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Gentamicin and Gentamicin C_1 in the Treatment of Complicated Urinary Tract Infections: Comparative Study of Efficacy, Tolerance, and Pharmacokinetics

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The clinical efficacy, patient tolerance, and pharmacokinetics of gentamicin and the single component gentamicin C_1 were studied after single and multiple doses in elderly male patients. Patient tolerance was extremely good at the dose levels used. There was some evidence of renal function impairment due to repeated intramuscular doses of gentamicin, but not gentamicin C_1. The antibiotics were equally effective against the organisms present in the urine of these patients. The pharmacokinetics of the two antibiotic forms were similar, although gentamicin C_1 appeared to have a larger distribution space.

Gentamicin, a broad-spectrum antibiotic complex, has been shown to consist of three components designated C_1, C_{1a}, and C_2 (2). The recent availability of each component in substantially pure form has permitted their comparative evaluation with the parent complex in a variety of in vitro and in vivo studies. It was noted that gentamicin C_1 (SCH 13706) required a significantly longer period of administration to produce ataxia in cats than did the gentamicin complex. Similar observations, together with reduced nephrotoxicity due to gentamicin C_1, were made in the squirrel monkey. Studies in other species also demonstrated reduced eighth cranial nerve and renal toxicity with gentamicin C_1 (2).

In vitro bacteriological studies and in vivo mouse protection studies indicate that gentamicin C_1 is slightly less active than the gentamicin complex against most strains of *Enterobacteriaceae*. Cross-resistance between gentamicin C_1 and the parent complex is generally noted, although the former is not inactivated by bacterial acetylases (2).

Since it thus appears that gentamicin C_1 may offer therapeutic advantages over gentamicin, the two antibiotics were compared in the clinical treatment of complicated urinary tract infections, with particular emphasis on efficacy, tolerance, and pharmacokinetics.

MATERIALS AND METHODS

Thirty elderly male patients, on the urology ward of the Veterans Administration Hospital, aged between 45 and 83 years (mean 71) and weighing between 121 and 220 pounds (mean 155) (about 55 to 100 kg, mean 70) were divided in a prospective randomized fashion into two groups of 15 patients. Almost all patients had complicated urinary tract infections associated with lower urinary tract obstruction from benign hypertrophy or cancer of the prostate, or urethral strictures. Many also had indwelling bladder catheters. All patients had relatively normal renal function for this type of patient population as defined by a serum creatinine $\leq$1.5 mg/100 ml and/or a blood urea nitrogen $\leq$25 mg/100 ml. Creatinine clearances were, as expected, low, suggesting some impairment of renal function. The two patient groups were considered comparable since there were no statistically significant differences between the groups regarding age, weight, underlying pathology, incidence of indwelling catheters, or renal functions, and there were no major differences in the types of bacteria isolated from the urines in the two groups. All patients had gram-negative urinary tract infections susceptible to gentamicin as defined by the standardized disk susceptibility method (1), and all had significant bacteriuria ($\geq 10^5$ colonies per ml) before treatment.

All patients received gentamicin or gentamicin C_1 by intravenous injection at a dose level of 1 mg/kg on the first day of treatment. (Gentamicin C_1 was supplied as the sulfate in 2-ml ampoules containing 50 mg/ml by Schering Laboratories, Bloomfield, N.J.) This was followed by 1 mg/kg every 8 h intramuscularly for 7 days. On the 8th day the patients again received 1 mg/kg of one of the two antibiotics intravenously. Simultaneously with the intravenous injections on the first and last days of treatment, patients received injections of 20 μCi each of [^{125}I]sodium iothalamate and [^{131}I]o-iodohippurate ([^{125}I]Glofil and [^{131}I]Hippuran; Abbott Laboratories, North Chicago, Ill.) as indicators for glomeruler filtration rate

(5) and effective renal plasma flow (8), respectively. Serum samples for bioassay and radioactivity counting were obtained immediately before and at 15 min, 30 min, and 1, 2, 4, and 8 h after each intravenous injection. Urine was collected quantitatively at 0 to 2, 2 to 4, and 4 to 8 h after dosing. All urine and serum samples were assayed for antibiotic activity by a disk diffusion method using *Staphylococcus aureus* ATCC-6538P as test organism. Radioactivity in serum and urine was measured in a Packard automatic scintillation spectrometer and appropriate corrections were made for radioactivity decay and simultaneous reading of the two isotopes.

Plots of the logarithms of serum concentrations of antibiotic versus time were approximately linear between 1 and 6 h after intravenous injection, and the resulting regressions were used to calculate elimination half-lives ($t_{1/2}$), associated elimination rate constants ($\beta = \ln 2/t_{1/2}$), distribution volumes (V_d), and serum and renal clearances. Serum clearances of antibiotic were calculated from the formula $S_{C_1} = (V_d \times 0.693)/t_{1/2}$, where V_d is the distribution volume obtained by the method of extrapolation (7). Although this method tends to overestimate the total distribution space of a drug that obeys two-compartment model kinetics (10), its use may be justified on a comparative basis in this study for two compounds with similar pharmacokinetic characteristics.

Serum clearances of the renal diagnostic agents were obtained from the relationship $S_{C_1} = V_1K_2$, where V_1 is the volume of the central compartment of the two-compartment model and K_2 is the elimination rate constant of compound from the central compartment (6). Complete details of the pharmacokinetics of these diagnostic agents will be published separately. Renal clearances were calculated from the relationship $R_{C_1} = (U \times V)/S_m$, where U is the urinary concentration of antibiotic (in micrograms per milliliter) or diagnostic agent (in counts per minute per milliliter), V is the urine flow rate (in milliliters per minute), and S_m is the serum concentration calculated as a weighted mean from a plot of log serum concentrations versus time during a urine collection interval.

Audiograms were carried out and blood chemistry values were obtained before and immediately after treatment. Blood urea nitrogen, serum creatinine, and creatinine clearances were determined before and at the end of a treatment. Urine cultures with colony count were carried out before treatment, on the 3rd and last day of treatment, and at the 1-week follow-up.

Therapeutic results were defined according to the urine cultures: cure, negative culture at 1 week after treatment; persistence, >100,000 colonies/ml of the original bacteria during treatment; relapse, negative culture during therapy and >100,000 colonies/ml of the original organism at follow-up; reinfection, >100,000 colonies/ml different from the original bacteria at the follow-up; and superinfection, >100,000 colonies/ml different from the original bacteria during therapy. Microorganisms were identified by routine bacteriological methods without specific typing.

RESULTS

Clinical efficacy. The bacteriological results from the two treatments are given in Table 1. Similar results were obtained with both treatments. Although a slightly higher cure rate was obtained with gentamicin, the differences observed between the treatment were not clinically significant.

Tolerance. The intramuscular injections of the two antibiotics caused only minimal discomfort. There were no changes in values for serum alkaline phosphatase, glutamic oxaloacetic transaminase, serum bilirubin, hemoglobin, or leukocyte count with differential before or after treatment with either compound, and no changes in audiograms were observed.

Table 2 illustrates renal function as expressed by blood urea nitrogen, serum creatinine, and creatinine clearance before and after treatments. No changes were observed except for an increase in serum creatinine after gentamicin dosing, which was of borderline significance.

Serum and urine antibiotic levels. Mean serum and urine antibiotic concentrations after both treatments, together with cumulative urinary excretion, are given in Table 3, and mean serum levels are illustrated in FIG. 1. Serum concentrations of gentamicin were generally higher than those for gentamicin C_1, and higher concentrations of both antibiotics were obtained after multiple dosing due to accumulation. Both treatments resulted in similar urinary concentrations and cumulative urinary excretion of antibiotic after the first and last doses. The data for gentamicin are similar to those

TABLE 1. *Results of treatment of complicated urinary tract infections with gentamicin and gentamicin C_1*

Time	Negative culture		Persistence or relapse		Reinfection or superinfection	
	Gentamicin	C_1	Gentamicin	C_1	Gentamicin	C_1
3rd day of therapy	13/15	10/15	0/15	1/15	2/15	4/15
End of therapy	14/15	13/15	0/15	1/15	1/15	1/15
1-week follow-up	9/15	8/15	3/15	5/15	3/15	2/15

TABLE 2. *Renal function parameters before and after treatment with gentamicin or gentamicin C_1*

Group	Determination	Blood urea nitrogen (mg/100 ml)		Serum creatinine (mg/100 ml)		Creatinine clearance (ml/min per 1.73 m²)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Gentamicin	Mean ± SE[a]	21.4 ± 2.2	21.4 ± 1.9	1.25 ± 0.07	1.32 ± 0.08	75 ± 7	78 ± 10
	Range	9-44	11-34	0.8-1.9	0.9-2.1	39-131	33-130
	Paired *t* test	N.S.[b]	N.S.	$0.05 < P < 0.1$		N.S.	N.S.
Gentamicin C_1	Mean ± SE	18.5 ± 2.0	19.9 ± 2.3	1.28 ± 0.12	1.32 ± 0.10	79 ± 8	78 ± 7
	Range	10-42	10-44	0.7-2.8	0.8-2.8	35-121	25-132
	Paired *t* test	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

[a] SE, Standard error.
[b] Not significant; $P > 0.1$.

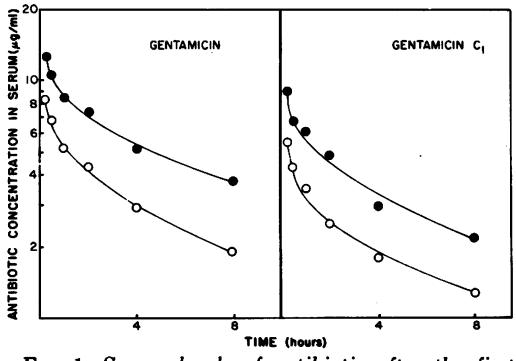

FIG. 1. *Serum levels of antibiotic after the first and last intravenous injections of gentamicin and gentamicin C_1.*

obtained by other investigators (3, 10). However, the serum concentrations were higher than those reported previously, and this may have been due to resistance to drug diffusion into extravascular spaces in these older patients. The distribution volume of gentamicin after the first intravenous dose was 17 ± 1% (standard error) of body weight, whereas that of gentamicin C_1 was 25 ± 1.5% of body weight, and it appears that this single component penetrates into extravascular spaces more readily than the other components of gentamicin or a combination of all three components. Serum half-lives of gentamicin and gentamicin C_1 after the first intravenous doses were 272 ± 28 (standard error) and 258 ± 40 min, respectively. Almost identical values of 279 ± 31 and 253 ± 65 min were obtained after the final intravenous doses.

Uncorrected serum and renal clearances (10) of the antibiotics, and also the renal function indicators, are given in Table 4. Clearance values for gentamicin were lower than those obtained in younger subjects (4), and renal clearances of gentamicin were approximately one-half creatinine clearance values (Table 2). Clearance values for gentamicin C_1 were higher than those for gentamicin, and for both treatments renal and serum clearances were similar. Serum clearances of [^{125}I]iothalamate were almost identical to creatinine clearances and, as observed in other studies (A. Mosegaard, P. G. Welling, F. L. S. Tse, and P. O. Madsen, submitted for publication), were somewhat higher than renal [^{125}I]iothalamate clearances. The only values influenced by repeated administration of either drug were the renal clearance of gentamicin, which increased slightly, and the renal clearance of [^{125}I]iothalamate, which significantly decreased after repeated doses of gentamicin. Although creatinine clearance values, antibiotic clearance values, and effective renal plasma flow were essentially unaltered after the gentamicin treatment, increased serum creatinine levels and decreased renal clearance of [^{125}I]iothalamate suggest some degree of renal function impairment.

DISCUSSION

From the above results it is evident the both gentamicin and gentamicin C_1 were well tolerated locally and systemically with the dosage regimens used. Although gentamicin has been shown in this and other studies to have some effect on renal function (9), no adverse effects were associated with the present gentamicin C_1 treatment. Due to the similarity in the clinical efficacy of the two treatments and the absence of any toxic symptoms with gentamicin C_1, it appears that this single component may offer some slight advantage over gentamicin.

The present results were obtained in a special patient population, and therefore further studies will be needed to compare the relative efficacy and tolerance of the two antibiotics in a

TABLE 3. *Serum and urine concentrations and cumulative urinary excretion after intravenous gentamicin or gentamicin C_1 injections on the first and last days of treatment*

Time (h)	Gentamicin						Gentamicin C_1					
	Serum concn[a]		Urine concn[a]		Cumulative excretion[b]		Serum concn		Urine concn		Cumulative excretion	
	1st day	Last day	1st day	Last day	1st day	Last day	1st day	Last day	1st day	Last day	1st day	Last day
0.25	8.3 ± 0.8	12.1 ± 0.8					5.5 ± 0.2	9.0 ± 1.6				
0.5	6.8 ± 0.5	10.6 ± 0.5					4.3 ± 0.3	6.7 ± 0.6				
1	5.2 ± 0.4	8.5 ± 0.9					3.5 ± 0.2	6.1 ± 1.2				
2	4.3 ± 0.3	7.4 ± 0.8					2.5 ± 0.2	4.8 ± 0.7				
4	2.9 ± 0.3	5.1 ± 0.6					1.8 ± 0.2	2.9 ± 0.3				
8	1.9 ± 0.2	3.8 ± 0.4					1.3 ± 0.2	2.3 ± 0.4				
0–2			133 ± 33	235 ± 33					187 ± 36	224 ± 40		
2–4			101 ± 26	207 ± 49					107 ± 21	143 ± 27		
4–8			55 ± 8	125 ± 31					65 ± 12	84 ± 16		
0–2					22 ± 4	42 ± 5					34 ± 4	38 ± 4
0–4					36 ± 6	71 ± 7					48 ± 5	62 ± 6
0–8					49 ± 6	96 ± 8					60 ± 5	87 ± 10

[a] Expressed as micrograms per milliliter ± 1 standard error.
[b] Expressed as percentage ± 1 standard error.

TABLE 4. *Serum and renal clearances of gentamicin, gentamicin C_1, and [^{125}I]iothalamate, and serum clearances of [^{131}I]o-iodohippurate on the first and last days of treatment*[a]

Treatment	Clearance	Drug clearance		Paired *t* test	[^{125}I]iothalamate clearance		Paired *t* test	[^{131}I]o-iodohippurate clearance		Paired *t* test
		1st day	Last day		1st day	Last day		1st day	Last day	
Gentamicin	Serum	32 ± 3	35 ± 4	NS[b]	84 ± 11	81 ± 12	NS	293 ± 78	297 ± 52	NS
	Renal	25 ± 3	31 ± 5	$0.05 < P < 0.1$	61 ± 6	43 ± 6	$P < 0.05$	[c]	[c]	
Gentamicin C_1	Serum	55 ± 7	57 ± 8	NS	88 ± 11	83 ± 12	NS	338 ± 36	325 ± 45	NS
	Renal	50 ± 6	47 ± 5	NS	64 ± 8	62 ± 9	NS	[c]	[c]	

[a] Clearances are expressed as milliliters per minute ± 1 standard error.

[b] NS, Not significant.

[c] Renal clearance of [^{131}I]o-iodohippurate could not be obtained due to very low radioactivity levels in all except the 0- to 2-h urine samples.

broader patient population. To establish possible therapeutic efficacy differences between the two drugs, studies in much larger series of patients with urinary tract infection will be required.

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