

Pharmacology of Amikacin in Humans

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Amikacin is a new aminoglycoside antibiotic which is active in vitro against most isolates of gram-negative bacilli. A dose of 300 mg/m² intramuscularly produced a highest mean serum concentration of 25.4 µg/ml with a mean serum concentration of 3.1 µg/ml at 8 h. The same dose intravenously produced a highest mean serum concentration of 52.4 µg/ml with a mean serum concentration of 2.1 µg/ml at 8 h. The mean urinary excretion during the first 6 h was 75 and 66%, respectively. When amikacin was administered at a dose of 150 mg/m² every 6 h, there was evidence of some drug accumulation. A loading dose of 150 mg/m² administered intravenously over 30 min followed by 200 mg/m² administered as a continuous infusion every 6 h maintained serum concentrations of 8 µg/ml. No major toxicity was observed with any of these drug regimens.

Gram-negative bacilli infections have become an increasingly serious problem among hospitalized patients. Many of these organisms are resistant to kanamycin sulfate. Recently, infections caused by gram-negative bacilli which are resistant to gentamicin sulfate have been reported (7). Consequently, the search for new antibiotics continues to be of considerable importance.

Amikacin (BB-K8) is a new aminoglycoside antibiotic which is a chemical derivative of kanamycin (4). The drug is of interest because it has broad-spectrum activity against gram-negative bacilli, including *Pseudomonas aeruginosa* (1, 6). Amikacin is also active in vitro against many isolates of gram-negative bacilli which are resistant to other aminoglycoside antibiotics. Because of its potential value for the therapy of infections caused by gram-negative bacilli, pharmacological studies of amikacin were initiated.

MATERIALS AND METHODS

All patients included in this study had metastatic cancer or leukemia but were not debilitated. All had normal renal function as evidenced by a serum creatinine of 1.5 mg/100 ml or less and a blood urea nitrogen of 22 mg/100 ml or less. Creatinine clearances were obtained from most patients and were greater than 90 ml/min (corrected to a body surface area of 1.73 m²). All but two of the patients had normal liver function as evidenced by a normal bilirubin and serum glutamic oxalacetic transaminase (SGOT). The two exceptions were patients who received the drug as therapy for infections. The patients ranged in

age from 14 to 62 years old (median 43 years old). Their body surface area varied from 1.4 m² to 2.5 m² (median 1.8 m²). Informed consent was obtained according to institutional policy.

Nine patients participated in single-dose studies of amikacin administered intramuscularly (i.m.) and intravenously (i.v.) at a dose of 300 mg/m² of body surface area. The i.v. dose was given in 50 ml of 5% dextrose solution over 15 min. The same nine patients also received kanamycin sulfate (300 mg/m²) i.v. as above. The interval between each of the three studies was at least 2 days. Each of the three studies was conducted initially with one-third of the patients who were assigned on a random basis. Serum specimens were obtained before drug administration, and at 0.25, 0.5, 1, 2, 4, 6, and 8 h after drug administration. Urine specimens were collected before drug administration and during the first 6 h of the study.

Sixteen patients were studied while receiving amikacin as therapy for infections. Six patients received a dose of 150 mg/m² every 6 h for at least 7 days. The drug was administered i.v. in 50 ml of 5% dextrose solution over 30 min. Studies were conducted on day 3 and 7 of therapy. Serum specimens were obtained just before a dose of drug and at 0.25, 0.5, 1, 2, 4, and 6 h after onset of a dose of drug. Five patients received a loading dose of 100 mg/m² administered i.v. in 50 ml of 5% dextrose solution over 15 min. This was followed immediately by a dose of 150 mg/m² administered i.v. in 200 ml of 5% dextrose solution over 6 h, every 6 h. As experience was gained, the dosage was escalated. Five additional patients received a loading dose of 150 mg/m² given i.v. in 50 ml of 5% dextrose solution over 30 min. This was followed immediately by a dose of 200 mg/m² administered i.v. in 200 ml of 5% dextrose solution over 6 h, every 6 h. An infusion pump was used to administer the 6-h infusions (IVAC TH500, IVAC Corp., San Diego, Calif.). Serum specimens

were obtained before drug administration and at 0.25, 0.5, 1, 2, 4, and 6 h thereafter.

The concentrations of amikacin and kanamycin sulfate in blood and urine specimens were determined by an agar well method with *Bacillus subtilis* ATCC 6633 as the test organism (3). The organism was incubated in brain heart infusion agar (BBL) for 1 week at 37 C, harvested, washed with normal saline, and heat-shocked at 65 C for 30 min to release the spores. The spores were washed and suspended in normal saline so that there were approximately 5×10^7 viable spores per ml. A 1.5-ml portion of this suspension was added to 1 liter of antibiotic medium no. 2, the pH was adjusted to 7.8 with phosphate buffer, and petri dishes were filled with 14-ml portions. Wells (0.75 mm in diameter and 0.4 mm in depth) were cut into the agar and filled with 0.05 ml of each specimen. The plates were incubated at 37 C for 18 h. Zones of inhibition were measured and compared to a standard curve. Assays were performed in triplicate.

The standard error of the mean was calculated by the method of Mantel (5). The 95% confidence limits were calculated as twice the standard error of the mean. Statistical analyses of the differences in serum concentrations were performed with the Student's *t* test. The amikacin used in these studies was supplied by Bristol Laboratories, Syracuse, N.Y.

RESULTS

The mean serum concentrations obtained after the i.m. and i.v. administration of single doses of 300 mg of amikacin per m^2 to the same nine patients are shown in Fig. 1. The highest mean serum concentration after i.m. administration was 25.4 $\mu\text{g/ml}$ and was obtained at 30 min. The mean serum concentrations at 6 and 8 h were 7.0 $\mu\text{g/ml}$ and 3.1 $\mu\text{g/ml}$, respectively. The serum half-life was 2.8 h. The highest mean serum concentration after the 15-min i.v. infusion was obtained at the end of the infusion and

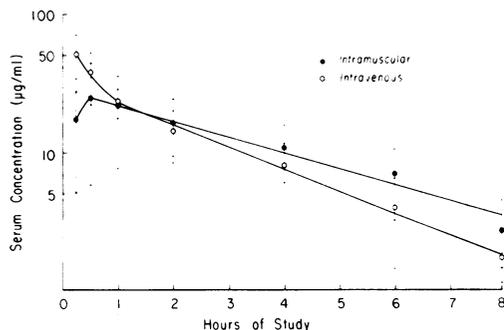


FIG. 1. Serum concentrations after single doses of 300 mg of amikacin per m^2 administered i.m. and i.v. The same nine patients participated in both studies. The i.v. dose was given over 15 min. The bars represent the 95% confidence limits.

was 52.4 $\mu\text{g/ml}$. The mean serum concentrations at 6 and 8 h were 4.0 $\mu\text{g/ml}$ and 2.1 $\mu\text{g/ml}$, respectively. The serum half-life was 2 h. The same nine patients also received 300 mg of kanamycin sulfate per m^2 , administered i.v. over a 15-min period (Fig. 2). The highest mean serum concentration was 45.0 $\mu\text{g/ml}$, and the mean serum concentrations at 6 and 8 h were 2.8 $\mu\text{g/ml}$ and 1.6 $\mu\text{g/ml}$, respectively. The serum half-life was 1.9 h.

Five patients received a dose of 150 mg of amikacin per m^2 , administered i.v. over 30 min every 6 h as therapy for infections (Fig. 3). Pharmacological studies were conducted on days 3 and 7 of therapy. On day 3, the initial mean serum concentration was 2.5 $\mu\text{g/ml}$. The highest mean serum concentration was obtained at the end of the infusion and was 18.3 $\mu\text{g/ml}$. The mean serum concentration at 6 h (before initiation of the next infusion) was 2.4 $\mu\text{g/ml}$. On day 7, the initial mean serum concentration was 4.1 $\mu\text{g/ml}$. The highest mean

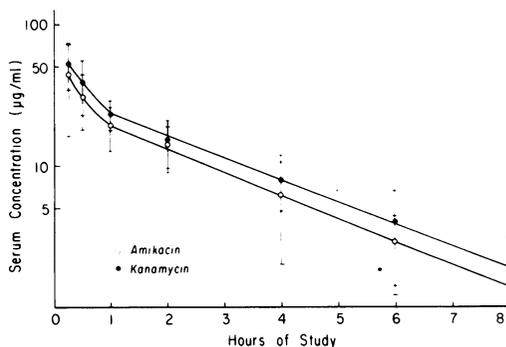


FIG. 2. Serum concentrations after single doses of 300 mg of amikacin per m^2 and kanamycin sulfate administered i.v. to the same nine patients.

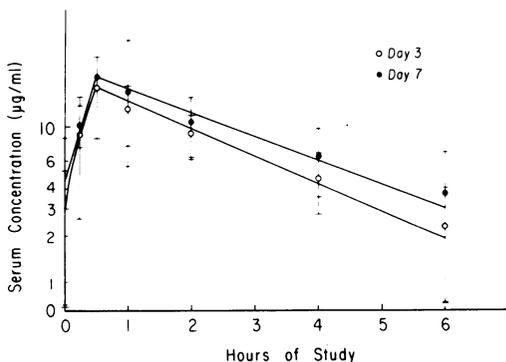


FIG. 3. Serum concentrations after multiple doses of amikacin. A dose of 150 mg/ m^2 was administered i.v. over 30 min to five patients. Studies were conducted on days 3 and 7 of therapy.

serum concentration was 20.6 $\mu\text{g/ml}$ and the mean serum concentration at 6 h was 3.9 $\mu\text{g/ml}$. The serum half-life on day 3 was 1.7 h and on day 7 was 1.9 h. The differences between the serum concentrations on day 3 and day 7 were statistically significant for every sampling period except the 15-min samples ($P = <0.02$ to 0.05).

Ten patients received a loading dose of amikacin followed by a continuous i.v. infusion as therapy for infections (Fig. 4). Five patients received a loading dose of 100 mg of amikacin per m^2 administered i.v. over a 15-min period, followed immediately by a dose of 150 mg/m^2 administered as a continuous infusion every 6 h. The highest mean serum concentration was obtained at 30 min and was 18.4 $\mu\text{g/ml}$. Thereafter, the mean serum concentration gradually decreased to 4.9 $\mu\text{g/ml}$ by 6 h. Since our interest was to maintain the serum concentration above 8 $\mu\text{g/ml}$, the dose of amikacin was increased. The remaining five patients received a loading dose of 150 mg of amikacin per m^2 administered i.v. over a 30-min period, followed immediately by a dose of 200 mg/m^2 administered as a continuous infusion every 6 h. Two of these patients had impaired liver function studies as manifested by serum bilirubins of 1.7 and 2.4 mg/100 ml. One patient also had an elevated SGOT of 245 U. The highest mean serum concentration was obtained at 30 min and was 24.8 $\mu\text{g/ml}$. The mean serum concentration at 1 h was 11.0 $\mu\text{g/ml}$ and remained above 8.0 $\mu\text{g/ml}$ thereafter.

The urinary excretion of amikacin and kanamycin sulfate was determined during the 6 h

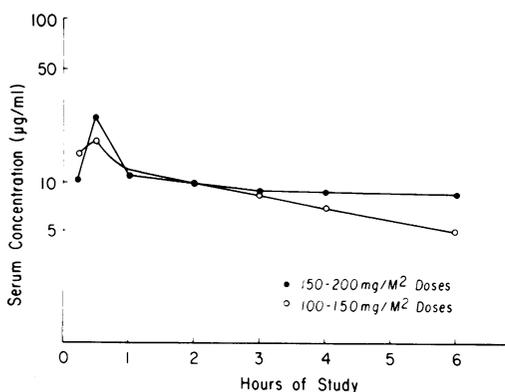


FIG. 4. Serum concentrations with continuous i.v. infusions of amikacin. Five patients received a loading dose of 100 mg/m^2 over 15 min followed by 150 mg/m^2 over 6 h. Another five patients received a loading dose of 150 mg/m^2 over 30 min followed by 200 mg/m^2 over 6 h.

after a single dose of drug (Table 1). The mean urinary excretion of amikacin was 75% after i.m. administration and 66% after i.v. administration. Urinary concentrations of the drug were very high, exceeding 2 mg/ml in a few patients. Results with kanamycin sulfate were similar to those obtained with amikacin.

No toxicity was observed after the single-dose studies of amikacin. None of the patients receiving multiple-dosage regimens developed nephrotoxicity or ototoxicity. However, elevations in SGOT were observed in 8 of these 15 patients during therapy with amikacin. Six of the patients received the drug as a continuous i.v. infusion. In most of the patients other factors such as antitumor agents were a more likely explanation for these abnormalities.

Serum specimens obtained from the patients receiving 150 mg of amikacin per m^2 every 6 h were tested in vitro against isolates of gram-negative bacilli (Fig. 5). The specimens tested had been collected on day 3 of therapy, just before an infusion and at the end of the 30-min infusion. Six isolates each of *P. aeruginosa*, *Klebsiella* spp., and *Escherichia coli* were used. Three isolates each had a minimal inhibitory concentration (MIC) of 0.78 $\mu\text{g/ml}$, and the remaining had an MIC of 3.12 $\mu\text{g/ml}$. Twofold serial dilutions of each specimen were made, and the greatest dilution which inhibited the growth of each organism was determined. There was good correlation between the serum inhibitory activity and the actual serum concentration. For example, a serum concentration of 6.3 $\mu\text{g/ml}$ would be expected to inhibit an organism with an MIC of 0.78 $\mu\text{g/ml}$ at a 1:8 dilution. The majority of isolates of *P. aeruginosa* were not inhibited by the expected serum dilution, whereas a majority of the isolates of *Klebsiella* spp. were more sensitive than expected.

DISCUSSION

Amikacin is a new aminoglycoside antibiotic of potential importance because of its broad-spectrum activity against gram-negative bacilli, including organisms resistant to other similar antibiotics. At a concentration of 3.12 $\mu\text{g/ml}$, amikacin inhibited over 90% of isolates of all gram-negative bacilli, except *Proteus* spp. (1). Although it is not as active in vitro as gentamicin and tobramycin, it has less toxicity in experimental animals. Consequently, it should be possible to administer this drug to humans at doses sufficient to produce much higher serum concentrations. Since this drug is similar to kanamycin, a dosage schedule of 150 mg/m^2

TABLE 1. Urinary excretion after administration of amikacin and kanamycin sulfate^a

Drug	Mean urinary excretion		Mean urinary concn (μg/ml)
	Amount (mg)	Percentage	
Amikacin i.m.	468 (154-729) ^b	75 (29-97)	1,001 (270-2900)
Amikacin i.v.	401 (209-618)	66 (31-96)	788 (170-1720)
Kanamycin sulfate i.v.	402 (225-600)	75 (38-102)	943 (250-3100)

^a Determined during first 6 h after drug administration.

^b Numbers in parentheses indicate ranges.

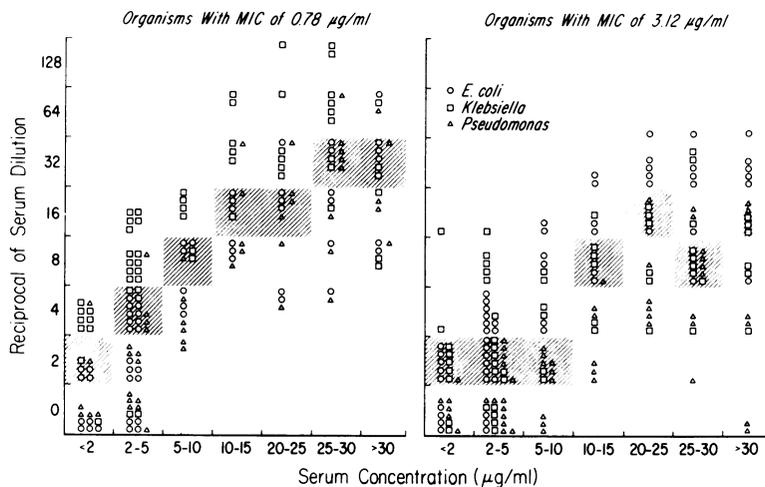


FIG. 5. Serum inhibitory activity against gram-negative bacilli. Serum specimens were obtained from patients receiving 150 mg of amikacin per m^2 every 6 h and tested *in vitro* against isolates of gram-negative bacilli. The specimens tested had been collected on day 3 of therapy, just before an infusion and at the end of the 30-min infusion. The hatched areas indicate the median for each serum concentration.

every 6 h or 300 mg/ m^2 every 12 h was selected for pharmacology studies. The highest serum concentration after a dose of 300 mg of amikacin per m^2 administered i.m. was 25.4 μg/ml compared to 52.4 μg/ml after a 15-min i.v. infusion. At 6 h the serum concentration was still above the MIC for most organisms but this was no longer true at 8 h. Hence, an every-12-h schedule may be suboptimal for treatment of serious infections. It is probably also advisable when administering the drug i.v. to prolong the infusion time to avoid the risk of neuromuscular blockade.

Pharmacological studies were conducted while patients were receiving several dosage schedules for therapy of infections. A dosage of 150 mg/ m^2 every 6 h of amikacin administered as a 30-min i.v. infusion resulted in a peak serum concentration of 18.3 μg/ml on day 3 of therapy. The serum concentration was maintained above 2 μg/ml. After 7 days of therapy, the serum concentrations were somewhat higher, suggesting accumulation of the drug

with duration of administration. Amikacin is excreted primarily in the urine. It also can cause renal impairment which results in a reduction of its renal excretion. Although nephrotoxicity was not observed in these patients, it is possible that subclinical nephrotoxicity occurred, resulting in higher serum concentrations with increasing duration of therapy.

In patients with impaired host defense mechanisms, we attempted to devise a dosage regimen which would maintain serum levels of 8 to 12 μg/ml. A dose of 100 mg of amikacin per m^2 administered i.v. over 15 min followed by 150 mg/ m^2 as a continuous infusion every 6 h resulted in a peak serum concentration of 18.4 μg/ml but failed to maintain serum concentrations above 5 μg/ml. By increasing the loading dose to 150 mg/ m^2 administered over 30 min followed by a continuous infusion of 200 mg/ m^2 every 6 h, the peak serum concentration was 24.8 μg/ml and the serum concentration was maintained above 8 μg/ml. Since no nephrotoxicity or ototoxicity was observed with this

regimen, it may be possible to administer even higher doses safely.

Aminoglycoside antibiotics are excreted mainly by glomerular filtration and are not metabolized in the body. Over 70% of amikacin was excreted in the urine during the first 6 h after an i.m. dose and 66% was excreted after an i.v. dose. Urinary excretion of kanamycin sulfate was similar to amikacin.

The activity of amikacin in the patient serum correlated with the serum concentration and the in vitro sensitivity of the organisms tested. Hence, serum factors do not significantly interfere with the activity of this antibiotic against some gram-negative bacilli. However, its activity against *P. aeruginosa* was suboptimal, suggesting that serum factors may interfere with the activity of amikacin against this organism. The activity of some aminoglycoside antibiotics against *P. aeruginosa* is reduced in the presence of magnesium and calcium (2).

A dose of 300 mg/m² (7.5 mg/kg) every 12 h or 200 mg/m² every 8 h i.m. of amikacin probably will be adequate for the treatment of many infections, especially urinary tract infections. However, patients with serious infections may benefit from more frequent dosage (150 mg/m² every 6 h). For patients with impaired host defense mechanisms it may be more important to maintain adequate serum concentrations. A regimen of 150 mg/m² as a loading dose followed

by 200 mg/m² every 6 h maintains serum concentrations of at least 8 µg/ml, which should be adequate against most organisms.

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