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Cefotiam Disposition in Markedly Obese Athlete Patients, Japanese Sumo Wrestlers

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Markedly obese athletes like Japanese sumo wrestlers may frequently suffer various traumas which result in the prophylaxis or treatment of posttraumatic infection with antibiotics. However, appropriate dosage regimens in this group of patients have not been fully known for many antibiotics. Therefore, we studied the kinetic disposition of cefotiam, a parenteral, broad-spectrum cephalosporin with activity against gram-positive and -negative bacteria, after an intravenous dose (2 g) infused over 30 min into 15 sumo wrestler patients with an excess body weight (130 to 220% of ideal body weight) and 10 control patients with a normal weight (90 to 102% of ideal body weight). Mean (± standard deviation) clearance and steady-state volume of distribution were significantly greater in the sumo wrestler than in the control group (38.3 ± 9.4 versus 23.5 ± 6.0 liters/h, $P < 0.001$, and 30.2 ± 8.0 versus 17.9 ± 6.1 liters, $P < 0.001$). Mean elimination half-life was slightly but significantly longer in the sumo wrestler than in the control group (0.91 ± 0.14 versus 0.74 ± 0.20 h, $P < 0.05$). However, mean residence time did not differ between the two groups (0.79 ± 0.10 versus 0.75 ± 0.14 h). The statistical differences in clearance and volume of distribution between the two groups disappeared when these kinetic parameters were corrected for body surface area, but not for total body weight or ideal body weight. The results suggest that the dosage calculation of cefotiam, a hydrophilic antibiotic, should be made on the basis of body surface area in morbidly obese athlete or sumo wrestler patients. However, whether this recommendation should extend to other nonathlete obese subjects remains to be determined.

Sumo, a unique form of wrestling with a 2,000-year-old history, is the national sport of Japan (5, 18). There are more than 700 professional sumo wrestlers in the country. The most prominent physical characteristic of sumo wrestlers is obesity (5, 18). Since physical essentials for success in sumo wrestling are heavy weight and low center of gravity, wrestlers desire to gain weight and ingest many calories so that they have a tendency to be markedly obese. The heaviest professional sumo wrestler in the major league weighs 241 kg with a height of 187 cm. Since sumo wrestlers move about actively with an excess body weight in a small ring (4.55 m in diameter), they frequently suffer various traumas (e.g., abrasions, meniscus injuries, or fractures) and therefore often receive antibiotic therapy to prevent or treat posttraumatic infection. This may also be true for other heavyweight or obese athlete groups (e.g., football players).

Determination of the dosage of drugs for extremely obese subjects like sumo wrestlers frequently leaves clinicians in a quandary since the obesity produces an alteration of drug disposition, but the extent of dosage modification may vary from drug to drug (1, 2). Apparent volume of distribution in obese subjects has been reported to be dramatically increased for benzodiazepines (3), moderately increased for aminoglycosides (7, 9), and unchanged for digoxin (5). The mechanism for the variable drug distribution in obesity is unclear, although it is partially attributed to the lipophilic character of the drug molecule (2). Drug conjugation is uniformly increased as a function of body weight, whereas oxidative drug metabolism is minimally changed in obesity (2). The renal clearance of drugs in markedly obese subjects has been reported to be little affected for digoxin (5) but to be increased for aminoglycosides (7) and vancomycin (8).

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Cefotiam is an intravenously or intramuscularly administered broad-spectrum cephalosporin antibiotic (19). The drug is active against a wide variety of bacterial pathogens and can be used for the prophylaxis and treatment of infections caused by *Staphylococcus aureus*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* (19). The purposes of the present study were to investigate the pharmacokinetics of cefotiam in markedly obese sumo wrestlers and to verify a dosage modification in such an obese athlete patient group.

MATERIALS AND METHODS

Patients and drug administration. Participants in the study were 15 sumo wrestlers and 10 control subjects, who had been admitted to the Department of Orthopedics, Doai Memorial Hospital, Tokyo, and considered to need an antibiotic therapy for the prophylaxis of bacterial infection. They were inpatients with various types of fracture but had no clinical signs or symptoms of infection, cardiovascular abnormality, hepatic dysfunction, or impaired renal function when studied. The mean ± standard deviation (SD) data on demographic characteristics of participants in the present study are given in Table 1. Ideal body weight (IBW) was obtained from a height-weight table of the Japanese population (12), and body mass index (BMI) was calculated as described by Bray (10). Body surface area (BSA) was determined by the equation of DuBois and DuBois (14). Because normal limits of BMI and the ratio of total body weight (TBW) to IBW (TBW/IBW) are considered to be <26 (10) and <120% (1), respectively, all the sumo wrestlers were judged to be markedly obese from either their BMI (32 to 48) or TBW/IBW (130 to 220%). All the control subjects had normal heights and weights. Their body weights were within 10% of IBW, and their BMIs ranged from 19 to 22.

Informed written consent was obtained from each of the subjects before the study.

Cefotiam (2 g) was administered over 30 min with an intravenous infusion. Blood samples were obtained just before and at 0, 10, 20, and 30 min and 1, 2, 3, 4, and 5 h after the infusion ceased. The plasma was separated and frozen at −20°C until analyzed.

Sample assay. Concentrations of cefotiam in plasma were determined by a modification of the high-performance liquid chromatographic method reported by Brisson et al. (11). Briefly, 1 ml of acetonitrile and a 0.1-ml aqueous solution containing 0.1 or 1.0 mg (depending on measuring a low or high concentration of cefotiam, respectively) of cefotaxime per ml (internal standard) were added to a 0.5-ml plasma sample. The mixture was vortexed for 3 s and centrifuged for 5 min. The upper layer was transferred into a 10-ml glass-stoppered centrifuge tube containing 3 ml of dichloromethane and shaken for 5 min. After centrifugation, 20 μl of the aqueous phase was injected onto an Eicompak MA-ODS reversed-phase column (250 by 4.6 mm, inner diameter, packed with 7-μm particles; Eicom Corp., Kyoto, Japan). The mobile phase consisted of a mixture of 0.01 M acetate buffer (pH 4.2)–acetonitrile (85:15, vol/vol). Analytes (i.e., cefotiam and cefotaxime) were monitored by using a UVILOG-5111 variable wavelength UV detector (Oyo Bunko Kiki, Tokyo, Japan) at a wavelength of 254 nm. Retention times for cefotiam and cefotaxime were 2.3 and 4.1 min, respectively. Peak height ratio of cefotiam to cefotaxime was linear over the concentration range of 0.1 to 100 μg/ml. Within-day and day-to-day variations at concentrations of 0.5 and 5.0 μg/ml were less than 5%.

Mathematical analyses. Plasma concentration-time data after the intravenous infusion of cefotiam were analyzed by model-independent methods (15, 20). The slope (β) of the terminal log-linear portion of plasma cefotiam concentration versus time curve was determined by a log-linear least-squares fit. The elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/\beta$. The area under the plasma concentration-time curve (AUC) and the area under the moment curve (AUMC) were computed by the trapezoidal rule, with the respective area extrapolated to infinity. Clearance (CL) was calculated as CL = dose/AUC. The steady-state volume of distribution (V_{ss}) was calculated from the following relationship: $V_{ss} = [(\text{dose} \times \text{AUMC})/\text{AUC}^2] - [(\text{dose} \times T)/(2 \times \text{AUC})]$, where T is the infusion time (15). Mean residence time (MRT) was calculated from the equation, MRT = (AUMC/AUC) − $T/2$ (15).

Results are expressed as mean ± SD. Unpaired Student's t test was used to compare the mean values for pharmacokinetic parameters and concentrations of cefotiam in plasma between the two study groups. Linear regression analysis was performed for analyzing the relationship between BSA and CL or V_{ss}, and the coefficient of correlation (r) was calculated. A P value less than 0.05 was considered statistically significant.

RESULTS

Mean (± SD) plasma concentration versus time plots after an intravenous dose (2 g) of cefotiam infused over 30 min into the sumo wrestler and control patient groups are presented in Fig. 1. The concentrations of cefotiam in plasma were significantly ($P < 0.05$ or $P < 0.001$) lower from 30 min to 2.5 h postinfusion in the sumo wrestler than in the control group.

The mean pharmacokinetic parameters for cefotiam in the

TABLE 1. Data on demographic characteristics in the two study groups[a]

Study group (no.)	Age (yr)	Ht (cm)	TBW (kg)	IBW (kg)	TBW/IBW (%)	BMI (kg/m²)	BSA (m²)
Sumo wrestler (15)	21.7 ± 3.8 (15–28)	181 ± 6.3[b] (172–196)	124 ± 16.1[b] (92–155)	71.2 ± 5.3[b] (64–79)	175 ± 25.3[b] (130–220)	38.1 ± 5.4[b] (32–48)	2.41 ± 0.15[b] (2.13–2.64)
Control (10)	21.0 ± 4.9 (16–30)	169 ± 6.2 (160–180)	58 ± 5.0 (51–66)	62.3 ± 4.4 (56–70)	94 ± 4.6 (90–102)	20.2 ± 1.0 (19–22)	1.67 ± 0.10 (1.53–1.80)

[a] Values are given as mean ± SD, and those given in parentheses are the ranges observed.
[b] $P < 0.001$ compared with the control group.

TABLE 2. Pharmacokinetic parameters of cefotiam in the two study groups[a]

Study group (no.)	CL (liter/h)	V_{ss} (liter)	MRT (h)	β (h^{-1})	$t_{1/2}$ (h)
Sumo wrestler (15)	38.3 ± 9.4[b] (27.4–61.2)	30.2 ± 8.0[b] (20.6–51.4)	0.79 ± 0.10 (0.56–0.94)	0.80 ± 0.14[c] (0.44–0.92)	0.91 ± 0.14[c] (0.74–1.56)
Control (10)	23.5 ± 6.0 (14.3–35.0)	17.9 ± 6.1 (9.1–30.9)	0.75 ± 0.14 (0.50–1.05)	0.97 ± 0.20 (0.56–1.22)	0.74 ± 0.20 (0.57–1.25)

[a] Values are given as mean ± SD, and those given in parentheses are the ranges observed. β, Slope of the elimination phase.
[b] $P < 0.001$ compared with the control group.
[c] $P < 0.05$ compared with the control group.

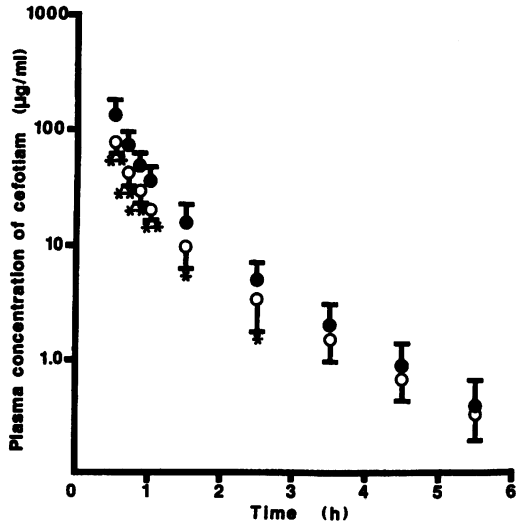

FIG. 1. Plasma concentration-time data of cefotiam after an intravenous dose of 2 g infused over 30 min in 15 sumo wrestler (○) and 10 control (●) patients. Each point represents the mean ± SD. *, $P < 0.05$ compared with the control; **, $P < 0.001$ compared with the control.

two groups are listed in Table 2. Both mean CL and V_{ss} values, when expressed without taking body weight units (e.g., IBW) into account, were significantly ($P < 0.001$) greater in the sumo wrestler than in the control group, whereas MRTs were virtually similar between the two groups. The mean $t_{1/2}$ value was significantly ($P < 0.05$) longer in the sumo than in the control patients (Table 2).

Table 3 shows the mean kinetic parameters corrected for TBW, IBW, and BSA. The significant differences ($P < 0.05$) in CL and V_{ss} between the two groups were still observed when these parameters were corrected for either TBW or IBW. However, the statistical differences vanished when the parameters were corrected for BSA (Table 3). The percentage differences in CL and V_{ss} between the two groups, when the parameters were not corrected and when they were corrected for TBW, IBW, and BSA were: for CL, 63.0 and 24.4, 42.1, and 14.3%; and for V_{ss}, 68.4 and 25.0, 53.6, and 18.1%, respectively.

Figure 2 illustrates the correlation between BSA and CL or V_{ss} in all study subjects ($n = 25$). The CL was significantly ($r = 0.705$, $P < 0.001$) correlated with BSA (Fig. 2, left). The V_{ss} also showed a significant ($r = 0.738$, $P < 0.001$) correlation with BSA (Fig. 2, right).

DISCUSSION

The observation that concentrations of cefotiam in plasma at several postinfusion times were significantly lower in the sumo wrestler than in the control patients (Fig. 1) may suggest that a dosage modification is needed for groups like obese athletes who have to be treated with this antibiotic. Because the dosage rate is usually known for the population with normal weights, determining the differences in the pivotal kinetic parameters (e.g., CL) between subjects with markedly heavy weights and subjects with normal weights seems to be an adequate indicator of the dosage of a drug for sumo wrestler patients. With this approach, a dosage modification using BSA was found to be a reasonable method for calculating cefotiam doses in the markedly obese athlete patients (i.e., sumo wrestlers) since the results showed that

TABLE 3. Pharmacokinetic parameters of cefotiam adjusted for TBW, IBW, and BSA in the two study groups[a]

Study group (no.)	CL/TBW (liter/h per kg)	V_{ss}/TBW (liter/kg)	CL/IBW (liter/h per kg)	V_{ss}/IBW (liter/kg)	CL/BSA (liter/h per m^2)	V_{ss}/BSA (liter/m^2)
Sumo wrestler (15)	0.31 ± 0.07[b]	0.24 ± 0.06[b]	0.54 ± 0.13[c]	0.43 ± 0.10[c]	16.0 ± 3.6	12.4 ± 2.9
Control (10)	0.41 ± 0.11	0.32 ± 0.11	0.38 ± 0.10	0.28 ± 0.09	14.0 ± 3.6	10.5 ± 2.9

[a] Values are given as mean ± SD.
[b] $P < 0.05$ compared with the control group.
[c] $P < 0.01$ compared with the control group.

both differences in CL and V_{ss} between the two groups were eliminated when the parameters were corrected for BSA, but not for TBW or IBW (Table 3). However, regarding the dosing interval, no modification appears to be needed, because the MRT did not differ between the two groups and only a slight increase (23%) in $t_{1/2}$ was seen in the sumo wrestler group compared with the control group.

In adults with normal renal function, the dosage regimen of cefotiam generally used is 1 g twice daily for the treatment of mild to moderately severe infections and the daily dose can be raised to 4 g for more severe infections (16). This dosage may be adjusted without changing the dosing interval for sumo wrestler patients as follows: daily dose = (2 or 4 g) × (BSA/1.7 m^2) administered in two divided doses, where the m^2 value of 1.7 indicates the average BSA in Japanese male adults (12). Because the MICs of cefotiam for most strains of clinically isolated *E. coli*, *S. aureus*, *K. pneumoniae*, *H. influenzae*, and *P. mirabilis* are within a range of 0.2 to 0.78 μg/ml (10), the pharmacokinetics of cefotiam described in this study suggest that an intraveneous dose of 1 g × (BSA/1.7 m^2) and 2 g × (BSA/1.7 m^2) infused over 30 min in the obese patient group would produce respective concentrations in plasma of greater than 0.78 μg/ml (with respective peaks of 52.0 ± 10.7 and 103.9 ± 21.4 μg/ml) for 3.72 ± 0.63 and 4.65 ± 0.58 h after the infusion began and therefore would readily inhibit these bacterial pathogens for at least approximately 3.7 and 4.7 h, respectively. These values predicted from the mean disposition data in the sumo wrestler patient group are comparable to the respective values calculated after a 1-g dose (3.54 ± 0.54 h) and actually observed after a 2-g dose of cefotiam (4.46 ± 0.68 h) in the normal weight patient group, respectively.

Our findings on the relation between BSA and changes in kinetic parameters (i.e., CL and V_{ss}) of cefotiam in sumo wrestlers are consistent with the observation recently reported by Yost and Derendorf (21) describing cefotaxime kinetics in morbidly obese subjects. They found that kinetic parameters of cefotaxime in morbidly obese subjects can be compensated for if the parameters are corrected for BSA and recommended that a dosage adjustment of cefotaxime should be made on the basis of BSA (21). The correlation of our findings with those of Yost and Derendorf may come from the similar physicochemical and pharmacokinetic properties of cefotiam and cefotaxime, since both cephalosporins have a common chemical structure (6). Although available data are limited, a different dosage regimen has been recommended for other groups of antibiotics in morbidly obese subjects (7, 8); a hybrid of TBW and IBW has been used to calculate the dosages of gentamicin, tobramycin, and amikacin (7), whereas vancomycin doses have been best calculated by using TBW (8).

The changes in cefotiam distribution volume observed in sumo wrestlers resemble those previously reported from other water-soluble antibiotics in extremely obese subjects (1, 2). The mean increase in V_{ss} (expressed in liters) observed in the sumo wrestler group was 68% compared with the value in the control group which was not proportional to the 100% increase in body weight. A similar or lower magnitude of changes in distribution volume has been reported for water-soluble antibiotics such as gentamicin (37%) (7), tobramycin (58%) (7), amikacin (44%) (7), vancomycin (51%) (4), and cefotaxime (39%) (21) in morbidly obese subjects. These findings point to a correlation between lipophilicity and kinetic changes in highly lipophilic drugs which are dramatically increased in distribution in obese subjects, whereas water-soluble drugs undergo a small change in distribution in obese subjects (2). Since cefotiam is a hydrophilic antibiotic, it may distribute only to a limited

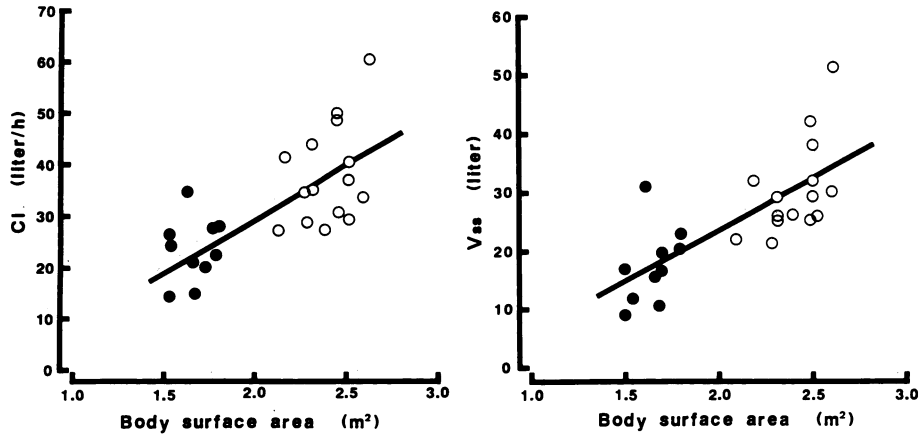

FIG. 2. Relationship between BSA and CL or V_{ss} observed in all study subjects ($n = 25$). The equations for the regression line are : CL = 20.0 × BSA − 9.9 and V_{ss} = 18.2 × BSA − 13.3. Both correlations were statistically significant ($r = 0.705$, $P < 0.001$ for BSA versus CL; and $r = 0.738$, $P < 0.001$ for BSA versus V_{ss}). Symbols: ○, sumo wrestlers; ●, control subjects.

extent in adipose tissues which are greatly increased in sumo wrestlers.

The CL value of cefotiam (expressed as liters/hour) was also increased by 59% in the sumo wrestler group compared with that of the control group. The mechanism of this change is not known. However, an elevated CL of antibiotics has been reported in obese subjects for gentamicin (42%) (7), tobramycin (50%) (7), amikacin (58%) (7), and vancomycin (130%) (4). The increase in CL values of these antibiotics in morbidly obese subjects was explained by the increased renal function (4, 7), since the CL values for these antibiotics showed a good correlation with creatinine clearance rates (4, 7). The observation that obese subjects have a much higher creatinine clearance rate (19) should support the above-mentioned findings (4, 7). Other likely reasons may include an increased renal blood flow secondary to the changes in blood volume and cardiac output due to the increase in body weight of obese subjects (2, 13). Since about 50 to 70% of the cefotiam is excreted unchanged in urine (11, 16, 17), the larger CL of cefotiam found in the sumo wrestler group is probably attributable to enhanced renal function.

Caution must be exercised, however, when our results are applied to other morbidly obese patients. Although the sumo wrestlers we investigated were markedly obese, they may be somewhat different from so-called morbidly obese subjects in that sumo wrestlers are relatively muscular compared with nonathlete obese subjects. Thus, in a strict sense, it remains unclear whether and to what extent an increase in muscular tissue relative to total obese body mass would contribute to the overall alteration in the kinetics of cefotiam obtained from sumo wrestlers.

In summary, the pharmacokinetics of cefotiam are significantly altered in sumo wrestlers. CL and V_{ss} in the sumo group were increased by approximately 60% compared with the control group, whereas MRT was unchanged in the markedly obese athlete group. The differences in cefotiam kinetics among the sumo wrestler and control groups were almost compensated for when the parameters were corrected for BSA. The results suggest that using BSA as a physiological variable is a reasonable means for optimizing a cefotiam dosage calculation in the treatment of bacterial infections for which this cephalosporin antibiotic is indicated in obese Japanese sumo wrestler patients. Although this approach is likely to be applicable to other markedly obese athlete groups (e.g., sumo-like football players), the results should be viewed as preliminary until further studies are conducted using an adequate athlete patient group under a research design similar to the present study. It should be emphasized that appropriate dosage guidelines are not available for many antibiotics for obese athlete patients who frequently suffer various traumas which require antibiotic treatment.

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