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Amikacin: Clinical and Laboratory Studies

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Amikacin was evaluated in vitro against S aureus *and a variety of gram negative bacilli. In concentrations of 12.5 μg/ml or less, it suppressed the growth of all organisms except 15% of* Proteus mirabilis. *Peak serum levels in patients, following a 7.5 mg/kg IM dose, averaged 21 μg/ml at one hour. Most of the drug appeared in the urine during the first six hours after administration. Of six patients receiving an adequate course of treatment, all but one were cured. Treatment in that patient also failed with a subsequent course of gentamicin and carbenicillin and he was cured only by extensive surgical excision of the infected bone. One patient developed an asymptomatic high frequency hearing loss. Another patient, who had a staggering gait after each of her first two doses, was withdrawn from the study. The data suggest that amikacin is an effective agent for the treatment of infections caused by susceptible pathogens.*

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Amikacin, formerly known as BB-K8, is a new semi-synthetic aminoglycoside antibiotic derived from kanamycin A. Its antibacterial activity is similar to kanamycin but amikacin is highly resistant to aminoglycoside inactivating enzymes,[1] and is active against *Pseudomonas aeruginosa.* Furthermore, Bodey and Stewart reported that about 50% of gram negative bacilli resistant to gentamicin were susceptible to amikacin in vitro. Of further importance, they reported amikacin to be less ototoxic and nephrotoxic than kanamycin, and significantly less nephrotoxic than gentamicin in animal experiments.[2]

Based on these preliminary data, we compared the in vitro activity of amikacin with that of gentamicin. We also evaluated the pharmacology and efficacy of amikacin in adult hospitalized patients with susceptible infections.

Methods and Materials

Test antibiotics. The standard assay powders of amikacin and of gentamicin, supplied by Bristol-Myers and Company and Schering Corporation respectively, were dissolved in phosphate buffer at pH8. Discs containing 10 μg of amikacin and of gentamicin were used in determining antibiotic susceptibility.

Biological activity. The minimum inhibitory concentration (MIC) of amikacin and of gentamicin against clinical isolates were

determined for 17 strains of *Pseudomonas* species, 23 strains of *Klebsiella* species, 19 strains of indole positive Proteus and 20 strains each of *S aureus, Enterobacter* species, *E coli* and of *Proteus mirabilis*. MICs were determined by the replicate plate method of Steers, Foltz and Graves.[3] Two-fold serial dilutions of amikacin and of gentamicin in a final concentration from 50 to 0.024 μg/ml were incorporated into Mueller-Hinton agar (BBL) and plated. The final inoculum deposited on the plate was approximately 10^5 organisms. Each antibiotic was also tested against the organisms in the Food and Drug Administration's standardized disc procedure.

Clinical studies. Adult patients with infections susceptible to this agent gave informed, written consent. They were given 7.5 mg/kg of this agent by deep intramuscular injection every 12 hours for seven or more days. Serum was obtained at 1, 2, 8 and 12 hours after the dose at various times throughout the course of treatment. Patient urine was collected for six hours after the first injection. This was repeated later in the course of treatment in some patients. Sera were frozen at −20°C until tested. Amikacin was assayed by the modified cup plate method with *B subtilis* (ATC 6633) as the test organism.[4] Undiluted pooled human serum was used as the diluent for the assay of drug levels. Urine was similarily handled and assayed except that phosphate buffer (pH8) was used as the diluent. All patients had renal, hepatic and hematological tests as well as vestibular and cochlear evaluation before, during and after treatment.

Results

Antibacterial activity. Table 1 shows the MIC of amikacin and of gentamicin respectively for the seven species tested. The average MIC for most organisms tested was two times greater for amikacin than for gentamicin. *S aureus* and *Proteus mirabilis* were exceptions, the mean MICs being five times greater of amikacin against *S aureus* and three times greater against *P mirabilis*.

In Figures 1 through 4, the cumulative percentage of organisms inhibited are plotted on the vertical axis and the MIC of the particular drug on the horizontal axis. The first figure shows that *E coli* and *P mirabilis* were inhibited by 6.25 μg/ml of gentamicin. At 12.5 μg/ml all *Pseudomonas* species were inhibited. Figure 2 presents the in vitro data for the same three organisms tested against amikacin. All *E coli* were inhibited by 6.25 μg/ml of amikacin and all *Pseudomonas* species by 12.5 μg/ml. Fifteen percent of *P mirabilis* tested required between 12.5 and 25 μg/ml of amikacin for inhibition.

Figure 3 shows the results obtained when the remaining organisms were tested against gentamicin. All *Klebsiella* species were inhibited by 1.56 μg/ml and *S aureus* by 3.125 μg/ml of this agent. Indole positive *Proteus* and *Enterobacter* species were inhibited by 12.5 μg/ml of gentamicin or less. Figure 4 shows that all *Klebsiella* species, *S aureus*, indole positive *Proteus* and *Enterobacter* species were inhibited by 12.5 μg/ml of amikacin or less.

Figure 5 correlates the MICs as obtained in the agar dilution method with the zone diameters measured in the Food and Drug Administration's standardized disc procedure. Correlating these analyses with the results of our clinical studies indicates that a zone diameter of 15 mm or more with a 10 μg amikacin disc would differentiate susceptible from resistant organisms.

Clinical studies. As shown in Figure 6, the average peak serum concentration of 21 μg/ml occurred at one hour after injection. The average serum concentrations were 20.4 μg/ml at two hours, 5.85 μg/ml at eight hours and 3.0 μg/ml at twelve hours. An average 50% of the injected dose appeared in the urine during the first six hours after the first dose and 66% following subsequent injections given after three or five days of initiating therapy. Concentrations of amikacin in all urine collected averaged 1150 μg/ml.

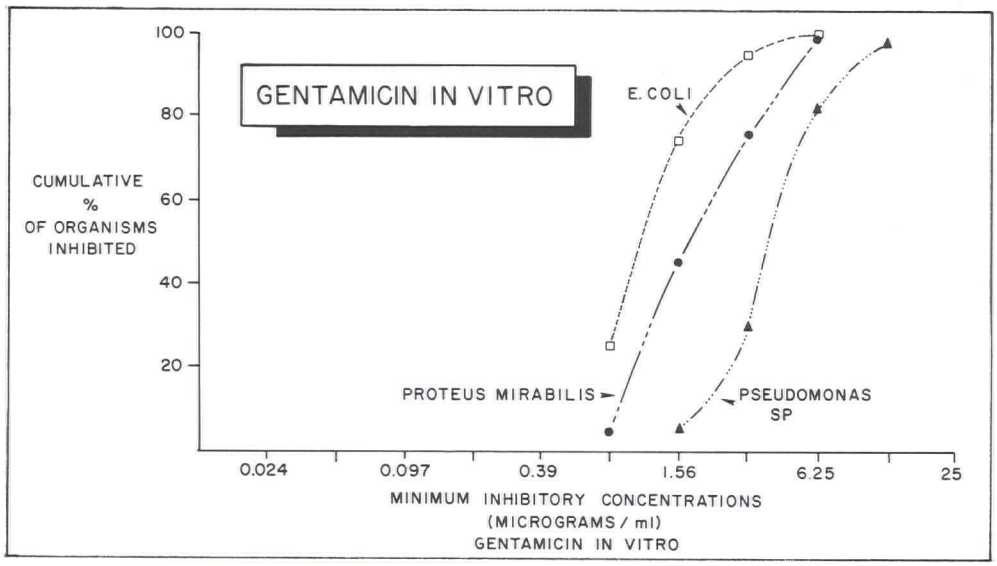

Figure 1

Cumulative percentage of organisms inhibited by increasing concentrations of gentamicin. Twenty strains of *E coli,* 20 strains of *Proteus mirabilis* and 17 strains of *Pseudomonas* species were tested.

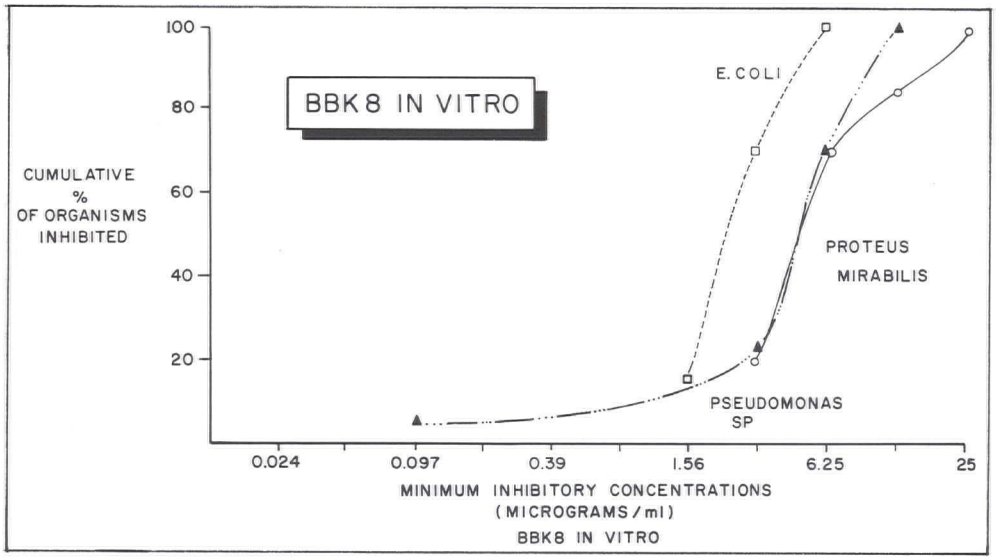

Figure 2

Cumulative percentage of organisms inhibited by increasing concentrations of amikacin (BB-K8). Twenty strains of *E coli,* 20 strains of *Proteus mirabilis* and 17 strains of *Pseudomonas* species were tested.

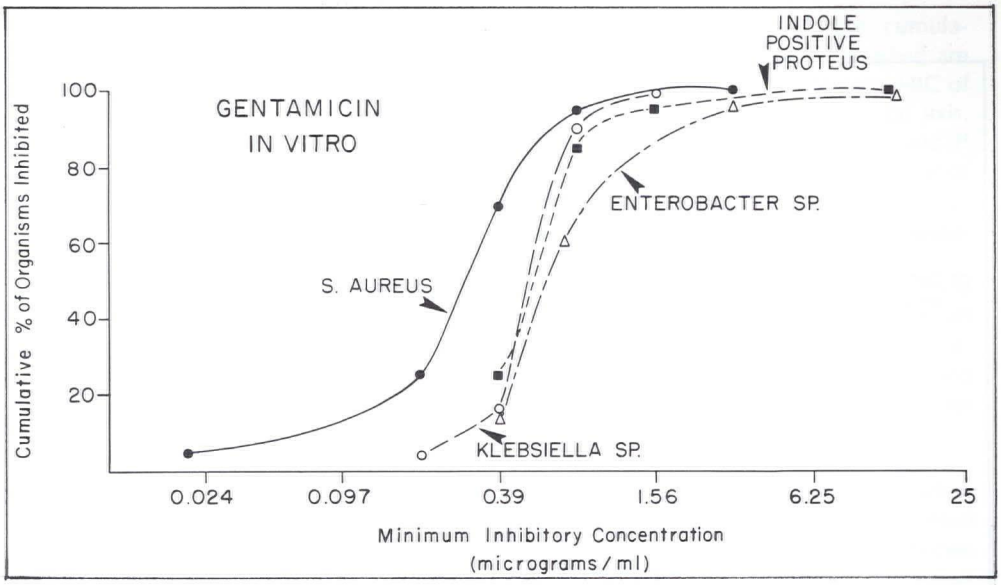

Figure 3

Cumulative percentage of organisms inhibited by increasing concentrations of gentamicin. Twenty strains of *E coli,* 20 strains of *Proteus mirabilis* and 17 strains of *Pseudomonas* species were tested.

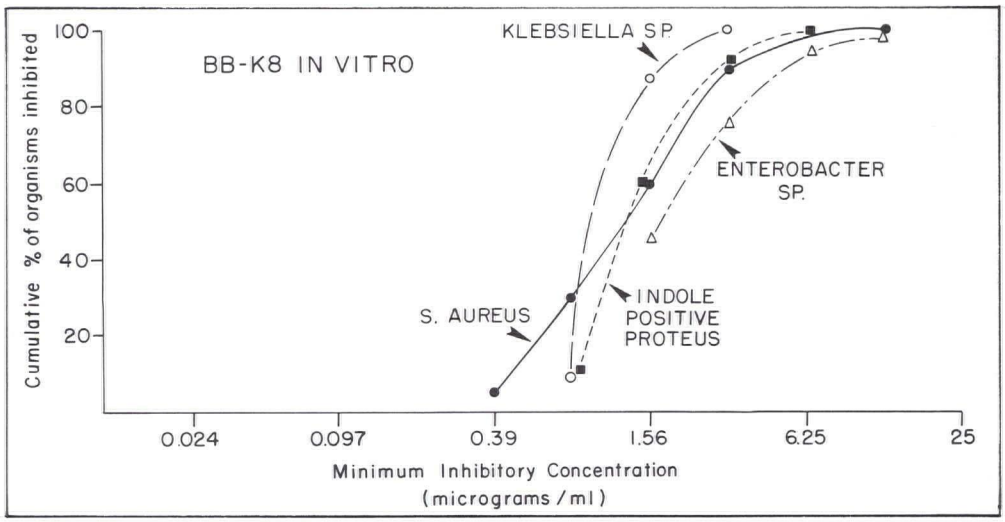

Figure 4

Cumulative percentage of organisms inhibited by increasing concentrations of amikacin (BB-K8). Twenty strains of *E coli,* 20 strains of *Proteus mirabilis* and 17 strains of *Pseudomonas* species were tested.

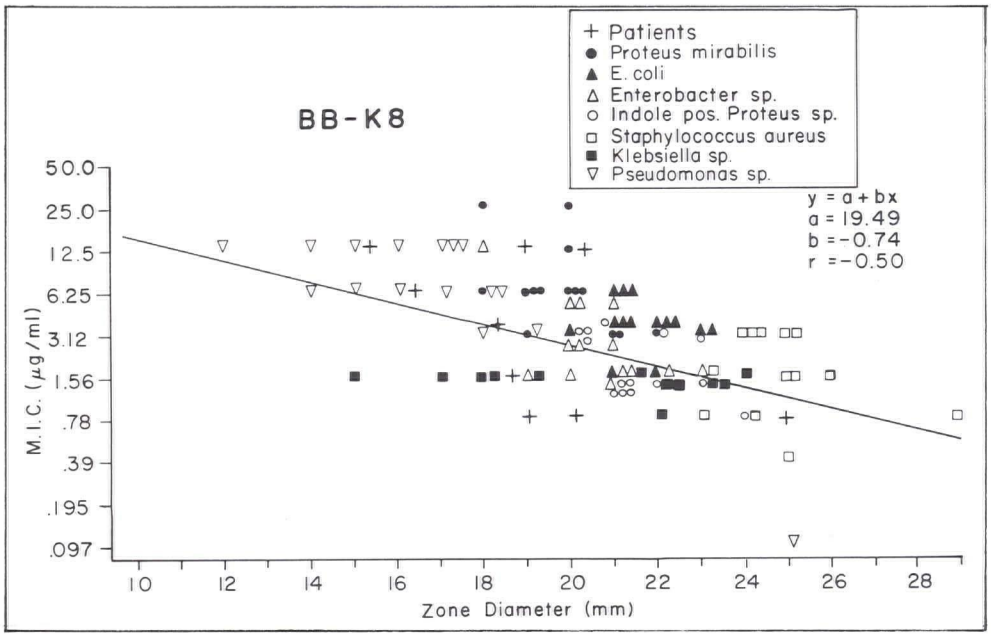

Figure 5

Regression line correlating disc zone sizes with MIC's for 119 clinical isolates.

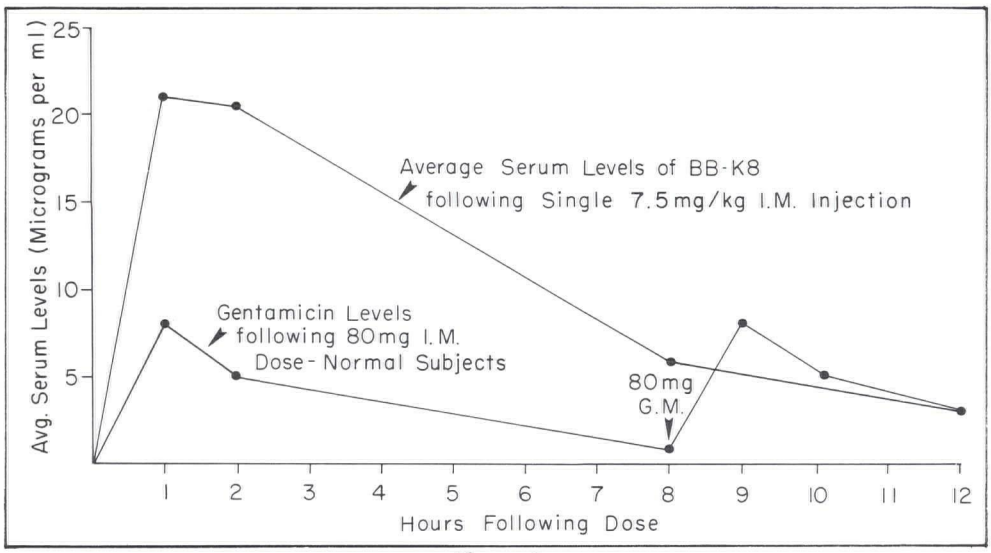

Figure 6

Serum levels of amikacin (BB-K8) were 21 μg/ml at one hour (5 specimens), 20.4 μg/ml at two hours (7 specimens), 5.85 μg/ml at eight hours (3 specimens) and 3.0 μg/ml at twelve hours (10 specimens).

All four patients with acute urinary tract infections became abacteriuric in 48 to 72 hours and remained abacteriuric after cessation of therapy for 8 to 15 months. The fifth patient, a paraplegic with an indwelling Foley catheter, fever, bacteremia and polymicrobial urinary tract infection became abacteriuric and abacteremic on treatment. Bacteriuria with *E coli* of a different antibiotic sensitivity pattern occurred following cessation of amikacin therapy.

Another patient who had a chronic *Pseudomonas* bacteriuria and multiple unsuccessful courses of gentamicin had to be withdrawn from the study because she staggered after each of her first two doses of amikacin. Otological and neurological examinations, however, gave normal results in this patient.

The seventh patient was a 49-year-old diabetic heroin user who had osteomyelitis of the sternum. Surgical drainage of the infected bone yielded *Pseudomonas aeruginosa*. He was given amikacin for six weeks. During treatment he experienced less pain and his wound showed healing, but cultures continued to grow *Pseudomonas*. Following treatment he complained of increasing pain in his sternum. Four weeks later the infected lower one-third of the sternum and adjacent costal cartilages were removed. He was then given a combined course of gentamicin and carbenicillin but a third surgical procedure was necessary to arrest the infection.

Most patients complained of moderate pain at the injection sites. Renal, hepatic and hematological tests remained normal during and after treatment. The seventh patient developed an asymptomatic high frequency hearing loss in his sixth week of treatment with amikacin. His hearing loss remained stable during four months of followup.

Discussion

Infections caused by *Pseudomonas aeruginosa* are increasing in incidence in many hospitals. Furthermore, organisms which are resistant to gentamicin have become a serious problem in burn units and some other areas where the drug has been used.[5–8] Amikacin is a drug which may prove to be effective against *Pseudomonas aeruginosa* and gentamicin-resistant *Enterobacteriaceae*. The compound was shown to be resistant to those enzymes that inactivate kanamycin and gentamicin through O-phosphorylation, O-adenylation or N-adenylation.[1]

Results of our in vitro studies were similar to those of others.[2, 9] *S aureus* and a wide range of enteric gram negative bacilli were suppressed by a concentration of 12.5 μg/ml of amikacin or lower. The only exceptions among our clinical isolates were 15% of *Proteus mirabilis*. One strain of *Pseudomonas stutzeri* isolated from a patient with septic arthritis of the knee was found to be resistant to amikacin in vitro.[10]

Our studies support previous reports that amikacin would be an effective agent for the treatment of infections caused by susceptible pathogens.[7, 11] Although it was only about one half as potent as gentamicin in vitro, peak serum levels were over two times greater for amikacin than those published for gentamicin. In the dosages which we employed, serum levels were over 20 μg/ml in specimens taken after one and two hours.

Most of the drug was excreted in the urine in a biologically active form. Levels averaged 1150 μg/ml in the urine, far higher than the MICs of any organism which we tested. Gentamicin is known to be incompletely excreted following the first several doses but excretion is virtually 100% of

the injected dose after three to five days of therapy. Our data suggest but do not prove that a similar phenomenon occurs with amikacin. One of the seven patients had subclinical high frequency hearing loss after prolonged treatment with this agent. Another patient had a staggering gait occurring after each of the first two doses but was asymptomatic before objective testing could define the nature of the derangement. Only 6.4% of 436 patients in a collected series were reported to have had possible otological effects due to treatment with amikacin.*

Based on these preliminary data, amikacin may represent a valuable addition to the therapeutic armamentarium of certain infections caused by susceptible organisms, particularly organisms which are not susceptible to any other agent.

*Summary of BB-K8 (amikacin) clinical data. Bristol Laboratories. 1974.

TABLE I

Comparison of Mean MIC's of Amikacin and Gentamicin for 119 Clinical Isolates

	Mean MIC of amikacin μg/ml	Mean MIC of gentamicin μg/ml
Staphylococcus aureus	2.56	0.57
Klebsiella sp	1.63	1.21
Indole positive *Proteus*	2.22	1.38
Enterobacter sp	3.50	1.44
E coli	3.83	1.89
Proteus mirabilis	9.38	3.16
Pseudomonas sp	7.9	5.16

Acknowledgment

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