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Bronchial Secretion Levels of Amikacin

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Amikacin was given to 14 noninfected men as three consecutive intramuscular injections (7.5 mg/kg) at 12-h intervals. Serum and bronchial secretion specimens were obtained at various times during flexible fiberoptic bronchoscopy after the final dose. Serum and bronchial secretion concentrations obtained between 1.5 and 2.0 h after the final dose ranged from 17 to 40 μg/ml and 2.3 to 8.4 μg/ml with a mean of 23.7 ± 2.9 and 5.23 ± 1.5 μg/ml, ±1 standard error of the mean, respectively. The highest bronchial secretion concentration in each subject correlated with the highest serum concentration ($r = 0.83$, $P < 0.001$), and all concurrent serum and bronchial secretion concentrations demonstrated a significant correlation ($r = 0.82$, $P < 0.001$). Clearance occurred at the same rate (half-life serum = 2.84 h; half-life of bronchial secretion = 2.60 h, $P > 0.5$). The mean bronchial secretion concentration of the 15 specimens obtained more than 7 h after the final dose was less than 1.0 μg/ml, with a range from 0.3 to 1.6 μg/ml. It is concluded that amikacin may achieve minimal inhibitory concentrations for many gram-negative bacteria in the bronchial secretions of noninfected patients 1 to 2 h after the final dose. However, levels fall below the reported minimal inhibitory concentrations against negative bacteria 6 to 7 h after the final dose. Furthermore, bronchial secretion levels may never reach the minimal inhibitory concentration against *Pseudomonas aeruginosa*.

The aminoglycosides are widely used for the treatment of gram-negative bronchopneumonia. A critical factor in their effectiveness is their ability to reach adequate concentrations in the infected lung or bronchial secretions. Since it is difficult to measure antibiotic concentrations in the lung, it has been suggested that the concentration gradient between blood and bronchial secretions may provide indirect evidence of parenchymal concentrations (19). In addition, the concentration of antibiotics in bronchial secretions may be an important factor in their activity in the lung.

Conventional doses of amikacin have been shown to achieve serum concentrations above the minimal inhibitory concentrations (MICs) for many gram-negative organisms (12, 13). If a similar level were also produced by these doses in bronchial secretions it might explain, at least in part, the documented effectiveness of this aminoglycoside in the therapy of gram-negative pneumonias (2, 22).

This study reports the concentration of amikacin in the blood and bronchial secretions of noninfected patients.

MATERIALS AND METHODS

Fourteen adult males, ranging from 47 to 71 years of age, gave informed consent to participate in the study. These patients were to have diagnostic flexible fiberoptic bronchoscopy for suspected pulmonary carcinoma. All had normal blood urea nitrogen, serum creatinine, and urinalysis results and were afebrile. The chest roentgenograms did not suggest infection and none of the patients was receiving other antibiotics.

To achieve steady-state concentrations, three consecutive intramuscular injections of amikacin (7.5 mg/kg) were administered at 12-h intervals. Thirty minutes before flexible fiberoptic bronchoscopy, patients were premedicated intramuscularly with 5 to 10 mg of morphine sulfate.

Flexible fiberoptic bronchoscopy was scheduled so that blood and bronchial secretion specimens could be collected in four patients for each of the following time intervals after the final dose of amikacin: 0 to 3, 4 to 6, and 7 to 9 h, respectively. It was intended to obtain three concomitant specimens from each patient at 30-min intervals during the time span for each of the three groups; because of technical problems this was not possible in every instance. Furthermore, since flexible fiberoptic bronchoscopy was performed for diagnostic purposes it was never intentionally prolonged to obtain specimens. Thus, three concomitant bronchial secretion and blood specimens at the planned intervals were not obtained at the desired time in every patient.

Endobronchial intubation and bronchoscopy were performed in the usual manner (24). Lidocaine was not applied to the area from which bronchial secretions were sampled. Bronchial secretions were ob-

tained from the lobar orifices of either lung and, together with the serum specimens, were frozen at −20°C until completion of the study. Amikacin concentrations were determined by radioimmunoassay (15).

Least-squares linear regression analysis was performed for all correlations and to determine the slope of the line and calculate the indicated half-life depicted in Fig. 1 and 2.

RESULTS

Serum and bronchial secretion concentrations for each patient are listed in Table 1. Concomitant specimens could not be obtained in every instance, either because of bronchial bleeding during the diagnostic procedure or lack of adequate bronchial secretions. The highest concentrations of amikacin in serum (40.0 μg/ml) and bronchial secretions (8.4 μg/ml) were encountered 1.5 h after the final dose (patient 1). The mean concentrations at this time were 27.3 μg/ml (four specimens) and 6.7 μg/ml (two specimens) in blood and bronchial secretions, respectively. Mean concentrations 2 h after the last dose were 19.0 μg/ml (three specimens) and 3.6 μg/ml (two specimens), respectively. Concurrent serum and bronchial secretion concentrations ($n = 30$) were significantly correlated ($r = 0.82$, $P < 0.001$) (Fig. 3). The highest serum concentra-

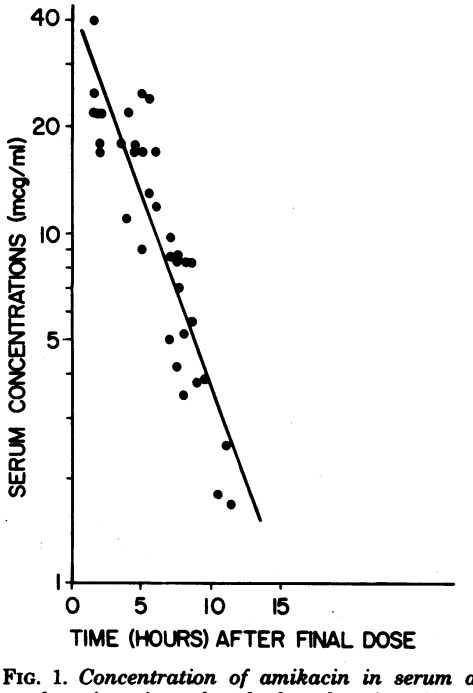

FIG. 1. *Concentration of amikacin in serum as plotted against time after the last dose ($n = 37$, $r = -0.90$).*

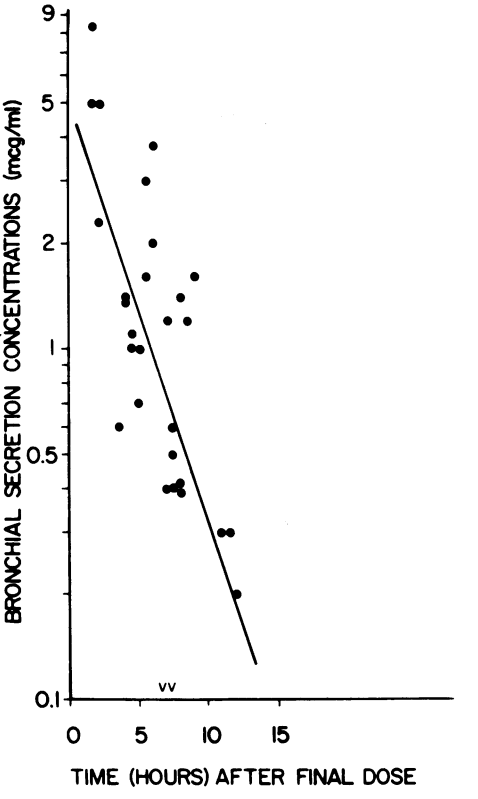

FIG. 2. *Concentration of amikacin in bronchial secretions as plotted against time after the last dose ($n = 30$, $r = -0.67$). V indicates the two levels below 0.1 μg/ml.*

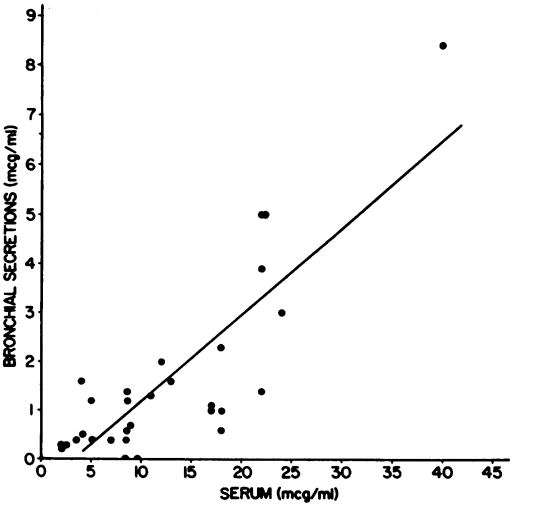

FIG. 3. *Correlation of serum and bronchial secretion concentrations of amikacin ($n = 30$, $r = 0.82$).*

TABLE 1. *Amikacin concentrations in serum and bronchial secretions*

Patient	Time[a]	Concn (μg/ml)					
		Serum			Bronchial secretion		
		Initial[b]	+0.5	+1	Initial	+0.5	+1
1	1.5	40			8.4		
2	1.5	22	18			2.3	
3	1.5	22	22		5.0	5.0	
4	1.5	25	17				
5	3.5	18	11	17	0.6	1.3	1.1
6	4	22	18	17	1.4	1.0	1.0
7	5	25	24	17		3.0	3.9
8	5	9	13	12	0.7	1.6	2.0
9	7	9.6	8.4	8.4	0	0	
10	7	5.0	4.2	3.5	1.2	0.5	0.4
11	7	8.6	7.0	5.2	0.4	0.4	0.4
12	7.5	8.6	8.4	8.4	0.6	1.4	1.2
13	8.5	5.6	3.8	3.9		1.6	
14	11	1.8	2.5	1.7	0.3	0.3	0.2

[a] Each value indicates hours after last dose.

[b] Initial refers to the specimen obtained at the time indicated; 0.5 and 1 refer to specimens obtained 30 min and 1 h later, respectively.

TABLE 2. *Mean concentration of amikacin in serum and bronchial secretions*

Time (h) after last dose	Concn (μg/ml)[a]		Bronchial secretion/serum
	Serum	Bronchial secretion	
1.5 to 2.0	23.70 ± 2.90	5.20 ± 1.50	0.21
3.5 to 6.0	16.90 ± 1.46	1.60 ± 0.30	0.09
7.0 to 9.5	6.57 ± 0.56	0.73 ± 0.15	0.11
11.0 to 12.0	2.00 ± 0.25	0.26 ± 0.03	0.13

[a] Each value indicates mean ± standard error of the mean.

tion in each subject ($n = 14$) was significantly correlated with the highest bronchial secretion concentration of that individual ($r = 0.83$, $P < 0.001$).

Clearance of amikacin from serum (Fig. 1) and bronchial secretions (Fig. 2) occurred at approximately the same rate ($t½$ of serum = 2.8 h, $t½$ of bronchial secretion = 2.6 h, $P > 0.5$). The mean concentration of amikacin in bronchial secretions fell below 4.0 μg/ml (Table 2) 3.5 h after the final dose. Only 3 of 15 bronchial secretion concentrations were greater than 1.0 μg/ml (mean = 0.73 ± 0.15 μg/ml) 7 h after the last dose of antibiotic.

Individual bronchial secretion to serum concentration ratios were less than 0.2 in all but two patients, both assayed 1.5 h after their last dose. Mean ratios for various time intervals are listed in Table 2, where it can be seen that the highest serum to bronchial secretion ratios occurred during the 1.5- to 2.0-h interval. Subsequent ratios were smaller, about 0.1, than those observed during the 1.5- to 2.0-h period.

DISCUSSION

The serum concentrations noted in the patients of this study were similar to the concentrations reported in other investigations (4, 17). Since most pathogenic gram-negative bacteria are inhibited by 1 to 4 μg of amikacin per ml (6, 12, 13), the conventional doses used in this study produced a high serum-to-MIC ratio.

The highest bronchial secretion concentrations noted by us occurred in the earliest specimens obtained 1.5 h after the final dose of amikacin, with an observed mean level of 6.7 μg/ml. This concentration would be expected to inhibit most gram-negative organisms (6, 12, 13). However, the rate of clearance of amikacin from bronchial secretion was similar to serum ($P > 0.5$), so that 7 h after the final dose, 12 of 15 of the bronchial secretion concentrations determined were below 1.0 μg/ml, which has been reported to be inadequate to inhibit most gram-negative organisms (6, 12, 13). Moreover, the reported MIC of amikacin against *Pseudomonas*

aeruginosa usually is greater than 6.0 μg/ml (6, 12, 13). Thus, the amikacin levels in bronchial secretions, as assayed by radioimmunoassay, were substantially below those generally accepted as the MICs against this species of bacteria in the specimens obtained more than 1.5 h after the last dose.

Some of the variation in both serum and bronchial secretion levels of amikacin in the earliest group assayed may have been affected by the design of this study. Since the first sample was obtained 1.5 h after the last injection of antibiotic, it is possible that the peak serum level of amikacin may have occurred before the initial assay. Peak amikacin levels in serum have been reported to occur within 2 h in most individuals (4). As a result, it would seem likely that the initial levels reported here were obtained close to the peak for most individuals in that group, but some variation in concentration caused by this effect cannot be excluded.

Other factors should also be considered in interpreting the levels reported here and may partially explain the patient-to-patient variation in bronchial secretion levels noted. It has been noted that pulmonary perfusion is greatest in the dependent regions of the lung (10). Since tissue antibiotic concentrations depend on blood levels (5), sampling from various lung regions with different rates of perfusion may have affected amikacin concentrations (23). It has also been postulated that inflammation increases the passage of antibiotics through the blood-bronchial barrier (3, 8, 21). As a result, some of the variation in bronchial secretion levels may reflect a regional variation in bronchitis. Since five of our patients were active smokers or had a history compatible with chronic bronchitis at the time of flexible fiberoptic bronchoscopy, this may have resulted in some of the differences in amikacin levels observed.

Several studies have been previously published which reported aminoglycoside concentrations in either lung parenchyma or bronchial secretions of noninfected patients. Kroening et al. (14) measured tobramycin concentrations in lung parenchyma, and Odio et al. (18) determined bronchial secretion concentrations of gentamicin. The levels of aminoglycoside in neither study were considered high enough to inhibit *Pseudomonas aeruginosa*. We have recently reported a mean bronchial secretion level of tobramycin, assayed biologically, of 3.75 μg/ml between 0.6 and 4 h after the final dose (1). This concentration is above the reported MIC against most tobramycin-susceptible gram-negative organisms, including *P. aeruginosa* (12).

Bronchial secretion concentrations of three aminoglycosides have also been reported in infected patients. Hall et al. measured tracheal secretion concentrations of tobramycin in three patients with clinical pneumonia (7). The levels were higher than the MICs for the cultured pathogen from 4 to 8 h after the final dose. Wong and associates measured bronchial secretion concentrations after eight intravenous injections of gentamicin (1.7 mg/kg of body weight) in five patients with either pneumonia or bronchitis (23). The absolute bronchial levels were 40% or more of the corresponding serum values. These authors concluded that gentamicin readily penetrates the blood-broncho-alveolar barrier. Marks et al., however, measured sputum concentrations of gentamicin in patients with cystic fibrosis who were presumed to have inflamed lungs and demonstrated drug levels that did not reach the MIC of the *Pseudomonas* strains tested (16). Finally, Klastersky et al. encountered such low concentrations of sisomicin in bronchial secretions after intravenous or intramuscular injection (75 mg every 8 h), that they suggested that endotracheal therapy with aminoglycosides should be part of the therapy for severe gram-negative pneumonias (11).

All of these studies, including the present one, must be interpreted with some caution because there are many factors that determine passage of drugs across a barrier, such as the bronchial membranes and the activity of these agents in tissue. These factors include modecular size of the antimicrobial drug (23), pH (23), lipid solubility (9), and the degree of inflammation present (3, 8, 21). The lipid content, pH, and membrane integrity may be different in the infected or inflamed lung than in the lungs of the patient population reported here who did not have evidence of overt parenchymal infection.

It should be pointed out, however, that at present there are several published reports, including this one, which suggest that the concentration of aminoglycosides measured in the secretions of the lung are often low, especially when compared with their reported MICs for *Pseudomonas*. Well-recognized problems associated with the therapy of *Pseudomonas* pneumonia with aminoglycosides in certain clinical situations support this position.

In summary, our results indicate that on occasion some aminoglycosides penetrate poorly into bronchial secretions. In noninfected patients, conventional doses of amikacin produce bronchial secretion concentrations that would be expected to inhibit most gram-negative organisms, but probably not *P. aeruginosa*. However, bronchial secretion levels of amikacin may fall so rapidly that concentrations below the

accepted MICs (6) against many gram-negative bacteria may prevail for approximately one-half the dosage interval.

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LITERATURE CITED

1. **Alexander, M. R., E. M. Berglund, J. E. Kasik, A. Fox, and W. M. Chinn.** 1979. The concentration of tobramycin in bronchial secretions. Chest **75**:675–678.
2. **Bartlett, J. G.** 1977. Amikacin treatment of pulmonary infections involving gentamicin-resistant gram-negative bacilli. Am. J. Med. **62**:945–948.
3. **Bergogne-Berezin, E., C. Morel, Y. Benard, G. Berthelot, and H. Kafe.** 1978. Pharmacokinetic study of β-lactam antibiotics in bronchial secretions. Scand. J. Infect. Dis. **14**(Suppl.):267–272.
4. **Clarke, J. T., R. D. Libke, C. Regamey, and W. M. M. Kirby.** 1974. Comparative pharmacokinetics of amikacin and kanamycin. Clin. Pharmacol. Ther. **15**:610–616.
5. **Crofton, J.** 1969. Some principles in the chemotherapy of bacterial infection. II. Br. Med. J. **2**:209–212.
6. **Finland, M., C. Garner, C. Wilcox, and L. D. Sabath.** 1976. Susceptibility of recently isolated bacteria to amikacin in vitro: comparisons with four other aminoglycoside antibiotics. J. Infect. Dis. **134**(Suppl.):S297–307.
7. **Hall, W. H., D. N. Gerding, and E. A. Schierl.** 1977. Penetration of tobramycin into infected extravascular fluids and its therapeutic effectiveness. J. Infect. Dis. **135**:957–961.
8. **Halprin, G. M., and S. M. McMahon.** 1973. Cephalexin concentrations in sputum during acute respiratory infections. Antimicrob. Agents Chemother. **3**:703–705.
9. **Hoeprich, P. D.** 1972. Antimicrobies and anthelmintics for systemic therapy, p. 177. *In* P. D. Hoeprich (ed.), Infectious diseases. Harper & Row, Publishers, Hagerstown, Md.
10. **Kaneko, K., J. Milic-Emili, M. B. Dolovich, A. Dawson, and D. V. Bates.** 1966. Regional distribution of ventilation and perfusion as a function of body position. J. Appl. Physiol. **21**:767–777.
11. **Klastersky, J., F. Carpentier-Meunier, L. Kahan-Coppens, and J. P. Thys.** 1979. Endotracheally administered antibiotics for gram-negative bronchopneumonia. Chest **75**:586–591.
12. **Kluge, R. M., H. C. Standiford, B. Tatem, V. M. Young, W. H. Greene, S. C. Schimpff, F. M. Calia, and R. B. Hornick.** 1974. Comparative activity of tobramycin, amikacin and gentamicin alone and with carbinicillin against *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. **6**:442–446.
13. **Knothe, H.** 1976. In vitro susceptibility of recently isolated gram-negative bacteria to gentamicin, sisomicin, tobramycin, and amikacin. J. Infect. Dis. **134**(Suppl.): 271–274.
14. **Kroening, V., S. Liebig, and M. Wundschock.** 1978. Tobramycin—Spiegel in Menschlichen Lungengewebe. Eine Untersuchung an 30 intravital gewonnenen Lungengewbsproben. Infection **6**:231–235.
15. **Lewis, J. E., J. C. Nelson, and H. A. Elder.** 1975. Amikacin: a rapid and sensitive radioimmunoassay. Antimicrob. Agents Chemother. **7**:42–45.
16. **Marks, M. I., R. Prentice, R. Swarson, E. K. Cotton, and T. C. Eickhoff.** 1971. Carbinicillin and gentamicin: pharmacologic studies in patients with cystic fibrosis and pseudomonas pulmonary infections. J. Pediatr. **79**: 822–828.
17. **Meyer, R. D., R. P. Lewis, E. D. Carmalt, and S. M. Finegold.** 1975. Amikacin therapy for serious gram-negative bacillary infections. Ann. Int. Med. **83**:790–800.
18. **Odio, W., E. VanLaer, and J. Klastersky.** 1975. Concentrations of gentamicin in bronchial secretions after intramuscular and endotracheal administration. J. Clin. Pharmacol. **15**:518–524.
19. **Pennington, J. E., and H. Y. Reynolds.** 1973. Concentrations of gentamicin and carbinicillin in bronchial secretions. J. Infect. Dis. **128**:63–68.
20. **Smith, C. R., K. L. Baughman, C. Q. Edwards, J. F. Rogers, and P. S. Lietman.** 1977. Controlled comparison of amikacin and gentamicin. N. Engl. J. Med. **296**: 349–353.
21. **Stewart, S. M., M. Fisher, J. E. Young, and W. Lutz.** 1970. Ampicillin levels in sputum, serum and saliva. Thorax **25**:304–307.
22. **Trenholme, G. M., P. P. McKellar, N. Rivera, and S. Levin.** 1977. Amikacin in the treatment of gram-negative pneumonia. Am. J. Med. **62**:949–953.
23. **Wong, G. A., T. H. Peirce, E. Goldstein, and P. D. Hoeprich.** 1975. Penetration of antimicrobial agents into bronchial secretions. Am. J. Med. **59**:219–223.
24. **Zavala, D. C.** 1975. Diagnostic fiberoptic bronchoscopy: techniques and results of biopsy in 600 patients. Chest **68**:12–19.