ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1976, p. 633-638

Vol. 9, No. 4
Printed in U.S.A.

Safety of the Bolus Administration of Gentamicin

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Received for publication 19 November 1975

A study was done to assess the safety of gentamicin administration by a bolus method. A total of 63 patients were randomly treated with intravenous gentamicin by bolus administration (3 to 5 min) and by slow infusion (2 h). Serum gentamicin levels were measured. Renal and audiovestibular function were monitored. Pure-tone audiometry was performed at the beginning, on day 3, and at the end of therapy. The study revealed that the bolus administration was safe and nontoxic.

It has been recommended by some that when gentamicin is administered intravenously it be infused over a period of 1 to 2 h (2). This recommendation was based on the assumption that more rapid administration would result in serum levels that are "potentially" oto- and nephrotoxic. The present study was undertaken to determine the safety of the "slow-bolus" (3- to 5-min) method of administration as compared with the infusion method (2 h) in patients with normal and with impaired renal function.

MATERIALS AND METHODS

Patients. Sixty-three patients receiving gentamicin for various infections were studied. The patients were randomly divided into two groups. Groups 1 received gentamicin diluted in 100 ml of 5% glucose and water or saline and infused over approximately a 2-h period. Group 2 received gentamicin diluted in 50 ml of 5% glucose and water or saline and administered over 3 to 5 min using a Soluset system. The flow rate was monitored by a nurse assigned to this study.

Blood samples for gentamicin assay were drawn between days 3 and 5 of therapy on all except three patients. Group 1 was treated for a mean of 6.4 days and group 2 was treated for a mean of 6.1 days.

In the 63 patients studied, 7 received gentamicin only and 56 received gentamicin in addition to other antibiotics. Renal function studies (serum creatinine, blood urea nitrogen, and urinalysis with microscope examination of sediment) were performed before the initial dose of gentamicin and every third day of treatment.

In the present study, 49 of 57 patients with normal renal function before therapy was instituted received 120 mg/dose. Only eight with normal renal function received 60 to 100 mg/dose. Four of the six patients with impaired renal function received 60 to 80 mg/dose, one received 120 mg every 12 h, and one received 120 mg every 8 h. Six of the 63 patients in the present study had impaired renal function before gentamicin was started.

Audiology. All patients were tested, in their hospital rooms, with a portable MAICO H-I audiometer with TDH-39 earphones. The audiometer was calibrated before the onset of the investigation, and the calibration was checked biweekly thereafter.

At the onset of gentamicin therapy, each patient received a pure-tone audiogram at 250 to 8,000 Hz. All pure-tone averages were calculated for 500, 1,000, and 2,000 Hz on examination. Significant change in the audiogram was defined as one greater than 10 dB in pure-tone averages or pure-tone levels. Pure-tone audiometry was performed at the beginning, on the third day, and at the end of therapy.

Several patients were subsequently tested in a sound-proof room with a MAICO-24 audiometer, and the results did not differ significantly from those obtained with the portable audiometer used in the hospital rooms.

Vestibular function was checked daily during therapy; patients were questioned regarding dizziness, lightheadedness, and tinnitus and were examined when possible for evidence of nystagmus. Electronystagmography was not performed.

Specimens. Blood samples for gentamicin assay were drawn between days 3 and 5 of therapy in all except three patients. For the 3- to 5-min slow-bolus method, a preinfusion sample was drawn, and samples were obtained at 1 to 2 min, 10 min, 1 h, and 8 h postinfusion. For the 2-h infusion method, a preinfusion sample was drawn, and samples were obtained 1 h intrainfusion. Upon completion of infusion, samples were drawn at 1 to 2 min, 1 h, and 6 h postinfusion. Blood samples were allowed to clot and the sera were frozen at −20 C until the assay.

Microbiological assay. Sera with gentamicin only were assayed in quadruplicate as described previously (7). Sera containing gentamicin in addition to other antibiotics were assayed in a similar manner but with 1.5 ml of an overnight culture of *Serratia marcescens* 74-34651 (Jewish General Hospital reference number) diluted 1:1 in Mueller-Hinton broth and reincubated at 43 C for a further 4 h as the

TABLE 1. *Two-hour infusion*

Patient	Sex	Age (yr)	BUN[a]	Creatinine	Dose (mg) /duration (day)[b]	Other antibiotics	Gentamicin level (μg/ml) at time:				
							Preinfusion	1 h intra-infusion	1–2 min post-infusion	1 h post-infusion	6 h post-infusion
1	M	24	N	N	120/4		0.3	2.1	2.35	1.6	
2	M	58	N	N	120/7	Clindamycin	0.2	2.6	5.0	2.7	<0.2
3	M	53	N	N	120/10	Ampicillin	<0.2	4.5	3.35	1.3	
8	M	44	N	N	120/7	Penicillin G	<0.2	<0.2	4.4	1.95	<0.2
9	M	59	N	N	80/8[c]	Penicillin G	<0.2	<0.2	3.25	2.1	0.5
10	M		N	N	120/8	Penicillin G	0.6	2.7	7.05	3.0	0.9
14	M	73	N	N	120/4 80/6	Cephalothin	<0.2	3.9	4.55	3.1	0.9
18	M	56	N	N	120/7	Clindamycin	<0.2	2.4	3.95	2.25	<0.2
22	M	17	N	N	120/5	Penicillin G	<0.2	<0.2	4.0	2.2	<0.2
25	M	60	N	N	120/5	Carbenicillin	<0.2	<0.2	5.4	0.2	
26	M	29	N	N	120/6	Penicillin G	<0.2	2.65	7.3	0.8	<0.2
27	M	40	N	N	120/7	Penicillin G	<0.2	1.0	6.1	2.1	0.3
5	M	49	44.5–42	2.3–2.1	120/1	Penicillin G	1.4	1.75	5.6	3.9	3.05
7	M	84	44–40–45	1.8–2.7	80/2 80/4[c] 120/2[d]	Penicillin G	<0.2	5.1	8.1	6.45	3.3
17	M	79	55–48–50	3.1–2.7–3.3	60/14[c]	Penicillin G	1.0	2.9	4.3	3.9	2.0
4	F	18	N	N	120/4	Ampicillin	<0.2	5.45	5.9	4.05	
6	F	71	N	N	120/7		3.4	4.7	7.85	5.25	2.85
11	F	39	N	N	120/8	Ampicillin	1.35	0.35	10.25	4.3	1.4
12	F	53	N	N	120/4	Penicillin G	<0.2	1.65	4.8	1.05	<0.2
13	F	46	N	N	120/5	Clindamycin	<0.2	4.8	4.05	0.9	<0.2
15	F	71	N	N	80/4	Penicillin G	2.55	2.35	2.4	1.7	0.75
16	F	25	N	N	120/10	Clindamycin	<0.2	<0.2	3.45	0.35	
19	F	44	N	N	120/5	Ampicillin	<0.2	2.3	5.7	3.55	<0.2
20	F	41	N	N	80/7		<0.2	2.1	0.9	<0.2	<0.2
21	F	41	N	N	120/11	Penicillin G, clindamycin	<0.2	2.65	3.25	1.75	<0.2
23	F	61	N	N	120/5	Sulfasoxazole	0.5	4.15	4.55	2.95	<0.2
24	F	30	N	N	120/5	Clindamycin	<0.2	0.65	3.8	1.2	0.45

[a] Blood urea nitrogen.
[b] All gentamicin doses were given every 8 h unless otherwise indicated.
[c] Every 12 h.
[d] Every 16 h

TABLE 2. *Slow-bolus infusion*

Patient	Sex	Age (yr)	BUN[a]	Creatinine	Dose (mg) /duration (day)[b]	Other antibiotics	Gentamicin level (μg/ml) at time:				
							Preinfusion	2 min post-infusion	10 min post-infusion	1 h post-infusion	8 h postinfusion
A	M	19	N	N	120/5	Nafcillin	<0.2	5.5	3.3	1.6	<0.2
D	M	34	N	N	120/5		<0.2	5.65	3.55	1.2	<0.2
E	M	71	N	N	120/2	Oxacillin	0.3	11.05	6.8	2.95	<0.2
F	M	55	N	N	120/3	Penicillin G	<0.2	5.3	3.7	1.65	0.3
J	M	76	N	N	80/2 120/5 80/2		<0.2	3.85	3.3	2.35	1.1
K	M	64	N	N	120/6	Penicillin G	<0.2	4.3	3.75	2.35	<0.2
N	M	71	N	N	100/5 80/3 (intramuscular)	Sulfasoxazole	<0.2	5.3	5.8	3.9	
O	M	26	N	N	60/5	Oxacillin	<0.2	5.1	4.45	2.6	0.4
P	M	78	N	N	120/7	Penicillin G	<0.2	12.1	5.15	4.35	
R	M	29	N	N	120/4		<0.2	10.05	8.0	5.1	<0.2
T	M	69	N	N	80/13[c]		<0.2	2.75	4.1	<0.2	<0.2
V	M	61	N	N	120/8	Clindamycin	<0.2	9.95	6.05	3.35	4.95
Z	M	62	N	N	120/5	Penicillin G	<0.2	7.4	4.7	0.35	<0.2
Ba	M	60	N	N	120/7	Nafcillin	<0.2	5.1	2.35	1.5	<0.2
Da	M	57	N	N	120/5	Nafcillin	<0.2	10.25	7.4	4.85	<0.2
Ga	M	65	N-32	N-3-2.5	80/8	Clindamycin	<0.2	7.05	4.2	2.9	<0.2
Ja	M	41	N	N	120/5	Oxacillin	<0.2	9.85	8.2	2.4	
Ka	M	45	N	N	80/1 120/5	Nafcillin	<0.2	7.45	4.1	1.1	<0.2
C	M	68	28-26	1.9-2.3	80/2	Penicillin G	1.45	5.2	5.1	2.65	0.55
S	M	79	41-37	1.8-N	80/4	Penicillin G	1.05	0.9	1.0	1.45	<0.2
B	F	44	N	N	120/4	Clindamycin	<0.2	7.9	8.8	2.1	<0.2
G	F	26	N	N	120/7	Ampicillin	0.4	9.05	10.0	4.35	<0.2
H	F	28	N	N	120/4	Ampicillin	<0.2	9.05	5.25	1.9	<0.2
L	F	74	N	N	100/4	Penicillin G, sulfasoxazole	0.8	9.25	6.85	3.9	1.05
M	F	83	N-25.5	N	80/5	Penicillin G	1.9	8.95	8.3	6.45	2.9

U	F	48	N	N	120/5	Clindamycin	<0.2	4.1	4.4	2.1	
					80/3						
W	F	37	N	N	120/4	Ampicillin	<0.2	5.9	3.4	2.25	<0.2
X	F	67	N	N	120/14	Clindamycin	<0.2	6.6	3.3	1.7	
Y	F	45	N	N	120/4	Clindamycin	<0.2	10.0	8.4	3.45	<0.2
Aa	F	60	N	N	120/6	Clindamycin	<0.2	6.4	2.9	0.85	
Ca	F	37	N	N	120/12	Nafcillin	<0.2	5.0	4.1	0.8	<0.2
Ea	F	27	N	N	120/6	Ampicillin	<0.2	4.2	6.9	1.3	<0.2
Fa	F	36	N	N	120/5	Clindamycin (prior kanamycin)	<0.2	6.75	3.95	1.75	<0.2
Ha	F	59	N	N	120/4	Clindamycin	<0.2	7.85	4.55	3.45	<0.2
Ia	F	71	42–N	N	120/8	Clindamycin	0.4	12.15	9.85	6.15	1.05
Q	F	61	N–36	1.6–N	120/6[c]	Clindamycin	2.3	16.7	13.65	8.2	1.45

[a] Blood urea nitrogen.
[b] All gentamicin doses were given every 8 h unless otherwise indicated.
[c] Every 12 h.

inoculum in 50 ml of melted 1% Mueller-Hinton agar. The *Serratia* strain was resistant to the penicillins, lincomycin, erythromycin, cephalosporins, streptomycin, and sulfonamides and was sensitive to kanamycin, gentamicin, polymixin B, chloramphenicol, and tetracycline. *Serratia* plates were incubated for 18 to 20 h before zone diameters were measured.

Enzymatic assay. *Escherichia coli* W 677/HJR66, a mutant bearing an R-factor for the enzyme gentamicin adenyl transferase (GAT), (kindly provided by M. Brazeau, Hôpital Nôtre-Dame, Montréal, Québec) was grown in brain heart infusion broth (Difco Laboratories, Detroit, Mich.) containing 5 μg of gentamicin per ml (Schering Corp, Pte. Claire, Québec), and the osmotic lysate was prepared essentially as described by Benveniste and Davies (1). Protein content of the bacterial extract was measured by the method of Lowry et al. (6). The lysate was kept at −70 C and diluted to contain 1 mg of protein per ml of buffer immediately before use (this was the source of the crude GAT). (The activity of the enzyme must be sufficient to adenylate 30 μg of gentamicin per ml serum under assay conditions.) The reaction mixture was prepared in duplicate at 0 C. A 15-μl volume of the bacterial extract was added to 25 μl of serum containing standard or unknown amounts of antibiotic; to this was added 50 μl of buffer solution consisting of 1:1 tritium-labeled adenosine 5′-triphosphate ([^{3}H]ATP) (New England Nuclear, 1.04 Ci/mmol) and 0.0024 M unlabeled ATP in a buffer solution of 0.016 M $MgCl_2$-0.04 M dithiothreitol-0.1 M tris(hydroxymethyl)aminomethane-hydrochloride (pH 8.1). The reaction mixture was incubated at 37 C for 20 min, and 50 μl was removed and pipetted onto a phosphocellulose paper disk (2-cm diameter, Whatman P-81). The disk was allowed to stand 1 min to absorb the basic antibiotic, dried for 5 min at 80 C, washed for 20 min in flowing distilled water to remove unbound radioactivity, and dried. Phosphocellulose-bound radioactivity was counted in a Nuclear-Chicago Unilux IIA liquid scintillation spectrophotometer and plotted against the concentration of the antibiotic standards.

Since the results of serum gentamicin levels measured by both the biological and enzymatic assays were similar, in this paper only the values obtained by the enzymatic assay are reported.

RESULTS

Patients receiving gentamicin by 2-h infusion method. Twenty-seven patients 17 to 84 years old were studied. There were 15 males and 12 females (Table 1). All except 5 received 120 mg of gentamicin every 8 h. Peak serum gentamicin levels were noted at 2 h (Fig. 1). Only one patient, no. 11 (Table 1), had a peak serum level in excess of 10 μg/ml. In no instance was there evidence of ototoxicity as determined by audiological and vestibular monitoring, as was expected from the levels obtained. Nephrotoxicity was not observed. Three

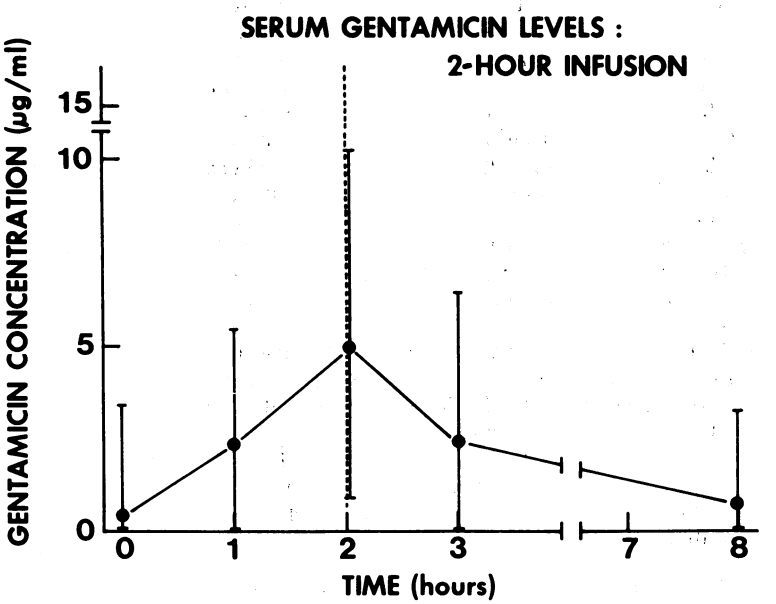

FIG. 1. *Serum gentamicin levels: 2-h infusion method. Range* (I) *and mean* (●——●) *concentrations in micrograms of gentamicin per milliliter for 27 patients. The vertical dotted line indicates completion of the infusion.*

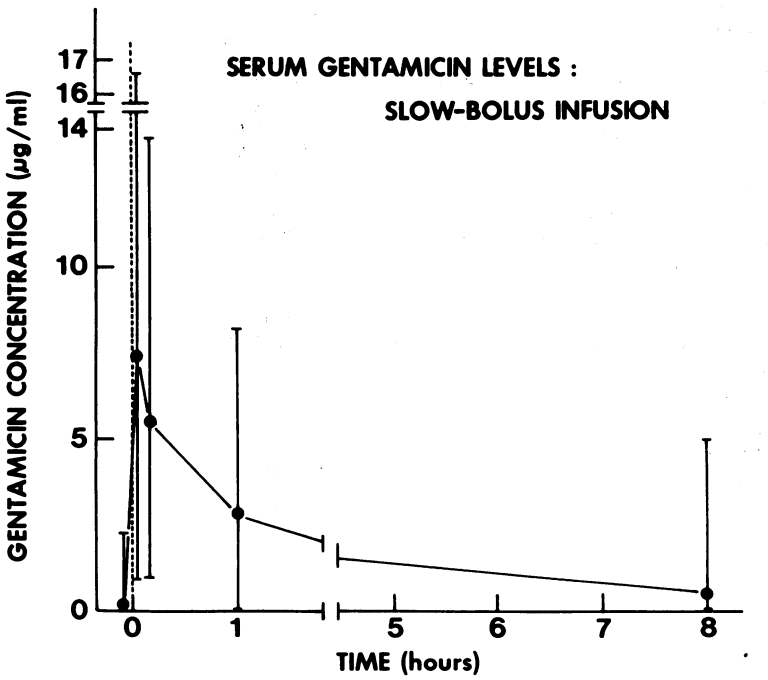

FIG. 2. *Serum gentamicin levels: slow-bolus infusion method. Range* (I) *and mean* (●——●) *concentration in micrograms of gentamicin per milliliter for 36 patients. The vertical dotted line indicates completion of the infusion.*

patients, no. 5, 7, and 17 (Table 1), had impaired renal function at the onset, but there was no evidence of further deterioration after gentamicin therapy.

Patients receiving gentamicin by bolus infusion (3 to 5 min). Thirty-six patients 19 to 83 years old were studied. There was 20 males and 16 females (Table 2); all except 10 received 120 mg of gentamicin every 8 h. Peak serum gentamicin levels were observed at 2 min postinfusion (Fig. 2). Only 6 patients, E, P, R, Da, Ia, and Q, had peak serum levels in excess of 10 μg/ml. In no instance was there evidence of ototoxicity as determined by audiological and vestibular monitoring. Nephrotoxicity after therapy was noted in one patient, Ga (Table 2), and was minimal and appeared to be reversing itself. Three patients, C, S, and Q, had impaired renal function before the administration of gentamicin; after therapy there was no evidence of further impairment.

DISCUSSION

There has been recent discussion in the literature as to what are the "potentially" nephro- and ototoxic serum levels of gentamicin (3). Hewitt (4) suggests that levels from 10 to 15 μg/ml may be ototoxic but, in fact, no investigation has been carried out to demonstrate this conclusively. In spite of this, there has been general reluctance to administer gentamicin by the bolus method for fear of increased toxicity. One study by Korner (5) on the IV bolus administration of gentamicin demonstrated no toxicity, but another by Nielsen and Elb (8) showed possible nephrotoxicity. However, the dose of gentamicin used in both of these studies was less than that used in the present report. In one of the studies (5), the standard dosage was 80 mg three times daily, whereas in the other (8) the doses ranged from 2 to 4 mg/kg per day.

Audiological and renal function were followed in all patients before and after therapy, and in only one instance was there evidence of toxicity when the bolus method of infusion was compared to slow-infusion administration. Of the six patients with impaired renal function, three received the drug by slow infusion and three received it by the bolus method. There was no evidence of ototoxicity or nephrotoxicity in any patient and, in fact, there was improvement in renal function in two. In one of these patients, Q (Table 2), this occurred in spite of a peak serum gentamicin level in excess of 15 μg/ml. In only one patient was there some deterioration of renal function (patient Ga), which was moderate. It is interesting that this patient's gentamicin serum levels were not in excess of 7.1 μg/ml.

The discouragingly low serum concentrations observed in the majority of patients 1 h after completion of the dose of gentamicin was reported previously (7).

Based on these data, it may be concluded that the bolus administration of gentamicin is safe and nontoxic.

ACKNOWLEDGMENTS

We wish to thank K. Dubitsky and F. Brender for their assistance.

This research was supported by Schering Corporation, Ltd.

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