TABLE I. PELVIC RADIOGRAPHS OF 727 WHITES

Age (yrs)	Male		Female	
	Without phleboliths	With phleboliths	Without phleboliths	With phleboliths
0 - 20	30	1	45	3
21 - 30	48	14	62	8
31 - 40	39	30	37	30
41 - 50	27	30	19	35
51 - 60	23	31	20	48
61+	31	36	21	59
Total	198	142	204	183

TABLE II. PELVIC RADIOGRAPHS OF 823 BLACKS

Age (yrs)	Male		Female	
	Without phleboliths	With phleboliths	Without phleboliths	With phleboliths
0 - 20	54	0	54	0
21 - 30	70	4	85	7
31 - 40	54	6	81	16
41 - 50	87	9	96	24
51 - 60	38	11	41	15
61+	18	8	34	11
Total	321	38	391	73

RESULTS

Tables I and II indicate the frequency of phleboliths according to race, age and sex. Blacks have far fewer phleboliths than Whites and the results are meaningful at the 1% level of significance.

Fig. 1 shows the differing rates of increase with age in the proportion of people with phleboliths. It is possible that the dip in the graph of the Black group is due to an increasing incidence in younger, westernized people.

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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.

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Department of Medicine, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

F. P. THERON, M.B. CH.B., M. MED.

M. A. DE KOCK, M.B. CH.B., M. MED., F.C.P. (S.A.), M.D., F.R.C.P., F.A.C.C.P.

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Reprint requests to: Professor M. A. de Kock, Department of Medicine, University of Stellenbosch Medical School, PO Box 63, Parowvallei, 7503 RSA.

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.[1] 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.[2,3]

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.[4,5] 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 I. SUMMARY OF PATIENT DATA

Case No.	Age	Primary diagnosis	Causative organism	Duration of illness (days)	Prior therapy	Amikacin dosage (mg/kg/d)	Duration of treatment (days)	Result
1	64	Bronchopneumonia	*Klebsiella pneumoniae*	10	Ampicillin	12,0	17	Fair
2	63	Bronchopneumonia	Gram-negative	5	Penicillin, ampicillin	12,0	13	Excellent
3	25	Septicaemia	*Pseudomonas aeruginosa*	2	Nil	19,5	8	Excellent
4	36	Empyema	*Proteus mirabilis*	30	Streptomycin, INH, ethambutol	17,8	21	Excellent
5	45	Lobar pneumonia	*Klebsiella pneumoniae*	14	Nil	15,1	9	Excellent
6	45	Lung abscess	Gram-negative	7	Nil	19,6	44	Good
7	55	Bronchopneumonia	*Klebsiella pneumoniae*	10	Nil	14,2	5	Excellent
8	65	Bronchopneumonia	*Enterobacter*	14	Nil	27,0	10	Poor
9	51	Lobar pneumonia	*Klebsiella pneumoniae*	2	Nil	16,6	22	Good
10	18	Bronchopneumonia	*Klebsiella pneumoniae*	7	Nil	24,3	8	Excellent
11	70	Bronchopneumonia	Unknown	7	Nil	15,3	8	Excellent
12	14	Bronchiectasis	*Pseudomonas aeruginosa*	14	Nil	27,3	12	Good
13	60	Lobar pneumonia	*Klebsiella pneumoniae*	2	Nil	19,2	10	Good
14	61	Bronchiectasis	*Pseudomonas*	4	Amoxycillin	20,8	7	Excellent
15	53	Bronchopneumonia	*Klebsiella pneumoniae*	3	Ampicillin	19,2	10	Excellent
16	45	Lobar pneumonia	*Klebsiella pneumoniae*	14	Nil	17,5	10	Excellent
17	48	Bronchiectasis	*Klebsiella pneumoniae*	21	Nil	15,0	7	Excellent
18	25	Bronchopneumonia	*Klebsiella pneumoniae*	10	Nil	22,6	10	Excellent
19	67	Lung abscess	*Klebsiella pneumoniae*	14	Nil	15,1	19	Excellent
20	40	Lobar pneumonia	*Klebsiella pneumoniae*	5	Nil	15,3	9	Excellent

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 I.

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 nature of the pathology and the difficulty experienced in eradicating a variety of Gram-negative pathogens. On the 44th day of therapy the patient developed a non-bullous form of erythema multiforme, which regressed promptly after withdrawal of the drug and the administration of a short course of steroids. The overall clinical response was good and the patient's progress to recovery continued on alternative antibiotic therapy.

Patient 1, a 64-year-old man in a pre-terminal state associated with advanced lymphocytic lymphoma, was treated with amikacin when a bronchopneumonic infection could not be controlled with ampicillin. The clinical improvement observed with trial drug therapy was initially encouraging, but *Klebsiella pneumoniae* was persistently cultured from the sputum, necessitating a change to alternative aminoglycoside therapy with gentamicin and, subsequently, tobramycin. The bacteriological response to the latter drugs was, however, indifferent and at the time of the patient's death 6 months later, sputum culture was still positive for *Klebsiella*.

The clinical response to the drug achieved in patient 8 was coded as poor. This elderly woman had severe chronic obstructive airways disease complicated by bronchopneumonia. *Enterobacter* was implicated and amikacin therapy was commenced. The patient's temperature chart showed a swinging pyrexia which subsided after several days, and sputum culture became negative. Antibiotic and other supportive therapy failed to halt the progressive parenchymal destruction, however, and the worsening respiratory failure resulted in death from irreversible hypoxaemia.

Patient 4 is worthy of comment. This patient was treated for empyema but was also receiving antituberculosis therapy, including streptomycin. We were reluctant to use two aminoglycosides simultaneously, but this was thought justified in view of the patient's life-threatening Gram-negative infection — amikacin in a dosage of 17,8 mg/kg/d was given.

CONCLUSIONS

Our experience, although limited, suggests that amikacin is a valuable adjunct to current antibiotic therapy, particularly in respect of Gram-negative pathogenic organisms which are likely to prove resistant to all but aminoglycoside treatment.

In view of the severity and refractoriness of the infection in a number of cases, the dosage employed 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.[3,4]

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.

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