Single-Dose Daily Gentamicin Therapy in Urinary Tract Infection

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Patients with urinary tract infection were treated for 8 to 15 days with one daily intramuscular injection of 160 mg of gentamicin or 60 or 80 mg every 8 h. Ten of 11 patients treated with one injection daily were cured as compared with 8 of 10 patients treated with three injections daily. Urinary concentrations of gentamicin were 3.2 to 600 $\mu\text{g/ml}$ in all 8-h collections in patients receiving one injection daily and were 22 to 440 $\mu\text{g/ml}$ in all 8-h collections in patients receiving three injections daily. The group treated once daily demonstrated a significant but reversible increase in mean serum creatinine concentration and decrease in mean creatinine clearance during therapy as compared with no change in the group treated with three injections daily. Decreases in renal function were correlated with higher milligram per kilogram doses and higher 1-h serum concentrations.

Gentamicin, an aminoglycoside antibiotic, has the broadest spectrum against gram-negative bacilli of any commercially available antibiotic (9). It is not absorbed when given orally and must be given intramuscularly or intravenously in treatment of systemic infection.

Gentamicin has been shown to be effective in treatment of urinary tract infection (3). The daily therapeutic dose has usually been administered in two to three divided doses each day, which makes its use in out-patients with urinary tract infections quite difficult. Gentamicin is excreted almost entirely by the kidneys after injection. In one study (2), urinary levels of 6 to 12 $\mu\text{g/ml}$ were found in the urine of four healthy subjects 12 to 24 h after injection of 1.6 to 3.2 mg of gentamicin per kg. This suggested that gentamicin administered once daily might be effective in treatment of urinary tract infection. The availability of gentamicin as an agent for treatment of urinary tract infection requiring only one injection each day would have obvious advantages in out-patients with urinary tract infections caused by bacteria resistant to other antibiotics.

The present study was undertaken to evaluate the efficacy and tolerance of gentamicin administered by one injection each day in comparison with multiple daily injections in treatment of patients with urinary tract infection.

MATERIALS AND METHODS

Patients. Twenty-one patients, 3 males and 18 females, with urinary tract infections were treated

with gentamicin at The Hospital of The Medical College of Pennsylvania from April 1972 to September 1973. The criteria for inclusion in the study were: in symptomatic patients, significant bacteriuria in one urine culture ($\geq 10^5$ bacteria per ml of urine), and in asymptomatic patients, significant bacteriuria in two urine cultures on different days with the same organism.

Patients were excluded from the study if there was: a serum creatinine concentration > 1.5 mg per 100 ml; a history of abnormal vestibular function (labyrinthitis, vertigo, or tinnitus); impairment of hearing for conversational speech; evidence of gross upper or lower urinary tract obstruction, renal calculi, a neurogenic bladder, urinary diversion (e.g., foley catheter); or pregnancy. Also excluded were patients who had received ototoxic or nephrotoxic drugs within the previous month (i.e., streptomycin, kanamycin, neomycin, viomycin, vancomycin, polymyxin B, colistin, or cephaloridine).

The patients were treated with regimens of either 160 mg of gentamicin intramuscularly every 24 h (usually given at 8 AM) or 60 or 80 mg of gentamicin intramuscularly every 8 h. Patients were assigned to the regimens of one or three injections a day in a randomized fashion.

Repeat urine cultures were obtained on days 4, 5, or 6 of therapy, the last day of therapy, and 3 to 4 weeks after therapy was discontinued. Urine for culture was a midstream specimen of voided urine obtained after cleaning and drying the perineum and external urethra and was processed immediately or after several hours of refrigeration at 4 C. Bacteria isolated in titers of $\geq 10^5$ per ml of urine were tested for susceptibility to gentamicin by the Kirby-Bauer method (1) and by an antibiotic dilution method in heart infusion broth (5).

Determinations were made of the serum creatinine concentrations and 24-h urines were collected and stored for determination of the endogenous creatinine

clearance (Ccr) before initiation of gentamicin therapy and on the last day of therapy.

Vestibular function was tested daily during therapy by finger to nose, vertical passed pointing, and gait. Subjective complaints of lightheadedness, loss of coordination, dizziness, giddiness, and tinnitus were sought.

Serum and urinary concentrations of gentamicin.

Serum and urinary concentrations of gentamicin were determined during the 1st day, 4th, 5th, or 6th day, and last day of therapy. Blood was obtained 1 h after the dose of gentamicin. Twenty-four-hour urine specimens were collected in three 8-h samples. The beginning of the urine collection coincided with the administration of the drug. Serum was separated and stored at -20°C until the time of assay. Urine was stored at -20°C .

The concentrations of gentamicin in serum and urine were determined by an agar diffusion method with the use of paper disks. A volume of 0.25 ml of *Bacillus subtilis* spore suspension (Difco 0453-52-9) was mixed with 100 ml of melted heart infusion agar. Pour plates were made with 10 ml for each plate and were allowed to harden. Sterile paper disks were submerged in known concentrations of gentamicin freshly prepared in pooled human serum and in the sera to be tested. The disks were placed on the pour plates and incubated at 37°C for 24 h. Each known and unknown serum was plated in quadruplicate. A known serum was plated on each pour plate to measure uniformity of the plates. Zones of inhibition were determined with an antibiotic zone reader, and a standard curve was constructed from the known concentrations of gentamicin. Concentrations of gen-

tamicin in the patients' sera were determined from this curve. Urine concentrations of gentamicin were determined in the same manner with two exceptions: (i) the urine specimens were diluted in heart infusion broth before the determinations were performed, and (ii) the standard curve was constructed from known concentrations of antibiotic in heart infusion broth.

RESULTS

Results of therapy. The clinical data are summarized in Table 1. Eleven patients (three males and eight females) 22 to 80 years of age (mean, 53 years) were treated with a single daily intramuscular injection of 160 mg of gentamicin for 8 to 11 days (except for one patient who received 15 days of treatment). Ten females 20 to 74 years of age (mean, 40 years) were treated with 60 mg (six patients) or 80 mg (four patients) of gentamicin intramuscularly every 8 h for 8 to 12 days (except for one patient who was treated for 15 days). The age difference between the two groups was not significant ($P > 0.05$ by t test).

The species of infecting organisms were similar in both groups (Table 1). However, all of the infecting organisms in the group treated with three daily injections of gentamicin were highly susceptible to gentamicin (i.e., inhibited by $1.6\text{ }\mu\text{g/ml}$ or less). In contrast, in the group treated with one injection each day, the *Escherichia coli* isolated from patient 3 required $3.1\text{ }\mu\text{g}$ of

TABLE 1. Results of therapy with gentamicin

Patient	Age (years)	Sex	Daily dose of gentamicin (mg/kg) ^a	Infecting organism	Results
1	59	M	2.46	<i>Escherichia coli</i>	Cure
2	80	F	2.35	<i>Proteus mirabilis</i>	Cure
3	64	F	2.55	<i>E. coli</i>	Cure
4	34	F	2.35	<i>E. coli</i>	Cure
5	37	F	1.56	<i>E. coli</i>	Persistence during therapy
6	49	M	1.76	<i>Pseudomonas aeruginosa</i>	Cure
7	49	F	1.64	<i>E. coli</i>	Cure
8	22	F	3.14	<i>Enterobacter cloacae</i>	Cure
9	68	F	2.71	<i>Enterococcus</i>	Cure
10	68	F	2.07	<i>Enterococcus</i>	Cure
11	55	M	2.15	<i>E. coli</i>	Cure
12	21	F	2.71	<i>Enterobacter liquefaciens</i>	Cure
13	35	F	3.42	<i>E. coli</i>	Cure
14	74	F	2.55	<i>Enterobacter aerogenes</i>	Cure
15	58	F	2.48	<i>E. coli</i>	Cure
16	30	F	3.81	<i>E. coli</i>	Cure
17	36	F	4.40	<i>E. coli</i>	Relapse
18	20	F	3.55	<i>E. coli</i>	Cure
19	47	F	4.12	<i>E. coli</i>	Cure
20	45	F	2.81	<i>E. coli</i>	Cure
21	37	F	3.05	<i>Klebsiella pneumoniae</i>	Relapse

^a Patients 1 through 11 received a single daily dose of 160 mg intramuscularly; patients 12 through 21 received 60 or 80 mg intramuscularly every 8 h.

gentamicin per ml for inhibition, the *Proteus mirabilis* from patient 2 required 12.5 µg/ml, and the enterococcus from patient 9 required 50 µg/ml for inhibition.

Four of the 11 patients treated with single daily injections had symptoms of urinary tract infection as compared with 6 of the 10 treated with injections every 8 h. In all symptomatic patients, the symptoms disappeared within the first 72 h of treatment. In 10 of the 11 patients treated with one daily injection of gentamicin, urine cultures were negative during therapy and at followup, 3 to 4 weeks after therapy was discontinued. In one patient (number 5) *E. coli* persisted in the urine during and after treatment in titers of $>10^4$ /ml. This patient was subsequently discovered to have a renal calculus.

The urine cultures were negative during therapy in all 10 of the patients who were treated with injections of gentamicin every 8 h. Eight of these patients had negative urine cultures 3 to 4 weeks after discontinuation of therapy, but in two (patients 17 and 21) the urinary infection relapsed by 3 to 4 weeks after discontinuation of therapy.

Serum and urinary concentrations of gentamicin. Table 2 lists serum concentrations for the patients in both groups. Serum concentrations of gentamicin determined 1 h after the first injection of gentamicin were significantly higher ($P < 0.01$) in patients receiving 160 mg (1.56 to 3.14 mg per kg per dose) than in patients receiving 60 or 80 mg (0.83 to 1.47 mg per kg per dose) three times a day. For those receiving the single daily dose, the mean serum gentamicin concentration was 8.4 µg/ml as compared with 4.0 µg/ml for those receiving three doses each day. The mean concentration of gentamicin in serum 1 h after injection on the last day of therapy was not significantly higher ($P > 0.05$) than on the first day in either group.

There was a relationship between 1-h serum concentrations and the dose injected. For example, in the group that received one injection of gentamicin each day, the patients (numbers 5, 6, 7, and 10) who received the lowest milligram per kilogram dose of gentamicin (1.56 to 2.07 mg/kg) had mean 1-h blood levels significantly below the patients (numbers 1, 2, 3, 4, 8, 9, and 11) who received larger doses (2.15 to 3.14 mg/kg); the mean levels were 6.0, 6.4, and 5.9 µg/ml on day 1, day 4, 5, or 6, and the last day of therapy, respectively, as compared with 9.4, 8.9, and 10.1 µg/ml ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively).

Table 3 lists the urinary concentrations of gentamicin. The urinary levels in the group

receiving three injections of gentamicin each day were 22 to 440 µg of gentamicin per ml in all 8-h collections. The two patients in this group who relapsed (numbers 17 and 21) had urinary concentrations of at least 42 µg/ml in all collections. The group receiving one injection of gentamicin each day had urinary levels of at least 54 µg of gentamicin per ml in all first 8-h collections, 8.8 µg/ml in all second 8-h collections, and 3.2 µg/ml in all third 8-h collections. In this group, 3 of 11 patients had urinary concentrations of less than 10 µg/ml in the third 8-h collection on the first day of treatment. However (with the exception of one patient on the last day of therapy), concentrations were at least 16 µg/ml in the third 8-h urine collections obtained on day 4, 5, or 6 and on the last day of therapy. The patient (number 5) who had persistence of bacteriuria while receiving 160 mg of gentamicin each day had relatively low urinary levels during the second and third 8-h urine collections on the first day (11 and 3.2 µg/ml, respectively); however, the levels were 52 and 64 µg/ml on day 6 of therapy and 50 and 62

TABLE 2. Gentamicin in serum

Patient	Gentamicin (mg per kg per dose) ^a	1-h gentamicin concn (µg/ml)	
		Day 1 (1st dose)	Last day (day 9-12)
1	2.46	6.2	8.2
2	2.35	5.2	7.6
3	2.55	8.8	10.0
4	2.35	14.0	11.0
5	1.56	6.0	5.8
6	1.76	6.6	6.0
7	1.64		4.6
8	3.14	11.2	10.5
9	2.71	9.6	10.5
10	2.07	5.3	7.2
11	2.15	10.7	13.0
Mean (range) ± SD ^b		8.4 (5.2-14) ± 2.8	8.6 (5.8-11.0) ± 2.5
12	0.90	5.0	3.4
13	1.14	3.3	3.0
14	0.85	4.2	5.6
15	0.83	1.8	4.2
16	1.27	4.3	6.5
17	1.47	3.6	5.0
18	1.18	4.2	4.2
19	1.37	5.4	4.8
20	0.94	3.0	5.4
21	1.02	5.0	5.5
Mean (range) ± SD		4.0 (1.8-5.4) ± 1.0	4.8 (3.0-6.5) ± 1.0

^a Dosages were as in Table 1.

^b SD, Standard deviation.

TABLE 3. *Gentamicin in urine*

Time of determination	Gentamicin concn on:		
	Day 1 (1st dose)	Day 4, 5 or 6	Last day (9-12)
160 mg intramuscularly once a day			
First 8 h	225 (76-460) ^a	282 (54-600)	220 (110-400)
Second 8 h	72 (11-180)	110 (40-290)	56 (8.8-102)
Third 8 h	28 (3.2-54)	86 (16-252)	54 (5.4-124)
60 or 80 mg intramuscularly every 8 h			
8 h after first dose	164 (40-440)	147 (48-280)	116 (22-160)
8 h after second dose	174 (48-360)	171 (50-360)	133 (54-201)
8 h after third dose	150 (50-368)	119 (60-240)	163 (80-306)

^a Mean (range) in micrograms per milliliter.

μg/ml on the last day of therapy.

The patients receiving 60 to 80 mg of gentamicin every 8 h excreted a mean of 70% of the initial (first dose, first day) gentamicin dose in the first 8-h urine collection; this group excreted 92% of the amount injected in the 8-h urine collections after both the second and third doses on the first day. A mean of 96% of the dose injected was recovered from the three 8-h urine collections on days 4, 5, or 6 and on the last day of therapy. The group receiving 160 mg of gentamicin once each day excreted means of: 78% of the injected dose on day 1 (54% in the first 8 h, 18% in the second 8 h, and 6% in the third 8 h); 93% of the dose on day 4, 5, or 6 (55% in the first 8 h, 25% in the second 8 h, and 13% in the third 8 h); and 101% of the dose on the last day of therapy (64% in the first 8 h, 19% in the second 8 h, and 18% in the third 8 h).

Side effects. The data on renal function are listed in Table 4. Prior to gentamicin therapy renal function (as measured by serum creatinine concentrations and endogenous Ccr) was better in the group treated with three injections each day than in the group treated with one injection each day. Although these differences were not significant for the group as a whole ($P > 0.05$ for both creatinine and Ccr by t test for independent groups), five patients (numbers 1, 2, 9, 10, and 11) treated with one injection each day had a creatinine clearance of less than 70 ml/min (range, 36 to 62) as compared with only one patient (number 14, who had a Ccr of 47 ml/min) in the group treated with three injections a day. The group treated with three injections of gentamicin each day did not have a significant change ($P > 0.05$ by t test for paired observations) in serum creatinine concentration or Ccr during therapy. However, renal function decreased in 2 of the 10 patients (numbers 12 and 14). The change was most marked in patient 14, who had the poorest renal function

TABLE 4. *Serum creatinines and endogenous creatinine clearances^a*

Determination	Before therapy	Last day of therapy
160 mg intramuscularly once a day		
Serum creatinine (mg/100 ml)	1.1 ± 0.2	1.4 ± 0.4
Endogenous creatinine clearance (ml/min)	80.6 ± 37.0	69.3 ± 41.1
60 or 80 mg intramuscularly every 8 h		
Serum creatinine (mg/100 ml)	1.0 ± 0.1	1.1 ± 0.1
Endogenous creatinine clearance (ml/min)	89.6 ± 25.1	85.7 ± 30.0

^a Mean ± standard deviation.

at the initiation of gentamicin therapy; in this patient the Ccr decreased from 47 to 25 ml/min. The group treated with one injection each day demonstrated a significant increase in serum creatinine concentration ($P < 0.05$ by t test for paired observations) and a significant decrease in Ccr ($P < 0.01$ by t test for paired observations) during therapy. Renal function decreased in 6 of the 11 patients (numbers 1, 2, 3, 4, 9, and 11), four of whom had Ccr less than 70 ml/min prior to therapy with gentamicin. The Ccr decreased by 8 to 11 ml/min in three patients and by 17, 24, and 29 ml/min in the other three. Four of these patients were reevaluated 2 to 6 weeks after discontinuation of gentamicin and renal function had returned to the pretherapy level. Renal function did not change in the four patients (numbers 5, 6, 7, and 10) who received the lowest milligram per kilogram of body weight dose (1.56 to 2.07 mg/kg) or in the patient (number 8) who received the highest dose (3.14 mg/kg).

In the group receiving three injections of

gentamicin each day there was no apparent relation between serum gentamicin concentrations and development of decreases in renal function. However, in the group receiving one injection each day the serum concentrations of gentamicin were higher in the patients that developed decreases in renal function than in those who did not. One hour after injection the mean serum concentrations in the six patients whose function decreased were 9.1, 8.3, and 10.1 $\mu\text{g/ml}$ (on day 1, day 4, 5, or 6, and the last day of therapy) as compared with 7.3, 8.1, and 6.8 $\mu\text{g/ml}$ in the five patients whose function did not decrease.

Audiometric evaluation revealed a slight decrease in hearing acuity after gentamicin therapy in only one patient (number 10). This patient had gentamicin serum concentrations of 5.3, 6.8, and 7.2 $\mu\text{g/ml}$ 1 h after the 160 mg of gentamicin on days 1, 4, and 9, respectively. The half-life in serum of gentamicin in this patient was 5.5 h as calculated by the method of least squares (6). Vestibular function did not change in any patient.

DISCUSSION

Cure of urinary tract infection is related more to achieving inhibitory urinary levels of an antimicrobial agent rather than serum levels (8). Therefore, as might be expected, the results of therapy with one daily dose of gentamicin were at least as good as with three daily doses. In this study, even 16 to 24 h after a single injection of 160 mg of gentamicin, urinary levels were high enough to inhibit the vast majority of gram-negative bacilli that cause urinary tract infection (7, 9).

As expected, concentrations of gentamicin in serum were significantly higher after 160-mg doses of gentamicin than after 60- or 80-mg doses.

In contrast to the group receiving three injections each day where renal function did not change, renal function decreased significantly during therapy in the group treated with one injection each day. As the total daily dose (in milligrams per kilogram of body weight) of gentamicin was higher in the group treated with divided doses, the decrease in renal function seemed to be more a function of peak serum levels than amount of gentamicin administered. Furthermore, in the group receiving 160 mg each day, those who developed nephrotoxicity had higher 1-h serum levels of gentamicin than those who did not. These results are in contrast to studies recently reported in rabbits (P. Frame, T. Bannister, J. Tan, and J. Phair,

Abstr. Clin. Res., 1973) where nephrotoxicity appeared to be related more to increased frequency of administration rather than to total daily dose or peak serum levels of gentamicin.

Some investigators have recently implicated trough levels of gentamicin in serum as more important than peak levels in producing nephrotoxicity (J. Dahlgren and W. Hewitt, Abstr., 13th Int. Conf. Antimicrob. Ag. Chemother., 1973). In the present study the serum half lives of gentamicin calculated on the first day of therapy were 5.5 h or less (mean 3.6 h) in the group receiving one injection of gentamicin each day and 4.5 h or less (mean 2.9 h) in the other group. Therefore calculated trough levels in the group receiving one injection each day would be lower (at least initially) than in the group receiving three injections each day because of the 24 h between injections. As noted by others (10), the nephrotoxicity was reversible when therapy was discontinued.

It is of interest that the patient who developed a decrease in hearing acuity had 1-h serum gentamicin concentrations well below the mean of the group. Furthermore, although nephrotoxicity was related to high serum concentrations of gentamicin in the group treated with one injection each day, the correlation was by no means perfect. One patient (number 2) developed nephrotoxicity with all 1-h serum levels 7.6 $\mu\text{g/ml}$ or lower, and one patient (number 8) whose 1-h levels were 11.2, 11.5, and 10.5 $\mu\text{g/ml}$ (on days 1, 5, and 10) did not develop nephrotoxicity.

These studies have shown that 160 mg of gentamicin injected once a day is as effective in treatment of urinary tract infection as 180 to 240 mg injected in three equal daily divided doses. Although the nephrotoxicity of gentamicin given as a single daily 160-mg dose seemed to be greater than when given as three daily 60- or 80-mg doses, the reductions in renal function were reversible after therapy was discontinued.

The urine levels achieved in the three patients with normal renal function (numbers 5, 6, and 7) who received 1.56 to 1.76 mg of gentamicin per kg of body weight in one 160-mg injection each day were high enough to inhibit most gram-negative bacilli. Furthermore, urinary tract infection was cured in two of these three patients, and none of the three developed ototoxicity or nephrotoxicity. In fact, none of the four patients who received the lowest milligram per kilogram daily dose in one injection (1.56 to 2.07 mg/kg) developed nephrotoxicity and as would be expected serum levels of gentamicin were lower in these four patients than in

most of the patients receiving higher milligram per kilogram single doses; the highest serum level in any of these patients 1 h after injection of gentamicin on the 1st day, 4th, 5th, or 6th day, or on the last day of therapy was 7.2 $\mu\text{g/ml}$. These data suggest that, in therapy of many patients with normal renal function and urinary tract infections caused by bacteria susceptible to gentamicin, a dose of 1.7 mg of gentamicin per kg injected once a day would probably be successful.

This dose, which is one-third of the 5 mg/kg daily dose recommended for therapy of serious infections (4), should certainly not result in any more toxic side effects than the 5 mg/kg daily dose and would probably be less toxic.

Although gentamicin used in a single daily dose may prove useful in treatment of urinary tract infection in certain patients, it seems clear that other less toxic antimicrobial agents should be used when antimicrobial susceptibility studies indicate that the infecting organism is susceptible. Furthermore, single daily-dose gentamicin therapy should be reserved for the patient who does not have systemic infection for which therapeutic blood levels are required throughout the day. The indications for use of single daily-dose gentamicin therapy would be uncommon, because urinary tract infections caused by bacteria resistant to all forms of oral therapy in patients with normal renal function are unusual.

Special attention should be directed to patients likely to have diminished renal function such as elderly or wasted patients and to patients with changing renal function. Careful monitoring of creatinine clearance and measurement of gentamicin levels in the blood are indicated since the blood urea nitrogen and serum creatinine concentration alone may not reflect the degree of renal impairment present

in these patients (e.g., patient 14 with creatinine at 1 mg/100 ml and Ccr at 47 ml/min) and the need to reduce the drug dosage.

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