Clinical Experience with Amikacin, a New Aminoglycoside Antibiotic

F. P. THERON, M. A. DE KOCK

SUMMARY
Amikacin, a new semisynthetic aminoglycoside antibiotic, was administered parenterally to 20 patients suffering from severe Gram-negative bacterial infections. The antibiotic was found to be highly effective in controlling infection. It was well tolerated and no signs of nephro- or ototoxicity were observed. The few side-effects which were seen appeared to be dose-related. The recommended 12-hourly dosage regimen has also proved useful in medium- to long-term management of refractory pulmonary infections.


Amikacin (BB - K8) is a semisynthetic aminoglycoside antibiotic derived from kanamycin. It has pharmacological properties similar to those of the parent substance, kanamycin. Amikacin has an extremely broad spectrum of antibacterial activity, and is claimed to be more resistant to aminoglycoside-inactivating enzymes than any aminoglycoside in current clinical use. In common with related aminoglycosides, amikacin might be expected to possess

toxic properties, particularly in respect of the patient with impaired renal function. Gentamicin, for example, has been shown to produce acute nephrotoxicity and ototoxicity, and to possess neuromuscular blocking potential.\(^{1,2}\)

Animal experimentation has suggested that the tendency to cause toxicity noted in the specific drug under trial was probably dose-related, occurring consistently in the dosage range of 30 mg/kg/d.\(^{1,2}\) Such levels exceed by a substantial margin the recommended daily dose (15 mg/kg) of amikacin for clinical use.

The purpose of this study was to evaluate the preclinical therapeutic claims made for the efficacy of amikacin in combating Pseudomonas organisms and other Gram-negative bacteria frequently implicated in drug-resistant microbial infections, particularly of the lungs.

**PATIENTS AND METHODS**

**Patient Selection**

All the subjects participating in the trial had given written informed consent to the administration of amikacin in the treatment of their disease. It was explained to them that the wider effects of the drug were unknown, although the limited clinical trials conducted elsewhere to date had yielded very few untoward effects, and that the latter had been similar to those encountered with other drugs in the aminoglycoside group currently in general use.

There were 20 patients with mixed Gram-negative infections which had, in 25% of cases, previously been treated unsuccessfully with other antibiotic drugs. The seriousness of the patients' illnesses did not permit the incorporation of double-blind techniques employing alternative aminoglycoside drugs in the design of the trial, and no control could be exercised other than thorough and objective clinical and laboratory observation.

The age of the patients varied from 14 to 70 years (average 47.5 years) and there were 14 male and 6 female subjects. Fourteen of these patients could be classified as seriously ill with life-threatening infections, while the remainder had moderately severe infections. The primary diagnoses are detailed in Table I, and these included a variety of bronchial, parenchymal and pleural pulmonary infections and a single case of septicaemia proved on blood culture.

**Methods**

All patients were individually evaluated by the authors before undergoing a predetermined set of investigations prior to the institution of amikacin therapy. This documentation included the following:

(a) the measurement of height and body mass;
(b) the maintenance of fluid balance charts, with regular microscopical and biochemical urinalysis;
(c) complete blood cell counts;
(d) liver function tests;
(e) the evaluation of auditory and vestibular function — after consulting our Ear, Nose and Throat Department, we considered the following tests adequate for our purposes: audiography and enquiry after conversational deafness, vertigo and tinnitus and examination for nystagmus;
(f) serum creatinine and blood urea determinations;
(g) records of arterial blood pressure, pulse rate and oral temperature, charted 6-hourly;
(h) daily bacteriological culture of collected sputum.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Primary diagnosis</th>
<th>Causative organism</th>
<th>Duration of illness (days)</th>
<th>Prior therapy</th>
<th>Amikacin dosage (mg/kg/d)</th>
<th>Duration of treatment (days)</th>
<th>Result</th>
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These investigations were repeated at regular intervals or continued throughout the period of drug trial therapy, and were maintained for some days after the cessation of treatment, subject to the emergence of side-effects ascribed to the drug. The results of therapy were assessed in terms of the clinical response, being adjudged excellent, good, fair or poor, according to such criteria as improvement in toxic-febrile state, diminished cardiac and respiratory rates, favourable leucocyte and sedimentation rate response, and, most important, the persistent absence of the offending pathogen from the patient's sputum, signifying eradication of the Gram-negative infection.

RESULTS

A summary of the patient data is provided in Table 1.

The findings in 6 patients deserve further discussion in view of the opportunistic nature of the infection in a compromised host situation, presumably unrelated supervening clinical events, the emergence of side-effects of the drug, or failure of antibiotic therapy to prevent irreparable loss of function.

The clinical and bacteriological response to amikacin in patient 7 was excellent. He made rapid progress towards complete recovery, only to succumb unexpectedly to acute anterolateral myocardial infarction on the fifth day of therapy.

Patient 12, a 14-year-old girl with mucoviscidosis and proven secondary amyloidosis and a long history of recurrent pulmonary infection in relation to bronchiectasis, developed acute bronchitis with marked central cyanosis. *Pseudomonas aeruginosa* was cultured from the sputum and amikacin was commenced as primary antibiotic therapy. In view of the severity of the infection, and the critical general condition of the patient, she received a very high dosage, 27.3 mg/kg/d. The clinical response to the drug was good and the pathogen was eradicated from the sputum within 14 days, but the blood platelet count had decreased from the control value of 340 000/µl to 62 000/µl at this stage and the drug was discontinued. The thrombocyte count gradually returned to normal levels within 2 weeks and the patient's further clinical progress was satisfactory.

The only other untoward effect of the drug noted in this series occurred in patient 6. He was a 45-year-old man who received amikacin as initial antibiotic treatment for a lung abscess. The dosage of the drug was high (19.6 mg/kg/d), and was of necessity prolonged in view of the patient's life-threatening condition. However, the daily dose administered frequently exceeded the manufacturer's recommendation of 15 mg/kg/d. Patients 8, 10, 12 and 18 in particular were thought to deserve high dosages by virtue of their life-threatening condition. However, the daily dose administered fell short of the 30 mg/kg/d level which has been quoted in the literature as consistently producing toxicity in animals treated with gentamicin and other aminoglycoside drugs.

Side-effects ascribable to the use of the drug in the present study were limited to two instances where exceptionally high dosages were used and were 'nonspecific' in nature, suggestive of a hypersensitivity response. Both were reversible, and unrelated to the nephrotoxic, ototoxic and neuromuscular blocking effects previously documented in respect of drugs in this group. It is concluded that amikacin is an effective antibiotic which may be employed with confidence in patients with life-threatening aerobic Gram-negative infections, provided that there is reasonable renal function and that the dosage does not exceed 20 mg/kg/d.

We should like to thank the BM Group (Pty) Ltd for the supply of amikacin.

REFERENCES