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# Influence of Age on Amikacin Pharmacokinetics in Patients without Renal Disease. Comparison with Gentamicin and Tobramycin

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**Summary.** The influence of age on amikacin pharmacokinetics was examined in 87 patients with normal renal function. All patients had a gram negative infection, were febrile, weighed within 20% of their ideal body weight, did not receive penicillin antibiotics concurrently, had normal hematocrits and had a measured 24 h creatinine clearance greater than 80 ml/min/1.73 $m^2$. 31 patients were 20–39 years old, 27 patients were between the ages of 40–59 years, and 29 patients were 60–79 years old. These patients were compared to patients in similar previous studies who received gentamicin or tobramycin. No significant differences in clearance, volume of distribution or half-life were found due to age within a single drug group (amikacin, gentamicin, or tobramycin) or among the 3 drug groups. However, a substantial amount of intersubject variability existed in the calculated pharmacokinetic parameters. Patients over 40 years old tended to be underdosed with amikacin and the other 2 aminoglycosides. The average amikacin dose needed to achieve the desired steady-state concentrations was 18.9 mg/kg/day. 52% of the amikacin patients required doses greater than the recommended maximum (15 mg/kg/day). Since aminoglycoside pharmacokinetics do not change as age increases, doses do not need to be arbitrarily changed in older patients with normal renal function.

**Key words:** amikacin, pharmacokinetics; gram negative infection, normal renal function, gentamicin, tobramycin, interpatient variability

The aminoglycoside antibiotics are widely used in the treatment of gram negative infections. Serious toxicities are possible when serum concentrations exceed therapeutic levels. Excessive peak concentrations have been associated with ototoxicity [1], and high trough concentrations may cause nephrotoxicity [2]. Because of the narrow therapeutic range, any changes in aminoglycoside pharmacokinetics that occur due to aging could be clinically important. The purpose of this study was to examine the influence of aging on amikacin pharmacokinetics in a group of patients with normal renal function and gram negative infections. Additionally, we compared these results to those previously obtained with gentamicin [3] and tobramycin [4].

## Methods

Eighty-seven patients with normal renal function (24 h creatinine clearance > 80 ml/min/1.73 $m^2$) receiving intravenous amikacin for the treatment of a gram negative infection were studied (Table 1). Sites of infection are given in Table 2. All patients were within 20% of their ideal body weight [5], had a normal haematocrit, did not receive concurrent penicillin therapy, and were febrile (range: 37.4–38.7 °C orally).

Amikacin pharmacokinetic parameters were determined as a part of these patients' routine medical care. Initial serum concentrations were obtained during the first 2 days of therapy. The elimination rate constant (K) was determined by means of linear regression from the slope of the post-infusion serum concentration versus time graph plotted on natural logarithum coordinates. Serum samples were obtained before the dose was administered and at 0.25, 1 to 2, and 3–5 h after a 1 h infusion. Half-life was computed by taking the quotient of 0.693 and K. The volume of distribution was calculated using the following formula [6, 7]:

$$V = \frac{ko\ (1 - e^{-Kt'})}{K\ [C_{max} - (C_{min}\ e^{-Kt'})]}$$

**Table 1.** Patient characteristics (mean ± SD)

| Age group [years] | Number of patients | Age [years] | Weight [kg] | Sex | Length of therapy [days] |
|---|---|---|---|---|---|
| Amikacin | | | | | |
| 20–39 | 31 | 31.2 ± 6.2 | 71.3 ± 5.1 | 18M/13F | 11 ± 3 |
| 40–59 | 27 | 49.1 ± 5.6 | 74.5 ± 6.5 | 14M/13F | 13 ± 4 |
| 60–79 | 29 | 71.2 ± 5.9 | 70.3 ± 5.9 | 14M/15F | 12 ± 3 |
| Gentamicin[a] | | | | | |
| 20–39 | 51 | 28.8 ± 5.4 | 72.8 ± 6.0 | 27M/24F | 14 ± 4 |
| 40–59 | 59 | 51.2 ± 6.1 | 70.6 ± 7.1 | 35M/24F | 12 ± 2 |
| 60–79 | 63 | 70.5 ± 5.7 | 74.2 ± 5.3 | 30M/33F | 14 ± 3 |
| Tobramycin[b] | | | | | |
| 20–39 | 25 | 30.1 ± 6.1 | 72.6 ± 5.3 | 15M/10F | 13 ± 3 |
| 40–59 | 23 | 50.5 ± 5.4 | 69.8 ± 6.3 | 12M/11F | 11 ± 4 |
| 60–79 | 29 | 69.6 ± 5.7 | 74.1 ± 7.1 | 14M/15F | 14 ± 3 |

[a] Reference 3; [b] reference 4

**Table 2.** Site of infection[c]

| Infection type | Amikacin | Gentamicin[a] | Tobramycin[b] |
|---|---|---|---|
| Pneumonia | 63 (72) | 120 (69) | 57 (73) |
| Urinary tract | 11 (13) | 19 (11) | 12 (16) |
| Wound | 8 (9) | 24 (14) | 5 (7) |
| Sepsis | 5 (6) | 10 (6) | 3 (4) |

[a] Reference 3; [b] reference 4; [c] numbers in parenthesis are percentages

where ko is the amikacin infusion rate in mg/h, t′ is the infusion time in h (always 1 h), $C_{max}$ is the amikacin serum concentration in μg/ml immediately after a 1 h infusion as computed by the regression program, and $C_{min}$ is the actual serum concentration in μg/ml immediately before infusion. Total body clearance was calculated by taking the product of K and V. This method has been shown to reliably calculate pharmacokinetic constants for aminoglycosides so that doses may be rapidly individualized [6, 7]. To confirm the pharmacokinetic values in our patients, steady-state $C_{max}$ and $C_{min}$ amikacin serum concentrations were obtained 2 to 3 days after the initial determination and compared with those projected using a linear one-compartment intermittent infusion model [8]. Doses for each group were adjusted to keep $C_{max}$ levels between 20 and 30 μg/ml and $C_{min}$ less than 5 μg/ml at steady-state.

Serum and urine creatinine concentrations were determined by autoanalyzer using a modified Jaffe kinetic reaction (Astra, Beckman Instruments, Fullerton, CA, USA).

A radioimmunoassay (Monitor Science, Newport Beach, CA, USA) was used to determine serum amikacin concentrations. Specimens were analyzed in duplicate and the mean was reported. The interday coefficient of variation was < 7% over the therapeutic range.

For the purpose of statistical analysis, amikacin patients were divided into 3 arbitrary age groups: 20–39, 40–59, and 60–79 years. Linear regression was performed individually for each of the 3 pharmacokinetic parameters versus age. The amikacin patients were also compared to patients receiving gentamicin [3] or tobramycin [4] in similar previous studies. Analysis of variance was used to test for statistical significance among drugs and age groups. Chi-square analysis was performed to detect population differences in site of infection, sex, or incidence of toxicities among the 3 drug treatments. A $p < 0.05$ was considered to be statistically significant.

## Results

The pharmacokinetic parameters for the amikacin patients are given in Table 3. Amikacin clearance, volume of distribution, and half-life were not significantly different among the age groups. Linear regression was performed individually for each of the 3 pharmacokinetic parameters versus age. Poor correlation coefficients ($r$) were found for the clearance ($r = -0.013$), half-life ($r = 0.032$), and volume of distribution ($r = 0.041$) plots.

Dosage adjustments were necessary in 76% of the patients in order to achieve the desired steady-state concentrations. Daily doses increased significantly from 13.7 ± 3.3 to 18.9 ± 4.3 mg/kg/day ($p < 0.01$, paired Student's $t$-test). Doses were administered every 8 h. The measured steady-state concentrations compared favorably with the projected values. The actual steady-state concentrations were $C_{max}$ = 26.3 ± 3.7 μg/ml and $C_{min}$ = 3.0 ± 1.2 μg/ml, and the projected steady-state values were $C_{max}$ = 24.7 ± 4.3 μg/ml and $C_{min}$ = 2.6 ± 1.0 μg/ml ($p > 0.05$, paired Student's $t$-test).

There were no significant differences for any of the pharmacokinetic parameters among the aminoglycosides. Half-lives, volumes of distribution and clearance were similar for all 3 drugs in each of the 3 patient age groups (Table 3). Toxicity rates were also similar for the drugs in this patient population with normal renal function. 5 amikacin patients (5.8%) had an increase in serum creatinine greater than 0.5 mg/dl over baseline. This compares with 3.5% for gentamicin [3] and 3.9% for tobramycin [4]. None of the drugs produced clinically detectable ototoxicity. There were no significant differences for any patient characteristics among the 3 drug groups (Tables 1 and 2).

**Table 3.** Pharmacokinetic parameters (mean ± SD)

| Age group [years] | Serum creatinine [mg/dl] | Creatinine clearance (ml/min/1.73 $m^2$) | Half-life [h] | Volume of distribution [l/kg] | Total body clearance [ml/min/kg] |
|---|---|---|---|---|---|
| Amikacin | | | | | |
| 20–39 | 0.7 ± 0.4 | 105.1 ± 10.8 | 2.3 ± 0.44 | 0.27 ± 0.06 | 1.32 ± 0.55 |
| 40–59 | 0.9 ± 0.3 | 101.3 ± 11.7 | 2.1 ± 0.40 | 0.24 ± 0.04 | 1.27 ± 0.47 |
| 60–79 | 0.8 ± 0.2 | 98.6 ± 9.9 | 2.5 ± 0.55 | 0.22 ± 0.05 | 1.23 ± 0.53 |
| Gentamicin[a] | | | | | |
| 20–39 | 0.8 ± 0.4 | 102.7 ± 12.3 | 2.2 ± 0.51 | 0.23 ± 0.05 | 1.29 ± 0.52 |
| 40–59 | 0.7 ± 0.4 | 103.9 ± 11.1 | 2.1 ± 0.41 | 0.27 ± 0.04 | 1.35 ± 0.48 |
| 60–79 | 0.8 ± 0.3 | 99.1 ± 10.0 | 2.4 ± 0.50 | 0.26 ± 0.05 | 1.31 ± 0.39 |
| Tobramycin[b] | | | | | |
| 20–39 | 0.8 ± 0.2 | 104.2 ± 11.4 | 2.3 ± 0.54 | 0.25 ± 0.04 | 1.34 ± 0.48 |
| 40–59 | 0.9 ± 0.3 | 100.7 ± 10.7 | 2.2 ± 0.51 | 0.26 ± 0.03 | 1.44 ± 0.38 |
| 60–79 | 0.9 ± 0.3 | 97.6 ± 9.3 | 2.4 ± 0.48 | 0.25 ± 0.04 | 1.25 ± 0.36 |

[a] Reference 3; [b] reference 4

## Discussion

The influence of age on drug pharmacokinetics is an important area of investigation. Because of the complex changes that occur during the aging process, it is very difficult to predict the impact that age will have on the kinetics of a particular drug. When studying the effects of aging on drug pharmacokinetics, it is important to exclude other factors that may influence the disposition of the drug. Our patients had normal renal function and haematocrit values, were febrile, weighed within 20% of their ideal body weight, and did not receive penicillin therapy concurrently. Each of these factors can influence aminoglycoside pharmacokinetics [9–13]. By examining this relatively homogenous group of patients, the effect of age on amikacin pharmacokinetics can be better studied.

A large amount of interpatient variability was found in the kinetic parameters of the patients receiving amikacin. Half-lives ranged from 1.0–3.6 h, clearance ranged 0.67–2.82 ml/min/kg and volumes of distribution ranged from 0.15–0.32 l/kg. Similar ranges have been found for tobramycin [4] and gentamicin [3].

Dosage adjustments were required in 66 patients in order to attain the desired steady-state concentrations. Seven needed dosage reductions while 59 required dosage increases. Before individualization of dosage, there was a tendency to underdose patients over 40 years old.

47 (80%) of the patients requiring increased doses were greater than 40 years old. The reason for the arbitrary dosage reduction in older patients was probably due to the reported decline in creatinine clearance with age [14]. However, recent studies reveal that the decline may not be as severe as originally thought. Rowe et al. [15] studied the relationship between creatinine clearance and age in 548 men with an age range 17–84 years. While the average creatinine clearance declined with age, the mean creatinine clearance for the 75–84 year age group was 96.9 ml/min/1.73 $m^2$. The present investigation and previous studies with tobramycin [4] and gentamicin [3] indicate that older patients with normal renal function have pharmacokinetic constants similar to younger patients with normal renal function (Table 3). Elderly patients with decreased renal function may need smaller doses [16]. Individualization of dose may be particularly useful in older patients.

The model used to calculate the pharmacokinetic parameters worked well in achieving the desired steady-state concentrations. This helped to varify the validity of the parameters. The daily amikacin dose required to attain the desired concentrations was 18.9 ± 4.3 mg/kg/day. This value exceeds the maximum suggested daily dose of 15 mg/kg/day. 52% of the patients required doses that exceeded the maximum. These findings are similar to those reported for gentamicin [3] and tobramycin [4].

In summary, amikacin pharmacokinetics were not influenced by age in patients with normal renal function. When amikacin was compared to gentamicin and tobramycin, no significant differences in kinetic parameters were found due to age or type of aminoglycoside. Based on our data, aminoglycoside doses do not need to be changed arbitrarily in older patients with normal renal function. Due to the large amount of interpatient variability, individualization of aminoglycoside doses using serum concentrations may help to rapidly achieve desired steady-state levels.

## References


1. Mawer GE, Ahmad R, Dobbs SM (1974) Prescribing aids for gentamicin. Br J Clin Pharmacol 1: 45–50
2. Dahlgren JG, Anderson ET, Hewitt WL (1975) Gentamicin blood levels: a guide to nephrotoxicity. Antimicrob Agents Chemother 8: 58–62
3. Bauer LA, Blouin RA (1982) Gentamicin pharmacokinetics: Effect of aging in patients with normal renal function. J Am Geriatrics Soc 30: 309–11
4. Bauer LA, Blouin RA (1981) Influence of age on tobramycin pharmacokinetics in patients with normal renal function. Antimicrob Agents Chemother 20: 587–9
5. Devine BJ (1974) Gentamicin therapy. Drug Intell Clin Pharm 8: 650–655
6. Sawchuk RJ, Zaske DE (1976) Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions. J Pharmacokinet Biopharm 4: 183–195
7. Sawchuk RJ, Zaske DE, Cipolle RJ, Wargin WA, Strate RG (1977) Kinetic model for gentamicin dosing with the use of individual patient parameters. Clin Pharmacol Ther 21: 362–369
8. Gibaldi M, Perrier D (1975) Pharmacokinetics. Marcel Dekker, New York
9. Cutler RE, Gyselynck AM, Fleet P, Forrey AW (1972) Correlation of serum creatinine concentration and gentamicin half-life. J Am Med Assoc 219: 1037–41
10. Barza M, Brown RB, Shen D, Gibaldi M, Weinstein L (1975) Predictability of blood levels of gentamicin in man. J Infect Dis 132: 165–174
11. Pennington JE, Dale DC, Reynolds HY (1975) Gentamicin sulfate pharmacokinetics: Lower levels of gentamicin during fever. J Infect Dis 132: 270–275
12. Bauer LA, Blouin RA, Griffen WO, Record KE, Bell RM (1980) Amikacin pharmacokinetics in morbidly obese patients. Am J Hosp Pharm 37: 517–522
13. Ervin FR, Bullock WE, Nuttall CE (1976) Inactivation of gentamicin by penicillins in patients with renal failure. Antimicrob Agents Chemother 9: 1004–1011
14. Gault MH, Cockcroft DW (1975) Creatinine clearance and age. Lancet 2: 612–613
15. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW (1976) The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. J Gerontol 31: 155–163
16. Zaske DE, Irvine P, Strand LM, Strate RG, Cipolle RJ, Rotschafer J (1982) Wide interpatient variations in gentamicin dose requirements for geriatric patients. J Am Med Assoc 248: 3122–3126


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