IN VITRO, PHARMACOLOGICAL AND CLINICAL STUDIES WITH AMIKACIN

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ABSTRACT

Amikacin, a new aminoglycoside antibiotic, was found to have broad spectrum in vitro activity against most gram-negative bacilli. Amikacin was also effective against 74% of 26 isolates of gram-negative bacilli known to be resistant to gentamicin. Pharmacological studies in humans demonstrated that adequate serum concentrations of amikacin could be safely reached and maintained by continuous infusions. Using these two schedules, amikacin cured 64% of 155 episodes of identified infections occurring in cancer patients. The majority of infections were pneumonia and septicemia. The most commonly identified pathogens were E. coli, organisms of the Klebsiella-Enterobacter-Serratia group and P. aeruginosa. The cure rate for infections produced by these organisms was 79%. Included were 5 of 8 infections produced by organisms resistant to gentamicin. The results with continuous infusions of amikacin in patients with severe neutropenia were as good as the results with intermittent infusions in patients with adequate neutrophil counts. Optimum results were obtained in neutropenic patients when a serum concentration of approximately 15 μg/ml was maintained.

INTRODUCTION

Patients with cancer are frequently affected by infections produced by gram-negative bacilli. Results of therapy for these infections are still suboptimal particularly during periods of severe...
neutropenia. Consequently, they remain the most common immediate
case of death in cancer patients (3,4,5). The recent emergence of
pathogenic organisms which are resistant to multiple antibiotics,
including gentamicin, has complicated the problem. Thus, the need
for continuing studies of promising new antibiotics is of importance.

Amikacin is a new aminoglycoside antibiotic which is chemically
related to kanamycin (6). Amikacin is of special interest because
of its broad spectrum of activity in vitro against most gram-nega­
tive bacilli, including some organisms which are resistant to other
aminoglycoside antibiotics (2). A review of our experience with
amikacin indicates that this is a very effective antibiotic for the
treatment of gram-negative bacilli infections in cancer patients.

MATERIALS AND METHODS

The sequential in vitro, pharmacologic and therapeutic studies
with amikacin were begun in the Department of Developmental Thera­
peutics of the University of Texas M.D. Anderson Hospital and Tumor
Institute in 1972. The in vitro activity of this antibiotic was
studied in 466 clinical isolates of gram-negative bacilli (2). All
organisms were cultured from blood specimens obtained from patients
previously admitted to this institution. Susceptibility tests were
conducted by use of the broth dilution technique.

The therapeutic efficacy of amikacin was investigated during
216 febrile episodes occurring in 178 cancer patients. All patients
were presumed or proven to have infection caused by gram-negative
bacilli and had a temperature of 101 or greater. Half of the
patients received amikacin after 48 to 72 hours of unsuccessful
therapy with a combination of cephalosporin and carbenicillin.

After appropriate cultures and other indicated tests, amikacin
was administered intravenously, either intermittently, or by con­
tinuous infusion. Patients with adequate neutrophils (>1000/mm^3)
received the drug by the intermittent schedule: 150 mg/M^2 admin­
istered in 50 ml of 5% dextrose solution over a 30 minute period
every 6 hours. Patients with neutropenia (<1000 neutrophils/mm^3)
received the continuous schedule. The first 14 neutropenic patients
received a loading dose of 100 mg/M^2 followed by a total daily dose
of 600 mg/M^2. All subsequent patients received a loading dose of
150 mg/M^2 followed by a total daily dose of 800 mg/M^2. An infusion
pump was used to administer the continuous infusions (IVAC TH500,
IVAC Corp., San Diego, California).

Pharmacologic studies were performed in 16 patients who were
receiving amikacin as therapy for infection. There were 6 patients
receiving the intermittent schedule and 10 patients receiving the