A prospective study of long-term use of amikacin in a paediatrics department

Indications, administration, side-effects, bacterial isolates and resistance

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Summary

Amikacin (Amikin; B-M) was used as the only aminoglycoside for 18 months in a paediatric department within a general hospital because of high levels of resistance of *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Enterobacter cloacae* isolates to tobramycin, gentamicin and netilmicin. Between 1 February 1987 and 31 July 1988, 816 children were treated with a slow intravenous injection at a standardised dose adjusted for weight and age. Respiratory disease was present in 35,8% of 537 neonates, 56,4% of 190 infants and 70,9% of 89 older children. *Escherichia coli* (65 isolates), *Klebsiella* species (59 isolates), *Enterobacter* species (26 isolates) and *P. aeruginosa* (22 isolates) constituted the most common Gram-negative pathogens. The positive blood culture yield was 7,8%. Satisfactory median peak and trough serum amikacin levels were achieved. No significant renal side-effects were noted. Severe bilateral hearing loss in 1 low-birthweight infant resulted from inadvertent overdosage. At the end of this 18-month surveillance period 97,7% of *E. coli*, 98,6% of *K. pneumoniae*, 96,3% of *E. cloacae*, and 98,0% of *P. aeruginosa* isolates remained sensitive to amikacin, while resistance of *K. pneumoniae* to tobramycin, netilmicin and gentamicin decreased significantly ($P < 0,003$, $P < 0,001$ and $P < 0,007$ respectively; chi-square test).

S Afr Med J 1990; **78:** 192-195.

The world-wide phenomenon of increasing bacteral resistance to gentamicin and tobramycin following prolonged hospital use[1,2] became evident at Tygerberg Hospital during 1986 (Table I). In that year, tobramycin constituted 70% of all the aminoglycosides prescribed in the medical and surgical paediatric wards and amikacin (Amikin; B-M) 12% of those prescribed in paediatric wards and 11,7% of those administered to adults. Since the unrestricted use of amikacin as the aminoglycoside of first choice has not resulted in increased resistance to amikacin in other studies and may decrease resistance to other aminoglycosides,[3-5] antibiotic policy was changed in the medical paediatric wards with effect from 1 February 1987. Amikacin became the only aminoglycoside available for routine use in the medical paediatric wards, while the rest of the hospital continued with an unrestricted aminoglycoside policy.

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Accepted 21 Feb 1990.

The objective of this study was to record the clinical indications for treatment and evidence of infection, to monitor the effect of a standardised amikacin dosage and administration schedule with blood levels, and to record possible side-effects of therapy in all children treated during the first 6 months of the new antibiotic policy. A second objective was to measure the change in the sensitivity of Gram-negative pathogens to aminoglycosides resulting from this policy in this institution over 18 months.

Patients and methods

Patient selection

The paediatric department occupies 15% of beds in this 1 981-bed general teaching hospital. The medical paediatric wards in which the study was carried out are located all over the hospital.

Amikacin was prescribed only to patients who had suspected Gram-negative infection or were infected by organisms proven to be sensitive to amikacin. The clinical indications for aminoglycoside therapy were recorded and patients were categorised by age as neonates (0 - 28 days), infants (1 - 12 months) or older children (1 - 12 years). The majority of patients simultaneously received a β-lactam antibiotic.

Amikacin therapy and control

The dosage schedule for neonates with a birth weight below 1 000 g was 7,5 mg/kg every 18 hours and that for neonates weighing 1 000 - 2 000 g and less than 8 days old 7,5 mg/kg every 12 hours; all other infants and children received 15 mg/kg/d in 2 or 3 divided doses. Amikacin was administered as a slow intravenous bolus at the butterfly connection of the infusion set over a period of 1 - 2 minutes, after which the connection was flushed with 0,5 ml sterile water over 1 minute. Capillary heel-prick or venous blood samples were collected in 0,5 ml Eppendorf centrifuge tubes for analysis of serum amikacin levels by the EMIT method (Syva, Palo Alto, Calif., USA) within 12 hours after collection. Trough levels were recorded immediately before and peak levels approximately 20 minutes after amikacin administration, only after 3 doses had already been administered.[6] The normal duration of treatment was 5 days. Many patients were switched to other antibiotics after 5 days if infection was still present or presumed to be present. The subsequent data were obviously excluded from the analysis. Dosages were adjusted if serum levels were unsatisfactory. Two hospital pharmacists controlled the ward dispensing of amikacin and supervised compliance with standard treatment instructions. All neonates (forming the largest group of patients, namely 537 of 816) were prescribed antibiotics when infection was suspected on clinical or other grounds. This is accepted neonatal practice and is associated with a much lower morbidity and mortality due to infection than a policy where antibiotics are only started after definite direct or indirect proof of infection.

TABLE I. BACTERIAL SENSITIVITIES TO AMINOGLYCOSIDES AT TYGERBERG HOSPITAL DURING 1986

	Amikacin		Gentamicin		Netilmicin		Tobramycin	
	No.	%	No.	%	No.	%	No.	%
Klebsiella pneumoniae	**1 929**	**99,2**	**1 932**	**56,7**	**1 909**	**71,9**	**1 932**	**56,5**
Escherichia coli	**1 391**	**98,4**	**1 389**	**95,8**	**1 382**	**97,4**	**1 388**	**94,5**
Pseudomonas aeruginosa	**1 217**	**97,0**	**1 217**	**85,2**	**1 217**	**82,9**	**1 218**	**81,8**
Enterobacter cloacae	**533**	**98,1**	**532**	**80,4**	**531**	**90,5**	**532**	**78,7**

Other investigations

All specimens submitted for microbiological culture were processed by the routine microbiology service. Only pathogens isolated from patients 3 days before and 1 day after the onset of antibiotic therapy were recorded for the purpose of this investigation. Blood C-reactive protein (CRP) screening measurements were performed at the onset of therapy, with a latex agglutination test where possible. A positive screening test was followed by quantitative rocket electrophoresis with a value of 20 μg/ml or above taken as elevated. A Coulter blood count (Model 5880) was scheduled for day 1. In view of the wide range of the normal white cell count (WCC) from birth to age 12 years, a WCC under 5 or over 15 x 10^9/l was considered abnormal in all age groups for the purpose of this study. These two investigations were used as supportive evidence of infection. Blood urea and creatinine levels were measured at the onset and at completion of treatment where possible.

Treated neonates with a birth weight below 1 500 g who had been admitted to the intensive care unit underwent hearing assessment at 3 and 12 months' corrected age respectively. Behavioural response audiometry was performed by presenting low-frequency (250 - 500 Hz) and high-frequency (4 000 - 8 000 Hz) test sounds in the freefield using Uni-pex horn speakers in conjunction with a Madsen OB822 clinical audiometer. Tympanometry with a Grason Stadler 28A automatic tympanometer recorded the middle ear pressure and physical volume of the external auditory meatus. When normal hearing could not be demonstrated with behavioural response audiometry and middle ear status was normal, acoustic brainstem reflex (ABR) audiometry was performed under sedation with a Cadwell 5200A audiometer and TBH-39P earphones.

Results

A total of 816 children received a course of amikacin between 1 February 1987 and 31 July 1988. Of 537 neonates treated, 71,3% (383) were premature and 34,6% (186) small for gestational age on assessment by the Finström method[7] and perinatal growth charts.[8]

The incidence of major clinical problems among 537 neonates, 190 infants and 89 older children are listed in Tables II and III. Respiratory disease was present in 35,8% of neonates, 56,4% of infants and 70,9% of older children.

TABLE II. MAJOR CLINICAL PROBLEMS AMONG 537 NEONATES TREATED DURING 1 FEBRUARY 1987 - 31 JULY 1988

	No.	%*
Respiratory distress syndrome/pneumonia	**192**	**35,8**
Infection (suspected clinically)	**89**	**16,6**
Prolonged rupture of membranes	**80**	**14,9**
Various confirmed infections	**47**	**8,8**
Patent ductus arteriosus	**41**	**7,6**
Septicaemia	**40**	**7,4**
Haemolytic disease	**39**	**7,2**
Gastro-enteritis/enterocolitis	**37**	**6,9**
Major congenital abnormalities	**37**	**6,9**
Diverse conditions	**49**	**9,1**
Total	**651**	

*% of 537 neonates. Some had more than one major clinical problem.

TABLE III. MAJOR CLINICAL PROBLEMS AMONG INFANTS AND OLDER CHILDREN

	% of 190 infants	% of 89 older children
Pneumonia	**43,2**	**52,9**
Other respiratory infections	**13,2**	**18,0**
Tuberculosis	**2,1**	**9,0**
Gastro-enteritis	**21,1**	**10,1**
Kwashiorkor/marasmus	**4,7**	**14,6**
Cancer	**0,0**	**21,3**
Septicaemia	**8,4**	**6,7**
Urinary tract infection	**8,4**	**6,7**
Infectious diseases	**5,8**	**5,6**
Neurological disorders	**8,4**	**9,0**
Cardiac conditions	**7,9**	**3,4**
Surgical conditions	**4,2**	**9,0**
Diverse conditions	**12,6**	**11,2**

Measurement of serum peak and trough amikacin levels was repeated if blood levels were unsatisfactory and dosages had been adjusted. The median value, standard error and range of the peak and trough values are set out in Table IV.

TABLE IV. AMIKACIN PEAK AND TROUGH SERUM LEVELS (μg/ml)

	Peak			Trough		
	Children	Infants	Neonates	Children	Infants	Neonates
Sample size	**103**	**226**	**502**	**111**	**237**	**525**
Median	**13,50**	**15,05**	**18,90**	**1,70**	**2,60**	**5,70**
Standard error	**1,12**	**0,68**	**0,53**	**0,38**	**0,20**	**0,27**
Range	**79,30**	**68,40**	**120**	**28,30**	**28,10**	**60,90**

TABLE V. NATURE AND ORIGIN OF PATHOGENS ISOLATED IN 816 PATIENTS

	Blood	Urine	Stool	Tracheal aspirate	Pus swabs	Umbilicus	Other sites	Total
Gram-positive organisms								
Escherichia coli	10	23	7	6	12	2	5	65
***Klebsiella* species**	14	13	4	13	7	4	4	59
Pseudomonas aeruginosa	0	0	0	17	3	1	1	22
Enterobacter cloacae	3	2	0	8	3	0	1	17
Serratia marescens	3	0	0	6	0	0	3	12
Other organisms	6	4	4	4	5	0	1	24
Gram-negative organisms								
Staphylococcus aureus	3	1	0	4	8	5	4	25
β-haemolytic streptococci	6	0	0	0	0	2	4	12
α-haemolytic streptococci	5	0	0	0	2	0	0	7
Streptococcus faecalis	8	0	0	0	2	1	0	11
Other organisms	6	1	0	2	0	0	1	10
Total	64	44	15	60	42	15	24	264

Pathogenic bacteria were isolated in 32,4% of the 816 patients and blood culture was positive in 7,8%. *Escherichia coli* (65 isolates), *Klebsiella pneumoniae* (59 isolates), *Pseudomonas aeruginosa* (22 isolates) and *Enterobacter cloacae* (17 isolates) accounted for 81,9% of all Gram-negative isolates, while *Staphylococcus aureus* and β-haemolytic streptococci were the major Gram-positive pathogens. The most common Gram-negative and Gram-positive pathogens and their sites of origin are listed in Table V.

Blood urea and/or creatinine values were measured in 471 patients on day 1 of therapy and in 464 patients on days 4 - 6. Renal function was abnormal (on the basis of our normal laboratory values for neonates, infants and older children) in 154 patients at the start and 128 patients towards the end of amikacin therapy. Nineteen patients with documented abnormal renal function died in hospital during or after amikacin therapy. These deaths could not be linked to amikacin toxicity (hyaline membrane disease 5, septicaemia 3, neoplasm 2, intracranial bleeding 2, motor vehicle accident 1, drowning 1, pneumonia 1, miliary tuberculosis 1, cardiac failure 1, necrotising enterocolitis 1, extreme prematurity 1).

A CRP level above 20 μg/ml was recorded in 347 cases, a WCC above 15×10^9/l in 247, and a WCC below 5×10^9/l in 80. Multivariate analysis of raised CRP levels, abnormal WCC and blood culture was not performed because blood samples for these investigations were not always collected simultaneously. However, it may be of interest to note that a raised CRP value was recorded in 16,1% of 64 patients with a positive aerobic blood culture, while a significant change in the WCC was recorded in 40% of cases (raised WCC 21%, depressed WCC 18,8%). This may suggest that the cut-off level for CRP of 20 μg/ml was too insensitive. However, this cut-off level was decided upon by our local laboratory after pilot studies to investigate the sensitivity and specificity of the test. Neonates, who constituted the majority of the study group, do not always respond with a quick rise in CRP to infection in the first 24 hours of life.

Of 113 very-low-birth-weight neonates (< 1 500 g) treated with amikacin in the neonatal intensive care unit 20 died and 30 were lost to follow-up; 63 survivors were evaluated for hearing loss (Table VI). Infants with serous otitis media were treated medically and followed up. One infant with 60 dB bilateral hearing loss had received too high an initial dose of amikacin. The report from the laboratory that the peak serum level was 120 μg/ml was not acted upon promptly and the neonate received a further 3 excessive doses of the drug. Two neonates, who had grade III and grade IV intraventricular haemorrhage respectively in the neonatal period (confirmed by ultrasound), had unilateral hearing loss of 20 dB. The fourth neonate required a tracheostomy from birth to 5 months, is severely globally retarded and has 65 dB hearing loss, which is largely conductive.

TABLE VI. ASSESSMENT OF HEARING IN HIGH-RISK NEONATES WITH A BIRTH WEIGHT BELOW 1 500 g

	No.
Normal	39
Serous otitis media	20
Impaired hearing	4
Total	63

The restricted use of other aminoglycosides for the period 1 February 1987 - 31 July 1988 applied to medical paediatric wards only. The relative use of different aminoglycosides for the whole hospital for 1986, 1987 and 1988 was calculated from dispensing data supplied by the central hospital pharmacy. The use of amikacin in all children (medical and surgical) increased from 12,8% during 1986 to 79,3% during 1987, and from 11,7% to 15,7% in all adults for the same period. Gentamicin and tobramycin remained the most commonly dispensed aminoglycosides in adult patients.

The data reported in the present study formed part of a larger study of changes in antibiotic sensitivity conducted for the whole hospital. The changes in sensitivity of the four most common Gram-negative pathogens to aminoglycosides in the whole hospital during the trial are illustrated in Table VII. The monthly changes in sensitivity patterns and differences between the paediatric wards and the rest of the hospital will be recorded elsewhere. Resistance of *K. pneumoniae* to gentamicin ($P < 0{,}007$), netilmicin ($P < 0{,}001$) and tobramycin ($P < 0{,}003$) decreased significantly. Resistance of *P. aeruginosa* to gentamicin increased significantly ($P < 0{,}003$; chi-square test), while the sensitivity pattern against amikacin showed no change.

Discussion

Because of the high incidence of infectious diseases, constant surveillance of microbial sensitivities is mandatory to ensure an appropriate antibiotic policy. The high incidence of low-birth-weight neonates, respiratory infections, tuberculosis, malnutrition and gastro-enteritis reflects the health of the

TABLE VII. MICROBIAL SENSITIVITY TO AMINOGLYCOSIDES AT TYGERBERG HOSPITAL IN FEBRUARY 1987 AND AUGUST 1988

	Amikacin		Gentamicin		Netilmicin		Tobramycin	
Sensitivity	Feb. '87	Aug. '88	Feb. '87	Aug. '88	Feb. '87	Aug. '88	Feb. '87	Aug. '88
Escherichia coli								
No.	137	180	135	180	131	180	134	180
%	97,8	97,7	96,2	93,3	96,9	95,0	94,7	92,7
Klebsiella pneumoniae								
No.	218	146	218	146*	216	145**	218	146***
%	94,0	98,6	55,9	70,5	69,9	82,0	55,9	71,9
Pseudomonas aeruginosa								
No.	102	105	102	105	101	105	102	105
%	98,0	98,0	94,1	79,0	91,0	89,5	91,1	90,4
Enterobacter cloacae								
No.	56	55	56	55	56	55	56	55
%	87,5	96,3	75,0	76,3	76,7	83,6	67,8	76,3

*$P < 0{,}007$; chi-square test.
**$P < 0{,}001$; chi-square test.
***$P < 0{,}003$; chi-square test.

mainly Third-World population who attend this academic hospital.

The administration of amikacin as a slow intravenous bolus (a practice not routinely recommended by the manufacturer) was necessary in our department, where an excessive patient load and insufficient nursing staff to supervise intravenous lines made it impossible to administer amikacin effectively as a slow intravenous infusion. This practice resulted in satisfactory median and peak trough levels and was not associated with significant impaired renal or auditory function, as in other reports where standard administration techniques were used.[9-11] The single high-risk neonate who developed cochlear deafness related to amikacin therapy clearly did so because of overdosage.

During a wash-out period of 12 months during 1986, amikacin represented only 12,8% of total paediatric and 11,7% of total adult aminoglycoside use. This was followed by relative amikacin use of 79,3% in children and 15,7% in adults during 1987. The policy of restricted use of other aminoglycosides was maintained in medical paediatric wards until August 1988. This practice did not induce bacterial resistance to the major Gram-negative pathogens encountered in medical paediatrics, e.g. *E. coli, K. pneumoniae, P. aeruginosa* and *E. cloacae,* in the hospital.

This aminoglycoside policy in a department representing 15% of all hospital beds was associated with a significant decrease of *K. pneumoniae* resistance to gentamicin, netilmicin and tobramycin in isolates from the whole hospital. However, resistance to these drugs still remained at an unacceptably high level at the end of the 18-month surveillance period (Table VII).

This study confirms other reports that the long-term intensive use of amikacin in a large hospital department does not induce bacterial resistance and that the drug is not associated with significant side-effects if used appropriately.[3-5]

We gratefully acknowledge the support of Bristol Myers and assistance of Mrs H. Bingham, Mrs K Drayton, the central hospital pharmaceutical service and the Statistics Department of Tygerberg Hospital in this investigation.

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