receiving busulfan orally every 6 h. The dosing varied between 13 and 20 mg/kg with seven patients receiving a dose of 600 mg/m^2. The busulfan formulations administered varied considerably. They included 2-mg tablets (Myleran), gelatine capsules, crushed tablets suspended in water and suspension for administration via nasogastric tube. Samples were analysed for busulfan either by HPLC using postcolumn photolysis or by LC-MS. Plasma concentration-time data were analysed by population pharmacokinetic modelling using NONMEM. *Results*: Busulfan kinetics were best described by a one-compartment model (subroutine ADVAN 2 TRANS 2). Residual variability was modelled using a combined additive and proportional error model. The influence of different covariates on the pharmacokinetic parameters was tested. The best results were obtained by inclusion of body surface area (BSA) as a covariate for clearance (Cl/F) and volume of distribution (V/F). The final population estimates were: Cl/F 4.13 l/h per m^2 ±26%, V/F 21.3 l/m^2 ±31% and ka 1.31 h^{-1} ±110% (population mean ± interindividual variability, IIV). Variability in one patient during the 4 days of treatment (interoccasion variability, IOV) for Cl/F (10%) and V/F (19%) were calculated to be less than interindividual variability, fulfilling the condition for individualization of busulfan dosage regimens. *Conclusions*: In our paediatric population, BSA, not body weight, is the best predictor of Cl/F and V/F. Our final estimations reflect the wide interpatient variability after oral administration of busulfan with an IIV for ka of 110%.

Keywords Busulfan · Haematopoietic stem cell transplantation · Population pharmacokinetics · NONMEM · Paediatrics

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Introduction

Busulfan, an alkylating agent, is an important part of many high-dose conditioning regimens before haematopoietic stem cell transplantation (HSCT) for

haematological malignancies in adults and children [10, 11, 24, 31, 32] and for certain genetic diseases [9, 21, 26]. It is always combined with one or two other drugs such as cyclophosphamide, melphalan, thiotepa and fludarabine. In most cases, busulfan is administered every 6 h over four consecutive days with a total standard dose of 16 mg/kg as defined by Santos et al. [30].

As have most alkylating agents, busulfan has a narrow therapeutic window. The dose-limiting toxicity of busulfan in HSCT regimens is hepatic veno-occlusive disease (VOD), a liver toxicity with an incidence varying from 0 in children with a genetic disease [7] up to 50% in adults with haematological malignancies [19, 22]. Children show a high inter- and intrapatient variability in the pharmacokinetic parameters of oral busulfan. Busulfan is extensively biotransformed in the liver. Conjugation of busulfan with glutathione, the major route of biotransformation, is predominantly catalysed by the isoenzyme glutathione S-transferase A1 (GSTA1). First results have shown that GSTA1 polymorphisms are not likely to be related to VOD because they do not appear to be associated with changes in GSTA expression or function [4]. Despite the fact that busulfan is mainly metabolized by GSTA1 it has been shown that drugs metabolized by the cytochrome P-450 system of the liver may alter the kinetics of busulfan. In adults, busulfan dose adjustment can decrease the morbidity and mortality due to liver toxicity (VOD). An area under curve (AUC) of < 1500 $\mu M \cdot$min (6160 μg/l·h) in adults is correlated with a low incidence of VOD [13]. So far, studies in children have failed to establish a toxic level or a therapeutic window of systemic exposure (measured as AUC).

It has been reported that after administering the standard dose of 16 mg/kg, busulfan clearance and volume of distribution are significantly higher in young patients than in adults or in older children [15, 16]. Consequently, as the systemic exposure (AUC) is two to four times lower in children than in adults [33], a higher dosage for children, normalized to body surface area (BSA), was suggested. In fact, several studies have shown that a dosage of 480 or 600 mg/m^2 in children is able to overcome the low systemic exposure compared to adults [33, 35]. However, even with a dose based on BSA, there is still a high intersubject variability in the systemic exposure in children with a coefficient of variation (CV) of 37% [33]. Apart from age, other factors contributing to the wide intra- and interpatient variability of busulfan disposition are the variability in drug absorption [13, 33], disease status [12, 34], circadian rhythmicity [16], drug interactions (anticonvulsive drugs) [5, 8, 17, 18, 29] and hepatic function [13, 16]. Recent studies have shown a correlation between hepatic GST activity and busulfan clearance and plasma levels [27].

The objective of this study was to characterize the population pharmacokinetics of oral busulfan in a large paediatric population with the aim of identifying patient-specific factors contributing to the variability in busulfan pharmacokinetics and to identify covariates which could be used for dose calculation. Furthermore, interoccasion variability (IOV), i.e. intraindividual variations of the pharmacokinetic parameters during the 4 days of treatment, needed to be quantified.

Table 1 Patient demographics

	Mean (CV)	Median	Range
Age (years)	9.9 (48%)	10.4	0.4–18.1
Weight (kg)	37 (52%)	34	5.49–80
BSA (m^2)	1.2 (38%)	1.15	0.29–2
Height (cm)	137 (24%)	144	56–185
Dose (mg)	37.9 (49%)	40	5–80

Materials and methods

Patients

A total of 48 children (32 male, 16 female) from three hospitals receiving high-dose conditioning therapy before HSCT between December 1997 and July 2001 were enrolled in this retrospective pharmacokinetic analysis. The patient demographics are given in Table 1. The children were treated for acute myelogenous leukaemia (21 patients), Ewing sarcoma (8 patients), myelodysplastic syndrome (5 patients), chronic myelogenous leukaemia (4 patients), acute lymphocytic leukaemia (3 patients) and non-malignant disorders (7 patients) with high-dose busulfan in combination with one or two other chemotherapeutic agents (cyclophosphamide, melphalan, thiotepa, etoposide, fludarabine). Except for one patient, busulfan was the first drug administered according to the protocol. To prevent busulfan-induced seizures, the children received short-term infusions of clonazepam or phenobarbital starting the day before the first busulfan therapy. Thus, 28 children received clonazepam (0.09 mg/kg per day) and the remainder were treated with phenobarbital (5 mg/kg per day). Because of the retrospective character of this analysis, we had no information about the liver status or the remission status prior to transplantation of the patients. The patients and/or their parents gave informed consent to the blood sampling.

Drug administration and dosage forms

Busulfan was given orally four times daily every 6 h over 4 days for a total of 16 doses. Of the 48 patients, 35 received a total dose of 16 mg/kg, 1 a total dose of 13 mg/kg, 3 a total dose of 18 mg/kg, 2 a total dose of 20 mg/kg and 7 a total dose of 600 mg/m^2. The administered formulations of busulfan varied considerably and included: (1) 2-mg tablets (Myleran) (13 patients); (2) gelatine capsules (27 patients); (3) a combination of tablets and gelatine capsules (2 patients); (4) crushed tablets suspended in water (4 patients); and (5) suspensions for administration via nasogastric tube (2 patients). Myleran (2-mg tablets) is the only licensed formulation of oral busulfan; the other formulations were prepared by the pharmacies on individual request.

Blood sampling and busulfan assays

Overall, a total of 508 plasma samples from 250 administrations in three hospitals with one to eight samples per administration were collected and analysed (mean 9 samples per patient over 4 days of treatment). Heparinized blood samples were drawn, and plasma was isolated and stored at −20°C until analysis. All samples were collected during the day. Because of the retrospective character of

this pharmacokinetic investigation and the intention to reflect clinical reality, no standardized blood sampling scheme was applied. In hospital 1, one plasma sample per administration was drawn (giving trough levels 1 h before the next busulfan dose) resulting in a sparse dataset. In hospitals 2 and 3, up to eight plasma samples per administration (within 0 to 6 h) were drawn. Samples were analysed for busulfan either by a validated LC-MS method (assays 1 and 2) or by a modified validated HPLC-UV method based on a method reported by Blanz et al. [1] (assay 3). Table 2 summarizes the number of samples per patient and per hospital and the busulfan assays used.

In assay 1, busulfan concentrations were quantified with a new LC-MS assay requiring only 200 µl plasma and using d_8-busulfan as internal standard [23]. After liquid-liquid extraction with diethyl ether, busulfan and d_8-busulfan were detected as ammonium adducts in selected-ion monitoring mode. Apart from the small plasma volume, the absence of a derivatization step and the low limit of quantification (5 µg/l) are further advantages of this method. Linearity was shown over a concentration range of 5–2000 µg/l. Assay 2 was a validated LC-MS method comparable with assay 1 (unpublished data). The limit of quantification for this assay was 20 µg/l, and linearity was shown over the range of 20–2000 µg/l.

In assay 3, busulfan plasma levels were measured with a new modified HPLC method based on a precolumn derivatization of busulfan to 1,4-diiodobutane, followed by a postcolumn photochemical dissociation of iodide anions for UV detection (226 nm). The quantification in assay 3 was performed using an internal standard. The limit of quantification for this assay was 50 µg/l, and linearity was shown over the range of 50–10,000 µg/l. The intra- and interassay imprecision (coefficient of variation) was $< 15\%$ for all assays.

NONMEM analysis

The data analysis was performed using NONMEM version V using the first-order conditional estimate method [3]. Examination of the minimum value of objective function (OF) on each NONMEM run supported the combined additive and proportional error model as being the best for residual variability. To determine differences between the three hospitals, the residual variability was modelled dependent on each hospital.

The influences of the following covariates were investigated consecutively: age, weight, height, hospital, gender, BSA, body mass index (BMI) and anticonvulsive prophylaxis (phenobarbital or clonazepam). The other chemotherapeutic agents administered in combination with busulfan were not tested as covariables because busulfan was always the first drug administered according to the protocols (except for one patient). IOV, i.e. variability of the pharmacokinetic parameters in a patient from one day of busulfan treatment to another day of treatment, was introduced into the model as proposed by Karlsson et al. [20].

To select the final model, the change in the OF as a goodness-of-fit parameter was used, values before and after adding a covariate to the model were compared. A decrease in the OF of more than 3.84 or 6.63 (log likelihood ratio test) was considered as a significant improvement to the model ($P < 0.05$ or $P < 0.01$). In addition, improvement in the fit of the data was determined by the precision of the parameter estimates (standard errors) and by a visual inspection of plots of data against the population model and the individual predictions as well as plots of the data against the weighted residuals.

Statistical analysis

All statistical analyses were performed using SigmaStat 2.03 (SPSS, Erkrath, Germany) with parameters being log-transformed before analysis. The correlations between Cl/F (corrected for BSA), V/F (corrected for BSA), ka and age were examined using linear regression. The values of Cl/F corrected for BSA of patients treated in hospitals 1 and 3 and patients treated in hospital 2 were compared using the unpaired *t*-test. To examine the potential enzyme-inducing effects of phenobarbital and clonazepam during the 4 days of treatment, the values for Cl/F corrected for BSA on day 1 and day 4 were compared by the paired *t*-test.

Results

A one-compartment model described the data sufficiently. The pharmacokinetic parameters estimated were apparent clearance (Cl/F), apparent volume of distribution (V/F) and absorption rate (ka). Interindividual variability was assessed in an exponential manner for each of them. The area under the curve (AUC) was calculated for all patients for each day of treatment according to the formula AUC = dose/apparent clearance. Figure 1 shows the measured plasma concentrations and the model for a representative patient.

Among the tested covariates, the strongest correlations were seen between BSA and V/F and Cl/F, which were slightly stronger than the correlations between body weight and V/F and Cl/F, respectively. The best method to include BSA in the model was found to be according to the formulas:

$$Cl/F_{pop} = Cl/F_{ind} \times BSA \quad (1)$$

$$V/F_{pop} = V/F_{ind} \times BSA \quad (2)$$

where Cl/F_{pop} and V/F_{pop} are the mean population estimates and Cl/F_{ind} and V/F_{ind} are the individual parameter estimates. The other covariates were tested in the same manner. Other models, such as additive or exponential models, gave unstable or inconclusive

Table 2 Number of samples per patient and per hospital, busulfan assays and anticonvulsive prophylaxis

Hospital	No. of patients	Busulfan assay	No. of samples		
			Total	Per patient per administration	Per patient (mean over 4 days)
University of Jena (1)	13[a]	LC-MS (assay 1)	52	1	4
University of Tuebingen (2)	20[b]	LC-MS (assay 2)	349	1–8	17
University of Muenster (3)	15[a]	HPLC-UV (assay 3)	107	1–5	7

[a]Patients received clonazepam (0.09 mg/kg/d) as anticonvulsive prophylaxis
[b]Patients received phenobarbital (5 mg/kg/d) as anticonvulsive prophylaxis

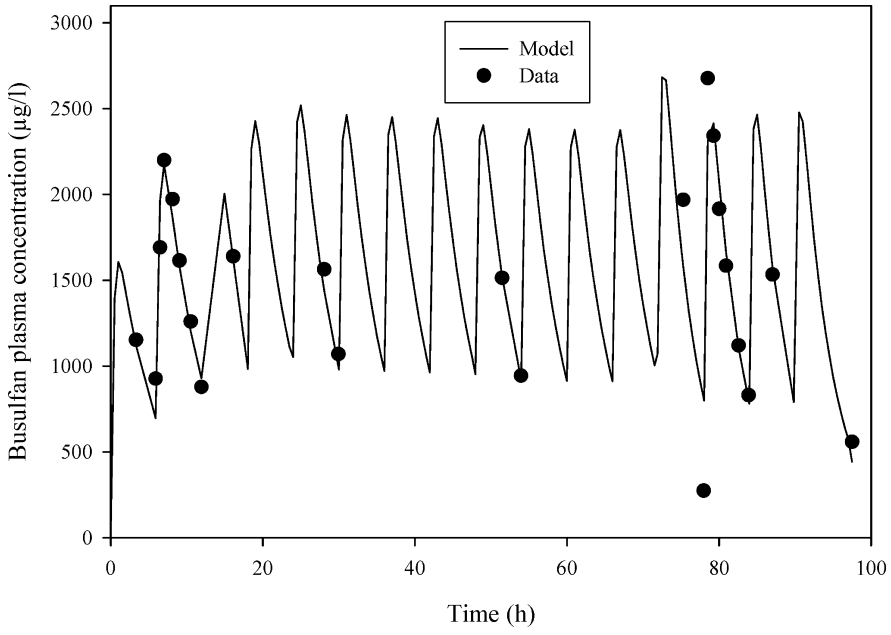

Fig. 1 Measured plasma concentrations (*Data*) vs individual model predictions (*Model*) of the final population model for one representative patient (ID 1)

Table 3 Population model development (*BSA* body surface area, *OF* objective function, *IOV* interoccasion variability, *IIV* interindividual variability)

Run	Description/ covariates	IOV	OF	Cl/F (l/h)[a]	IIV Cl/F (%)	V/F (l)[a]	IIV V/F (%)	ka (h^{-1})	IIV ka (%)	Residual error	
										Additive (µg/l)	Proportional (%)
129	Weight on Cl/F + V/F	–	6424	0.14	24	0.71	28	1.17	105	173	24.5
130	Age on Cl/F + V/F	–	6495	0.54	36	2.30	33	0.93	111	227	20.1
131	Length on Cl/F + V/F	–	6456	0.03	35	0.16	35	1.19	110	197	21.5
126	BSA on Cl/F + V/F	–	6412	4.03	25	21.40	30	1.24	106	161	24.5
128	BSA on Cl/F + V/F	Cl/F 10%, V/F 20%	6400	4.04	25	22.00	27	1.30	107	148	23
Final	BSA on Cl/F + V/F (hospital in error model)	Cl/F 10%, V/F 20%	6381	4.13	26	21.30	31	1.31	110	123[b], 192[c]	14.9[b], 23[c]

[a]If covariates are included, units are divided by the respective covariate
[b]Residual error for hospitals 1 and 3
[c]Residual error for hospital 2

results (data not shown). Inclusion of the hospital or the applied anticonvulsive prophylaxis in the model did not improve the fit. In addition, neither the introduction of IOV on ka nor the introduction of a lag time resulted in further improvement in the model.

The most important steps of model development are listed in Table 3. The best results were obtained by inclusion of BSA as a covariate on Cl/F and V/F and by introduction of IOV on Cl/F and V/F. Regarding IOV, each day of busulfan treatment was defined as one occasion. The IOV for Cl/F (10%) was calculated to be smaller than the IOV for V/F (19%).

The final parameter estimates are given in Table 4 and the individual estimates are summarized in Table 5. Figure 2 shows a goodness-of-fit plot of the model (observed concentrations versus individual model-predicted concentrations). In addition, the deviations (weighted residuals) from the data measured were evenly distributed over the whole concentration range (data not shown).

Residual variability was most appropriately modelled as a combined additive and proportional error model making a distinction between the three hospitals. As a result, the residual variability was determined to be

Table 4 Final parameter estimates. Values in parentheses are relative standard errors (in percent) of the estimates

	Estimate	IIV %	IOV %
Cl/F (l/h/m^2)	4.13 (5)	26 (27)	10 (37)
V/F (l/m^2)	21.3 (10)	31 (44)	19 (18)
ka (h^{-1})	1.31 (22)	110 (31)	–
Residual error			
Additive (μg/l)	123[a]/192[b] (21)	–	–
Proportional (%)	15[a]/23[b] (19)	–	–

[a]Errors represent additive/proportional errors for patients from hospitals 1 and 3
[b]Errors represent additive/proportional errors for patients from hospital 2

Table 5 Individual parameter estimates of all patients (*AUC* area under the curve, *Cl/F* individual model predicted clearance corrected for bioavailability, *V/F* individual model predicted volume of distribution corrected for bioavailability, *ka* absorption rate, *CV* coefficient of variation)

	Mean (CV%)	Median	Range
Cl/F (l/h/m^2)	4.18 (25)	4.18	2.53–7.73
Cl/F (ml/min/kg)	2.42 (32)	2.28	1.42–5.46
V/F (l/m^2)	21.07 (21)	20.92	11.41–38.93
V/F (l/kg)	0.73 (30)	0.69	0.38–1.62
Ka (h^{-1})	1.59 (105)	1.32	0.18–10.92
AUC (μ*M*·min)[a]	1893 (24)	1865	559–2901

[a]AUC values after total busulfan doses of 13 mg/kg (1 patient), 16 mg/kg (35 patients), 18 mg/kg (3 patients), 20 mg/kg (2 patients) or 600 mg/m^2 (7 patients)

smaller in patients from hospitals 1 and 3 than in patients from hospital 2. The additive errors were predicted to be 123 μg/l for plasma samples from hospitals 1 and 3 and 192 μg/l for plasma samples from hospital 2. The corresponding proportional errors were estimated to be 14.9% for plasma samples from hospitals 1 and 3 and 23% for plasma samples from hospital 2. According to the applied combined error model, at higher concentrations, the proportional error component would dominate, at lower concentrations (e.g. near to the limit of quantification of the assay), the additive error component would dominate.

To examine a possible age-dependency of the pharmacokinetic parameters Cl/F, V/F and ka in our population, Cl/F and V/F were normalized to BSA. Figure 3 shows Cl/F in relation to age. There was no correlation between Cl/F (corrected for BSA) and age ($r = 0.0243$) or between V/F (corrected for BSA) and age ($r = 0.0295$, data not shown). In addition, there was no correlation between ka and age ($r = 0.0056$, data not shown).

Phenobarbital and clonazepam are known to be inducers of the cytochrome P-450 system of the liver. Clonazepam is also known to be an inhibitor of these enzymes [8, 25]. To examine the role of phenobarbital and clonazepam as potential inducers of liver enzymes, the values for Cl/F corrected for BSA on day 1 and day 4 were compared using the paired *t*-test. There was no statistically significant difference in the values for Cl/F between day 1 and day 4 in the patient group treated with phenobarbital ($P = 0.157$) or in the patient group receiving clonazepam ($P = 0.974$).

Furthermore, we compared the Cl/F corrected for BSA of the patient groups during the 4 days of treatment (Fig. 4). The values of Cl/F corrected for BSA during the 4 days of treatment were found to be 24% lower in patients treated in hospital 2 than in patients treated in hospitals 1 and 3, with the difference being statistically significant ($P < 0.001$). Finally, the pharmacokinetic parameters of the patients with different diagnoses were compared, but we found no effect of the different diagnoses.

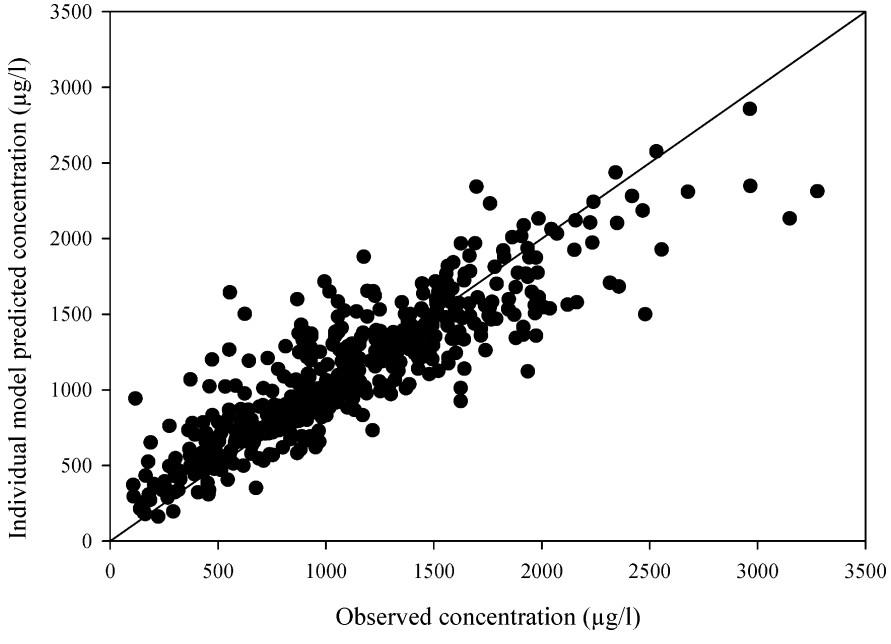

Fig. 2 Goodness-of-fit plot for the final model

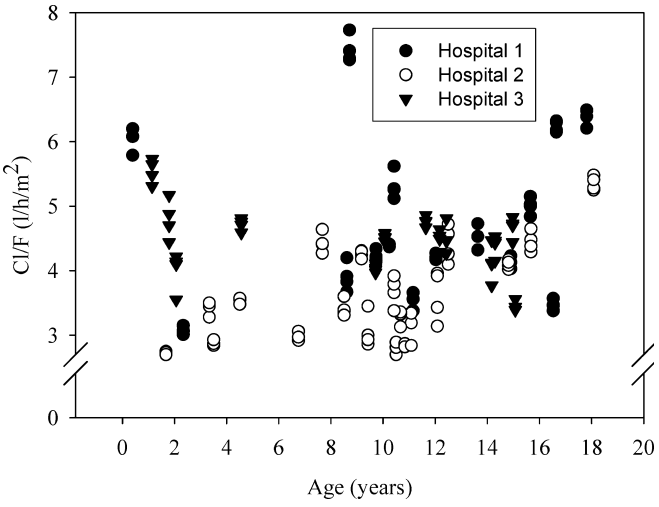

Fig. 3 Plot of age vs apparent oral clearance (Cl/F) (expressed relative to BSA, different symbols display the origin of the individual clearance values)

Discussion

To our knowledge, this is the largest investigation in which population pharmacokinetic modelling of oral busulfan has been applied to children. The population pharmacokinetics in our paediatric population were adequately characterized by a one-compartment model.

The mean individual estimates in our population were 2.42 ml/min per kg for Cl/F, 0.73 l/kg for V/F and 1.59 h^{-1} for ka. Our findings for V/F are in good agreement with estimates previously reported for oral busulfan (0.73–1.6 l/kg) [31, 34] and intravenous busulfan (0.85 l/kg) in children [6]. Our estimated mean value of ka is comparable with mean values reported from oral busulfan in adults (1.02–1.97 h^{-1}) but smaller than previous estimates in children (2.47–4.99 h^{-1}) [14, 28]. Regarding Cl/F in our population, our mean estimate of 2.42 ml/min per kg seems to be smaller compared to the findings of recent studies in children (3.6–8.4 ml/min per kg) [15, 31]. The systemic exposure (measured as AUC) in our population after different total doses of busulfan varied from 559 to 2901 $\mu M \cdot$min with a CV of 24%. This is comparable with data from children after administration of 600 mg/m^2 [33] and 16 mg/kg [15].

The pharmacokinetic evaluation in our population did not confirm the often-described age-dependency of oral busulfan pharmacokinetics in Cl/F, V/F or ka. For example, Hassan et al. have reported a significantly higher clearance in young children (<5 years) as compared to older children or adults [16]. One possible explanation for this discrepancy is perhaps the small number of young patients in our population (11 patients <5 years, 9 patients <4 years, 6 patients <3 years). Another influencing factor could be a possible variation in GST activity in children. For example, Poonkuzhali et al. have found that plasma GST levels are five to ten times higher in children (2–15 years) with thalassaemia than in age-matched leukaemic patients [27]. This was explained by increasing GST levels when there was acute or chronic liver damage or by elevated expression of the enzyme per se, or both. Therefore, other factors than age seem to play an important role in busulfan clearance.

Our final population parameter estimates are in good agreement with reports describing high interpatient variability in children after oral administration of busulfan with an IIV of 26% for Cl/F, 31% for V/F and 110% for ka. Sources of variability may be related to the different administration formulations of the drug (tablet, gelatine capsule, crushed tablet), administration technique (nasogastric vs oral, administration of crushed vs intact tablets, administration in gelatine capsules), age, differences in bioavailability and hepatic metabolism. Our findings for the IOV of Cl/F (10%) and V/F (19%) are in good agreement with the results

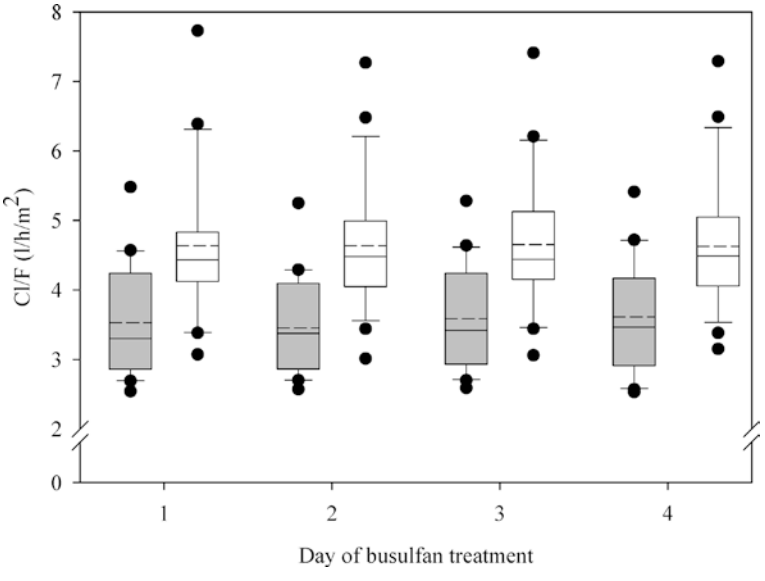

Fig. 4 Comparison of Cl/F (normalized to BSA) of patients from hospital 2 (*grey boxes*) with patients from hospital 1 and 3 (*white boxes*) between the 4 days of treatment (as boxplots). The *solid line* within each box marks the median; the *dotted line* marks the mean. The boundary of the box closest to zero indicates the 25th percentile, and the boundary of the box farthest from zero indicates the 75th percentile. The 10th and 90th percentile are indicated by the whiskers above and below each box. The circles represent outliers

of another population pharmacokinetic study of oral busulfan in children [28]. The IOV for Cl/F and V/F was estimated to be smaller than the IIV (10% vs 26% for Cl/F and 19% vs 31% for V/F), fulfilling the condition for individualization of busulfan dosage regimens (TDM).

With regard to possible drug interactions, it is important to know that busulfan is mainly metabolized in the liver through conjugation to reduced glutathione. Interactions of busulfan with other drugs are not well documented. In mice, Fitzsimmons et al. have shown that induction of the cytochrome P-450 system of the liver by phenobarbital results in reduced myelotoxicity of high-dose busulfan. This might occur due to enhanced liver metabolism of busulfan and a higher busulfan clearance [8]. Regarding the clinical use of busulfan, some authors have recommended anticonvulsants such as benzodiazepines with fewer enzyme-inducing properties for adequate antiseizure prophylaxis during oral busulfan treatment [17]. We found no statistically significant difference in Cl/F between day 1 and day 4 of treatment in patients treated with phenobarbital or in patients treated with clonazepam. This indicates that there was no enzyme-inducing or -inhibiting effect of phenobarbital or the benzodiazepine clonazepam in our population during the 4 days of treatment which would have resulted in a higher or lower apparent clearance of busulfan on day 4 compared with day 1.

The observation regarding clonazepam (which is an analogue of diazepam) is in good agreement with the finding of Hassan et al. who showed that diazepam does not induce busulfan clearance over 4 days of treatment [17]. Interestingly, during the 4 days of treatment, we found a 24% lower apparent clearance in patients from hospital 2 (receiving phenobarbital) compared to those treated in hospitals 1 and 3 (receiving clonazepam). We conclude from this that (1) induction of busulfan hepatic metabolism by phenobarbital or clonazepam did not occur in our population, and (2) hospital-specific factors, e.g. different hydration and/or different (pre)analytical conditions may play an important role in explaining the differences in apparent busulfan clearance between the patient groups.

In our final model, we found a high residual variability in busulfan kinetics varying between the hospitals. The additive errors were estimated to be 123 μg/l for plasma samples from hospitals 1 and 3 and 192 μg/l for plasma samples from hospital 2. The corresponding proportional errors were 15% and 23%, respectively. Initially, we expected differences to be mainly due to different assay errors and were surprised that the error with the LC-MS assay 2 was higher than with the LC-MS assay 1 and the HPLC assay 3 using postcolumn photolysis with derivatization. It is important to consider that residual variability also includes errors in recording sampling times, different ways of handling the blood samples (i.e. preanalytical conditions), and many other sources of variability between hospitals. For example, a standardized blood sampling scheme did not exist because of the retrospective character of this pharmacokinetic evaluation. In our opinion, these different preanalytical conditions seem to play a more important role in explaining the differences in residual intrapatient variability between the hospitals than the different analytical methods.

In summary, our finding that BSA is the best predictor of Cl/F and V/F confirms that busulfan dosing in children according to BSA is preferable over dosing according to body weight as proposed in recent studies. In our population, induction of busulfan hepatic metabolism by phenobarbital or clonazepam was not observed. Our population-based pharmacokinetic model confirms the high intra- and interpatient variability of oral busulfan in children. In addition, the age-dependency of busulfan kinetics was not confirmed. Possibly, the new intravenous formulations of busulfan may be able to overcome the unpredictable absorption of oral busulfan. Furthermore, it is a standardized and licensed application formulation that replaces the varying and non-standardized oral administration formulations in children. Dose individualization based on a test dose and Bayesian pharmacokinetic individualization of busulfan dosage regimens done by Bleyzac et al. [2] is another possible way to reduce the variability in systemic exposure to oral busulfan. As a result of cooperation between three German hospitals, we created a large set of oral busulfan data from 48 paediatric patients which could be the basis for further evaluations of oral busulfan kinetics and the basis for comparison with data from the use of new intravenous formulations in children.

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