

Aminoglycoside Dosing Weight Correction Factors for Patients of Various Body Sizes

ANNE M. TRAYNOR,¹ ANNE N. NAFZIGER,^{1,2,3} AND JOSEPH S. BERTINO, JR.,^{1,2,3,4*}

*Departments of Medicine,¹ The Clinical Pharmacology Research Center,² the Research Institute,³
and Pharmacy Services,⁴ Bassett Healthcare, Cooperstown, New York 13326*

Received 27 June 1994/Returned for modification 14 October 1994/Accepted 11 December 1994

Prior investigations have suggested the use of a dosing weight correction factor of ideal body weight (IBW) plus 40% excess body weight (EBW, where $EBW = \text{total body weight [TBW]} - IBW$) to determine the weight to use for aminoglycoside dosing in morbidly obese (TBW/IBW ratio, >2) patients. Little data are available to provide dosing information for underweight or moderately obese patients. We investigated aminoglycoside pharmacokinetics in 1,708 patients receiving gentamicin and tobramycin. Patients were stratified into under-average-weight or overweight weight categories based on both TBW/IBW ratio and body mass index (weight/height² ratio), which has been shown to correlate with physiologic estimates of body fat. Regression analyses revealed that the TBW/IBW ratio predicts the volume of distribution. Dosing weight correction factors to give equivalent predicted peak aminoglycoside concentrations with a 2-mg/kg loading dose are 1.13 times the TBW for underweight patients and 0.43 times the EBW plus IBW for overweight patients. There were no large differences between the dosing weight correction factors derived from IBW- and body mass index-based classification systems. These data generate useful aminoglycoside dosing weight equations for both underweight and overweight patients.

Ascertainment of accurate pharmacokinetic parameters for aminoglycoside dosing remains critical, as the serum drug concentration relates directly to both therapeutic response and toxic effect. Both maximum 1-h postinfusion peak and overall mean peak serum drug concentrations have been identified as significant predictors of therapeutic success for treatment of gram-negative bacteremia and pneumonia (16, 17). Moore et al. demonstrated a linear dose-response effect correlating the ratio of peak serum aminoglycoside concentration/MIC to clinical response in treatment of a broad array of documented gram-negative infections (15). Deziel-Evans et al. also noted that this ratio served as an accurate determinant of response in patients treated with aminoglycosides (10). Conversely, inadequate serum drug concentrations may result in treatment failure (16, 17). In addition, the narrow therapeutic effect/toxicity ratio for aminoglycosides mandates accuracy in predicting dosing parameters when attempting to reduce the risk of nephrotoxicity (4).

The physiologically linked variable volume of distribution at steady state (V_{ss}) is an important determinant of serum drug concentration. However, V_{ss} remains a poorly predicted pharmacokinetic parameter affecting aminoglycoside dosing in morbidly obese patients (TBW/IBW ratio >2 , where TBW is total body weight and IBW is ideal body weight). This is due, in part, to the variable penetration of these highly polar polycationic compounds into adipose tissue. Additional factors influencing estimations of V_{ss} in the population include increased projections of lean body mass and blood volume, as well as organ hypertrophy (2, 12).

Past investigators have utilized dosing weight correction factors (DWCs) to normalize predictions of V_{ss} in morbidly obese subjects by using 40% excess body weight (EBW [TBW - IBW]) added to IBW (2, 3, 6, 21). Guidelines outlining

aminoglycoside pharmacokinetic dosing parameters have not been formulated for moderately overweight patients (TBW/IBW ratio, 1.25 to 2.00) or underweight patients (TBW/IBW ratio, <1).

Prior calculations of DWCs have utilized Devine's formulae for determination of IBW, which derive IBW from height and weight data (8). Body mass index (BMI), defined as the weight/height² ratio (kilograms per square meter), has demonstrated good correlation with physiologic estimates of body fat and may serve as a more accurate basis for DWCF determinations (18).

Accurate assessment of dosing weight for patients whose body weight deviates from average allows for greater precision in the initial dosing of aminoglycosides and results in the ability to attain adequate immediate peak serum drug concentrations, deemed crucial to therapeutic success (16, 17). The specific goals of this study include determination of aminoglycoside pharmacokinetic parameters both for morbidly obese and moderately overweight patients and for underweight patients in order to describe DWCs for these groups based upon body weight ratio or BMI.

(This work was presented in part at the 94th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Honolulu, Hawaii, March 1993.)

Adult medical, surgical, or gynecologic patients, 18 years of age or older, with suspected or documented infection who received gentamicin or tobramycin for 48 h or longer between May 1982 and August 1992 were candidates for this study. All data were collected prospectively by the Clinical Pharmacy Service (CPS) of Bassett Healthcare. Of all patients receiving aminoglycosides at the institution during this period, 96% were monitored by the CPS. Initial dosing schemes were selected by the patient's physician and were generally not altered by the CPS unless it was determined that the initial dosing regimen was an over- or underdose (for an overdose, estimated trough concentrations are $>2 \mu\text{g/ml}$; for an underdose, estimated peak concentrations are $<5 \mu\text{g/ml}$). These estimates were derived from regression equations used to predict aminoglyco-

* Corresponding author. Mailing address: Dept. of Pharmacy Services, Bassett Healthcare, 1 Atwell Rd., Cooperstown, NY 13326. Phone: (607) 547-3399. Fax: (607) 547-6914.

TABLE 1. Demographic data for patients receiving aminoglycoside therapy grouped by body weight and BMI

Wt classification	Body wt grouping					BMI grouping				
	No. of patients			IBW (kg)	TBW (kg)	No. of patients			BMI (kg/m ²)	TBW (kg)
	Total	Male	Female			Total	Male	Female		
Total	1,708	916	792	62.3 ± 17.1	71.9 ± 19.9	1,708	916	792	22.3 ± 3.0	71.9 ± 19.9
Underweight	65	46	19	67.8 ± 10.0	45.6 ± 8.6 ^a	666	356	310	17.0 ± 2.2	58.1 ± 12.5 ^a
Avg wt	1,119	675	444	63.4 ± 10.5	65.2 ± 12.8	791	462	329	23.0 ± 2.1	75.3 ± 11.5
Overweight	524	194	330	59.1 ± 10.8	89.9 ± 21.1 ^a	251	98	153	34.0 ± 8.2	100.5 ± 22.1 ^a

^a $P \leq 0.05$ versus the average-weight group.

side pharmacokinetic parameters that we have previously published (5). Patients were seen by the CPS for pharmacokinetic evaluation and dosing adjustment within 72 h of institution of aminoglycoside therapy.

Pharmacokinetic dosing was performed by obtaining a pre-dose serum aminoglycoside concentration and two or three postdose concentrations. Nursing staff were instructed to infuse each dose over 30 min. The actual duration of each infusion was recorded. Postdose serum drug concentrations were obtained 30 min or longer after completion of the infusion, with two or three serum aminoglycoside concentrations being obtained over the dosing interval in an attempt to sample over at least one (estimated) half-life.

Serum aminoglycoside concentrations were determined by the fluorescence polarization immunoassay technique (1). Between-run coefficients of variation for gentamicin at concentrations of 1.0, 4.0, and 8.0 mg/liter were 1.9, 1.4, and 1.43%, respectively (14). Serum drug concentration data were analyzed by the method of Sawchuck and Zaske, with data fitted to a one-compartment intravenous infusion pharmacokinetic model (20). Serum aminoglycoside concentrations were adjusted to obtain a 1-h peak concentration (1 h after the beginning of the infusion) of 5 to 10 mg/liter (7 to 10 mg/liter for pneumonia) and trough concentrations of less than 2 mg/liter, irrespective of the dosing interval.

Prospective data collected included age, TBW, height, total V_{ss} (V_{sst}), relative V_{ss} per kilogram of TBW, aminoglycoside total body clearance, half-life, and creatinine clearance. Other data were prospectively collected as previously described (5). IBW was determined by the method of Devine (9). Creatinine clearance was calculated by the method of Cockcroft and Gault by using IBW (8). Patients with pathophysiologic conditions known to affect aminoglycoside V_{ss} (i.e., pancreatitis and cystic fibrosis) were excluded from the analysis.

Categorization of patients into underweight, overweight, and average weight groups was performed by using two parameters: body weight ratio and BMI. For IBW-based classification, a ratio of TBW/IBW was calculated for each patient. On the basis of V_{ss} (liters per kilogram), three independent patient groups were identified: those with TBW/IBW ratios of <0.75 (underweight patients), those with TBW/IBW ratios of 0.75 to 1.24 (average-weight patients), and those with TBW/IBW ratios of ≥ 1.25 (overweight patients). Further breakdown of the three patient groups into smaller subgroups by ratio units of 0.24 (i.e., 1.25 to 1.49 and 1.50 to 1.74, etc.) revealed no difference in DWCF versus that for the final three groups.

Secondly, for BMI-based classification, the BMI of weight/height² ratio (kilograms per square meter) was calculated for each patient. Patients were then assigned into underweight, average-weight, and overweight groups according to standard BMI definition. The weight groups were as follows: overweight male, BMI of ≥ 27.8 kg/m²; overweight female, BMI of ≥ 27.3

kg/m²; underweight male, BMI of <20.7 kg/m²; underweight female, BMI of <19.1 kg/m². Average-weight patients had BMI values between those limits (24).

Aminoglycoside pharmacokinetic parameters of total V_{ss} , relative V_{ss} per kilogram of TBW, and predicted peak serum drug concentration following a 2-mg/kg dose were determined for each of the TBW/IBW ratio categories. Concentrations calculated from this dose for the average-body-weight groups were used to determine the DWCF for the under- and overweight groups.

The data were analyzed with a Microvax II computer system by using version 6.07 of SAS (19). Differences in continuous variables between the TBW/IBW ratio and BMI groups were examined by three-by-one analysis of variance. Scheffe's test was applied when significant differences were found. All continuous variables are expressed as the mean \pm standard deviation. A P value of ≤ 0.05 was considered statistically significant.

Aminoglycoside pharmacokinetic parameters were examined for 1,708 patients. Table 1 illustrates demographic data for the six patient groups for both the IBW-based and BMI-based categorizations. For patients grouped according to IBW, TBWs of the underweight and overweight groups were statistically different in comparison with that of the reference average-weight group. BMI-based classification assigned more patients into lower weight groups than did IBW-based classification (the significance of which is unremarkable given the similarities of the DWCFs calculated by the two methods [see Table 3]).

Table 2 illustrates the V_{sst} , relative V_{ss} per kilogram of TBW, total body clearance, and calculated creatinine clearance for the patient groups by both methods of categorization. Our finding of an inverse relation between adiposity and relative V_{ss} per kilogram of TBW for both methods of weight categorization confirms that of other investigators (3, 7, 21, 23). Significant differences between classification groups were found for V_{sst} and V_{ss} . Additionally, women had significantly smaller V_{sst} (but not V_{ss}) values than men (data not shown). Calculated creatinine clearance was significantly less in overweight patients categorized as such by TBW/IBW ratio but not in those classified as overweight by the BMI method. No differences between sexes in calculated creatinine clearance were seen (data not shown). Total body clearance of aminoglycoside did not differ by weight or sex breakdown (sex data not shown).

Table 3 demonstrates DWCFs obtained for the six patient groups when equivalent predicted peak serum aminoglycoside concentrations were determined for a 2-mg/kg loading dose by using V_{sst} of the two average-weight groups as the references for the TBW/IBW ratio and BMI weight categorization methods, respectively. Incorporation of the DWCF into aminoglycoside pharmacokinetics mitigates variability in serum drug concentration obtained after dosing based upon either TBW or

TABLE 2. Absolute and relative V_{ss} values versus patient weight groups

Classification method	Patient wt grouping	CL_{CR}^a (ml/min/1.73 m ²)	V_{sst} (liters)	V_{ss} (liters/kg)	CL^b (ml/min/1.73 m ²)
TBW/IBW ratio	Underweight	70.1 ± 59.1	17.9 ± 5.4	0.39 ± 0.11	66.1 ± 41.0
	Avg wt	65.7 ± 34.7	22.6 ± 7.9	0.35 ± 0.11	73.9 ± 36.7
	Overweight	57.2 ± 29.5 ^c	25.4 ± 10.1 ^c	0.30 ± 0.12 ^c	72.7 ± 38.3
BMI	Underweight	64.2 ± 18.2	20.8 ± 7.3	0.36 ± 0.12	71.2 ± 37.6
	Avg wt	60.5 ± 29.7	24.3 ± 8.4	0.33 ± 0.11	75.9 ± 38.3
	Overweight	66.4 ± 39.0	26.8 ± 11.2 ^c	0.29 ± 0.13 ^c	73.4 ± 36.1

^a CL_{CR} , creatinine clearance.

^b CL , total body clearance.

^c $P \leq 0.05$ versus values for underweight and average-weight groups.

IBW alone. DWCFs for the underweight patients are similar for classifications by body weight and BMI, as are DWCFs derived for overweight patients by the two methods of body size categorization.

Past investigators have detected an inverse relation between adiposity and relative V_{ss} per kilogram of TBW (3, 21, 23). In studying aminoglycoside pharmacokinetics in underweight patients whose TBW equals 85% of IBW, Tointon et al. found the mean relative V_{ss} per kilogram of TBW to be significantly larger than that of controls (23). Similarly, in a 1982 report of gentamicin pharmacokinetics in malnourished children, Bravo et al. demonstrated a slight increase in relative V_{ss} per kilogram of TBW (7).

Multiple physiologic alterations combine in states of chronic malnutrition to derange pharmacokinetic parameters. These alterations include expanded volumes of extracellular fluid and diminished glomerular filtration rates, changes in total body fat synthesis, and changes in protein synthesis (13). Our identification of a DWCF exceeding 100% of TBW in underweight patients to normalize dosing weight, as well as an inverse relationship between adiposity and relative V_{ss} per kilogram of TBW, suggests that physiologic alterations may exist in our hospitalized population. Likewise, physiologic alterations associated with morbid obesity affect aminoglycoside pharmacokinetics. Penetration of polar aminoglycosides into adipose tissue occurs to some extent, as evidenced by the relative underdosing when V_{ss} is determined by IBW alone. Adipose tissue is known to contain 40 to 50% extracellular fluid compared with the same amount of nonadipose tissue (21). Forbes and Welle estimate a 20 to 40% increase in lean body mass in morbidly obese persons as long as sufficient protein intake is maintained (12). Expanded blood volume and organ hypertrophy in morbidly obese individuals also increase total V_{ss} (2). In sum, adipose tissue contributes less per volume than does nonadipose tissue to aminoglycoside V_{ss} , but its contribution is clinically significant (21). Sketris et al., in a study of aminogly-

coside pharmacokinetics in adult obstetrics and gynecology patients, estimated the relative V_{ss} for adipose tissue to be 0.05 liters/kg (22).

Consequently, investigators have formulated DWCFs to account for this increase in aminoglycoside V_{ss} in morbidly obese patients (2, 3, 6, 21). Bauer et al. identified a DWCF of (0.38 times the EBW) plus IBW for morbidly obese patients receiving amikacin (2). Investigators in 1979 cited a DWCF of (0.58 times the EBW)+IBW for morbidly obese patients receiving tobramycin (6). Unfortunately, clinical utility of these DWCFs for morbidly obese persons has been limited by a broad range of variability, as confirmed in a 1983 examination of aminoglycoside pharmacokinetics that yielded DWCFs with a sevenfold range (3). Many clinicians have relied upon a consensus DWCF of 40% (21).

The wide range of DWCFs for morbidly obese patients is not surprising, given that DWCFs attempt to compensate for increases in the aminoglycoside V_{ss} in adipose tissue, which is an unpredictable variable. Additionally, most researchers have restricted their DWCF calculations to populations of morbidly obese persons, rather than examining aminoglycoside pharmacokinetic parameters for the more commonly encountered moderately obese or overweight patients (TBW/IBW ratios of 1.25 to 2.00) (2, 3, 6).

Our investigation of aminoglycoside pharmacokinetics in a large population of adult hospitalized patients utilized two methods of assigning patients to body size categories. Our data suggest that different DWCFs are needed to determine aminoglycoside dosing weight in order to compensate for physiologic derangements of aminoglycoside V_{ss} in under- and overweight patients. The similarity of our DWCF of (0.43 times the EBW)+IBW for moderately obese or overweight patients (TBW/IBW ratio of 1.25 to 2.00) to the consensus DWCF of (0.40 times the EBW)+IBW for morbidly obese patients (TBW/IBW ratio, >2.00) suggests that use of the consensus DWCF can be extended to a broader patient population.

TABLE 3. DWCFs for both body weight and BMI methods of patient classification

Classification method	Patient wt grouping	DWCF	Serum aminoglycoside concn following 2-mg/kg loading dose (mg/liter)		
			TBW	IBW	DWCF
TBW/IBW ratio	Underweight	TBW × 1.13	5.1 ± 1.0	7.6 ± 1.1	5.8 ± 1.1
	Avg wt		5.8 ± 1.1		
	Overweight	0.43(EBW) + IBW	7.1 ± 1.7	4.7 ± 0.9	5.7 ± 1.3
BMI	Underweight	TBW × 1.11	5.7 ± 1.2		6.2 ± 1.3
	Avg wt		6.2 ± 0.9		
	Overweight	0.37(EBW) + IBW	7.5 ± 1.6		6.2 ± 1.1

These DWCFs, formulated in an effort to maximize clinical efficacy while minimizing toxic potential, are clinically applicable and lend accuracy to aminoglycoside pharmacokinetics.

Furthermore, the similarity between the DWCFs we obtained by the IBW and BMI methods of weight categorization suggests that for the purpose of aminoglycoside pharmacokinetics, assigning patients to weight groups by Devine's formulae for IBW remains valid and further refinements in estimations of body fat are not necessary.

We conclude that DWCFs for determination of aminoglycoside doses are 1.13 times the TBW for patients with TBW/IBW ratios of <0.75 and (0.43 times the EBW)+IBW for patients with TBW/IBW ratios of ≥ 1.25 . DWCFs based upon IBW are credible for assessing aminoglycoside pharmacokinetics. Individualized pharmacokinetic monitoring is recommended in order to ensure appropriate maintenance dosing.

We thank Kevin R. Franck for his technical assistance and Elizabeth Kelman for her preparation of the manuscript.

REFERENCES

1. **Abbott Laboratories.** 1990. TDX systems assay manual. Abbott Laboratories, Abbott Park, Ill.
2. **Bauer, L. A., R. A. Blouin, W. O. Griffen, Jr., K. E. Record, and R. M. Bell.** 1980. Amikacin pharmacokinetics in morbidly obese patients. *Am. J. Hosp. Pharm.* **37**:519-522.
3. **Bauer, L. A., W. A. D. Edwards, E. P. Dellinger, and D. A. Simonowitz.** 1983. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur. J. Clin. Pharmacol.* **24**:643-647.
4. **Bertino, J. S., Jr., L. A. Booker, P. A. Franck, P. L. Jenkins, K. R. Franck, and A. N. Nafziger.** 1993. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J. Infect. Dis.* **167**:173-179.
5. **Bertino, J. S., Jr., L. A. Booker, P. A. Franck, and B. A. Rybicki.** 1991. Gentamicin pharmacokinetics in patients with malignancies. *Antimicrob. Agents Chemother.* **35**:1501-1503.
6. **Blouin, R. A., H. J. Mann, W. O. Griffen, Jr., L. A. Bauer, and K. E. Record.** 1979. Tobramycin pharmacokinetics in morbidly obese patients. *Clin. Pharmacol. Ther.* **26**:508-512.
7. **Bravo, M. E., A. Arancibia, S. Japra, P. M. Carpentier, and A. N. Jahn.** 1982. Pharmacokinetics of gentamicin in malnourished infants. *Eur. J. Clin. Pharmacol.* **21**:499-504.
8. **Cockcroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* **16**:31-41.
9. **Devine, B. J.** 1974. Gentamicin pharmacokinetics. *Drug Intell. Clin. Pharm.* **8**:650-655.
10. **Deziel-Evans, L. M., J. E. Murphy, and M. L. Job.** 1986. Correlation of pharmacokinetic indices with therapeutic outcome in patients receiving aminoglycosides. *Clin. Pharm.* **5**:319-324.
11. **Etzel, J. V., A. N. Nafziger, and J. S. Bertino, Jr.** 1992. Variation in the pharmacokinetics of gentamicin and tobramycin in patients with pleural effusions and hypoalbuminemia. *Antimicrob. Agents Chemother.* **36**:679-681.
12. **Forbes, G. B., and S. L. Welle.** 1983. Lean body mass in obesity. *Int. J. Obesity* **7**:99-107.
13. **Krishnaswamy, K.** 1989. Drug metabolism and pharmacokinetics in malnourished children. *Clin. Pharmacokinet.* **17**(Suppl. 1):68-88.
14. **Levy, R. H., and L. A. Bauer.** 1986. Basic pharmacokinetics. *Ther. Drug Monit.* **8**:47-58.
15. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J. Infect. Dis.* **155**:93-99.
16. **Moore, R. D., C. R. Smith, and P. S. Lietman.** 1984. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J. Infect. Dis.* **149**:443-448.
17. **Moore, R. D., C. R. Smith, and P. S. Lietman.** 1984. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am. J. Med.* **77**:657-662.
18. **Revicki, D. A., and R. G. Israel.** 1986. Relationship between body mass indices and measures of adiposity. *Am. J. Public Health* **76**:992-994.
19. **SAS Institute.** 1985. SAS user's guide: statistics. SAS Institute, Cary, N.C.
20. **Sawchuck, R. J., and P. E. Zaske.** 1976. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J. Pharm. Biopharm.* **4**:183-195.
21. **Schwartz, S. N., G. J. Pazin, J. A. Lyon, M. Ho, and A. W. Pascille.** 1978. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J. Infect. Dis.* **138**:499-505.
22. **Sketris, I., T. Lesar, D. E. Zaske, and R. J. Cipolle.** 1981. Effect of obesity on gentamicin pharmacokinetics. *J. Clin. Pharmacol.* **21**:288-293.
23. **Tointon, M. M., M. L. Job, T. A. T. Peltier, J. E. Murphy, and E. S. Ward.** 1987. Alterations in aminoglycoside volume of distribution in patients below ideal body weight. *Clin. Pharm.* **6**:160-162.
24. **Williamson, D. F., H. S. Kahn, P. L. Remington, and R. F. Anda.** 1990. The 10-year incidence of overweight and major weight gain in US adults. *Arch. Intern. Med.* **150**:665-672.