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Variation in the Pharmacokinetics of Gentamicin and Tobramycin in Patients with Pleural Effusions and Hypoalbuminemia

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The pharmacokinetic parameters of gentamicin and tobramycin were evaluated and compared for 260 patients with pleural effusions and 1,049 patients without pleural effusions by chest radiograph. Pharmacokinetic data were collected prospectively and analyzed by using our aminoglycoside data base. Univariate analysis revealed that the patients with pleural effusions demonstrated significantly lower serum albumin concentrations, greater aminoglycoside volumes of distribution, longer elimination half-lives, and lower peak and higher trough concentrations in serum than the patients without pleural effusions. Patients with pleural effusions were significantly older and had lower total body weight. Stepwise multiple linear regression analysis revealed that lower total body weight and serum albumin concentration, presence of pleural effusion, and greater age were associated with significantly greater volumes of distribution. Calculated creatinine clearance, age, total body weight, and shock were associated with reduced aminoglycoside clearance in these patients.

Despite the increased availability of extended-spectrum beta-lactam and fluorinated quinolone antimicrobial agents, the aminoglycosides remain an important group of antibiotics in the treatment of severe gram-negative infections (6). Individualization of aminoglycoside dosing by determining serum drug concentrations has been employed as a means of maximizing efficacy while minimizing drug toxicity (2, 13, 15). Over the past few years, however, several disease states and clinical conditions have been demonstrated to alter aminoglycoside pharmacokinetics from normally accepted parameters (4, 7, 14, 19–22). Several authors have demonstrated that these highly polar compounds are capable of penetrating the pleural cavity and can be detected in pleural fluid (8, 9). It is possible that patients with pleural effusions possess altered pharmacokinetic parameters for aminoglycosides. The purpose of our investigation was to assess and describe the pharmacokinetics of these agents for two discrete adult populations: patients with pleural effusions demonstrable by chest radiograph and patients without pleural effusions by chest radiograph. In addition, since hypoalbuminemia has been shown to affect aminoglycoside pharmacokinetics (20), the serum albumin concentrations for these patients were examined to determine whether this nutritional deficiency was an important cofactor or whether pharmacokinetic alterations exist for patients with hypoalbuminemia.

This investigation utilized data which were collected prospectively by the Clinical Pharmacy Service of The Mary Imogene Bassett Hospital from January 1983 through August 1991. Patients eligible for the study included all adult patients (ages 18 years or older) who received either gentamicin or tobramycin and who had no pathophysiology (aside from impaired renal function) known to alter aminoglycoside pharmacokinetics (4, 11, 19, 21, 22). Patients with malignancies were not excluded from analysis because, as has been previously reported, aminoglycoside pharmacokinetics in patients with hematologic or solid malignancies are not altered (3). The prospective data that were collected included age, total body weight, calculated lean body weight, initial serum creatinine, serum albumin concentration, initial creatinine clearance (calculated by the method of Cockcroft and Gault [5]), the presence or absence of pleural effusions by chest radiograph (as read by a board-certified radiologist), and the presence or absence of shock. Shock was defined as either a systolic blood pressure of less than 80 mm Hg with a urine output of less than 500 ml/24 h or a decrease in the systolic blood pressure of greater than 50 mm Hg when the final systolic blood pressure was less than 100 mm Hg.

Within 72 h of the initiation of treatment with the antibiotic, aminoglycoside pharmacokinetic parameters were determined by the method of Sawchuck and Zaske (18) by utilizing a 30-min infusion and a three- or four-point determination. Blood for analysis of serum aminoglycoside concentration was obtained predose, and two or three additional samples were obtained after the infusion. Serum aminoglycoside concentration data were analyzed by a one-compartment, intravenous-infusion pharmacokinetic model (12). Serum aminoglycoside concentrations were adjusted to obtain 1-h peak concentrations (1 h after the beginning of the infusion) of 5 to 10 mg/liter and trough concentrations of less than 2 mg/liter, regardless of dosing interval.

Serum aminoglycoside concentrations were determined by the fluorescence polarization immunoassay technique. Between-run coefficients of variation for gentamicin at concentrations of 1.0, 4.0, and 8.0 mg/liter were 2.2, 1.5, and 0.9%, respectively, while those for tobramycin at the same concentrations were 1.8, 1.9, and 1.2%, respectively (1).

The data were analyzed on a Microvax II computer system by using version 5 of SAS (SAS Institute) (17). Pearson's chi-square analysis was used to detect differences in discrete variables. Differences in continuous variables between the two groups (patients with and without pleural effusions by chest radiograph) were examined by a two-tailed Student's t test for unpaired observations. Stepwise multiple linear regression analysis was then utilized to determine whether the variables found to be significantly different affected the pharmacokinetic parameters of volume of distribution or total body clearance independently of other confounding variables. All variables found to be significantly different between the two groups by univariate analysis,

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TABLE 1. Patient demographics and pharmacokinetic characteristics

Parameter	Value for each patient group[a]		P value
	Pleural effusions present	Pleural effusions absent	
Gender distribution	132 (male) 128 (female)	562 (male 487 (female)	0.42
Aminoglycoside used			
Gentamicin	177	872	0.38
Tobramycin	38	222	
Age (yr)	64.0 ± 14.4	61.2 ± 17.4	0.008
Ideal body wt (kg)	61.1 ± 10.6	62.0 ± 10.8	0.24
Total body wt (kg)	67.7 ± 16.4	72.1 ± 20.3	0.0002
Serum albumin (g/dl)	2.8 ± 0.7	3.2 ± 0.7	0.0001
Estimated CL_{CR} (ml/min/1.73 m^2)[b]	59.6 ± 28.1	63.3 ± 31.5	0.06
Initial dose (mg/kg)	1.5 ± 0.4	1.4 ± 0.4	0.23
Vol of distribution (liter/kg of total body wt)	0.37 ± 0.12	0.33 ± 0.11	0.0001
Aminoglycoside clearance (ml/min/1.73 m^2)	72.5 ± 41.6	75.9 ± 35.9	0.2
Half-life (h)	5.2 ± 4.6	4.2 ± 3.0	0.0006
Initial peak concn (mg/liter)	4.5 ± 1.6	4.8 ± 2.6	0.03
Initial trough concn (mg/liter)	0.90 ± 0.8	0.80 ± 0.7	0.03

[a] Values are numbers of patients or means ± standard deviations. Presence or absence of pleural effusions was determined by chest radiograph.
[b] CL_{CR}, calculated creatinine clearance (by the method of Cockcroft and Gault [5]).

which would be identified prior to pharmacokinetic analysis, were included as independent variables in the multiple linear regression analysis. In addition, estimated creatinine clearance, although not significant by univariate analysis, was placed in the regression equation for aminoglycoside total body clearance, since aminoglycoside pharmacokinetics are known to be correlated to a degree with creatinine clearance. Interaction terms were used to determine whether significant interactions between the independent variables occurred. All continuous variables are expressed as the mean ± standard deviation. A P value of ≤ 0.05 was considered to be significant for all statistical tests.

A total of 1,309 patients were monitored over the specified time period and were eligible for inclusion in the study. A total of 260 patients had radiographically identifiable pleural effusions, while the remaining 1,049 patients demonstrated no evidence of effusion. Of the 260 patients with pleural effusions, 50 met the definition for shock, while 66 of the 1,049 patients without pleural effusions met the definition for shock ($P < 0.0001$).

Table 1 summarizes the demographic and pharmacokinetic parameters of the patients. Patients with pleural effusions by radiograph had total body weights significantly lower than those of patients without pleural effusions and were significantly older. Patients with pleural effusions also had significantly lower serum albumin concentrations, greater volumes of distribution, longer elimination half-lives, lower initial peak concentrations, and higher initial trough concentrations, compared with the control population. Univariate analysis failed to demonstrate significant differences in gender, dose of aminoglycoside administered, ideal body weight, initial aminoglycoside dose, initial calculated creatinine clearance, or initial total body clearance of drug between patients with and patients without pleural effusions by chest radiograph.

Stepwise multiple linear regression analysis revealed that four variables were associated with an increased volume of distribution: increasing age, decreasing serum albumin concentration, total body weight, and the presence of pleural effusion by chest radiograph (Table 2).

Multiple linear regression analysis failed to demonstrate any effect of pleural effusion on total body clearance of aminoglycoside (Table 3). Calculated creatinine clearance and total body weight were directly associated with aminoglycoside total body clearance, while age and shock were indirectly associated with total body clearance. No interaction terms were statistically significant.

It has been noted that several clinical conditions are associated with an increased volume of distribution for aminoglycoside antibiotics (11, 14, 19, 20, 22). Our investigation has demonstrated that patients with pleural effusions by chest radiograph have larger volumes of distribution resulting in significantly diminished peak drug concentrations in serum, compared with control patients. Therefore, the presence of pleural effusions in a patient may necessitate the use of relatively large aminoglycoside doses to achieve

TABLE 2. Stepwise multiple linear regression analysis of factors predicting volume of distribution

Variable	Value for		P value
	Parameter estimate	Total model variance[a]	
Total body wt	−0.0015	0.08	0.0001
Serum albumin concn	−0.023	0.1097	0.0001
Pleural effusions	0.0227	0.1158	0.008
Age	0.0004	0.1194	0.04

[a] Total model variance is the R^2 value for the significant variables.

TABLE 3. Stepwise multiple linear regression analysis of factors predicting aminoglycoside clearance

Variable	Value for		P value
	Parameter estimate	Total model variance[a]	
Calculated creatinine clearance	0.582	0.3437	0.0001
Age	−0.3933	0.3656	0.0001
Total body wt	0.1453	0.3713	0.0024
Shock	−7.425	0.3745	0.021

[a] Total model variance is the R^2 value for the significant variables.

desirable serum drug concentrations. This finding is not unexpected, since the diffusion of aminoglycoside antibiotics into pleural fluid has been established (8, 9).

Knowing whether disease states result in alterations in aminoglycoside pharmacokinetics is important, since Moore et al. have demonstrated the importance of the ratio of peak aminoglycoside concentration to MIC (13). These authors have demonstrated that this ratio is a major determinant of the clinical response to aminoglycoside therapy. Thus, knowledge of diseases which can alter aminoglycoside pharmacokinetics may result in more appropriate empirical dosing before individual pharmacokinetic parameters are obtained.

It was not possible to estimate the quantities or the compositions of the effusions in our patients. Pleural effusions were diagnosed by radiograph, and we are unaware of any accurate method of determining this information from radiograph analysis.

Volumes of distribution for our patients were dependent on age, total body weight, presence of pleural effusion, and serum albumin concentration. Our finding that patients with diminished serum albumin concentrations demonstrate expanded volumes of distribution confirms the findings of other investigators (20). However, the increased volume of distribution associated with advancing age for our patients with pleural effusions is in direct contrast to findings for the pediatric population (16). On the basis of body composition changes, one might expect that volume of distribution would decrease with increasing age because of a reduction in total body water (10). It is possible that the elderly patients studied had an increase in total body water as the result of congestive heart failure or other disease states that resulted in the development of pleural effusions and larger volumes of distribution.

The total body clearances of aminoglycosides were not found to differ significantly between patients with pleural effusions or hypoalbuminemia and controls ($P > 0.4$).

In summary, we evaluated aminoglycoside pharmacokinetics for two adult populations: patients with pleural effusions and patients without pleural effusions by chest radiograph. Even though no significant difference in total body clearance between the two groups was observed, patients with pleural effusions, lower total body weights, advanced ages, and lower serum albumin concentrations demonstrated significantly greater aminoglycoside volumes of distribution and, thus, longer elimination half-lives. These alterations in pharmacokinetic parameters resulted in lower peak and higher trough serum drug concentrations for patients with pleural effusions or hypoalbuminemia, compared with controls. Therefore, individualized pharmacokinetic monitoring is recommended in order to optimize aminoglycoside therapy for these patients.

REFERENCES

1. **Abbott Laboratories.** 1990. TDX systems assay manual. Abbott Laboratories, Abbott Park, Ill.
2. **Barza, M., and M. Lavermann.** 1978. Why monitor serum levels of gentamicin? Clin. Pharmacokinet. **3**:202–215.
3. **Bertino, J. S., Jr., L. A. Booker, P. Franck, and B. Rybicki.** 1991. Gentamicin pharmacokinetics in patients with malignancies. Antimicrob. Agents Chemother. **35**:1501–1503.
4. **Carr, M. R., S. P. Dick, J. Bordley, and J. S. Bertino, Jr.** 1988. Gentamicin dosing requirements in patients with acute pancreatitis. Surgery **103**:533–537.
5. **Cockcroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16**:31–41.
6. **Edson, R. S., and C. L. Terrell.** 1987. The aminoglycosides: streptomycin, kanamycin, gentamicin, tobramycin, amikacin, netilmicin and sisomicin. Mayo Clin. Proc. **62**:916–920.
7. **Gill, M. A., and J. W. Kern.** 1979. Altered gentamicin distribution in ascitic patients. Am. J. Hosp. Pharm. **36**:1704–1706.
8. **Higuchi, K., A. Kajiki, M. Takamoto, and T. Ishibashi.** 1982. Clinical trial of netilmicin in infections of respiratory organs and studies on its penetration in pleural fluid II. Jpn. J. Antibiot. **35**:667–674.
9. **Kiss, J. I., E. Faragio, L. Kionya, E. Fabian, and F. Moriczet.** 1975. Clinico-pharmacological examination of gentamicin in thoracic surgery. Int. J. Clin. Pharmacol. Biopharm. **12**:372–380.
10. **Lamy, P. P.** 1982. Comparative pharmacokinetic changes and drug therapy in an older population. J. Am. Geriatr. Soc. **30**(Suppl. 1):S11–S19.
11. **Levy, J., A. L. Smith, J. R. Koup, J. Williams-Warren, and B. Ransey.** 1984. Disposition of tobramycin in patients with cystic fibrosis: a prospective controlled study. J. Pediatr. **105**:117–124.
12. **Levy, R. H., and L. A. Bauer.** 1986. Basic pharmacokinetics. Ther. Drug. Monit. **8**:47–58.
13. **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 concentrations. J. Infect. Dis. **155**:93–99.
14. **Niemiec, P. W., M. D. Allo, and C. F. Miller.** 1987. Effect of altered volume of distribution on aminoglycoside levels in surgical intensive care. Arch. Surg. **122**:207–212.
15. **Noone, P., T. M. C. Parsons, J. R. Pattison, R. C. B. Slack, D. Garfield-Davies, and K. Hughes.** 1974. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. Br. Med. J. **1**:477–481.
16. **Pechere, J. C., and R. Dugal.** 1979. Clinical pharmacokinetics of aminoglycoside antibiotics. Clin. Pharmacokinet. **4**:170–199.
17. **SAS Institute.** 1985. SAS user's guide: statistics. SAS Institute, Cary, N.C.
18. **Sawchuck, R. J., and D. E. Zaske.** 1976. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions; gentamicin in burn patients. J. Pharmacokinet. Biopharm. **4**:183–195.
19. **Sketris, I., T. Lesar, D. E. Zaske, and R. J. Cipolle.** 1981. Effect of obesity on gentamicin pharmacokinetics. J. Clin. Pharmacol. **21**:288–294.
20. **Zarowitz, B. J., A. M. Pilla, and J. Popovich.** 1990. Expanded gentamicin volume of distribution in patients with indicators of malnutrition. Clin. Pharm. **9**:40–44.
21. **Zaske, D. E., R. J. Cipolle, R. G. Strate, and W. F. Dickes.** 1981. Increased gentamicin dosage requirements: rapid elimination in 249 gynecology patients. Am. J. Obstet. Gynecol. **139**:896–900.
22. **Zaske, D. E., R. J. Sawchuck, D. N. Gerding, and R. G. Strate.** 1976. Increased dosage requirements of gentamicin in burn patients. J. Trauma **16**:824–838.