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Clinical and bacteriological efficacy, and practical aspects of amikacin given once daily for severe infections

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In a multicentre non-randomized open prospective study, 124 patients hospitalized in medical infectious disease or intensive care units, with severe community and hospital-acquired bacterial infections were treated with 15 mg/kg body weight amikacin in a once-daily dose given as a 30 min iv infusion, combined with other antibiotics. Infections were bacteriologically proven in 101 patients

The clinical responses showed 83·1% primary success and 83·9% definitive cure predominantly in intensive care patients with hospital-acquired infections and pneumonia. Bacteriological eradication was achieved in 67·3%. Bacteria associated with true failures and colonizations were predominantly *Pseudomonas, Acinetobacter* and *Staphylococcus* spp. The risk of nephrotoxicity may be decreased with such a regimen of amikacin, but no conclusions could be drawn with regard to ototoxicity. In summary, a once-daily dosing regimen of amikacin 15 mg/kg is practical and probably efficacious and safe in severely infected patients.

Introduction

Current dosing strategies for aminoglycosides may not be ideal with regard to therapeutic efficacy and safety (Kapusnik & Sande, 1986). Optimal clinical efficacy is attained with high peak serum concentrations (Moore, Lietman & Smith, 1987) while cochleo-vestibular toxicity is minimized with lower trough concentrations (Nordström *et al.*, 1973) or less frequent dosing intervals (Tran Ba Huy, Bernard & Schacht, 1986).

A considerable number of in-vitro, animal and clinical studies have been conducted with once-daily administration of aminoglycosides (Kovarik, Hofpelman & Verhoef, 1989). In a preliminary study in eight patients we showed that amikacin 15 mg/kg in a single daily dose provided excellent bactericidal activity (Chidiac *et al.*, 1987). These results were supported by further clinical experience in 78 patients (Beaucaire *et al.*, 1989).

The aim of this study was to assess the clinical and bacteriological efficacy of once-daily doses of amikacin in severe systemic infections and to review the practical aspects of such a regimen.

Patients and methods

This study was approved by the Lille Medical University's Ethics Committee. Informed consent was obtained from each patient in accordance with the Helsinki Declaration.

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This was a prospective, open, non-comparative, multicentre study conducted, in a single medical infectious diseases unit and in eight intensive care units, from October 1987 to September 1989.

Patients

Patients were enrolled in the study if they had evidence of severe infection for which systemic aminoglycoside therapy was indicated, for a minimum duration of 3 days. The aminoglycoside was given in combination with another antibiotic in accordance with normal practice in France; when the infection was bacteriologically proven, strains had to be susceptible to at least one of the two antibiotics used.

The following patients were excluded: pregnant women; patients with meningitis, endocarditis or bacteraemia related to uncomplicated acute pyelonephritis; patients with septic shock which had not improved in the first 24 h; patients with acute or chronic renal failure with a serum creatinine greater than 17 mg/l; patients with myasthenia gravis, known cochleo-vestibular abnormalities, neutropenia of less than $0{\cdot}5 \times 10^9$/l polymorphonuclear neutrophil cells and patients who had received an aminoglycoside in the previous 2 weeks.

The principal characteristics of the 124 patients studied are detailed in Table I. Using the McCabe and Jackson classification 40 patients were assessed as class III severity (McCabe & Jackson, 1962). Of the 91 patients admitted to intensive care units (mean Simplified Acute Physiological Score, $14{\cdot}0 \pm 5{\cdot}8$) 35 underwent a surgical procedure. Empirical therapy was defined as antibiotic administration before the causative bacteria was identified and susceptibility determined, as opposed to documented

Table I. Details on the 124 patients: according to age, weight, McCabe classification, renal function, and clinical diagnosis

	Medical unit	Intensive care units	Total
Number of patients (*n*)	33	91	124
Mean age (years)	54 ± 21	61 ± 17	59 ± 18
Mean weight (kg)	61 ± 14	64 ± 15	63 ± 15
McCabe classification (*n*) I	4	13	17
II	13	54	67
III	16	24	40
Renal failure (*n*) (serum-creatinine > 12 mg/l)	6	22	28
Simplified Acute Physiological Score	—	$14 \pm 5{\cdot}8$	—
Mechanical ventilation (*n*)	—	48	—
Community-acquired infection (*n*)	22	35	57
Hospital-acquired infection (*n*)	11	56	67
Empirical therapy (*n*)	28	78	106
Pneumonia (*n*)	6	52	58
Bacteraemia (*n*)	12	21	33
Intra-abdominal sepsis (*n*)	5	28	33
Complicated urinary tract sepsis (*n*)	10	5	15
Other localized infections (*n*)	8	2	10

therapy prescribed only when this information was known. A total of 149 sites of infection were recorded in the 124 patient group.

Amikacin therapy and serum assays

Amikacin in a dose of 15 mg/kg body weight/day was given iv as a short term infusion over 30 min, in 108 patients. In 16 patients the daily dose was reduced to 10 mg/kg because they were older than 80 years, or had a body weight such that the amikacin daily dose would exceed 1500 mg, or had renal failure.

Blood samples for assays of serum concentrations of amikacin were drawn immediately before (trough value) and 1 h after (peak value) the onset of the infusion. The first peak and trough were defined as serum concentrations measured after the first infusion, the day 1–2 peak as the highest peak concentration measured on the first and second days of therapy, and the maximum peak and trough as the highest peak and lowest trough concentrations measured during the treatment. Amikacin serum concentrations were assayed by a fluorescence polarization immunoassay (Abbott TD_x). The limits for peak and trough values were set respectively between 25 and 60 and at $\leqslant 2$ mg/l.

Associated antibiotics

Amikacin was co-administered with one or more other drugs in all patients. The other drugs used were piperacillin (67), ceftazidime (26), imipenem (21), ofloxacin (13), cefotaxime (6), vancomycin (5), imidazoles (3), aztreonam and co-amoxyclav (1). A patient could be treated with more than one associated antibiotic during the infectious episode. Associated antibiotics were given at the recommended daily doses with a mean duration of treatment of $12{\cdot}5 \pm 5{\cdot}1$ days.

Bacteriological data

Before starting antimicrobial therapy samples for aerobic and anaerobic cultures of blood and accessible pus and cultures of urine were obtained. The susceptibility of the isolates to amikacin and other antibiotics was tested by a disc diffusion method on Mueller–Hinton Agar (Pasteur Diagnostics). Amikacin susceptibility was reported as 'sensitive' (equivalent to MIC < 8 mg/l), 'intermediate' (equivalent to MIC 8–16 mg/l), or 'resistant' (equivalent to MIC > 16 mg/l), with discs containing 30 μg amikacin (Pasteur Diagnostics). One hundred and one patients had a bacteriologically proven infection, and 125 causative bacteria were isolated (Table II). A single pathogen was responsible for infection in 85 patients. Susceptibility studies identified three Gram-negative bacilli resistant to amikacin and 13 resistant to other, co-administered antibiotics (Table III).

Laboratory tests and evaluation of toxicity

Assays of serum creatinine were performed repeatedly, before, during and at the end of treatment, and a few days later if renal failure was evident. Nephrotoxicity was defined as an increase of the serum creatinine concentration of 15% above the initial value (Nordström *et al.*, 1990). Tests for auditory and vestibular function were performed on an insufficient number of patients for analysis; only clinical signs of vestibular toxicity were noted.

Table II. Number of organisms (total 125) isolates from 101 patients

Organism	Medical unit	Intensive care units	Total
Gram-negative bacilli (*n*):	18	92	110
Acinetobacter anitratus	0	2	2
A. baumanni	0	8	8
A. calcoaceticus	0	5	5
A. haemolyticus	1	0	1
A. lwoffii	0	1	1
Moraxella catarrhalis	0	1	1
Enterobacter cloacae	1	4	5
E. hafniae	0	1	1
Escherichia coli	10	28	38
Haemophilus influenzae	0	7	7
Klebsiella oxytoca	0	4	4
K. pneumoniae	1	4	5
Levinea	0	1	1
Morganella morganii	0	2	2
Proteus mirabilis	1	6	7
Pseudomonas aeruginosa	2	14	16
P. cepacia	1	0	1
P. paucimobilis	0	1	1
P. putida	0	1	1
Salmonella enteritidis	1	0	1
Serratia liquefaciens	0	1	1
S. marcescens	0	1	1
Gram-positive cocci (*n*)	3	9	12
Enterococcus faecalis	1	2	3
Staphylococcus aureus	1	4	5
S. epidermidis	0	2	2
Streptococcus bovis	1	0	1
S. pneumoniae	0	1	1
Anaerobes (*n*):	0	3	3
Bacteroides fragilis	0	2	2
Clostridium perfringens	0	1	1

Evaluation of efficacy

Clinical response. Patients were evaluated for efficacy after a minimum of 3 days treatment. 'Primary success' was defined as the disappearance of all the initial abnormal clinical and radiological signs related to the initial infection, and eradication of the causative bacteria. This primary success could be definitive or followed by death due to underlying diseases or followed by a superinfection.

'Primary failure' was defined as no change or worsening of clinical manifestations, failure to eradicate the causative bacteria with or without superinfection.

Bacteriological response. 'Bacteriological success' was defined as the eradication of the causative bacteria, without reinfection or superinfection; true 'bacteriological failure' as persistence of the original pathogen(s) or superinfection associated with

Table III. Details of antibiotic resistant strains

Drug	Strains	Number
Amikacin		12
	Acinetobacter anitratus	2
	Bacteroides fragilis	2
	Clostridium perfringens	1
	Enteroccoccus faecalis	3
	Pseudomonas aeruginosa	1
	Staphylococcus aureus	1
	Streptococcus bovis	1
	S. pneumoniae	1
Piperacillin		9
	Enterobacter cloacae	1
	Escherichia coli	6
	Klebsiella pneumoniae	1
	S. aureus	1
Cefotaxime		2
	Acinetobacter baumanni	2
Ceftazidime		1
	A. baumanni	1
Imipenem		1
	P. aeruginosa	1

clinical manifestations; and 'bacteriological colonization' as persistence of the original pathogen(s) or superinfection, without clinical manifestations.

Data analysis. The Student's *t*-test was used to compare means. The χ^2 test, with Yates correction was used as necessary and the Fisher Exact Test to compare proportions. The tests were performed at the 5% level of significance.

Results

Clinical evaluation

The clinical response was generally favourable in all patients groups (Table IV).

Primary success occurred overall in 83·1% of patients; 90·9% for patients hospitalized in the medical unit and 80·2% for those in intensive care units. Definitive primary successes were more common in surgical intensive care unit patients (23/35–65·7%) than in medical intensive care unit patients (26/56–46·4%). Primary success was noted in 82·1% of hospital-acquired infections, and in 85·8% of patients treated empirically.

Primary failure occurred in 16·9% of patients, with more striking difference between medical unit patients (9·1%) and intensive care unit patients (19·8%). Primary failure of documented infection occurred in 6/18 (33·3%), compared with 15/106 (14·2%) in those treated empirically ($\chi^2 = 4{\cdot}02$, $P < 0{\cdot}05$).

In the case of hospital-acquired pneumonia, primary success rate was 79·1% (34/43). Pneumonia occurring in ventilated patients was associated with a primary success rate

Table IV. Details of the clinical response in the 124 patients

	n	Primary success (%)	Definitive cure (%)	Death related to infection (%)	Death not related to infection (%)
Total	124	103 (83·1)	104 (83·9)	7 (5·6)	13 (10·5)
Medical unit	33	30 (90·9)	32 (97·0)	0 (—)	1 (3·0)
Intensive care unit	91	73 (80·2)	72 (79·1)	7 (7·7)	12 (13·2)
Community-acquired infection	57	48 (84·2)	53 (93·0)	3 (5·3)	1 (1·8)
Hospital-acquired infection	67	55 (82·1)	51 (76·1)	4 (6·0)	12 (17·9)
Mechanical ventilation	48	40 (83·3)	32 (66·7)	6 (12·5)	10 (20·8)
Empirical therapy	106	91 (85·9)	91 (85·9)	4 (3·8)	11 (10·4)
Documented therapy	18	12 (66·7)	13 (72·2)	3 (16·7)	2 (11·1)
Pneumonia	58	46 (79·3)	42 (72·4)	6 (10·3)	10 (17·2)
Intra-abdominal sepsis	33	28 (84·9)	29 (87·9)	3 (9·1)	1 (3·0)
Bacteraemia	33	28 (84·9)	27 (81·8)	3 (9·1)	3 (9·1)
Complicated urinary tract sepsis	15	12 (80·0)	14 (93·3)	0 (—)	1 (6·7)

of 72·1% (31/43); the definitive primary success rate fell to 34·9% (15/43). In intra-abdominal sepsis, septicaemia and complicated urinary tract sepsis, the primary success rates were 84·8, 84·8 and 80% respectively.

Analysis of the clinical response (Table IV) showed a high rate of definitive cure (83·9%). Death directly related to infection occurred in only seven patients (5·6%). For intensive care unit patients, these rates were respectively 79·1 and 7·7%. Rates for pneumonia with mechanical ventilation were 69·8 and 11·6% respectively.

All infectious related deaths occurred in patients on intensive care units on a background of multi-organ failure (2), septic shock (3), broncho-pleural fistula (1) and acute respiratory distress syndrome (1). These deaths were all related to infection and occurred after a mean of $13{\cdot}6 \pm 10{\cdot}1$ days treatment with amikacin.

Thirteen deaths unrelated to infection occurred after a mean of $18{\cdot}5 \pm 10{\cdot}0$ days treatment with amikacin. Six occurred with a mean of $11{\cdot}7 \pm 5{\cdot}0$ days after stopping antibiotic therapy. The cause of death indicated acute respiratory insufficiency from pulmonary embolus (3) or pneumothorax (2), chronic respiratory insufficiency (3), cerebral haemorrhage (3), gastric bleeding (1) and cardiac arrest (1).

Bacteriological results

Among the 101 patients with documented infection, definitive eradication occurred in 68 patients (67·3%); 19/21 in the medical unit (90·5%) and 49/80 (61·3%) in intensive care units. True failures (Table V) occurred in 24 patients (23·8%), divided between persistence and superinfection in 12 and 14 patients respectively. Among the 25 causative bacteria resistant to amikacin ($n = 12$) or associated antibiotics ($n = 13$), 22 were definitively eradicated (12/12 amikacin resistant and 10/13 resistant to associated antibiotics). Twenty-two out of the 24 failures occurred in the intensive care units. *Pseudomonas* spp. and *Acinetobacter* spp. were the initial causative bacteria on seven and four occasions respectively and were persistent or superinfecting bacteria on eight and three occasions respectively. *Staphylococcus* spp. always occurred as superinfecting bacteria, and were always methicillin resistant. These three bacterial species were responsible for 15/24 true failures (62·5%). Of the six persistent Enterobacteriaceae, three were implicated in renal abscesses which required surgical drainage.

Table V. Organisms implicated in the 24 true failures, among the 101 patients with initially bacteriologically documented infection

Organism	Initial	Final	
		persistence	superinfection
Enterobacteriaceae	19 (1)[a]	7 (1)[a]	2 (1)[b]
Pseudomonas spp.	7 (1)[a]	4 (2)[a]	4 (2)[a]
Acinetobacter spp.	4 (1)[a]	1	2 (2)[b]
Staphylococcus spp.	0	0	7 (7)[b]
Others	2 (1)[a]	0	2 (2)[c]

[a]Strain resistant to the associated antibiotic but susceptible to amikacin.
[b]Strain resistant to the associated antibiotic and amikacin.
[c]Strain susceptible to the associated antibiotic but resistant to amikacin.

Twenty-four episodes of superinfection were noted in 22 patients, all of whom were hospitalized in an intensive care unit, and in 15/22 (68·2%) patients who required mechanical ventilation. These mainly occurred in patients with pneumonia, (30·4%), and represented 20/83 (24·1%) of those treated empirically.

Nine (8·9%) episodes of colonizations were noted; these persisted in four patients and resulted in superinfection in five patients. All occurred in intensive care unit patients, and were caused by *Pseudomonas* spp. (6), *Acinetobacter* spp. (2) and *Staphylococcus* spp. (3) which included three amikacin resistant strains.

Amikacin treatment

The mean initial amikacin daily dose was 903±197 mg which rose to a mean of 941±215 mg after the treatment had been completed. The initial daily dose in medical unit patients was reduced from 896±205 mg to 852±190 mg, whereas it had to be raised in intensive care unit patients from 906±195 mg to 973±225 mg. The mean duration of amikacin treatment was 11·0±4·2 days; it was shorter in 9·6±3·3 days for medical unit patients and 11·6±4·6 days for intensive care unit patients.

In order to achieve the defined peak and trough concentrations changes in the initial daily dose had to be made for 62 (50%) patients. The initial daily dose was unchanged in 62 patients and was changed once, twice, thrice and more, in 34, 21 and 7 patients respectively.

Serum concentrations

The results are summarized in the Table VI. Large inter-individual variation in the peak and trough concentrations were noted (8·7–110·0 mg/l peak, 0·0–17·8 mg/l trough). In the 28 patients who presented with impaired renal function, the mean first peak concentration value was 44·2±14·7 mg/l in the six medical unit patients and 32·3±12·8 mg/l in the 22 intensive care unit patients, the mean first trough values were 3·6±3·2 and 2·7±2·2 mg/l respectively. If the mean first peak and trough concentration values in patients with unchanged (62), decreased (19) and increased initial daily dose (43) are compared, the corresponding values were respectively 37·4±11·4, 46·2±12·1 and 25·8±7·8 and 1·5±1·9, 2·9±1·7 and 1·6±1·4 mg/l. The difference between the first

Table VI. Amikacin serum concentrations

	Assays	Medical unit mean±S.D.	Intensive care unit mean±S.D.
First peak	(n = 118)	38·6±13·9	33·5±14·8
Day 1–2 peak	(n = 118)	38·9±12·9	37·9±14·6
Maximum peak	(n = 124)	39·8±13·0	46·9±15·6
First trough	(n = 118)	1·9±2·6	1·7±1·9
Maximal trough	(n = 124)	1·9±2·6	2·7±2·9

S.D., Standard deviation.

peak concentration values in unchanged and increased initial daily doses was statistically significant ($t = 5{\cdot}24$, $P < 0{\cdot}001$).

Concerning the clinical evaluation, there were seven (11·3%), three (15·8%) and 11 (25·6%) failures, in the patients with unchanged, decreased and increased initial daily doses respectively. Though more failures were noted in patients who needed an increase of the initial daily dose, this difference was not significant ($\chi^2 = 3{\cdot}65$, $P < 0{\cdot}1$). The occurrence of superinfection or death related to infection was not correlated with changes in the initial daily dose.

If clinical evaluation in accordance with serum concentrations are considered (Table VII), although more primary failures appeared when first peak and day 1–2 peak serum concentration values were < 40 mg/l, this was not a significant difference. However, when definitive successes and deaths related to an infection were analysed, the first peak concentration value was a determining factor since there were more deaths when the first peak, day 1–2 peak and maximum peak concentration values were < 40 mg/l, and it was significant for the first peak concentration value (Fisher Exact Test; $P < 0{\cdot}02$). This was also the case for intensive care unit patients, with significantly more deaths related to an infection when the first peak was < 40 mg/l (0 death and 36 definitive successes vs seven deaths and 44 definitive successes; Fisher Exact Test, $P < 0{\cdot}05$) or the maximum peak concentration values (two deaths and 49 definitive successes vs five deaths and 23 definitive successes; $\chi^2 = 4{\cdot}35$, $P < 0{\cdot}05$) were $<$ 40 mg/l.

Toxic side effects

Only one patient, a 68-year-old man, with a previous history of aminoglycoside treatment for recurrent septicaemia, developed permanent vestibular toxicity.

Among the 27 medical unit patients who had normal renal function at the start of treatment, three had an increase of $> 15\%$ in serum creatinine above base line values

Table VII. Clinical evaluation and amikacin serum concentrations (mg/l)

Serum concentrations	Primary success	Primary failure	Definitive success	Death related to an infection
First peak				
⩾40 ($n=47$)	42	5 10·6%)	45	0*
26⩽ to 39 ($n=45$)	38	7 (15·6%)	32	4**
<25 ($n=26$)	22	4 (15·4%)	23	3***
Day 1–2 peak				
⩾40 ($n=47$)	41	6 (12·8%)	41	1 (2·4%)
26⩽ to 39 ($n=52$)	43	9 (17·3%)	40	5 (11·1%)
<25 ($n=19$)	16	3 (15·8%)	18	1 (5·3%)
Maximum peak				
⩾40 ($n=76$)	66	10 (13·2%)	66	2 (2·9%)
26⩽ to 39 ($n=38$)	29	9 (23·7%)	21	4 (11·4%)
<25 ($n=10$)	9	1 (10·0%)	9	1 (10·0%)

*vs **+ ***Fisher Exact Test; $P < 0{\cdot}02$.

during the first few days of treatment, but returned to base line values before the end of the treatment. Among the six medical unit patients who presented with renal failure at the start of treatment, four had a fall of serum creatinine to normal levels during the treatment, one had an increase of $> 15\%$ of serum creatinine which returned to the baseline value before the end of the treatment. Only one patient, an 83-year-old diabetic with cardiac insufficiency, hospitalized for pneumonia had a worsening of pre-treatment renal insufficiency, with a $> 100\%$ increase in serum creatinine, which returned to within normal limits once treatment had stopped.

Among the 69 intensive care unit patients with normal renal function, six had an increase in serum creatinine, five $> 50\%$ and one $> 25\%$. They were severely ill patients with a Simplified Acute Physiological Score of $18{\cdot}8 \pm 5{\cdot}6$ and a mean age of $67{\cdot}3 \pm 17{\cdot}6$ years, five of them being over 70. They all required mechanical ventilation and included three patients with septicaemia and six with pneumonia; all these infections were hospital-acquired. Two patients died from multi-organ failure; one patient died from gastric bleeding and persistent renal failure, after recovering from the initial infectious episode. Three patients showed a $> 50\%$ rise in serum creatinine during treatment, but this returned to normal once treatment had stopped. Among the 22 intensive care unit patients with a renal failure at the start of treatment, creatinine concentrations returned to normal values in 21; worsening of renal function was noted in the remaining patient, which returned to normal at the end of the treatment.

Considering these results the incidence of nephrotoxicity can be evaluated as 1/33 (3%) in medical unit patients and 5/89 (5·6%) in intensive care unit patients, if the two patients with a multi-organ failure are excluded from the analysis.

Discussion

To our knowledge, this is the first study using aminoglycosides in a single daily dose administered to critically ill patients, with pre-existing disease complicated by severe infections. The study supports the concept that a single daily dose of amikacin can constitute effective and safe treatment.

A randomized comparative study of the efficacy of once daily and conventional regimens of amikacin was not performed because the most published comparative studies have failed to show any superiority for aminoglycosides delivered in a single daily dose compared to the conventional regimens, although the number of subjects studied has been small (Cohen *et al.*, 1985; Tulkens *et al.*, 1988; Hollender *et al.*, 1989; Kovarik, Hoepelman & Verhoef, 1989; Sturm, 1989; de Vries *et al.*, 1990; Ter Braak *et al.*, 1990). We calculated that 650 patients would be required to demonstrate a 10% difference in efficacy between the once-daily and a conventional regimen, with limits of cure set at 75 and 85%, (two-tailed test, $\alpha = 5\%$, $1-\beta = 90\%$), and concluded that such a trial was not practical.

Within the limitations of an open study a primary and a definitive primary success rate of 80% in critically ill patients can be considered satisfactory. The outcomes for hospital-acquired infections, such as pneumonia and bacteraemia are in accordance with those encountered in patients treated with conventional multi-dose regimens of aminoglycosides (Maki, 1981; Martin *et al.*, 1983; Bartlett *et al.*, 1986; Bryan *et al.*, 1986; Craven *et al.*, 1986; Ruiz-Santana *et al.*, 1987; Celis *et al.*, 1988; Beuscart *et al.*, 1989; Bricaire *et al.*, 1989; Hollender *et al.*, 1989; de Vries *et al.*, 1990; Nordström *et al.*, 1990).

Pseudomonas, Acinetobacter and *Staphylococcus* spp. were responsible for most of the true failures and colonizations. In practice, such bacteria are frequently responsible for hospital-acquired infections, and are also commonly responsible for superinfection or colonization in intensive care unit patients (Nyström, Frederici & Von Euler, 1988). Almost all these emerging bacteria were multiresistant even to amikacin.

The mean duration of treatment with amikacin of 11 ± 4 days might appear prolonged, however this reflects the critical status of the intensive care unit patients. On the basis of amikacin serum concentrations we had to increase the initial daily dose in nearly half the patients. Many factors contribute to the difficulties in empirical dosing of aminoglycosides in critically ill patients: haemodynamic instability with cardiac failure and septic shock; fever; increases in the volume of distribution; use of drugs which modify cardiac output; reduced aminoglycoside clearance and excessive caution in patients with known or suspected renal failure. Haemodynamic disturbances, age and body weight, may explain the observed wide interpatient variability of peak and trough concentrations. A low initial daily dose appeared to be a bad prognostic factor with more primary failures including death in patients with first or a maximum peak concentration values < 40 mg/l ($P < 0{\cdot}02$). These data are in agreement with a previous study (Moore *et al.*, 1987).

In a previous study (Chidiac *et al.*, 1987) in patients receiving amikacin in a once-daily dose, auditory evoked brainstem potentials were unchanged before, during or after treatment. In the same way, the study of Nordström *et al.* (1990), after rigorous testing of the patients with serial electronystagmographs and audiograms concluded that there was no greater incidence of ototoxicity in patients who received the aminoglycoside once a day. In a recent published study of 141 elderly patients, auditory toxicity was documented in three patients and was no different in patients receiving once daily dosing or conventional regimen of netilmicin (Ter Braak *et al.*, 1990). Although we were unable to study ototoxicity in the present study, these previous studies suggest that once-daily dosing is safe.

Renal toxicity according to the criteria used by Nordström *et al.* (1990), was very mild in this study, estimated respectively at 3 and 5·6% in medical unit and intensive care unit patients. These data are consistent with the paper in this symposium by Tulkens *et al.* (1991).

Finally, a once-daily dosing regimen is more economical in time and the use of disposables such as syringes, intravenous bags and lines. In our study, this was estimated to be a 10 min reduction in nurse labour time and $3 for disposables, per day of treatment per patient. A lower risk of iv catheter-related hospital-acquired infection may also be an advantage of using a once-daily regimen. If the incidence of nephrotoxicity which is known to carry considerable additional costs is reduced by using once-daily dosing regimens, it could result in substantial savings in aminoglycoside treatment (Ter Braak *et al.*, 1990).

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