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NOTES

Pharmacokinetics of Aerosolized Tobramycin in Adult Patients with Cystic Fibrosis

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This study was performed to determine the clinical pharmacokinetics of tobramycin in six patients with cystic fibrosis (CF) after inhalation of 600 mg. Tobramycin was administered with an ultrasonic nebulizer (WISTO SENIOR). Blood and urine were sampled until 24 h after inhalation. Maximum tobramycin levels in serum varied from 0.19 to 2.57 mg/liter (mean, 1.27 mg/liter; standard deviation, 1.07 mg/liter). Systemic availability (calculated from urinary output) ranged from 6.0 to 27.4% (mean, 17.5%; standard deviation, 8.8%). The results illustrate that, provided that the systemic availability of tobramycin is a reflection of pulmonary deposition, inhalation studies with CF patients should have a concentration-controlled design. Furthermore, reliance on dose recommendations from the literature for a new patient starting on this treatment is not justified, but it is mandatory that deposition kinetics be studied for each patient and for each nebulizer. It may well be that, with higher levels of deposition, dosages lower than those recommended in the literature will suffice to obtain the desired clinical effect. In addition, the reverse may also be the case.

Clinical trails have demonstrated that patients with cystic fibrosis (CF) and chronic pulmonary infection with *Pseudomonas aeruginosa* may benefit from maintenance treatment with inhalation of antibiotics to prevent exacerbations and hospital admissions (19). When the appropriate antibiotic at the appropriate dose is inhaled, the annual decrease in their pulmonary function is slowed or even normalized (13). In these trials, various antibiotics at various dosages were investigated. For the aminoglycosides gentamicin and tobramycin, the dosage ranged from 20 mg three times daily to 600 mg three times daily. Ramsey et al. (13) demonstrated a significant improvement in pulmonary function during inhalation of 600 mg of tobramycin three times daily. These results were in good agreement with those of smaller studies (5, 7–9, 12, 17). On the basis of the results of those studies, inhalation therapy may be adopted as a maintenance treatment for *Pseudomonas* infections of the lungs of patients with CF. However, a potential adverse effect of aerosolized aminoglycosides is systemic toxicity due to absorption of the antibiotic. Most studies have focused on the clinical symptoms of toxicity, such as a rise in the serum creatinine concentration or aberrations upon audiometric examination. Only a few investigators have actually performed pharmacokinetic studies after the inhalation of the antibiotic by patients. Pharmacokinetic studies were compromised by the inability to measure the low concentrations that are usually achieved in serum after inhalation. With the opportunity to increase the sensitivity of a commercially available assay for tobramycin, this problem has been overcome (20). The present study was performed to investigate the clinical pharmacokinetics of tobramycin after inhalation by using standard aerosol equipment.

Pharmacokinetic study. Six patients with CF and chronic respiratory tract infections due to *P. aeruginosa* under the care of the Adult Cystic Fibrosis Center, Department of Pulmonology, Leyenburg Hospital, The Hague, The Netherlands, were studied. They were not having infectious exacerbations, and their pulmonary functions were within 10% of their usual values. Patient demographics are summarized in Table 1. The study was carried out according to the Helsinki Declaration and was approved by the Ethical Review Board of the Leyenburg Hospital. The patients received a single dose of 600 mg of tobramycin by inhalation. For patients who had been receiving previous treatment with aminoglycosides, treatment was stopped at least 3 days before the study began. Tobramycin for inhalation was manufactured by the hospital pharmacy by dissolving 600 mg of tobramycin in 10 ml of water for injection. The pH was adjusted to 6 to 7 with sulfuric acid, and tonicity was adjusted to 270 mosmol/kg with sodium chloride. The solution was aerosolized by using an ultrasonic nebulizer (WISTO SENIOR; Wisto, Woerden, The Netherlands). Sixty-six percent of the mass aerosol output was in droplets of <7 μm (cascade impaction analysis), which was in the respirable range (1 to 8 μm). Patients were instructed to inhale the aerosolized drug for at least 15 min. After inhalation, the dose of tobramycin that was retained in the nebulizer was collected for analysis by flushing the nebulizer with water. The amount administered to the patients was estimated from the dose in the nebulizer minus the amount found in the water used to flush the nebulizer. Venous blood samples were taken immediately before and after inhalation and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h later. Urine was collected for 24 h. The sera, urine samples, and flushings from the nebulizer were assayed by a fluorescence polarization immunoassay (TD_xFL_x system;

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TABLE 1. Patient demographics

Patient no.	Gender[a]	Age (yr)	Ht (cm)	Wt (kg)	FEV_1 (% predicted)[b]	Serum creatinine concn (μmol/liter)
1	m	17	165	41	28.6	36
2	f	24	164	48	28.7	45
3	f	30	163	47	21.3	41
4	m	24	179	72	68.3	65
5	m	28	186	65	40.3	66
6	m	27	180	72	26.6	48
Mean		25	173	57.5	35.6	50
SD		4.6	10	13.8	17.1	12

[a] m, male; f, female.
[b] FEV_1, forced expiratory volume in 1 s.

Abbott Diagnostics, North Chicago, Ill.). The lower limit of quantitation of this assay is 0.3 mg/liters. Since very low serum tobramycin concentrations were expected, a modified version of this assay with a lower limit of quantitation of 0.025 mg/liter was also used (20). Its intra-assay coefficient of variation was 6% at 0.050 mg/liter, 2.7% at 0.375 mg/liter, and 2.0% at 0.753 mg/liter (20). Pharmacokinetic calculations were performed using the MW/Pharm software (MediWare, Groningen, The Netherlands). The MW/Pharm software performs curve fitting according to a one-, two-, or three-compartment model and provides compartmental and noncompartmental pharmacokinetic parameters. Total bioavailability was estimated from the dose administered to the patient divided by the cumulative amount of tobramycin recovered from the urine over 24 h and multiplied by 100/85. It has been demonstrated in healthy individuals (2) and in patients with CF (22) that 85% of the dose administered can be recovered from the urine collected over 24 h. Variance is shown as standard deviation from the mean. In addition, serum concentration-time curves were simulated for three patients who received aerosolized tobramycin at 600 mg three times daily for 1 week: one patient having the lowest systemic availability (patient 5), one patient exhibiting the average bioavailability assessed in this study, and one patient exhibiting the highest systemic availability (patient 3). These curve simulations were performed by using the MW/Pharm program. Error and bias were not incorporated into the curve fittings and simulations.

Pharmacokinetic analysis. The individual serum concentration-time profiles of tobramycin after inhalation are presented in Fig. 1, and the calculated pharmacokinetic parameters are given in Table 2. Figure 2 presents the simulations of the serum concentration-time profiles of tobramycin after inhalation of 600 mg of tobramycin three times daily by patients 3 and 5 and a theoretically average patient and illustrate the wide interindividual variability. An important feature of the results of this study is the demonstration of the widely varying, and in some patients relatively high, bioavailabilities and maximum concentrations of tobramycin in serum after inhalation. It has been reported that after aerosolization a maximum of about 10% of the aerosolized drug actually reaches the bronchial tree and is available for systemic absorption (6, 11). In the present study we found a mean systemic availability of 17.5% on the basis of the renal recovery of tobramycin. The remaining excretion of tobramycin from previous administrations can be dismissed as an irrelevant source of recovery of drug in urine because of the period that had elapsed since treatment with the drug was stopped before the start of the current study. Notably, the patients for whom the recovery of tobramycin from the urine (patients 3 and 4) was highest did not receive any tobramycin or other aminoglycosides for several months preceding the study. Theoretically, enteral absorption may also contribute to the total bioavailability. However, aminoglycosides are hardly absorbed (<1%) after oral administration in non-CF patients (15), and this is not likely to be different in patients with CF. Studies on the pharmacokinetics of aminoglycosides after endotracheal administration to mechanically ventilated patients have shown that up to 34% of the dose administered could be recovered from the urine (3). This indicates that aminoglycosides are indeed absorbed from the respiratory tract, which is further substantiated in the present study. During inhalation of tobramycin, a depot of tobramycin is likely formed in the lung, from which the drug is slowly released. This can be deduced from our data on the average terminal half-life of tobramycin after inhalation (13.0 h). Historical data from studies in which tobramycin was given to CF patients intravenously showed a half-life in the range of 1.5 to 3.0 h, which is typical for CF patients (21). The prolonged half-life after inhalation of the drug is most probably due to the delayed absorption of tobramycin hypothesized above. One may therefore argue that the administration of aerosolized tobramycin three times daily is unnecessarily frequent. However, more studies must be performed to substantiate this statement. Two previous studies (9, 18) demonstrated hardly detectable (<1 mg/liter) concentrations in serum after the inhalation of small doses (80 mg twice daily and 80 mg three times daily respectively) of tobramycin

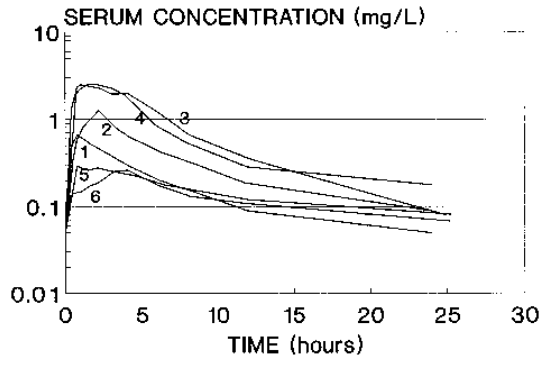

FIG. 1. Log concentration-time profiles for tobramycin in serum following inhalation of a single dose of 600 mg in six patients with CF. The numbers refer to the patients in the present study.

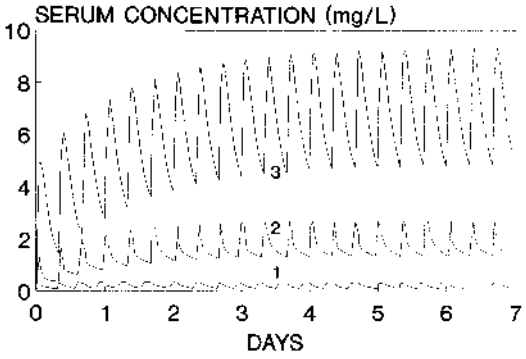

FIG. 2. Simulated serum concentration-time profiles during 1 week of inhalation of 600 mg of tobramycin three times daily. Curve 1, simulation for the patient with the lowest systemic availability (patient 5); curve 2, simulation for a hypothetical patient with the average systemic availability found in this study; curve 3, simulation for the patient with the highest systemic availability (patient 3). For details see the text.

TABLE 2. Calculated individual pharmacokinetic parameters after inhalation of 600 mg of tobramycin with an ultrasonic nebulizer[a]

Patient no.	Dose (mg)	AUC (h · mg/liter)	CL (liters/h)	V_{ss} (liters/kg)	K_a (1/h)	T_{max} (h)	C_{max} (mg/liter)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	Urinary recovery (mg)	F (%)
1	315	4.0	10.7	3.29	3.23	0.85	0.59	2.09	14.3	45.9	17.1
2	361	8.9	6.62	0.82	1.44	1.06	1.51	0.87	8.35	55.6	18.1
3	337	16.2	4.49	1.63	0.99	1.51	2.57	1.45	17.6	78.5	27.4
4	405	17.0	6.20	0.85	1.50	1.42	2.48	1.88	5.95	92.8	27.0
5	375	3.8	3.71	1.47	4.16	0.90	0.30	2.85	19.3	22.4	6.0
6	450	3.3	10.2	2.41	0.56	3.49	0.19	0.077	12.4	43.4	9.6
Mean	374	8.9	6.98	1.74	1.98	1.54	1.27	1.54	13.0	56.4	17.5
SD	48	6.3	2.89	0.96	1.40	0.99	1.07	0.97	5.2	25.5	8.8

[a] Dose, the dose placed in the nebulizer minus the dose recovered in the water used to flush the nebulizer; AUC, area under the curve; CL, total body clearance; V_{ss} volume of distribution at steady state; K_a, absorption rate constant; T_{max}, time to maximum concentration in serum; C_{max}, maximum concentration in serum; $t_{1/2\alpha}$ and $t_{1/2\beta}$, initial and terminal half-lives, respectively; urinary recovery, cumulative amount of tobramycin recovered from urine over 24 h; F, total bioavailability based on urinary recovery and corrected for 85% recovery.

by CF patients. In three more studies with patients with CF, higher dosages of inhaled aminoglycosides were applied. Zach (23) found maximum concentrations of gentamicin in serum varying from 1.5 to 4.2 mg/liter after inhalation of 120 to 600 mg in eight patients with CF, which is in the same range as our current findings with tobramycin. Mukhopadhyay et al. (10) found concentrations in serum ranging from <0.1 to 2.0 mg/liter after inhalation of 400 mg of tobramycin in 10 patients with CF. In one patient a concentration in serum of 9.9 mg/liter was measured at 30 min postdose, but this was attributed to an analytical or sampling error (1). Smith et al. (16) studied the inhalation of 600 mg of tobramycin three times daily for 3 months in 22 patients with CF (16). This dose was aimed at achieving therapeutic concentrations in the respiratory tract with specific respiratory equipment (DeVilbiss ultrasonic nebulizer equipped with a 1,250-ml spacer). The recovery of tobramycin in urine over 24 h was 0.15 to 25 mg (0.008 to 1.4% of the dose). In our view, this low recovery of tobramycin in the urine is to be attributed to the poor performance of the nebulizer used in combination with the 1,250-ml spacer, which may have greatly reduced the amount of nebulized tobramycin actually inhaled. Important factors that contribute to the bioavailability of aerosolized tobramycin are the efficiency of the nebulizer at producing droplets in the respirable range and the inhalation technique (19). In addition, it seems that subtle changes in the technique of administration (for example, using a spacer or not) may result in significant changes in the amount of tobramycin delivered to the lungs. This illustrates that dose and dosing regimen may need to be altered, based on the equipment used and the level of deposition observed in a given patient. Furthermore, the clinical condition of the patient, such as lung function, sputum production, and inflammation, may influence the bronchial bioavailability of tobramycin after inhalation (4). At present, no information is available on the intraindividual reproducibility of the bioavailability of tobramycin either during long-term inhalation treatment or with deterioration of the clinical condition of the patients. This requires further research. An important risk factor in the development of oto- and nephrotoxicities of aminoglycoside antibiotics is a long duration of aminoglycoside therapy (14). Furthermore, nephrotoxicity is linked to trough concentrations of >2 mg/liter and ototoxicity is linked to trough concentrations of >4 mg/liter (14). One may expect that continuous inhalation of 600 mg of tobramycin three times daily in those patients for whom bioavailability is high, as demonstrated in our study, will lead to continuous exposure to relatively high levels of the drug (Fig. 2), putting some patients at risk of nephro- or ototoxicity. Therefore, it is advisable to monitor every patient for nephro- and ototoxicity. To reduce the chance of toxicity in patients with a relatively high systemic availability, either a dose reduction or a longer interval between doses should be considered. It should be stressed, however, that safe tobramycin levels for this kind of long-term therapy must still be established.

This study provided preliminary data on the total bioavailability that can be reached after inhalation of 600 mg of tobramycin. Ramsey et al. demonstrated a beneficial effect on pulmonary function of the inhalation of the same dose of tobramycin three times a day (13), without measurable levels in serum and urinary recovery of only 0.008 to 1.4% (16). In our study, apparently, a superior way of administering the aerosolized tobramycin was practiced, as evidenced by the measurable concentrations in serum and urinary recovery. It thus appears that apart from the dose of aerosolized tobramycin, the inhalation device and inhalation technique are of paramount importance for the deposition and the dose-effect relationship. Determination of the levels of drug in serum may well be an important tool for determining the appropriate dosing schedule. Aerosolized antibiotics are an important treatment modality for CF patients (19). With the initiation of this treatment, reliance on dose recommendations from the literature is not justified. It is mandatory that the delivery characteristics be studied for each patient and each nebulizer before such therapy is started. The correct dose (either small or large) must be justified with prior documentation of equipment-specific delivery characteristics.

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