Intensive Care Med (2008) 34:755–762
DOI 10.1007/s00134-007-0935-1

EXPERIMENTAL

Stephan Ehrmann
Emmanuelle Mercier
Laurent Vecellio
David Ternant
Gilles Paintaud
Pierre-François Dequin

Pharmacokinetics of high-dose nebulized amikacin in mechanically ventilated healthy subjects

Received: 7 June 2007
Accepted: 21 October 2007
Published online: 29 November 2007

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-007-0935-1) contains supplementary material, which is available to authorized users.

S. Ehrmann (✉) · E. Mercier · P.-F. Dequin
Centre hospitalier universitaire de Tours,
Service de réanimation médicale polyvalente,
37044 Tours cedex 9, France
e-mail: stephanehrmann@gmail.com
Tel.: +33-6-71103302
Fax: +33-2-47396536

L. Vecellio
Université François Rabelais, Faculté de médecine, INSERM U-618, IFR 135,
37032 Tours cedex, France

D. Ternant · G. Paintaud
Centre hospitalier universitaire de Tours,
Laboratoire de Pharmacologie-Toxicologie,
Université François Rabelais Tours,
EA 3853, IFR 135,
37044 Tours cedex 9, France

Abstract *Objective:* Nebulized amikacin may be an attractive option for the treatment of lung infections. Low systemic absorption may permit the use of high doses, leading to high lung concentrations without systemic toxicity. We evaluated the pharmacokinetics and safety of an optimized high-dose amikacin nebulization technique. *Design:* in vitro and in vivo pharmacokinetic study. *Patients and participants:* Six healthy volunteers (age 21–30 years, weight 49–68 kg). *Interventions:* The Aeroneb Pro nebulizer with an Idehaler vertical spacer was evaluated in a bench study. Amikacin was administered intravenously (15 mg/kg) and nebulized (40, 50, and 60 mg/kg) during noninvasive pressure-support ventilation through a mouthpiece. *Measurements and results:* Median (interquartile range) in vitro inhaled fraction was 31% (30–32) and inhalable output was 681 mg/h (630–743). Serum concentrations after nebulization were less than or equal to those after infusion. The area under the serum concentration curve was significantly higher after infusion (138 mg $h^{-1}l^{-1}$, 122–143) than after nebulization (49 mg $h^{-1}l^{-1}$, 39–55, at 40 mg/kg; 63, 53–67 at 50; 66, 50–71, at 60). Peak serum concentration was also higher after infusion: 48 mg/l (45–49) after infusion compared to 8.2 (5.6–8.7), 9.2 (7.6–10.2), and 9.2 (5.2–10.3), respectively. Mean absorption times after nebulization were 2 h 24 min (2,07–2,45), 2 h 21 min (2,07–2,35), and 2 h 5 min (2,00–2,25), respectively. No side effect was observed. *Conclusions:* Nebulization of up to 60 mg/kg amikacin appears to be safe in healthy subjects and associated with lower serum concentrations than a 15 mg/kg infusion.

Keywords Administration, aerosol · Respiration, artificial · Drug evaluation

Introduction

Ventilator-associated pneumonia (VAP) is a frequent complication of mechanical ventilation (MV) which leads to significant morbidity and mortality [1, 2]. Aminoglycosides are often used intravenously to treat VAP in addition to a β-lactam antibiotic [3, 4]. Nevertheless systemic therapy is limited by the pulmonary diffusion of the antibiotic and the increasing level of bacterial resistances [5, 6]. Increasing the antibiotic dose is a method used to overcome these limits, but this is associated with systemic toxicity, particularly with aminoglycosides. Administration of antibiotics as an aerosol directly delivered to the respiratory tract is an appealing alternative. This route of administration of aminoglycosides has proven effective in patients with cystic fibrosis, colonized with *Pseudomonas aeruginosa* [7–9]. In ventilator-dependent tracheotomized patients nebulized amikacin proved effective in treating tracheobronchial infection [10]. The effectiveness of nebulized amikacin in treating pneumonia, a lung parenchyma infection, has still to be investigated. The low bioavailability of nebulized amikacin may allow

the administration of high doses with little systemic toxicity. In animal studies nebulization of 40–50 mg/kg amikacin allowed 3- to 30-fold higher lung parenchyma concentrations than conventional 15 mg/kg intravenous infusion [11–14]. To our knowledge, such high doses of nebulized amikacin have never been reported in humans. Optimization of the nebulization technique is a key issue in aerosol therapy during MV because up to 90% of the nebulizer load can be lost in the ventilator circuit, thus reducing the inhalable mass (amount of drug delivered to the lungs) [15–17]. Optimization of the nebulization technique in addition to the use of high amikacin doses may constitute an effective complement to standard therapy for VAP, but pharmacological and safety data in humans are lacking.

The aim of this study was to determine the pharmacokinetics and safety of high-dose nebulized amikacin in healthy subjects during noninvasive MV using an optimized nebulization technique. The nebulized doses were chosen to achieve serum levels close to those obtained after intravenous administration. The nebulization technique was validated in a preliminary bench study. Some of the results of this study have been previously reported as an abstract [18].

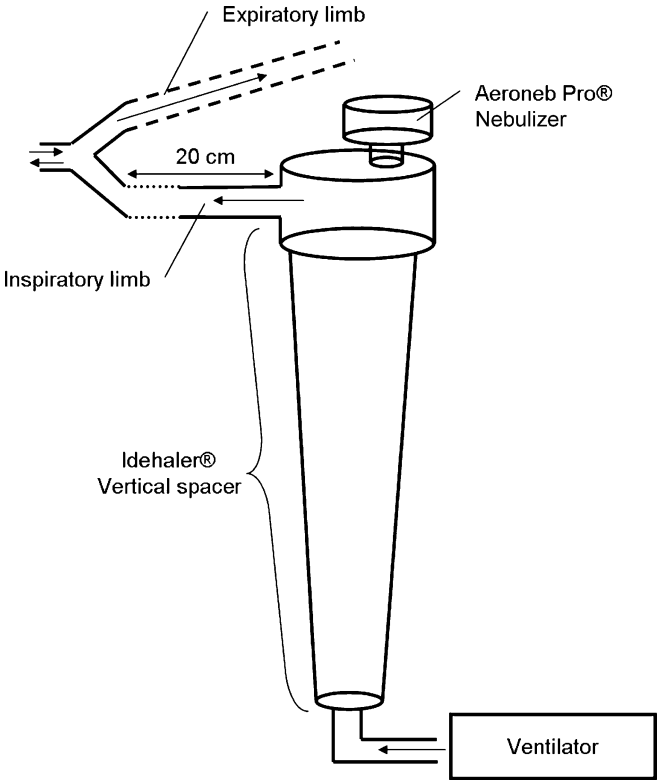

Fig. 1 Diagram of the nebulization setup

Methods

In vitro study

The vibrating mesh nebulizer Aeroneb Pro (Nektar Therapeutics, San Carlos, Calif., USA) was placed on the inspiratory limb just before the Y piece when used alone (manufacture's recommendations) and 20 cm before when used with the Idehaler spacer (La Diffusion Technique Française, St-Etienne, France), in vertical or horizontal position (Fig. 1). The ultrasonic nebulizer Atomisor Megahertz was placed 40 cm before the Y piece and tested without spacer [14]. Ventilatory pattern was standardized (Servo300 ventilator, Maquet, Rastatt, Germany: volume-controlled mode, square wave-flow pattern, 450 ml tidal volume, 16 breath/min, inspiratory/expiratory ratio 0.5, end expiratory pressure 5 cmH_2O, fraction of inspired oxygen 21%). Nebulization was performed continuously. Nebulization yield was determined using the filter method with sodium fluoride as a chemical tracer, as previously described [19]. Briefly, 1 g sulfite-free amikacin (Laboratoire Merck Générique, Lyon, France) was dissolved in a 0.9% NaF solution (8 ml with the Aeroneb Pro and 12 ml with the Atomisor Megahertz nebulizer). An absolute filter (Gelman, Ann Arbor, Mich., USA) was placed between the extremity of the 8 mm endotracheal tube (connected to the Y piece) and the lung model. Filters were changed every 6 min and desorbed for 12 h in 100 ml 25% aqueous TISAB (Reagecon, Shannon, Ireland). The NaF extracted was then assayed by electrochemical analysis (Combination Fluoride Electrode, Orion, Beverly Hills, Calif., USA). Amikacin mass was calculated using the measured NaF mass. Three measurements were made for each setup. The mass median aerodynamic diameter (MMAD) was measured for each setup through laser diffraction (Mastersizer X, Malvern Instruments, Malvern, UK).

In vivo study

Our institutional review board (Comité consultatif pour la protection de personnes se prêtant à la recherche biomédicale, Tours, France) approved the study protocol. Six healthy subjects (three men) aged 21–30 years and weighting 49–68 kg, without a history of respiratory, renal, or otological disease and with no contraindication to amikacin were included after written informed consent. The protocol consisted of four amikacin dosage sequences separated by a 7-day washout period. Sequence A consisted of a 1-h intravenous infusion of 15 mg/kg amikacin. The three following sequences consisted of nebulization of 40, 50, and 60 mg/kg amikacin (sequences B, C, and D, respectively; Fig. 2). Ten blood samples were collected by forearm venipuncture to measure amikacin serum concentrations over the 24-h period following each drug administration (Fig. 2). After centrifugation at 3,000 g

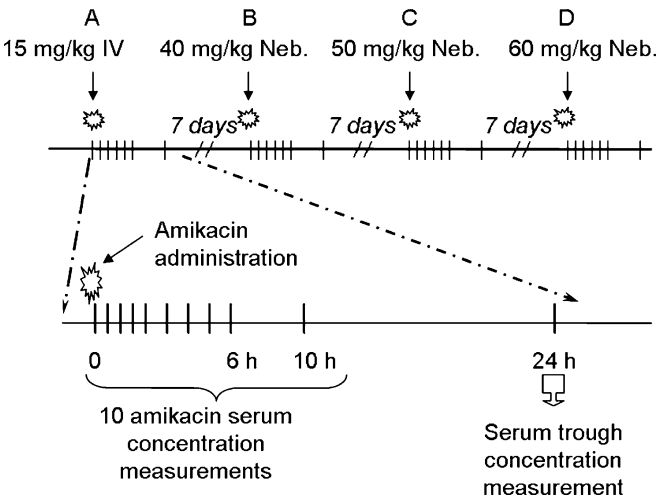

Fig. 2 Diagram of the study protocol. The study lasted 3 weeks, and each of the four sequences lasted 24 h. During each sequence pharmacokinetic measurements were performed as indicated for the first sequence. *IV*, Intravenous infusion; *Neb*, nebulization

for 10 min the supernatant was stored at –20 °C until completion of the study and analyzed using an enzyme multiplied immunomethod calibrated every 20 measurements (EMIT Amikacin assay, Cobas Mira+, Dade Behring, Paris, France). Amikacin was diluted in saline (1 g/8 ml); the nebulizer was refilled when sputtering until the total dose was nebulized. Throughout nebulization noninvasive MV was performed with a Servo300 ventilator in pressure-support ventilation (PSV) using a mouthpiece (Medi-test, Saclay, France). Subjects lay in a 45° semirecumbent position, PSV was adapted to achieve a respiratory rate of 12–20 per minute, positive end-expiratory pressure set at zero and fraction of inspired oxygen at 21%. The Aeroneb Pro nebulizer with the Idehaler vertical spacer was used (Fig. 1). Hemodynamic and respiratory monitoring was performed throughout amikacin administration and pulmonary functional testing was performed before and after sequence B. Creatinin clearance was calculated before each sequence and at 4 weeks' follow-up. Subjects underwent otological examination with otoacoustic emission test at enrollment and at 4 weeks' follow-up. Pharmacokinetics were analyzed using WinNonLin Professional 4.1 (Pharsight, Mountain View, Calif., USA).

Sequence A

After intravenous administration serum amikacin concentrations were analyzed using a compartmental and a noncompartmental approach [20]. A linear two-compartment model gave the best description of amikacin serum concentrations. Terminal elimination constant (λ_z) and half-life ($t_{1/2z}$) were derived from the compartment parameters. The area under the curve of serum amikacin concentrations vs. time after infusion (AUC_sinf) was estimated by the trapezoidal method, extrapolated AUC_s being estimated by C_{last}/λ_z, where C_{last} is the last concentration above the quantification limit. The area under the first moment of the amikacin concentration curve after infusion ($AUMC_s$inf) was calculated as $\sum\left\{\left(\left[t_iC_i + t_{i-1}C_{i-1}\right)/2\right] \times \left[t_i - t_{i-1}\right]\right\} + (t_{last}C_{last}/\lambda_z) + \left(C_{last}/\lambda_z^2\right)$ where C_i and t_i are measured concentrations and corresponding times, and t_{last} is the time of C_{last} [20]. Mean residence time after infusion (MRT_{inf}), was calculated by: $MRT_{inf} = AUMC_s\text{inf}/AUC_s\text{inf}$. The MRT of amikacin after bolus injection (MRT_{bolus}) was obtained by: $MRT_{bolus} = MRT_{inf} -$ (infusion duration/2) [20].

Sequences B, C, and D

Because of the slow absorption of amikacine during nebulization, leading to complex concentration vs. time curves, a compartmental pharmacokinetic analysis could not be used to describe nebulization sequences. Therefore amikacin serum concentrations measured during sequences B, C, and D were analyzed using a noncompartmental approach. AUC_sneb and MRT_{neb} were calculated with the same equations as for the infusion. During nebulization absorption was slow, hiding the elimination phase and thus yielding falsely low values of λ_z. As elimination kinetics are believed to be the same after infusion and nebulization, the values of λ_z obtained from sequence A were used for calculations. Mean absorption time (MAT: average time needed for an inhaled molecule of amikacin to reach the systemic circulation) was calculated for each subject by: $MAT = MRT_{neb} - MRT_{bolus} -$ (nebulization duration/2).

Fraction of amikacin absorbed (F,%: fraction of dose placed in the nebulizer that reaches the systemic circulation) was calculated by: $F = (AUC_s\text{neb}/D_{neb})/(AUC_s\text{inf}/D_{inf})$, with D_{neb} = amikacin nebulizer load and D_{inf} = amikacin dose administered by intravenous infusion.

Noncompartmental analysis of amikacin absorption was completed by estimating the pulmonary absorption rate as a function of time through the Iga deconvolution method using the macro constants derived from the two-compartment intravenous model [21]. The instantaneous pulmonary absorption [a(t)] was weighed by the administered doses $\left[a(t) = \text{absorption} \times D_{inf}/D_{neb}\right]$ and expressed as a cumulative fraction of the nebulizer load.

Values were reported as median (interquartile range). Variables were compared using the paired (in vivo study) or unpaired (in vitro study) Wilcoxon rang test (Statview, SAS Institute, Cary, N.C., USA). Probability of randomness below 5% was considered statistically significant.

Results

In vitro study

Placing the Idehaler vertical spacer underneath the Aeroneb Pro nebulizer significantly increased the inhalable mass (31%, 30–32, vs. 8% 8–9 of the nebulizer load) and inhalable output (681 mg/h, 630–742, vs. 235, 217–251; Table 1). Nebulization rate was stable throughout nebulization as no difference was noted in the amount of amikacin deposited on the various filters over time. MMAD was 4 μm (3.9–4.1) with the Atomisor Megahertz and 5 μm (4.9–5.1) with the AeronebPro nebulizer. The Idehaler vertical spacer did not influence the MMAD.

In vivo study

All patients completed the four sequences of the study; no side effect occurred. The pulmonary functional tests remained in the normal range. No renal, otological, or respiratory impairment was detected. Serum concentrations after nebulization were less than or equal to those after intravenous infusion throughout the 24 h after administration (Fig. 3). For each individual subject the serum amikacin concentration after nebulization remained lower or equal (± 5 mg/l) to the concentrations after intravenous infusion at each time point. All 24-h concentrations were below the quantification limit of the assay (2.5 mg/l). Peak serum concentrations and AUC_s values after intravenous infusion were significantly higher than after nebulization (Table 2). The pulmonary absorption rate was similar with the three nebulization doses, with MAT values above 2 h (n.s.; Table 2). No differences in the fraction of the nebulized dose absorbed were observed between the nebulization sequences: 13% (11–14), 12% (11–17) and 10% (8–15) with sequences B, C, and D, respectively (n.s.; Fig. 4, Table 2). Therefore the pulmonary absorption was not saturated in the healthy subjects, which allowed assuming linear absorption kinetics. This biodisponibility

Table 1 Results of the bench study for a 1 g amikacin nebulizer load; values are medians (interquartile range)

Nebulization technique	Inhalable mass (mg)	Inhalable output (mg/h)
Atomisor Megahertz	192* (183–200)	230 (220–240)
Aeroneb Pro	82 (79–87)	235 (218–251)
Aeroneb Pro + Idehaler spacer placed horizontally	213 (195–225)	425 (390–450)
Aeroneb Pro + Idehaler vertical spacer	312 (299–318)**	681 (630–743)**

* $p < 0.05$ vs. Aeroneb Pro, ** $p < 0.05$ vs. the three other nebulization setups

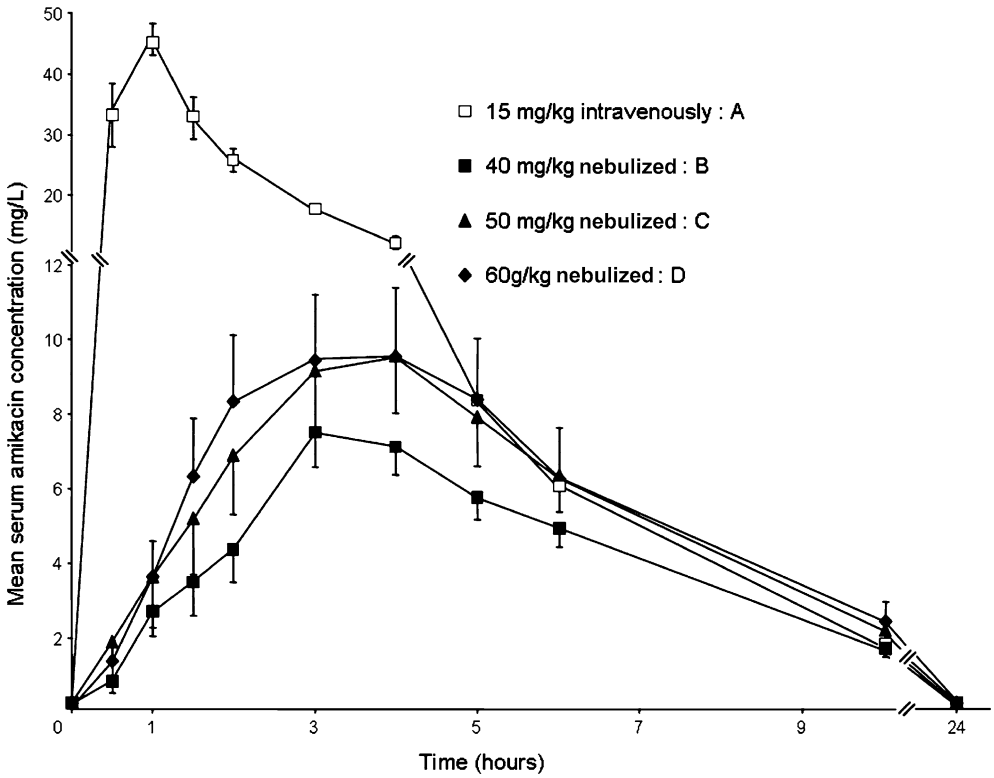

Fig. 3 Mean amikacin serum concentrations during the 24 h period following the beginning of administration. *Bars*, Standard error of the mean

Table 2 Comparison between nebulization and intravenous infusion sequences; values are medians (interquartile range) (*Peak*, peak amikacin serum concentration; AUC_s, area under the serum amikacin concentration vs. time curve; *MAT*, mean absorption time; *MRT*, mean residence time; *F*, fraction absorbed expressed as proportion of the nebulizer load; *IV*, 1-h intravenous infusion; *Neb*, nebulization using the vertical spacer)

	A (15 mg/kg IV)	B (40 mg/kg Neb)	C (50 mg/kg Neb)	D (60 mg/kg Neb)
Dose (mg)	877 (791–964)	2340 (2110–2570)	2925 (2637–3212)	3510 (3165–3855)
Peak (mg/l)	48 (45–49)*	8.2 (5.6–8.7)	9.2 (7.6–10.2)	9.2 (5.2–10.3)
AUC_s (mg h^{-1} l^{-1})	138 (122–143)*	49 (39–55)	63 (53–67)	66 (50–71)
MAT (h, min)	NA	2, 24 (2, 07–2, 45)	2, 21 (2, 07–2, 35)	2, 05 (2, 00–2, 25)
MRT (h, min)	2, 39 (2, 37–2, 58)	5, 41 (5, 40–5, 51)	5, 35 (5, 19–6, 11)	5, 32 (5, 16–5, 55)
F (%)	100	13 (11–14)	12 (11–17)	10 (8–15)

* $p < 0.05$ vs. sequences B, C, and D

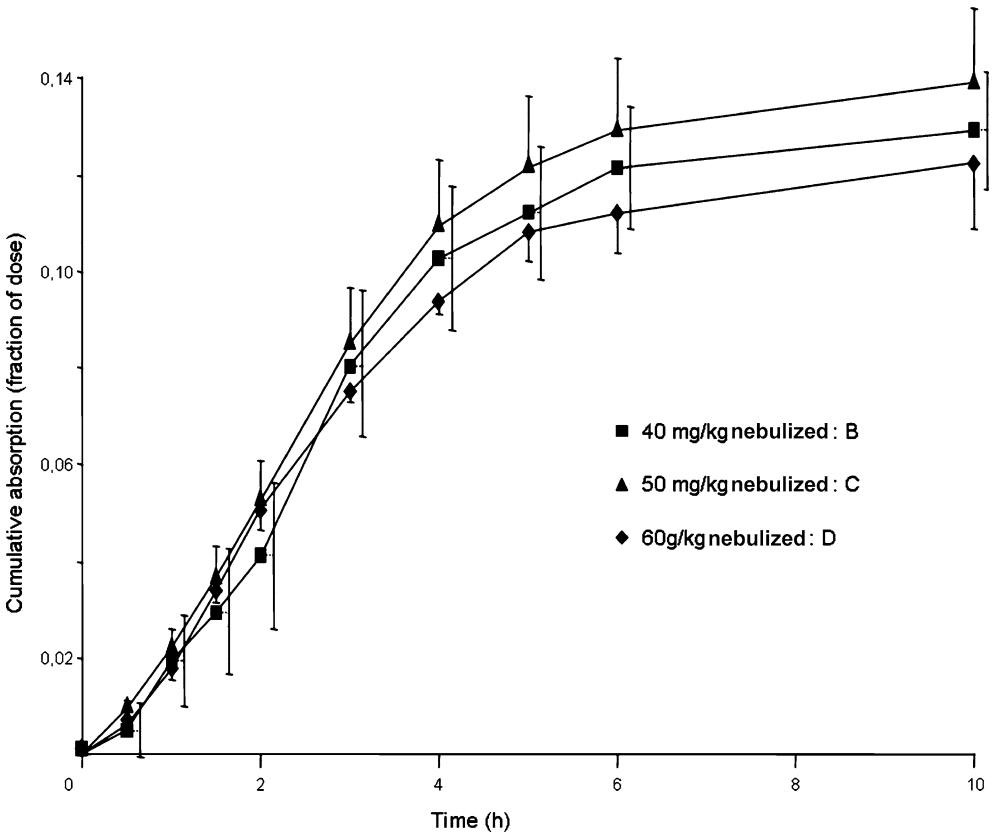

Fig. 4 Mean cumulative systemic absorption of amikacin as a function of time. Absorption is expressed as a fraction of the nebulizer load. The curves reached a plateau (corresponding to the fraction absorbed on the y axis) after about 6 h, which indicates that most of the systemically available amikacin had reached the serum. *Bars*, Standard error of the mean

corresponded to 41% (35–45), 39% (35–55), and 32% (26–48) of the inhalable mass considering the 31% yield of the nebulization technique (bench study). Nebulization durations were: 53 min (52–55), 1 h 09 min (1, 02–1, 16), and 1 h 15 min (1, 13–1, 17) with sequence B, C, and D, respectively.

Discussion

In this study the administration of up to 60 mg/kg amikacin by a nebulization technique yielding a 31% inhalable mass was associated with serum concentrations equal to or less than those obtained after intravenous infusion of 15 mg/kg amikacin, no side effects being noted in the six subjects studied. Otological and renal toxicity of aminoglycosides occurs through a saturable mechanism and is therefore not related to peak serum concentration. The AUC_s is a better indicator of potential otological or renal toxicity [22, 23]. In our study after nebulization the AUC_s remained significantly lower than after intravenous administration. Therefore nebulization of up to 60 mg/kg amikacin seems to carry a risk of renal or otological toxicity inferior to that of 15 mg/kg intravenous amikacin. Indeed, the fraction of amikacin absorbed after nebulization of 60 mg/kg was 10% of the nebulizer load;

therefore the systemic circulation was exposed to a total mass of amikacin comparable to the intravenous infusion of 6 mg/kg. This limited biodisponibility may allow the use of high doses in order to increase pulmonary drug levels, but as discussed below this may not fully apply in patients with infected lungs.

The bench study revealed a higher inhalable mass when the Aeroneb Pro nebulizer was used with the Idehaler spacer. These results confirm studies reporting an increase in inhalable mass with the use of horizontal spacers [15, 24, 25]. This increase in nebulization efficiency may be related to aerosol homogenization within the spacer. Our results suggest that the use of a vertically placed spacer further increases inhalable mass; higher aerosol droplet deposition during expiration in the horizontal spacer or inspiratory limb compared to a lower deposition in the vertical spacer may explain these results.

Our in vivo results are compatible with those reported by Goldstein et al. [14] in healthy ventilated piglets. The authors reported a peak serum concentration of 12 mg/l after nebulization of approx. 50 mg/kg amikacin and a ratio between AUC_s after nebulization and after intravenous infusion of 58% [14]. Our measurements showed a peak serum concentration of 9.2 (7.6–10.2) mg/l and a ratio between AUC_s after nebulization and after intravenous infusion of 46% with sequence C (50 mg/kg; Table 2). The lower serum concentrations in our study might be explained by higher oropharyngeal impaction of the aerosol in our study than endotracheal tube impaction, differences in ventilatory pattern, and interspecies differences in mucocilliary clearance and alveolocapillary diffusion. Caution is needed when comparing those study results because Goldstein et al. [14] reported a nebulization yield of 38% (measured by the mass balance technique), slightly higher than the yield of our nebulization setup (31%). We tested the Atomisor Megahertz nebulizer in the same conditions as reported by Goldstein et al. (40 cm before the Y piece on the inspiratory limb) to be able to compare our results with the animal data [11–14]; using the filter impaction method, the nebulization yield measured was much lower (19%); Table 1.

The systemic absorption after antibiotic nebulization is believed to occur mainly at the alveolar level as it exhibits the thinnest interface between aerial and vascular compartments. Therefore systemic pharmacokinetics reflect deposition of the nebulized drug in the distal pulmonary parenchyma [26, 27]. Goldstein et al. reported very high lung parenchyma amikacin concentrations [14]. As we found similar amikacin serum pharmacokinetics, we hypothesize that lung parenchyma concentrations, albeit not measured in our healthy subjects, were high.

MAT is the average time spend by molecules in the lung before diffusion to the serum. With all sequences MAT was above 2 h (Table 2), and therefore it may be hypothesized that amikacin molecules remained for a sufficiently long time in the pulmonary parenchyma to allow potential antibacterial activity. Furthermore, in addition to the systemically absorbed amikacin, the molecules eliminated by mucocilliary clearance contribute to the antibacterial activity. Aminoglycosides exhibit a concentration-dependent bactericidal activity with a marked postantibiotic effect. Achieving high tissue concentrations once daily seems a pharmacokinetic strategy adapted to amikacin pharmacodynamics and has proven effective after intravenous administration [28]. In contrast, clinical studies performed with nebulized aminoglycosides in cystic fibrosis or ventilator-dependent patients evaluated multiple daily administrations of relatively low doses [7, 10]; Palmer et al. [10] reported effective treatment of tracheobronchial infection with 400 mg amikacin nebulized every 8 h in ventilated tracheotomized patients. Whether once daily administration of high-dose nebulized amikacin is as effective or superior for treating lung infections warrants further clinical studies. Nevertheless in an animal model of pneumonia the reduction in lung bacterial burden was greater after 45 mg/kg nebulized amikacin once daily for 2 days than after standard intravenous treatment (15 mg/kg once daily) [13].

The results of our study should be applied only very cautiously, and after confirmatory clinical studies, to patients with VAP. Amikacin absorption may indeed be higher in patients with VAP than in our study, leading to potential risks of toxicity, for various reasons. First, pneumonia induces ruptures of the alveolocapillary barrier resulting in an increased diffusion from the lung to the serum. Using the above animal model of *Escherichia coli* pneumonia, Goldstein et al. [13, 14] observed higher serum peak concentrations than in their healthy lung animal model. Second, patients with VAP are ventilated through an endotracheal tube, which was not the case with the subjects in our study; oropharyngeal deposition of amikacin is very likely to have reduced the mass of amikacin delivered to the lungs. On the other hand, poor lung aeration may induce low alveolar concentrations and lower systemic absorption of amikacin in patients with VAP [11]. Thus, as demonstrated in animal models [29], the pharmacokinetics of nebulized amikacin may be less favorable in patients with infected lungs than in our study (lower antibiotic deposition in the poorly aerated infected lung segments with concomitant higher systemic absorption and toxicity). Studies in patients with infected lungs are therefore mandatory to draw conclusions regarding optimal dose and to assess short and long-term tolerance in patients. The subjects of our study were ventilated in PSV to maximize comfort, making it impossible to control inspiration/expiration ratio, tidal volume, or inspiratory flow which have been shown to influence aerosol delivery during MV [15, 16]. Respiratory rate (14 bpm, 12–15) and tidal volume (11 ml/kg, 9–12) measured were within the range usually recommended for optimal nebulization during MV [29], but lung protective ventilation of patients with VAP which may present acute respiratory distress

syndrome requires lower tidal volumes. Our results may therefore not strictly apply to this specific patient population.

The nebulization setup that we investigated produced a high inhalable amikacin output, which allowed nebulizing high doses of amikacin in a short period of time (median nebulization duration of 1 h 15 min for 60 mg/kg placed in the nebulizer). This is of interest as nebulization during MV requires modifications of the ventilatory parameters and discontinuation of the inhaled gas humidification; thus the duration of nebulization should be kept as short as possible [15, 17]. In contrast, the Atomisor Megahertz nebulizer, albeit exhibiting a significantly higher inhalable mass than the Aeroneb Pro nebulizer, showed a similar inhalable output (Table 1). Inspiratory phase synchronized nebulization, which is an effective method to increase the inhalable mass, presents the same shortcoming because it does not increase the inhalable output and therefore results in significantly increased nebulization duration [30].

This study carried out in subjects with healthy lungs showed that, using an optimized nebulization technique with a vertical spacer (Idehaler) placed underneath the Aeroneb Pro nebulizer, doses of 60 mg/kg amikacin are probably associated with high lung parenchyma concentrations of amikacin during a sufficiently long period of time for bactericidal activity. No side effect was observed in the limited number of healthy subjects studied. This dose could be used as a basis for clinical studies investigating the potential benefits of once daily administration of high-dose nebulized amikacin in the treatment of VAP.

Acknowledgements. The authors whish to sincerely thank Mrs. Christine Mabilat for her help with data collection, Mr. Daniel Grimbert for the pulmonary functional tests, Dr. Emmanuel Lescanne for otological tests, and Ms. Andrea Pritzker for editorial assistance.

References

1. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C (1999) The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 159:1249–1256
2. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, Kollef MH (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 122:2115–2121
3. Anonymous (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416
4. Rello J, Paiva JA, Baraibar J, Barcenilla F, Bodi M, Castander D, Correa H, Diaz E, Garnacho J, Llorio M, Rios M, Rodriguez A, Sole-Violan J (2001) International Conference for the Development of Consensus on the Diagnosis and Treatment of Ventilator-associated Pneumonia. Chest 120:955–970
5. Panidis D, Markantonis SL, Boutzouka E, Karatzas S, Baltopoulos G (2005) Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. Chest 128:545–552
6. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S (2003) Comparison of 8 vs. 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290:2588–2598
7. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev KM, Borowitz D, Bowman CM, Marshall BC, Marshall S, Smith AL (1999) Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 340:23–30
8. Moss RB (2002) Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest 121:55–63
9. Mukhopadhyay S, Singh M, Cater JI, Ogston S, Franklin M, Olver RE (1996) Nebulised antipseudomonal antibiotic therapy in cystic fibrosis: a meta-analysis of benefits and risks. Thorax 51:364–368
10. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A (1998) Aerosolized antibiotics in mechanically ventilated patients: delivery and response. Crit Care Med 26:31–39
11. Elman M, Goldstein I, Marquette CH, Wallet F, Lenaour G, Rouby JJ (2002) Influence of lung aeration on pulmonary concentrations of nebulized and intravenous amikacin in ventilated piglets with severe bronchopneumonia. Anesthesiology 97:199–206
12. Ferrari F, Goldstein I, Nieszkowszka A, Elman M, Marquette CH, Rouby JJ (2003) Lack of lung tissue and systemic accumulation after consecutive daily aerosols of amikacin in ventilated piglets with healthy lungs. Anesthesiology 98:1016–1019
13. Goldstein I, Wallet F, Nicolas-Robin A, Ferrari F, Marquette CH, Rouby JJ (2002) Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets. Am J Respir Crit Care Med 166:1375–1381
14. Goldstein I, Wallet F, Robert J, Becquemin MH, Marquette CH, Rouby JJ (2002) Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs. Am J Respir Crit Care Med 165:171–175
15. O'Doherty MJ, Thomas SH, Page CJ, Treacher DF, Nunan TO (1992) Delivery of a nebulized aerosol to a lung model during mechanical ventilation. Effect of ventilator settings and nebulizer type, position, and volume of fill. Am Rev Respir Dis 146:383–388

16. Vecellio L, Guerin C, Grimbert D, De Monte M, Diot P (2005) In vitro study and semiempirical model for aerosol delivery control during mechanical ventilation. Intensive Care Med 31:871–876
17. Miller DD, Amin MM, Palmer LB, Shah AR, Smaldone GC (2003) Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. Am J Respir Crit Care Med 168:1205–1209
18. E Mercier, S Ehrmann, L Vecellio, D Ternant, PF Dequin (2006) High dose of nebulized amikacin during non invasive positive pressure ventilation (NPPV) in healthy volunteers (HV): pharmacokinetic and tolerance. American Thoracic Society International Conference 2006, San Diego. Am J Respir Crit Care Med 173:A150
19. Dennis JH, Stenton SC, Beach JR, Avery AJ, Walters EH, Hendrick DJ (1990) Jet and ultrasonic nebuliser output: use of a new method for direct measurement of aerosol output. Thorax 45:728–732
20. Gibaldi M, D Perrier (1982) Noncompartmental analysis based on statistical moment theory. In: Pharmacokinetics. Dekker, Basel, pp 409–417
21. Lanao JM, Vicente MT, Sayalero ML, Dominguez-Gil A (1992) A computer program (DCN) for numerical convolution and deconvolution of pharmacokinetic functions. J Pharmacobiodyn 15:203–214
22. Beaubien AR, Desjardins S, Ormsby E, Bayne A, Carrier K, Cauchy MJ, Henri R, Hodgen M, Salley J, St Pierre A (1989) Incidence of amikacin ototoxicity: a sigmoid function of total drug exposure independent of plasma levels. Am J Otolaryngol 10:234–243
23. Begg EJ, Barclay ML, Duffull SB (1995) A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharmacol 39:605–609
24. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SH, Nunan TO, Treacher DF (1995) Effect of a spacer on pulmonary aerosol deposition from a jet nebuliser during mechanical ventilation. Thorax 50:50–53
25. Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO (1993) Delivery of ultrasonic nebulized aerosols to a lung model during mechanical ventilation. Am Rev Respir Dis 148:872–877
26. Diot P, Dequin PF, Rivoire B, Gagnadoux F, Faurisson F, Diot E, Boissinot E, Le Pape A, Palmer L, Lemarie E (2001) Aerosols and anti-infectious agents. J Aerosol Med 14:55–64
27. Dequin PF, Faurisson F, Lemarie E, Delatour F, Marchand S, Valat C, Boissinot E, de Gialluly C, Diot P (2001) Urinary excretion reflects lung deposition of aminoglycoside aerosols in cystic fibrosis. Eur Respir J 18:316–322
28. Barclay ML, Kirkpatrick CM, Begg EJ (1999) Once daily aminoglycoside therapy. Is it less toxic than multiple daily doses and how should it be monitored? Clin Pharmacokinet 36:89–98
29. Rouby J, Goldstein I, Luin Q (2006) Inhaled antibiotic therapy. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill, Columbus, pp 1311–1321
30. Dubus JC, Vecellio L, De Monte M, Fink JB, Grimbert D, Montharu J, Valat C, Behan N, Diot P (2005) Aerosol deposition in neonatal ventilation. Pediatr Res 58:10–14