New Schedule for Tobramycin Administration

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Ten patients received a loading dose of tobramycin of 60 mg/m² intravenously over 0.5 h followed immediately by 60 mg/m² over 2 h every 4 h. The highest mean serum concentration (at the end of the loading dose) was 6.0 ± 0.3 µg/ml (range, 3.2 to 10.9 µg/ml). The mean serum concentration 2 h after the end of the initial 2-h infusion was 3.0 ± 0.2 µg/ml (range, 1.6 to 3.9 µg/ml). This schedule of tobramycin was used to treat 117 patients with presumed or proven infection. There were no differences in the mean serum concentrations of tobramycin at comparable times on days 3 to 4 and 6 to 7. Only 60% of patients had serum levels between 3 µg/ml (trough) and 10 µg/ml (peak). This intermittent schedule of administration resulted in substantial fluctuations in serum concentrations of tobramycin and produced trough concentrations which were too low or peak concentrations which were too high in some patients.

Infection is the most frequent cause of morbidity and mortality in patients with malignant disease (4, 5). Gram-negative organisms are responsible for most episodes of infection. The aminoglycoside group of antibiotics have the broadest spectrum of activity against these organisms; however, their efficacy is diminished in neutropenic patients (1). Various schedules of administration of aminoglycosides have been investigated. Aminoglycosides have been given by an interrupted dosage schedule at 6- to 8-h intervals which results in a high peak serum concentration, but a low serum concentration 6 to 8 h after a dose (7). Tobramycin, gentamicin sulfate, sisomicin, and amikacin have been given by continuous infusion with a more constant serum concentration maintained throughout the period of infusion (2, 6). The continuous infusion of aminoglycosides has the disadvantage of requiring more nursing attention and requiring one intravenous site solely for the administration of the aminoglycoside. This pharmacology study was initiated to investigate a method of interrupted aminoglycoside (tobramycin) administration which would allow the administration of other antibiotics through the same intravenous site.

MATERIALS AND METHODS

Initially, a pilot study was conducted to determine the feasibility of utilizing this new intermittent schedule. Ten patients who had metastatic cancer or leukemia and had received ablative chemotherapy (BCNU, BCNU-VP-16-cyclophosphamide, or piperazine-dione) and total body irradiation followed by au-

tologous bone marrow transplantation were entered on this study (Table 1). All of these patients had normal renal function initially, as evidenced by a serum creatinine concentration of ≤1.5 mg/dl and a blood urea nitrogen of ≤22 mg/dl. The patients ranged in age from 17 to 66 years old (median, 41 years old). Because of the high frequency of gram-negative bacillary infections in the transplant population, all of the patients currently receive prophylactic antibiotics when their absolute granulocyte count decreases to less than 1,000/mm³. The antibiotic regimen consists of trimethoprim-sulfamethoxazole (2 tablets every 8 h), nystatin suppository administered orally (1 every 8 h) and tobramycin. A loading dose of tobramycin of 60 mg/m² in 50 ml of D5W is administered intravenously over a 30-min period and followed immediately by 60 mg/m² in 200 ml of D5W over 2 h and every 4 h thereafter (total daily dose, 9 mg/kg per day). Antibiotic prophylaxis is continued until the patient's absolute granulocyte count increases to greater than 1,000/mm³. Prophylactic antibiotics are discontinued if the patient develops a temperature greater than or equal to 101°F (ca. 38.3°C), at which time a therapeutic regimen is instituted.

Upon completion of the pilot study, this schedule of tobramycin administration was incorporated into a therapeutic antibiotic regimen. Neutropenic (neutrophil count of ≤1,000/mm³) patients who developed fever (≥101°F) presumed to be due to infection were entered on this study. During 358 febrile episodes, patients were randomly assigned to receive ticarcillin and tobramycin, or ticarcillin, cephalothin, and tobramycin. The dosage of drugs was: ticarcillin, 4 g in 200 ml of D5W over 2 h every 4 h; cephalothin, loading dose of 3 g in 50 ml of D5W over 30 min immediately followed by maintenance doses of 3 g in 200 ml of D5W every 6 h by continuous infusion; tobramycin, 60 mg/m² in 50 ml of D5W over 30 min immediately followed by maintenance doses of 60 mg/m² in 200 ml of D5W by infusion over 2 h every 4 h (total daily dose, 9.0 mg/kg per day). All patients received the

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antibiotics for a minimum of 7 days or 4 days after becoming afebrile, whichever was longer, unless untoward reactions, death, or clinical deterioration occurred. Serum tobramycin levels were measured on days 1, 3 or 4, and 6 or 7 during 117 febrile episodes and are included in this analysis (Table 1).

Tobramycin was administered by an infusion pump (IVAC T H 500, IVAC Corp., San Diego, Calif.). No patient had received aminoglycosides for at least 1 month before entry on study. Tobramycin was supplied by Eli Lilly & Co., Indianapolis, Ind. Patients treated with prophylactic tobramycin had serum specimens collected before tobramycin administration and at 0.5, 2.5, and 4.5 h after initiation of the loading dose. Subsequently, specimens were collected on days 3 or 4 and 6 or 7 immediately before and at 2, 3, and 4 h after initiation of a dose between 8 a.m. and 12 p.m. Patients treated therapeutically with tobramycin had serum concentrations measured before infusion, after the loading dose, and after the 2-h infusion on day 1. Subsequently, serum concentrations were determined before infusion (2 h after the completion of the preceding infusion) and at the end of the 2-h infusion on days 3 or 4, and 6 or 7, and every 3 days thereafter.

The radioimmunoassay method for the measurement of tobramycin in serum has been described elsewhere (3). The antiserum was produced by immunizing rabbits with a tobramycin-bovine albumin conjugate. Iodinated tobramycin competes with unlabeled tobramycin for binding sites on the antisera. Polyethyleneglycol is used to separate the unbound from the bound iodine. Serum levels are determined by comparison with a standard curve. This radioimmunoassay method is highly specific, with only minor cross-reaction occurring with other aminoglycoside antibiotics, and has a significant correlation ($P < 0.05$) with both the radioenzymatic and microbiological assays.

The standard error of the mean was calculated according to the equation: $S\bar{X} = S\bar{X}/\sqrt{n}$, where $S\bar{X} = (\Sigma \times^2 - n \bar{X}^2)/\sqrt{n-1}$. The 95% confidence limits were calculated as twice the standard error of the mean. Significance levels associated with distributions of serum levels were compared between groups of patients or on different days of treatment by unpaired or paired Wilcoxon tests.

RESULTS

The mean serum concentrations of tobramycin on days 1, 3 or 4, and 6 or 7 are shown in Fig. 1. The mean serum concentration after the infusion of the loading dose was $6.0 \pm 0.8 \mu\text{g/ml}$. Two hours later, upon completion of the first infusion, the mean serum concentration was 6.2

FIG. 1. Mean serum concentrations in 10 patients receiving tobramycin as infection prophylaxis. After a loading dose of 60 mg/m^2 over 30 min on day 1, the patients received 60 mg/m^2 over 2 h, every 4 h. The vertical lines indicate the 95% confidence limits. —, Day 1; ----, day 3; —, day 7.

$\pm 0.4 \mu\text{g/ml}$. Hence, this serum concentration was obtained after 120 mg of tobramycin per m^2 had been administered during a 2.5-h period. On day 3 (or 4), the mean peak serum concentration obtained after completion of a 2-h infusion was $6.3 \pm 0.4 \mu\text{g/ml}$, and the lowest (trough) mean serum concentration was $2.9 \pm 0.5 \mu\text{g/ml}$. On day 7 (or 6), the comparable concentrations were $7.4 \pm 0.6 \mu\text{g/ml}$ and $4.5 \pm 0.8 \mu\text{g/ml}$, respectively. The peak serum concentrations were higher on these days than on day 1 due to the residual trough concentration existing at the time of administration of the study dose. The mean serum concentrations of tobramycin were higher on the

TABLE 1. Characteristics of patients

Tobramycin administration	No. of patients	Age		Male	Underlying malignancy				Cause of fever		Median duration therapy (days, range)
		<35	>50		Acute leukemia	Chronic leukemia	Lymphoma	Solid tumor	FUO ^a	Identified infection	
Prophylactic	10	3	4	6	4	0	1	5			11 (6-18)
Therapeutic	117	41	50	76	74	4	4	35	72	45	10 (7-17)

^a FUO, Fever of undetermined origin.

last day of the study, suggesting drug accumulation with this schedule. Only the difference at 2 h was statistically significant ($P = 0.03$).

No patient developed nephrotoxicity from tobramycin as defined by an increase in serum creatinine to greater than 1.5 mg/dl and blood urea nitrogen to greater than 22 mg/dl. Tobramycin was discontinued in four patients when full hematopoietic recovery occurred, in two patients when they developed *Candida* infection, in one patient when he developed *Staphylococcus epidermidis* septicemia, and in three patients when they developed fevers of undetermined origin.

Subsequently, ticarcillin and tobramycin, or ticarcillin, cephalothin, and tobramycin were administered as initial antibiotic therapy to 117 patients with solid tumors and leukemia who developed fever presumed to be due to infection. Fever was proven to be due to infection in 45 patients, and no cause could be found for the fever in 72 patients. All patients had serum tobramycin concentrations measured on days 1, 3 or 4, and 7 or 8 of therapy. All patients had normal renal function before treatment as defined by serum creatinine less than 1.5 mg/dl and blood urea nitrogen less than 22 mg/dl. Serum was obtained immediately before (0 h) and at the end of a 2-h infusion of tobramycin on days 3 or 4, and 6 or 7 of therapy (Table 2). Mean serum concentrations of tobramycin were similar for patients with infection and fever of undetermined origin at all times studied. Mean preinfusion and postinfusion concentrations were similar on days 3 and 4, and 6 and 7.

Table 3 indicates the proportion of patients whose serum concentrations of tobramycin were unsatisfactory. Our intention was to maintain the serum concentration about 3 $\mu\text{g/ml}$ without the peak serum concentration exceeding 10 $\mu\text{g/ml}$. These serum concentrations were arbitrarily selected so that the trough serum values would exceed the minimum inhibitory concentration of most sensitive organisms and the peak serum

TABLE 3. Proportion of patients whose serum concentrations of tobramycin were unsatisfactory^a

Time (h)	Serum concn of tobramycin ($\mu\text{g/ml}$)	Day 3	Day 7
0	>3.0	48 ^a	58
	≤ 3.0	26	22
	≤ 2.0	23	17
	≤ 1.0	3	3
2	<10	78	83
	>10	15	13
	>12	4	3
	>14	3	1

^a Expressed as percentage of patients.

values would not be high enough to risk renal toxicity. Dosage adjustments were made only in patients who developed renal impairment. There was considerable variation in serum concentrations in different patients. Of the 117 patients, 22 to 26% had a serum concentration ≤ 3.0 $\mu\text{g/ml}$ before an infusion, and 13 to 15% had a serum concentration ≥ 10 $\mu\text{g/ml}$ at the end of the infusion. Hence, only about 60% of patients had serum concentrations within the anticipated range. Renal toxicity developed in only 3 of the 117 patients in whom serum tobramycin levels were determined. All three of these patients had peak serum concentrations of tobramycin greater than 10 $\mu\text{g/ml}$. Their highest peak serum tobramycin concentration and serum creatinines were 10.4 $\mu\text{g/ml}$ and 1.8 mg/dl; 13.0 $\mu\text{g/ml}$ and 2.4 mg/dl; and 17.4 $\mu\text{g/ml}$ and 2.6 mg/dl, respectively.

DISCUSSION

This schedule of administration permits the administration of two antibiotics through a single intravenous site by an alternating schedule. The actual serum concentration of aminoglycoside antibiotics that should be maintained to achieve optimum results against infecting orga-

TABLE 2. Serum concentrations of tobramycin during therapy

Day of therapy	Time of determination	Mean serum concn ($\mu\text{g/ml}$) $\pm$ standard error		
		72 patients with FUO ^a	45 patients with infection	All 117 patients
3-4	Preinfusion	3.5 $\pm$ 0.2 (0.7-10.3) ^b	3.2 $\pm$ 0.3 (0.4-8.8)	3.4 $\pm$ 0.2 (0.4-10.3)
3-4	Postinfusion	7.1 $\pm$ 0.3 (2.6-16.4)	7.3 $\pm$ 0.5 (<1-22.5)	7.2 $\pm$? (<1-22.5)
6-7	Preinfusion	3.7 $\pm$ 0.3 (<1-13.0)	3.4 $\pm$ 0.3 (<1-7.9)	3.6 $\pm$ 0.2 (<1-13.0)
6-7	Postinfusion	7.1 $\pm$ 0.3 (1.7-13.0)	7.3 $\pm$ 0.4 (2.9-18.0)	7.2 $\pm$ 0.2 (1.7-18.0)

^a FUO, Fever of undetermined origin.

^b Numbers in parentheses are the range.

nisms is not known. Our objective was to attempt to obtain a serum concentration of 3 to 6 $\mu\text{g/ml}$ (at least four times higher than the minimum inhibitory concentration of tobramycin against most gram-negative bacilli), without the peak concentration exceeding 10 $\mu\text{g/ml}$, and to maintain this optimal serum concentration as long as possible between doses. Our data indicate that with this schedule, about 25% of patients will have trough concentrations that may be too low and about 15% will have peak concentrations that may be too high. There were wide variations in the serum concentrations obtained from different patients, which has been true with other schedules of administration of aminoglycosides. Frequent assays are necessary to avoid inadequate or excessively high serum concentrations. Assays should be performed before (trough) and immediately after (peak) tobramycin infusion, and should be performed early in the course of therapy (probably day 2 or 3) and every 2 to 3 days thereafter. More frequent determinations should be obtained in patients who develop abnormalities in renal function.

This intermittent schedule of tobramycin administration allows higher doses to be given with no increase in renal toxicity. The 2-h administration allows other antibiotics, blood products, etc., to be given in one intravenous site in contrast to continuous infusion. A major advantage of the continuous infusion schedule is that it provides less fluctuation in the serum concentration of aminoglycoside. Excessive serum concen-

trations are less likely to occur by eliminating the peaks, and very low concentrations are avoided by administering the drug continuously. The 2-h infusion of tobramycin allows wide variations in the serum concentration, which increases the possibility of toxic concentrations as well as periods when the serum concentration is inadequate.

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