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Comparative Clinical Study of Tobramycin and Gentamicin

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Gentamicin and tobramycin have been compared in vitro and as single-drug therapy in patients with a serious infection caused by gram-negative rods. In vitro, a slight advantage of tobramycin over gentamicin has been found against *Pseudomonas aeruginosa*. Cross-resistance between gentamicin and tobramycin has been observed for gentamicin-resistant strains of *P. aeruginosa* and *Providence* but was not always present. The clinical effectiveness of gentamicin and tobramycin was similar: 14 (45.1%) out of the 31 patients in each series responded favorably. The clinical results were much better in urinary tract infections (66% of favorable responses) than in wound infections, pulmonary infections, septicemia, and meningitis (26% of favorable responses). The frequency of adverse reactions encountered in the present series was similar for both drugs.

Tobramycin is a new aminoglycoside antibiotic that has been reported to present an antibacterial activity similar to that of gentamicin against most strains of *Enterobacteriacae* and *Staphylococcus*. However, it has been suggested by several in vitro studies that tobramycin might have an anti-*Pseudomonas* advantage over gentamicin (5, 9, 12).

Only a few clinical investigations using tobramycin have been reported (W. W. King and C. E. Cox, Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 12th, Atlantic City, abstr. no. 32, 1972; L. S. Young, R. D. Meyer, and D. Armstrong, Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 12th, Atlantic City, abstr. no. 47, 1972). These studies suggest that tobramycin is effective as a therapy for urinary tract infections.

Severe infections caused by gram-negative bacteria, namely *Pseudomonas aeruginosa*, continue to be a major cause of morbidity and mortality in hospitalized patients, especially in those with impaired natural resistance to infection. Therefore it seemed important to evaluate further the clinical effectiveness of tobramycin and to compare it with that of gentamicin.

MATERIALS AND METHODS

Bacteriological studies. The bacteria tested were isolated from patients hospitalized at the Institut Jules Bordet, which is the clinical center for cancer therapy of Brussels University, between 1 January and 31 December 1972. Gram-negative bacteria were identified by the method of Edwards and Ewing (3). Only one isolate per bacterial species per patient was considered.

These clinical isolates included 318 *Staphylococcus aureus*, 530 *Escherichia coli*, 275 *Klebsiella*, 72 *Enterobacter* sp., 234 *P. aeruginosa*, 322 *Proteus mirabilis*, 42 indole-positive *Proteus* strains, and 57 *Providence*. Minimal inhibitory concentrations (MIC) of tobramycin and gentamicin were determined by the inocula replicating method (9) by using Mueller-Hinton agar (BBL) and an overnight bacterial suspension in Trypticase soy broth (BBL) diluted to a final concentration of 10^8 viable microorganisms in tests involving staphylococci and of 10^5 in those involving gram-negative bacilli.

Clinical studies. The patients studied here were hospitalized at the Institut Jules Bordet in 1972. The type of treatment was allocated to the patients by using a table of random numbers, and each form of therapy was given to 31 patients. The investigators did not know which antibiotic had been attributed to a patient until the complete evaluation of the present study had been completed. The two groups of patients received 320 mg of gentamicin or tobramycin daily. The patients in those series were approximately similar as far as age, sex, and underlying conditions were concerned. Depending upon the patient's weight, the daily dosage of the antibiotics ranged from 3.7 to 6.6 mg/kg. All the patients received 320 mg of gentamicin or tobramycin daily. No patient received concomitant therapy with other antibiotics. The mean duration of therapy was similar in both groups.

Clinical cure was considered to have been effected when the initial clinical signs and symptoms related to the infection disappeared during therapy or markedly improved. Bacteriological cure occurred when the offending microorganism had been eradicated. Bacterial colonization was defined as the presence of large numbers of any potential pathogen in cultures of sputum, urine, or wounds after antibiotic therapy was begun. Superinfection was defined as a newly clinically apparent infection caused by the colonizing microbial agent. It was recognized that the differenti-

ation between colonization and superinfection can be very difficult to make.

In all of the patients in this study, cultures of the sputum (or pharynx), urine, and wounds (when present) were performed before and on days 3 and 6 (when feasible) during therapy. Culture studies were repeated in most patients after the discontinuation of therapy. Similarly, complete hematological examination and determination of blood urea nitrogen, creatinine, alkaline phosphatase, bilirubin, oxalacetic-glutamic and glutamic-pyruvic transaminases were performed before, during, and after therapy with gentamicin or tobramycin.

Serum was obtained from all patients on the 2nd day of treatment just before and 1 h after the administration of the antibiotics. These sera were tested for bacteriostatic activity against the organism responsible for the infection in each case: suspensions of these organisms (10^4 to 10^5 per ml) in Trypticase soy broth were added to serial twofold dilutions of these sera. The highest dilution that failed to show evidence of macroscopic growth was considered to represent the bacteriostatic end point.

Assays for tobramycin and gentamicin were performed on these sera by the disk plate method described by Davis and Stout (2); *Bacillus subtilis* (Difco spore suspension) was used as the indicator organism, and Mueller-Hinton agar was used throughout.

Antibacterial activity and concentration of antibiotics within the urine was measured by the same techniques. Urine was collected on the 2nd day of treatment during the 8 h following an administration of the drug.

RESULTS

The antibacterial activity of tobramycin and gentamicin was similar in vitro for *S. aureus*, *E. coli*, *Klebsiella* and *Enterobacter* species, and indole-positive and indole-negative strains of *Proteus* (Fig. 1 and 2). A marked difference in the antibacterial activity of the two antibiotics could be shown for *P. aeruginosa* and to a lesser extent for *Providence*. For *P. aeruginosa*, the median MIC of tobramycin was 0.15 μg/ml and that of gentamicin was 0.9 μg/ml. At higher concentrations, the differences between the two drugs were less conspicuous.

Among the strains studied here, 29 (8 *Providence* and 21 *P. aeruginosa*) were found to be resistant to 3 μg of gentamicin per ml. The susceptibility of these strains to gentamicin and tobramycin is indicated in Table 1. It can be seen that 17 (58%) of these gentamicin-resistant strains could be inhibited in vitro by 3 μg or less of tobramycin per ml, making it clear that complete cross-resistance between gentamicin and tobramycin does not always exist, as already has been suggested by other workers (1). All of these strains were resistant to 50 μg of kanamycin per ml. No strains resistant to tobramycin and sensitive to gentamicin were encountered here. It should be observed that higher levels of resistance to gentamicin (MIC >12 μg/ml) were usually associated with cross-resistance with tobramycin.

The characteristics of the population studied here are summarized in Table 2. It is important to observe that in both groups most patients had a malignant tumor, making their prognosis as far as the outcome of gram-negative infection is concerned equally bad, because the types of tumors were uniformly distributed between the two treatment groups. In addition, in both groups a similar proportion of the patients was considered to be in a serious clinical condition when therapy was started.

None of the infections studied here was

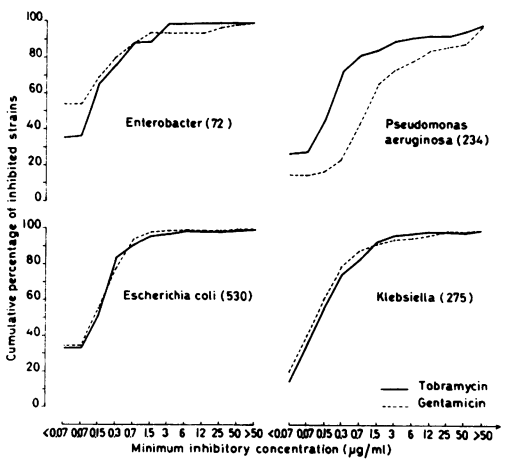

FIG. 1. *Cumulative percentage of strains inhibited by gentamicin and tobramycin.*

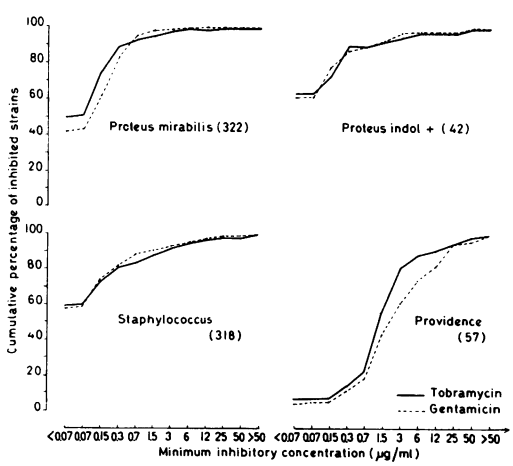

FIG. 2. *Cumulative percentage of strains inhibited by gentamicin and tobramycin.*

TABLE 1. *Cross-resistance between gentamicin and tobramycin on strains resistant to gentamicin*[a]

Microorganism	Gentamicin MIC (μg/ml)	Tobramycin MIC (μg/ml)
Providence	25	25
	25	12
	25	3
	12	12
	12	6
	12	1.5
	6	3
	6	3
Pseudomonas aeruginosa	>50	>50
	>50	>50
	>50	>50
	50	50
	50	12
	25	50
	25	25
	25	0.3
	12	3
	12	0.7
	12	0.7
	12	0.7
	12	0.7
	12	<0.07
	6	6
	6	3
	6	1.5
	6	0.3
	6	0.3
	6	0.3
	6	<0.07

[a] Gentamicin MIC >3 μg/ml.

caused by a microorganism resistant to the drug which has been given. However, the mean MIC of the offending microorganisms responsible for the infections in the gentamicin-treated patients was higher (1.08 μg of gentamicin per ml) than that found in the other group (0.4 μg of tobramycin per ml).

The blood levels observed in the patients treated with gentamicin were very similar to those found in the tobramycin-treated patients; the peak and trough levels were 3.94 and 0.76 μg/ml for tobramycin and 3.06 and 0.89 μg/ml for gentamicin, respectively.

As indicated in Table 3, 14 (45.1%) excellent responses, i.e., clinical and bacteriological cure without colonization or adverse effects, were observed in both groups. It should be stressed however that the results of both therapies in urinary tract infections were much better than those observed in patients with other types of infections such as wound infection, septicemia, broncho-pulmonary infection, and meningitis. In urinary tract infections, gentamicin or tobramycin resulted in 66% of favorable responses, whereas in other types of infection only 6 out of 29 (26%) patients responded well. This is a highly significant difference ($P < 0.01$). The overall results in broncho-pulmonary infections, which were associated with tracheostomy in all of the patients studied, were particularly poor. We previously found in this laboratory that endotracheal administration of antibiotics may be of value under these conditions (6).

All of the septicemias in this study arose from urinary foci; this might explain why excellent results, as defined earlier, were observed in two out of three cases.

Meningitis was the infection in two patients. Both died ultimately, in spite of several intrathecal daily injections of gentamicin or tobramycin (3 mg) in addition to intramuscular therapy. Levels of 0.3 to 3.1 μg of tobramycin or gentamicin per ml were observed in the cerebrospinal fluid 8 to 12 h after the injection. In one patient, with meningitis caused by *P. aeruginosa*, complicating a postoperative fistula of cerebrospinal fluid, eradication of the microorganism was obtained.

The importance of the site of the infection

TABLE 2. *Characteristics of the population studied, susceptibility of the offending pathogens, and serum levels observed during treatment with tobramycin and gentamicin*

Determination	Tobramycin	Gentamicin
No. of patients	31	31
Patient age (years)		
Mean	58.5	59.3
Range	(28-72)	(16-77)
Patient sex		
Females	16	11
Males	15	20
Patient underlying disease		
Cancer	24	28
Serious clinical condition[a]	16	17
Corticoids, cytostatic drugs	13	10
Local complicating factors[b]	17	16
Duration of therapy (days)		
Mean	7.7	7.8
Range	(3-12)	(4-11)
MIC (μg/ml)		
Mean	0.4	1.08
Range	(0.07-3.0)	(0.07-6.0)
Serum levels (μg/ml)		
Peak (mean and range)	3.94 (1.7-13.9)	3.06 (1.1-8.5)
Trough (mean and range)	0.76 (0.03-2.6)	0.89 (0.03-1.1)

[a] Rapidly fatal outcome was expected at the time of admission to the hospital.

[b] Tumor, urinary obstruction, tracheostomy, foreign body, etc....

TABLE 3. *Clinical and bacteriological data obtained with tobramycin and gentamicin*

Infection	Tobramycin[a]						Gentamicin[a]					
		Clin	Bact	Adv	Col	Excel	No	Clin	Bact	Adv	Col	Excel
Extraurinary infections												
Wound infection	4	2	2	0	1	2	7	5	3	0	1	2
Respiratory infection	9	1	0	0	0	0	3	1	1	0	1	0
Septicemia	3	2	3	0	0	2	1	0	1	1	0	0
Meningitis	1	0	0	0	0	0	1	0	1	0	0	0
Urinary infection	14	13	13	2	1	10	19	16	17	2	4	12
Total	31	18	18	2	2	14	31	22	23	3	6	14

[a] Clin, Clinical success; Bact, Bacteriological Success; Adv, adverse effects; Col, bacterial colonization; Excel, excellent response, i.e., clinical and bacteriological successes without bacterial colonization or adverse effects.

—urinary tract or not—played such a role in the outcome of the infection in this series that other factors such as sex, age, and nature of the underlying disease could not be assessed. The role of the nature of the offending microorganism did not significantly influence the outcome (Table 4). The clinical results were not significantly different regardless of whether *P. aeruginosa* or other gram-negative rods were responsible for the infection. Gentamicin and tobramycin appeared to be similarly effective against infections caused by *P. aeruginosa*.

The inhibitory activity attained in the serum of treated patients can be correlated to the outcome of serious infections: when the dilution of one-eighth of the serum is inhibitory against the offending pathogen the prognosis is better than when only lower dilutions are inhibitory (10). No clear differences could be detected between the inhibitory levels attained in the serum with gentamicin or tobramycin. In addition, it should be stressed that the inhibitory activities achieved were relatively low and could not be related to the outcome.

There were few untoward effects in this treatment series. Azotemia was seen in three patients (Table 5). In two of them the creatinine level was slightly elevated prior to therapy (1.6 mg/100 ml). In all cases, the signs of impaired renal function subsided when therapy with gentamicin or tobramycin was discontinued. Eighth cranial nerve dysfunction, manifested by dizziness and impaired hearing, was observed in three patients; in all three patients these symptoms disappeared after discontinuation of the drugs. Precise audiometric studies were performed in only a few patients however.

Bacterial colonization during therapy was observed in two patients treated with tobramycin and in six who received gentamicin. In all cases, the colonizing microorganisms were resistant to gentamicin or tobramycin (MIC >50 μg/ml). Bacterial colonization resulted in

TABLE 4. *Role of the nature of offending pathogen and of the antibacterial activity of the serum in the clinical course*

Antibiotic and type of infection	Total no. of patients	Number of patients		Inhibitory action of serum[b]	
		Micro-organism[a]			
		P. aeruginosa	Other micro-organisms[c]	Trough	Peak
Gentamicin					
Urinary infections					
Success	12	6	6	2	4
Failure	7	2	5	2	4
Nonurinary infections					
Success	2	1	1	4	4
Failure	10	4	6	4	8
Tobramycin					
Urinary infections					
Success	10	2	8	2	4
Failure	4	1	3	2	4
Nonurinary infections					
Success	4	3	1	<2	2
Failure	13	6	7	2	4
Total					
Urinary infections					
Success	22	8	14	2	4
Failure	11	3	8	2	4
Nonurinary infections					
Success	6	4	2	2	2
Failure	23	10	13	2	4

[a] Values represent number of patients.

[b] Maximum inhibitory dilution (reciprocal)—geometric means.

[c] *E. coli*, *Klebsiella* sp., and *Proteus* sp.

TABLE 5. *Untoward effects encountered in patients treated with tobramycin and gentamicin*

Untoward effects	Tobramycin (31 patients)	Gentamicin (31 patients)
Azotemia	1	2
Eighth cranial nerve dysfunction	1	2
Bacterial colonization	2[a]	6[b]
Clinical superinfection	1[c]	2[d]

[a] Yeasts (urine); beta-hemolytic streptococci (wound).

[b] *P. aeruginosa* (urine); beta-hemolytic streptococci and bacteroides (wound); *Providence* (urine); *P. aeruginosa* (sputum); yeasts (urine); *Providence* (urine).

[c] Beta-hemolytic streptococci (wound).

[d] Beta-hemolytic streptococci and bacteroides (wound); *Providence* (urine).

clinical superinfection in three patients; these complications were caused by beta-hemolytic streptococci, bacteroides, and *Providence* as summarized in Table 5.

DISCUSSION

Although the antibacterial activity of gentamicin and tobramycin is very similar for many strains of gram-negative rods tested in vitro, it would be erroneous to extrapolate results of an assay of the activity of only one agent to the other (1, 5, 9, 12): we have verified in the present study that tobramycin was more active in vitro against *P. aeruginosa* than was gentamicin and that cross-resistance was not always present between these two drugs, because different transferable R factors are in part responsible for resistance to gentamicin and tobramycin or to gentamicin alone (10). The present study failed to demonstrate any significant difference in clinical effectiveness or in tolerance between gentamicin and tobramycin, in spite of better in vitro susceptibility (lower MIC) of the offending pathogens to tobramycin than to gentamicin. The similar clinical effectiveness of gentamicin and tobramycin is also substantiated by similar, and rather low, inhibitory activities in the sera of the treated patients against the offending pathogens. *P. aeruginosa* infections did not respond more favorably in the tobramycin-treated patients than in those who received gentamicin; however, the present series of patients was small, and further investigations are required to determine whether there is a clinical advantage in using tobramycin rather than gentamicin in *P. aeruginosa* sepsis.

Perhaps our most striking finding was the difference in clinical effectiveness between both gentamicin and tobramycin in urinary tract infections, even when complicated by obstruction, and in other conditions such as wound infections, tracheo-bronchial infections, and meningitis. It is possible that in the latter situations, the relatively modest blood levels of both drugs do not result in adequate levels of the antibiotic at the site of infection. That the maximal serum level of gentamicin reached during therapy of serious infection is of considerable importance for the outcome has been shown by Jackson and Riff (4).

Gentamicin and probably also tobramycin are synergistic in vitro with penicillins and cephalosporins. Synergistic combinations seem to be more active clinically than nonsynergistic combinations (7) or single-drug therapy (8) in very debilitated patients presenting serious infections. It is therefore believed that under these special conditions, a combination of tobramycin or gentamicin with a penicillin or a cephalosporin might represent the most adequate therapy; additional controlled trials should assess the effectiveness of this form of treatment.

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