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ARTICLE

Impact of combination therapy with aminoglycosides on the outcome of ICU-acquired bacteraemias

P.-Y. Delannoy · N. Boussekey · P. Devos · S. Alfandari · C. Turbelin · A. Chiche · A. Meybeck · H. Georges · O. Leroy

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Abstract Pharmacodynamic studies report on the rapid bactericidal activity of aminoglycosides, conferring them as being of theoretical interest for bacteraemia treatment. We assessed this issue in a retrospective study of patients with intensive care unit (ICU)-acquired bacteraemias. To determine the impact of aminoglycosides in antimicrobial combination on the outcome of patients with bacteraemia, we performed a monovariate analysis and a logistic regression analysis comparing patients treated with or without aminoglycosides. Forty-eight bacteraemias in 48 patients were included. Eighteen patients received aminoglycosides. Baseline characteristics as well as adaptation and adequation of antibiotherapy did not differ in patients who did or did not receive aminoglycosides. Patients who received aminoglycosides had longer time alive away from the ICU (11.3 ± 8.9 (10 [0–20]) vs. 3.2 ± 6.6 (0 [0–2] days; p=0.002) and free from mechanical ventilation (12.5 ± 9.3 (14 [0–21] vs. 5.5 ± 9.2 (0 [0–10] days; p=0.02) on day 28. The ICU mortality was 16% in the aminoglycoside group versus 46% (p=0.03). In the multivariate analysis, patients treated with aminoglycosides were 6 times less likely to die than those treated without aminoglycosides (confidence interval [CI]=[1.3–28.9]; p=0.02). Our study supports the hypothesis that combination short-term antibiotherapy with an aminoglycoside for ICU-acquired bacteraemias could increase survival.

P.-Y. Delannoy · N. Boussekey (✉) · S. Alfandari · C. Turbelin · A. Chiche · A. Meybeck · H. Georges · O. Leroy
Intensive Care and Infectious Disease Unit,
Tourcoing Hospital, University of Lille,
135, rue du Président Coty, BP 619,
Tourcoing Cedex 59208, France
e-mail: nboussekey@ch-tourcoing.fr

P. Devos
Department of Biostatistics, University Hospital,
Lille, France

Introduction

Combination antimicrobial therapy with beta-lactams plus aminoglycosides (AGs) was widely used in the 1970s and 1980s. The advent of broader spectrum beta-lactams and reports on AG toxicity were the basis of the current controversy on combination therapy. Meta-analysis failed to demonstrate improved outcomes in patients treated with antibiotic combinations over those receiving monotherapy [1–4] and resulted in a decreased use of combination therapy. However, it remains frequently used in intensive care units (ICUs) due to the theoretical advantages of rapid bacterial killing and extending the spectrum of activity in the era of multidrug-resistant microorganisms.

Bacteraemia is a severe infection associated with increased morbidity and mortality [5–7]. Hospital-acquired bacteraemias are more often due to drug-resistant organisms. A delay in the administration of active antibiotics has been linked to an increased risk of death. AGs exhibit concentration-dependant activity, allowing for maximum efficacy with once-daily, short-duration therapy, which offers the added benefit of decreased toxicity. Moreover, the pharmacologic properties of AGs could be beneficial in the specific subgroup of critically ill patients presenting with ICU-acquired bacteraemia. We performed a retrospective study to evaluate the impact of AGs in antimicrobial combination on ICU-acquired bacteraemia in our university-affiliated ICU [8–11].

Materials and methods

Inclusion criteria and study goal

Eligible patients were those who developed ICU-acquired bacteraemia from January 2006 to July 2009 during their stay in the ICU of Tourcoing Hospital, France. Patients were recruited though the ICU ongoing database and the microbiology laboratory records. Neither approval of the ethics committee nor informed consent was required, considering our study was retrospective.

The aim of the study was to evaluate the impact of AGs in antibiotic combination on the outcome of patients with ICU-acquired bacteraemia.

Data collection and definitions

For each bacteraemia, the following covariates were collected: age, gender, comorbidities (cardiac disease, diabetes mellitus, chronic obstructive pulmonary disease [COPD], chronic hepatic failure, chronic renal failure, haematologic malignancies, non-haematologic malignancies). Patients were considered as being on immunosuppressive treatment if they had received corticosteroids (10 mg/d for at least two weeks), cytotoxic therapies or radiotherapy in the last three months. Organ transplant patients, human immunodeficiency virus (HIV)-positive patients and patients with splenectomy or neutropaenia (granulocyte count <500/ mm^3) were considered to be immunocompromised.

We collected all antibiotics administered during the month before bacteraemia. ICU-acquired bacteraemia was defined as any bacteraemia occurring in our unit more than 48 h after admission. Coagulase-negative staphylococci were considered if two successive blood cultures were positive with the same antibiogram. The source of infection was classified as follows: lower respiratory tract, intra-abdominal, genitourinary tract, catheter-related infection, endocarditis, meningitis, cutaneous infection, primary bacteraemia or other. Secondary bacteraemia was defined as an episode developing after a documented infection with the same microorganism at another body site [5].

The severity of illness was evaluated with the Simplified Acute Physiology Score (SAPS II) [12] and the Sepsis-related Organ Failure Assessment (SOFA) score [13]. We considered organ dysfunction if the score was greater 3. Haemodynamic instability was defined as a need for vasopressive drugs to maintain adequate blood pressure and respiratory failure was noted when PaO_2/FiO_2 <200 with ventilatory support was required. Acute renal dysfunction was defined by a serum creatinine >35 mg/l or urine output <500 ml/d, acute hepatic dysfunction by an increase in bilirubin level >60 mg/l, neurologic failure by Glasgow Coma Scale score <9. Platelet count <50,000/mm^3 was considered as a coagulopathy. We collected biological data including leukocyte and platelet counts, pH, urea, creatinine, PaO_2/FiO_2, prothrombin time, bilirubin and C-reactive protein (CRP).

Variables collected on antibiotherapy were as follows: time from the first positive blood culture to first antibiotic administration and antimicrobial agents used. The administration schedule of AGs was recorded. Following local guidelines, we performed peak serum dosages and trough dosages for patients with initial renal impairment. A trough over 2 μg/ml was considered to be toxic. Antibiotic therapy was considered as adapted if it followed the recommendations and adequate if it included at least one antibiotic active in vitro on the isolated pathogen [14]. We also recorded the use of activated protein C, hydrocortisone, intensive insulin therapy, and need for mechanical ventilation or renal replacement therapy (RRT).

The SOFA score evolution was recorded on days 3 and 7 following bacteraemia. We investigated whether the patient had developed infection-related complications, such as septic shock, acute respiratory distress syndrome (ARDS), renal failure, disseminated intravascular coagulopathy or hepatic dysfunction. To evaluate the renal function, we used the Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) criteria [15]. Patients were considered as having acute kidney injury when the RIFLE class increased to injury or failure after bacteraemia. We also searched for any other hospital-acquired infection and bacteraemia recurrence. The primary endpoint was 28-day survival. Secondary endpoints were number of days without mechanical ventilation, without vasopressive drugs, without RRT and with ICU discharge on day 28 from bacteraemia.

Statistical analysis

To evaluate the impact of AGs on patients' outcomes, we compared patients with or without AGs in their empirical antibiotic regimen for bacteraemia through a monovariate analysis. Comparisons between groups were performed using the Chi-square test or Fisher's exact test for categorical parameters. Continuous variables were analysed using Wilcoxon's test. Differences between groups were considered to be significant for variables yielding a p-value less than 0.05. All significant parameters in the monovariate analysis were evaluated in the multivariate logistic regression analysis. All analyses were performed using SAS software Version 8.2.

Results

Between January 2006 and July 2009, we identified 48 ICU-acquired bacteraemias in 48 patients.

Of the overall population, 70% were male, the mean age was 64 years ± 11, the mean SAPS II on the bacteraemia day was 49 ± 16 and the mean SOFA score was 5.8 ± 2.6. The baseline characteristics did not differ in patients who did or did not receive AGs (Table 1).

The most frequent portal of entry was a catheter-related bacteraemia (52%). The most frequent microorganisms were *Staphylococcus aureus* (33%) and Enterobacteriaceae (27%). No polybacterial bacteraemia was observed. The bacteriological data are presented Table 2. All but three

Table 1 Baseline characteristics of 48 patients with intensive care unit (ICU)-acquired bacteraemias whether they received or not an aminoglycoside as combination therapy

	Aminoglycoside not received		Aminoglycoside received		*p*-value
	n=30		*n*=18		
	n	%	*n*	%	
Female sex	14	46	7	38	0.59
Comorbidities					
Cardiac disease	8	26	4	32	1
Diabetes mellitus	7	23	8	44	0.13
COPD	11	37	11	61	0.1
Chronic liver failure	5	16	0	0	0.14
Chronic alcoholism	10	33	4	22	0.52
Chronic renal failure	2	7	1	6	1
Non-haematologic malignancy	3	10	1	6	1
Haematologic malignancy	3	10	0	0	0.28
Immunosuppression	5	16	0	0	0.14
Organ failure					
Cardiac failure	7	23	3	16	0.72
Renal failure	7	23	1	6	0.23
Respiratory failure	29	96	17	94	1
Coagulation failure	2	7	0	0	0.52
Hepatic failure	3	10	0	0	0.28
Neurologic failure	2	7	2	11	0.62
Severity of illness	Mean ± SD		Mean ± SD		*p*-value
SAPS II	49.5 ± 14.8		48.7 ± 18.6		0.71
SOFA score	6.1 ± 3.2		5.2 ± 1.8		0.57
Clinical and biological presentation					
Age (years)	62 ± 13		68 ± 8		0.12
Temperature (°C)	38.3 ± 1.1		38.6 ± 1.01		0.94
Leukocyte count (/mm^3)	15,489 ± 12,352		17,828 ± 10,439		0.24
Platelet count (1,000/mm^3)	255 ± 173		273 ± 143		0.50
pH	7.40 ± 0.07		7.39 ± 0.07		0.48
Lactate (meq/l)	1.63 ± 1.00		1.25 ± 0.41		0.60
Serum urea (g/l)	0.66 ± 0.38		0.59 ± 0.35		0.52
Creatinine (mg/l)	11 ± 5		12 ± 7		0.54
PaO_2/FiO_2	290 ± 108		266 ± 84		0.75
Bilirubin (mg/l)	66 ± 137		9 ± 8		0.03
Prothrombin time (%)	74 ± 17		84 ± 10		0.20
CRP (mg/l)	121 ± 78		107 ± 90		0.55
Treatment					
Vasopressive drugs	6	20	4	22	0.85
Mechanical ventilation	29	97	17	94	0.71
Renal replacement therapy	6	20	0	0	0.07

Table 2 Bacteriological data of 48 patients with ICU-acquired bacteraemias whether they received or not an aminoglycoside as combination therapy

	Aminoglycoside not received		Aminoglycoside received	
	n = 30		*n* = 18	
	n	%	*n*	%
Infection site				
Respiratory	9	26	5	27
Abdominal	0	0	2	11
Urinary	1	3	0	0
Catheter	19	63	6	33
Surgical site	0	0	2	11
Primary bacteraemia	1	3	3	17
Causative pathogens				
Gram-positive cocci	18	60	7	39
Streptococcus pneumoniae	3	10	0	0
Methicillin-susceptible *Staphylococcus aureus*	3	10	5	27
Methicillin-resistant *Staphylococcus aureus*	8	26	0	0
Coagulase-negative *Staphylococcus*	4	13	2	11
Gram-negative bacilli	12	40	9	50
Enterobacteriaceae	7	23	6	33
Ticarcillin-susceptible *Pseudomonas aeruginosa*	3	10	2	11
Ticarcillin-resistant *Pseudomonas aeruginosa*	2	7	0	0
Other	0	0	1	6
Anaerobes	0	0	2	11

patients received a beta-lactam as the primary therapy. Eighteen patients (37.5%) received combination therapy with an AG (12 with amikacin and six with gentamicin). Patients with AGs received a mean of 2.1 ± 1.2 AG injections. AGs were more frequently administered in Gram-negative than in Gram-positive bacteraemias (43 vs. 23%, $p=0.29$). Two patients developed acute renal failure in the AG group versus three in the non-AG group ($p=1$). In the AG group, 83% of patients received at least two antibiotics active on the isolated pathogen, whereas this was only 17% in the other group ($p<0.001$). The most frequent combination in the AG group was beta-lactam with AGs ($n=14$) for eight Enterobacteriaceae, for five methicillin-susceptible *S. aureus* and for one coagulase-negative *Staphylococcus* bacteraemias. The other combination in the AG group was glycopeptides plus AG for one coagulase-negative *Staphylococcus* bacteraemia. In the non-AG group, combinations were beta-lactam plus quinolone ($n=2$) and beta-lactam plus colistin ($n=2$) for Enterobacteriaceae bacteraemias, and one association of beta-lactam with linezolid for methicillin-susceptible *Staphylococcus*.

No difference was found between the two groups in the management and the occurrence of complications (Table 3). Antibiotherapy delay was not different between the two groups and the adaptation and adequation of antibiotherapy reached 97% in both groups. Patients who received AGs had longer time alive away from the ICU (11.3 ± 8.9 (10 [0–20]) vs. 3.2 ± 6.6 (0 [0–2]); $p=0.002$) and free from mechanical ventilation (12.5 ± 9.3 (14 [0–21]) vs. 5.5± 9.2 (0 [0–10]); $p=0.02$) on day 28. The ICU mortality was 16% in the AG group and 46% in the non-AG group ($p=0.03$). The occurrence of another nosocomial infection, complications of bacteraemia and SOFA score evolution did not differ between the two groups.

The univariate analysis identified five variables associated with a higher mortality:

- Hepatic failure ($p=0.001$)
- Oliguria ($p=0.05$)
- No AG ($p=0.03$)
- No vancomycin ($p=0.05$)
- SOFA score ≥5 ($p=0.01$)

These variables were included in a logistic regression multivariate analysis model. Two independent risk factors for mortality were identified:

- Patients treated with AG were 6 times less likely to die than those treated without AGs (CI=[1.3–28.9]; $p=0.02$)
- A SOFA score on the day of bacteraemia ≥5 was associated with 7.5 times increased ICU mortality (confidence interval [CI]=[1.6–35.1]; $p=0.01$)

Table 3 Prognosis of ICU-acquired bacteraemias in 48 patients whether they received or not an aminoglycoside as combination therapy

	Aminoglycoside not received		Aminoglycoside received		*p*-value
	n = 30		*n* = 18		
	n	%	*n*	%	
Bacteraemia complications	10	33	5	27	0.69
Septic shock	8	27	5	27	0.53
ARDS	1	3	0	0	1.00
Acute renal failure	3	9	2	11	1.00
Secondary nosocomial infection	16	54	8	44	0.55
Prognosis on day 28	Mean ± SD		Mean ± SD		*p*-value
Number of days alive free from mechanical ventilation	5.5 ±9.2 0 [0–10]		12.5 ± 9.3 14 [0–21]		0.02
Number of days alive free from vasopressors	11.3 ± 12.4 3 [0–24]		19.3 ± 10.5 24.5 [15–26]		0.18
Number of days alive free from RRT	5.4 ± 9.4 0 [0–8.5]		28 28		0.17
Number of days alive away from ICU	3.2 ± 6.6 0 [0–2]		11.3 ± 8.9 10 [0–20]		0.002
	n	%	*n*	%	*p*-value
ICU death	14	46	3	16	0.03
Patients discharged from ICU on day 28	8	26	13	72	0.002

Discussion

We found a survival benefit with the use of combination therapy with AGs for ICU-acquired bacteraemias. AGs have unique characteristics among antimicrobial agents. They exhibit extremely rapid bacterial killing, have a demonstrated synergy with beta-lactams on some bacteria and have a prolonged post-antibiotic effect [16]. In the ICU, inadequate empirical antibiotic therapy is associated with an increased mortality risk in patients with ventilator-associated pneumonia and bacteraemia. With the increasing occurrence of drug-resistant microorganisms, both community- and hospital-acquired, ICU physicians often use empirical combination therapy to increase the initial spectrum coverage. In our study, the rates of appropriate antibiotic treatment in the two groups were not statistically significant and do not explain our main result [17–20]. The bacteraemias' portals of entry, similarly, could not explain our results. Catheter-related bacteraemias were usually associated to a low mortality rate and were more frequent in the group without AGs.

The major adverse effects of AGs are dose-dependent nephrotoxicity and ototoxicity. In our study, the rates of adverse events were not increased by AGs. AG nephrotoxicity is influenced by the administration schedule, the duration of treatment and individual variability. The risk of nephrotoxicity is lower for once-daily AG dosing than for traditional twice- or thrice-daily dosing.

Our dosing regimen, drug level monitoring and duration of treatment are strictly adherent to our institution's guidelines. We only use once-daily high dosing, with a maximum of 3 days treatment duration. This might explain the lack of observed adverse events [21, 22].

ICU patients with or without bacteraemia have an increased volume of distribution. The usual dosages of beta-lactams might be less effective. These patients would be the most likely to benefit from the enhanced bactericidal activity offered by a beta-lactam-AG combination therapy. Most studies do not support a benefit for combination therapy. The comparison of AG/beta-lactam combination with beta-lactam monotherapy has been the subject of numerous studies and meta-analysis. Paul et al., in 2004, reviewed 7,586 patients from 64 clinical trials [1]. Combination therapy did not prevent the emergence of antimicrobial resistance and did not affect patient outcomes. Acute kidney injuries were mostly found in the combination group. Paul et al. found the same conclusions in another meta-analysis published in 2008 [23]. Furno et al., in 2002, performed a similar meta-analysis focussing mostly on immunocompromised patients [4]. Among 4,795 septic episodes with 1,029 bacteraemias, their conclusions were similar. Safdar et al. found a significant survival advantage with AGs for bacteraemia caused by *Pseudomonas aeruginosa* in comparative non-randomised studies [3] analysed in a meta-analysis. The meta-analysis by Bliziotis et al. concluded that combination therapy lacks benefit with respect to the selection of drug-resistant organisms, superinfection, treatment failure and mortality [2]. Leibovici et al., reviewing all of the previously mentioned meta-analyses, concluded to a lack of interest of the beta-lactam AG combination [24].

However, it has been objected [8] that most studies included suffered from limitations weakening this interpretation: the studies were heterogeneous and rarely compared the same beta-lactam in both arms. The latter means that it is difficult to relate the difference in efficacy to the AG and not the beta-lactam. Furthermore, the studies mainly used outdated AG administration schedules, such as thrice-daily administration, long treatment duration and lack of serum monitoring. These are related to treatment toxicity, which was counted as treatment failure in many studies. Finally, Bliziotis et al. suggested that once-daily AG therapy combined with a beta-lactam could have a beneficial effect on the development of resistance compared with beta-lactam monotherapy and should be the subject of further research. Recently, a systematic review of randomised trials focussing on the clinical implications of beta-lactam-AG synergy recommended avoiding the routine use of beta-lactam-AG combination therapy. In a subgroup of bacteraemic patients, they did not find any survival advantage for combination therapy [25]. Our study focussed on the most severe patients, i.e. ICU patients with hospital-acquired bacteraemia who need more rapidly active treatment than less severe patients.

Our study has several limitations that should be taken into account. First, this study is retrospective and low-powered. Second, our groups were statistically homogeneous, except for greater hepatic failure in patients without AG. This failure, a major prognostic factor associated with a high mortality, could have biassed our study. Third, we considered a very specific clinical scenario: ICU-acquired bacteraemias. Fourth, except for methicillin-resistant *S. aureus*, we observed only rarely drug-resistant organisms. However, considering the susceptibility pattern of drug-resistant bacteria now observed in our ICU, this would probably enhance our results. Mostly, treatment with AG permitted to reach an 83% rate of effective bi-therapy instead of only 17% without AG.

Conclusion

The debate about aminoglycoside (AG) interest is not closed. Our study suggests that short-term combination beta-lactams plus AGs therapy in intensive care unit (ICU)-acquired bacteraemia could reduce mortality. This should be confirmed in future prospective randomised trials.

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