INTRODUCTION

Busulfan is a bi-functional alkylating agent commonly used in preparative regimens prior to hematopoietic stem cell transplantation for treatment of various malignancies and inherited disorders. In hematopoietic stem cell transplantation, outcome at a fixed mg/kg dose has been related to area under the plasma concentration-time plot (AUC) and average steady-state concentration (C_{SS}). Excessively high busulfan AUC or C_{SS} is associated with an increase in hepatic veno-occlusive disease, low levels are associated with a higher relapse rate in patients with CML, and lower levels are associated with graft rejection in allogeneic transplantation.[1-4] Both AUC and C_{SS} are inversely proportional to CL/F, and are directly proportional to dose.

In many instances, busulfan is administered orally on a fixed mg/kg basis without dosage adjustment to achieve target busulfan plasma concentrations. The practice of normalizing doses to body size diminishes variability in clearance among patients.[5] However, the problem faced in dosing obese patients is choosing the appropriate measure of body size to apply to both dose and CL/F, as total body weight is intuitively questioned. Previously, we found that among the commonly used body size parameters (*i.e.*, BW, IBW, AIBW, and BSA), expressing busulfan CL/F relative to BSA produced the lowest coefficient of variation in 42 children and adults[3], although AIBW performed nearly as well. The body size measure that produces the minimum variability in CL/F is the most appropriate for the calculation of dose as it will minimize variability in the resultant AUC or C_{SS} in comparison to alternative measures of body size.

Disease has also been linked to alterations in busulfan pharmacokinetics. Previous studies have shown that the disposition of busulfan is altered in children with inherited disorders. Children with lysosomal storage diseases have been reported to have longer elimination half-lifes, and a trend towards higher CL/F compared to children with immune deficiencies, acute leukemias, and malignant lymphohistiocytosis.[6] Children with inherited genetic disorders have been reported to have enhanced elimination half-lifes after the first dose of busulfan and elevated busulfan CL/F compared to children with leukemias[7], although patient numbers were small.

The only known pathway for the elimination of busulfan involves glutathione (GSH) conjugation. Busulfan is uncommon in this respect, as there are few other drugs that are primarily eliminated by GSH conjugation. We have found that human cytosolic GST catalyzes THT⁺ formation[8], and that GSTA1-1, the major liver GST, is the predominant GST isoform in busulfan conjugation.[9] Less than 2% of an oral busulfan dose is excreted unchanged.[10] The effect of obesity on GSTA1-1 activity is unstudied.

The purpose of this report is to compare busulfan CL/F in obese and normal patients treated for various diseases to provide a pharmacokinetic rationale for the appropriate dosing of busulfan, and to gain insight on the activity of GSTA1-1 in obesity and disease. We used a base of 279 adult and adolescent patients undergoing hematopoietic stem cell transplantation at the Fred Hutchinson Cancer Research Center between January, 1992 and December, 1996, in whom busulfan CL/F had been measured on at least two occasions during conditioning for hematopoietic stem cell transplantation.

METHODS

Patients. Records collected as part of routine clinical busulfan monitoring between January, 1992 and December, 1996 at the Fred Hutchinson Cancer Research Center were examined retrospectively. All patients with complete information (consisting of age, dose, disease, height, weight, dose 5 CL/F, and dose 9 CL/F) were included in the analysis, and individuals less than 12 years (due to age-dependence in busulfan CL/F[3,11]) or greater than 60 years were excluded. The final database contained 279 patients who received 0.44-1.8 mg/kg oral busulfan tablets every 6 hrs for 4 days as part of their transplant preparative regimen. No other cytotoxic agents or irradiation was given immediately before or concomitantly with busulfan. Patients received a phenytoin for seizure prophylaxis. The diseases treated included acute myelogenous leukemia (AML; n = 60), breast cancer (BrCa; n = 55), chronic myelogenous leukemia (CML; n = 73), myelodysplastic syndrome (n = 49), multiple myeloma (MM; n = 25), non-Hodgkin's lymphoma (n = 10), and ovarian cancer (n = 7).

Determination of CL/F. Blood samples were collected just before and 60, 120, 240, and 360 min after the administration of busulfan. Plasma busulfan concentrations were determined by gas chromatography with mass selective detection, and mean CL/F was calculated for the 5th and 9th doses of busulfan as previously described.[3] Body size estimates were calculated using the following equations in which height is measured in cm and weight in kg.

$$\mathrm{BSA}\ (\mathrm{m}^2) = \sqrt{\frac{\mathrm{height} \times \mathrm{BW}}{3600}}$$

$$\mathrm{IBW}\ (\mathrm{kg;\ men}) = 50 + 0.91 \times (\mathrm{height} - 152)$$

$$\mathrm{IBW}\ (\mathrm{kg;\ women}) = 45 + 0.91 \times (\mathrm{height} - 152)$$

$$\mathrm{AIBW}\ (\mathrm{kg}) = \mathrm{IBW} + 0.25 \times (\mathrm{BW} - \mathrm{IBW})$$

$$\text{BMI} = \frac{\text{BW}}{(\text{height} \times 10^{-2})^2}$$

Patients were classified by BMI: underweight, BMI < 18 kg/m^2; normal, BMI 18-26.9 kg/m^2; obese, BMI 27-35 kg/m^2, and severely obese, BMI > 35 kg/m^2. BMI and the percentage of BW relative to IBW are correlated (BMI = 0.2 (%IBW) + 2.10, $r^2 = 0.907$), such that a BMI of 27 corresponds to 125% BW/IBW.

Statistical analysis. All statistical comparisons were performed using SPSS version 7.5 (Chicago, IL). In univariable linear regression analysis, the relationship between CL/F (mL/min) and each of the following individual patient variables was assessed: age, AIBW, BMI, BSA, height, IBW, gender, disease, and BW. Multiple stepwise linear regression analysis was performed with absolute CL/F as the dependent variable. A single variable describing body size (*i.e.*, BW, AIBW, BSA, or IBW) entered the model on the first step. BMI entered the model as the second step. In the third step, patient variables (*i.e.*, age, gender, and height) were incorporated. In the fourth step, disease was incorporated. Steps one and two were then reversed, and the analysis was repeated. One-way ANOVA was used to compare differences in body size-normalized CL/F among different disease categories with the Bonferroni correction for multiple comparisons. The Levene statistic was used to test for homogeneity of variance. Log transformation was used to normalize the distribution of a variable not conforming to a Gaussian distribution.

RESULTS

Busulfan CL/F is listed in Table I for patients in 4 BMI categories: underweight, normal, obese, and severely obese. The ratio of BW:IBW for each respective BMI category was: 78.4 ± 7.4% (range, 65.6-88.1%), underweight; 106 ± 12% (range, 76.4-138%), normal; 136 ± 13% (range, 117-166%), obese; and 177 ± 23% (range, 151-215%), severely obese. Statistically significant differences in CL/F between genders were noted within normal and obese categories.[a] Males had a higher absolute (mL/min) CL/F than females in both normal and obese patients. In addition, obese males had a 12% higher absolute CL/F expressed relative to BSA than obese females.

We compared the mean CL/F among underweight, normal, obese, and severely obese patients using one-way ANOVA (Table II). Absolute CL/F was elevated in obese (16%) and severely obese (34%) patients compared to normal patients, $p < 0.05$, and there was no statistical difference in CL/F for normal and underweight patients. CL/F relative to BW (mL/min/kg) was 13 and 20% lower in obese and severely obese compared to normal patients, respectively, and 28% higher in underweight compared to normal patients. CL/F relative to IBW (mL/min/kg IBW) was 13% greater in obese *vs.* normal patients, and 35% greater in severely obese *vs.* normal patients. CL/F relative to IBW was 5.5% lower in underweight *vs.* normal patients. There was not a statistically significant difference in CL/F relative to BSA (mL/min/m^2) or AIBW (mL/min/kg AIBW) among underweight, normal, obese, and severely obese patients.

In univariable linear regression analysis, the regression coefficients for absolute busulfan CL/F and each of the following variables were: BW ($r^2 = 0.308$), BSA ($r^2 = 0.290$), AIBW ($r^2 = 0.285$), IBW ($r^2 = 0.195$), height ($r^2 = 0.181$), BMI ($r^2 = 0.174$), and age ($r^2 = 0.023$). Figure 1 shows the relationship between absolute busulfan CL/F and BW, BSA, AIBW, and IBW. All correlations were statistically significant ($p < 0.001$; for age, $p = 0.011$). There was a statistically significant difference in the mean absolute clearance for

[a] We did not test for gender differences in the underweight and severely obese patients due to the small sample size of these BMI categories (n = 6 and n = 9, respectively).

males and females (223 ± 55 *vs.* 186 ± 42 mL/min, $p < 0.001$, respectively). There was not a significant difference in absolute CL/F among diseases.

We performed multiple regression analysis to assess the value of BMI in conjunction with one of the commonly used body size parameters (*i.e.*, BW, AIBW, BSA, and IBW) as predictors of busulfan CL/F (Table III). In addition, demographic characteristics (*i.e.*, age, disease, gender, and height) were incorporated to determine their possible role as predictors of busulfan CL/F after a measure of body size had been included. When BW, AIBW or IBW were respectively entered into the model first (as single predictors), there was a statistically significant improvement in the predictive ability of the model with the addition of BMI. Likewise, when BMI was entered into the model first, followed by the addition of BW, AIBW, or IBW, there was a statistically significant improvement in the predictive ability of the model ($p < 0.05$; Table III). Addition of height, age, and gender did not improve the model after the inclusion of BW, AIBW or IBW. There was a trend to statistically significant improvement with addition of disease for all models ($p = 0.05$-0.06).

Results of the multiple regression analysis with BSA were different (Table III). When BSA was entered into the model first, and BMI was added second, there was not a statistically significant improvement in the predictive ability of the model ($p = 0.5$). When BMI entered the model first, the addition of BSA significantly improved the regression model of busulfan CL/F ($p < 0.001$). The model of CL/F with BSA was improved by the addition of age, height, and gender ($p < 0.001$).

Busulfan CL/F was compared among disease categories after expressing busulfan CL/F relative to BW, AIBW, BSA, and IBW (Table IV). There was a statistical difference when comparing the mean CL/F expressed relative to BW in patients with AML to those with BrCa (3.09 ± 0.80 *vs.* 2.69 ± 0.55 mL/min/kg, $p < 0.038$, respectively), and AML *vs.* MM (3.09 ± 0.80 *vs.* 2.53 ± 0.51 mL/min/kg, $p < 0.006$, respectively). In addition, significant differences in mean busulfan CL/F expressed relative to BSA were found in patients with AML in comparison to those with BrCa (119 ± 27 *vs.* 105 ± 19 mL/min/m^2, $p < 0.024$, respectively), and AML *vs.* MM (119 ± 27 *vs.* 101 ± 19 mL/min/m^2, $p < 0.023$, respectively). There were no disease-dependent differences in busulfan CL/F when expressed relative to AIBW or IBW.

DISCUSSION

The major finding was that while CL/F varies among patient groups based on body weight, there are no differences in busulfan CL/F among BMI classes when CL/F is expressed relative to AIBW or BSA. In addition, patients with BrCa or MM had lower busulfan CL/F expressed relative to BW or BSA compared to patients with AML.

Based on these findings, it is most appropriate that dose be adjusted for AIBW. BSA-adjusted dosing will eliminate differences in busulfan CL/F among normal and obese patients, but it does not eliminate disease-specific differences. It would be prudent to lower the dose/m^2 in BrCa and MM patients if it were desired to produce equivalent mean AUC or C_{ss} in all patients. Dosing on the basis of AIBW eliminates the need for any special accommodation for obese patients, which would be required when dosing on the basis of BW or IBW. There were no differences in busulfan CL/F expressed relative to AIBW in underweight patients compared to obese and severely obese patients, nor were disease-specific differences seen. Therefore, this measure of body size is appropriate for calculating dose in any adult.

The relationship between busulfan C_{ss} and a variety of outcomes has been examined. Busulfan C_{ss} was related to regimen related toxicity (RRT) and graft rejection in 42 patients with a variety of diseases undergoing hematopoietic stem cell transplantation.[3] Severe grade 3-4 RRT was only observed in patients with $C_{ss} > 900$ ng/mL. The incidence of graft rejection for those receiving HLA partially-matched related or unrelated donor grafts with a busulfan $C_{ss} < 600$ ng/mL was 7/9, whereas graft rejection in patients with $C_{ss} > 600$ ng/mL was 1/7. Based on these findings, the therapeutic window for busulfan is C_{ss} of 600-900 ng/mL (which corresponds to mean AUC of 900-1350 μM × min) over 16 doses for these patients.[3] More recent findings suggest that tolerance to busulfan may vary by disease. CML patients tolerate busulfan $C_{ss} > 900$ ng/mL without severe grade 3-4 RRT.[4] In addition, the incidence of relapse was significantly higher in CML patients with busulfan C_{ss} levels below the median for the entire group of 45 patients (917 ng/mL).

Inter-patient variability in busulfan CL/F is large and is an important determinant of transplantation outcome. In the studies just cited (in which patients received a constant mg/kg dose), inappropriate busulfan AUC was the single most important determinant of toxicity, rejection, or relapse. The coefficients of variation for busulfan CL/F expressed relative to AIBW and BSA when including all patients in this study were 21.3 and 21.8%, respectively. Thus, given the frequency with which busulfan AUC will exceed thresholds associated with undesired outcomes even when dose is adjusted for AIBW or BSA, busulfan level monitoring is still required in certain situations.

As mentioned previously, busulfan is eliminated by GSH conjugation catalyzed by GST. The results of this study suggest that GSTA1-1 activity is most closely related to BSA or AIBW. In general, absolute clearances of xenobiotics (*i.e.*, caffeine, phenytoin, desmethyl-diazepam, carbamazepine, midazolam, and antipyrine) eliminated primarily by hepatic P450 oxidative metabolism (phase I enzymes) are similar in obese and lean subjects.[12-17] While absolute clearances of drugs eliminated primarily by phase II enzymes (*i.e.*, phenol sulfotransferase, glucuronyl transferase) are higher in obese subjects compared to lean controls.[18-21] The findings with busulfan are similar to those with other drugs eliminated by phase II enzymes (GST is a phase II enzyme).

Interestingly, MM and BrCa patients had lower busulfan CL/F when expressed relative to BSA or BW compared to patients with AML, whose CL/F relative to BSA and BW was 8.2 and 9.6% higher than the mean of all patients, respectively. The reason for this difference is not clear, but patients with MM and BrCa were generally transplanted later in the course of their disease. While the difference in CL/F in patients with MM and BrCa was small (< 20%), these differences in CL/F could explain previous findings of an apparent higher incidence of grade 3-4 RRT in patients with MM and BrCa compared with patients with hematologic malignancies after standard dose busulfan.[22-24] After the standard 1 mg/kg (BW) busulfan dose, a patient with CL/F of 2.94 mL/min/kg (the mean value for patients with BMI between 18 and 27 kg/m^2) will have a C_{ss} of 940 ng/mL (which corresponds to an AUC of 1380 µM × min). BrCa and MM patients administered a 1 mg/kg dose will have a C_{ss} of 1030 and 1100 ng/mL respectively, (which corresponds to AUC of 1510 and 1610 µM × min, respectively). Previous studies have identified the threshold for severe toxicity to be C_{ss} of 900-1000 ng/mL (AUC of 1350-1500 µM ×

min).[1-3] The small reduction in busulfan CL/F in BrCa and MM patients could result in enhanced toxicity after a fixed 1 mg/kg dose.

In conclusion, absolute busulfan CL/F is elevated in obesity. Expressing CL/F relative to AIBW or BSA eliminated mean differences in CL/F among underweight, normal, obese and severely obese patients. There are modest differences between AML patients and those with MM or BrCa in busulfan CL/F expressed relative to BW or BSA. Even when expressed relative to BSA, interpatient variability in busulfan CL/F expressed relative to any measure of body size is large relative to the therapeutic window in certain indications.[3,4] The need for adjusting busulfan dose based on AUC or C_{ss} measured in the individual patient remains in certain settings regardless of body size measure.

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Table I. Busulfan CL/F[a] in underweight (BMI < 18 kg/m^2), normal (BMI = 18-26.9 kg/m^2), obese (BMI = 27-35 kg/m^2), and severely obese patients (BMI > 35 kg/m^2).

	Underweight	Normal			Obese			Severely Obese
	Mean	Male	Female	Mean	Male	Female	Mean	Mean
n	6	76	99		46	43		9
Age, years	23.2 ± 12.7	39.3 ± 12.2	41.7 ± 11.8	40.7 ± 12.0	44.2± 10.3	43.8± 9.2	44.0 ± 9.7	47.0 ± 11.6
CL/F, mL/min[b]	161 ± 30	212 ± 51	176 ± 36[d]	192 ± 47	246 ± 39	199 ± 55[d]	223 ± 53	257 ± 44
mL/min/kg BW[b]	3.77 ± 0.93	2.93 ± 0.67	2.95 ± 0.62	2.94 ± 0.64	2.64 ± 0.58	2.47 ± 0.49	2.56 ± 0.54	2.36 ± 0.50
mL/min/m^2 [c]	115 ± 22	113 ± 25	107 ± 23	110 ± 24	116 ± 25	104 ± 20[d]	110 ± 24	117 ± 26
mL/min/kg AIBW[c]	3.09 ± 0.58	2.96 ± 0.67	3.11 ± 0.62	3.04 ± 0.65	3.16 ± 0.69	3.22 ± 0.65	3.19 ± 0.67	3.49 ± 0.79
mL/min/kg IBW[b]	2.92 ± 0.53	2.98 ± 0.69	3.17 ± 0.66	3.09 ± 0.68	3.38 ± 0.75	3.58 ± 0.75	3.48 ± 0.75	4.18 ± 1.01

[a]Data are mean ± SD.

[b]Statistical comparisons of CL/F among different BMI categories are made in Tables II.

[c]There were no statistically significant differences in the mean CL/F expressed relative to BSA or AIBW among underweight, normal, obese, and severely obese patients.

[d]Denotes a statistically significant difference ($p < 0.05$) for the mean CL/F in males and females within a BMI category.

Table II. Statistical comparisons of Table I mean busulfan CL/F among underweight, normal, obese, and severely obese patients.

BMI category (1)	BMI category (2)	% difference in absolute CL/F[a] (mL/min)	p	% difference in CL/F/BW[a] (mL/min/kg)	p	% difference in CL/F/IBW[a] (mL/min/kg)	p
underweight	normal	-19.5	0.716	22.0	0.007	-5.8	1.000
	obese	-38.8	0.014	32.1	0.000	-19.2	0.374
	severely obese	-59.6	0.001	37.7	0.000	-43.2	0.005
normal	underweight	16.4	0.716	-28.2	0.007	5.5	0.010
	obese	-16.2	0.000	12.9	0.000	-12.6	0.000
	severely obese	-33.6	0.001	19.7	0.034	-35.3	0.000
obese	underweight	28.0	0.014	-47.3	0.000	16.1	0.374
	normal	13.9	0.000	-14.8	0.000	11.2	0.000
	severely obese	-15.0	0.291	7.8	1.000	-20.1	0.032
severely obese	underweight	37.4	0.001	-60.2	0.000	30.1	0.005
	normal	25.1	0.001	-24.6	0.034	26.1	0.000
	obese	13.0	0.291	-8.5	1.000	16.7	0.032

[a] The percent difference in CL/F = $\left(\dfrac{\text{BMI category (1)} - \text{BMI category (2)}}{\text{BMI category (1)}}\right) \times 100.$

Table III. Summary of multiple stepwise linear regression model of absolute busulfan CL/F (mL/min).

In the first analysis, body size was entered in the first step. In the second step, BMI was added to the model with body size. In the third step, age, height and gender were added to the model with BMI and body size. In the fourth step, disease was added to the model with age, height, gender, BMI and body size. In the second analysis, steps 1 and 2 were reversed. The r^2 value for the full model and significance of the r^2 change with the addition of variables is shown.

Regression model	Step	Body Size Parameters							
		BW		AIBW		BSA		IBW	
		r^2	p	r^2	p	r^2	p	r^2	p
First analysis:									
Body size	1	0.308	0.000	0.285	0.000	0.290	0.000	0.195	0.000
+ BMI	2	0.323	0.015	0.331	0.000	0.291	0.538	0.332	0.000
+ Age, height, gender	3	0.337	0.129	0.337	0.529	0.341	0.000	0.335	0.522
+ Disease	4	0.367	0.055	0.367	0.055	0.370	0.060	0.365	0.050
Second analysis:									
BMI	1	0.174	0.000	0.174	0.000	0.174	0.000	0.174	0.000
+ Body size	2	0.323	0.000	0.331	0.000	0.291	0.000	0.332	0.000
+ Age, height, gender	3	0.337	0.129	0.337	0.529	0.341	0.000	0.335*	0.522*
+ Disease	4	0.367	0.055	0.367	0.055	0.370	0.060	0.365*	0.050*

*Tolerance limits (< 0.001) were reached during this analysis. Therefore, height did not enter the multiple regression analysis.

Table IV. Disease-dependent differences in busulfan CL/F expressed relative to BW or BSA.

Busulfan CL/F expressed relative to BW, AIBW, BSA, or IBW was compared among patients with AML (n = 60), BrCa (n = 55), CML (n = 73), myelodysplastic syndrome (n = 49), MM (n = 25), non-Hodgkin's lymphoma (n = 10), and ovarian cancer (n = 7). Statistical comparisons were made using one-way ANOVA with the Bonferroni correction for multiple comparisons. Only the statistically significant results were listed in the table.

Busulfan CL/F expressed relative to:	Disease (1)	Disease (2)	%, mean difference[a]	p
(log) BW (ml/min/kg)[b]	AML	BrCa	12.9[c]	0.038
	AML	MM	18.1[c]	0.006
BSA (mL/min/m²)	AML	BrCa	11.9	0.024
	AML	MM	15.3	0.023

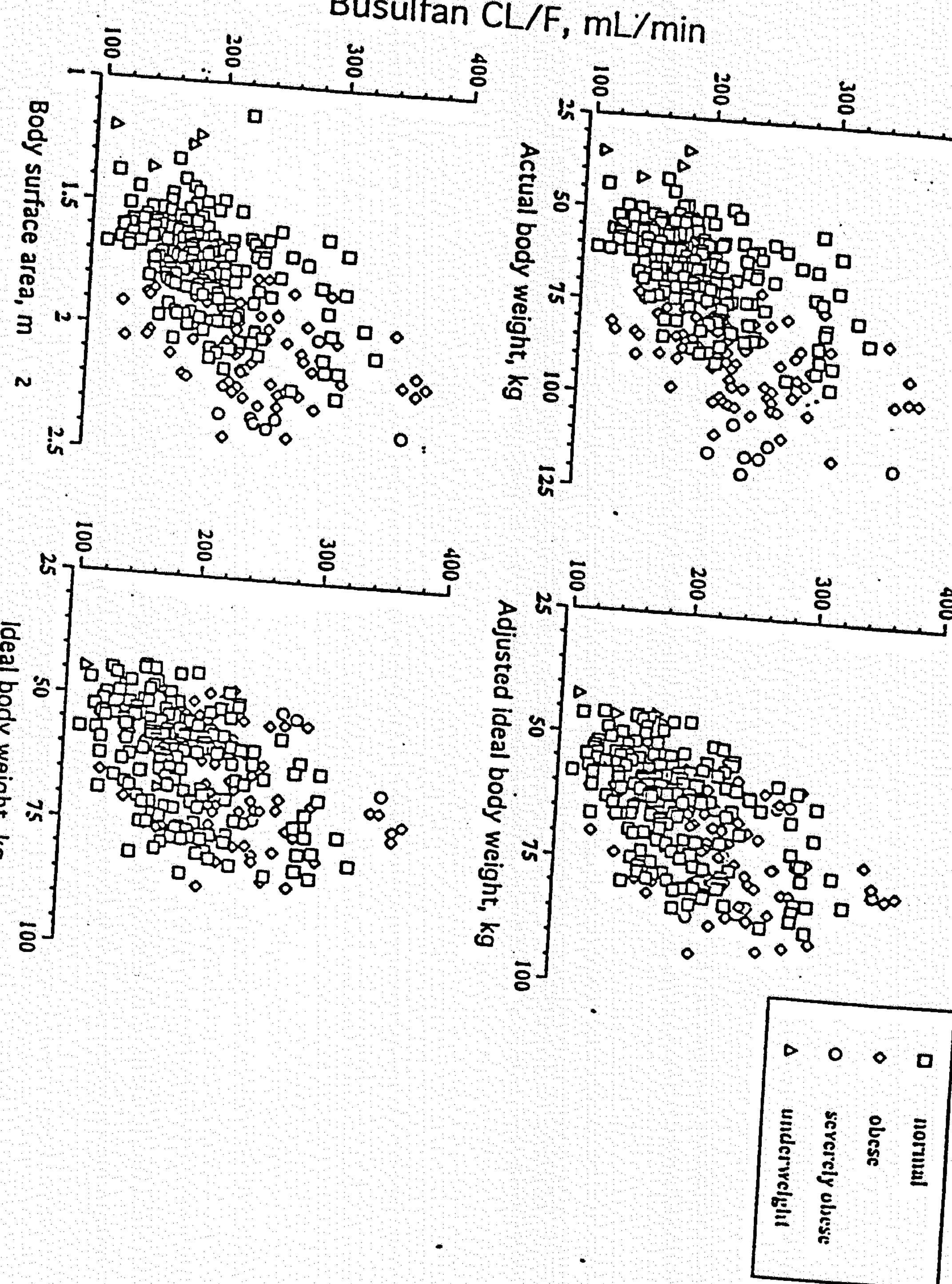
[a]The percent difference in CL/F $= \left(\frac{\text{Disease (1)} - \text{Disease (2)}}{\text{Disease (1)}}\right) \times 100$.

[b]CL/F expressed relative to BW were log transformed because the non-transformed data were not normally distributed and failed the Levene's distribution test. Log transformation resulted in a normally distributed variable.

[c]The value is the anti-log of the difference.

FIGURE LEGEND

Figure 1. The relationship between busulfan CL/F (mL/min) and BW, BSA, IBW, and AIBW in underweight (BMI < 18 kg/m2, n = 6), normal (BMI 18-26.9 kg/m^2; n = 181), obese (BMI = 27-35 kg/m^2; n = 89) and severely obese (BMI > 35 kg/m^2; n = 9) patients.


Busulfan CL/F, mL/min
Actual body weight, kg
Body surface area, m2
Adjusted ideal body weight, kg
Ideal body weight, kg
normal
obese
severely obese
underweight