Nebulized Antibiotics

Epithelial Lining Fluid Concentrations Overestimate Lung Tissue Concentrations

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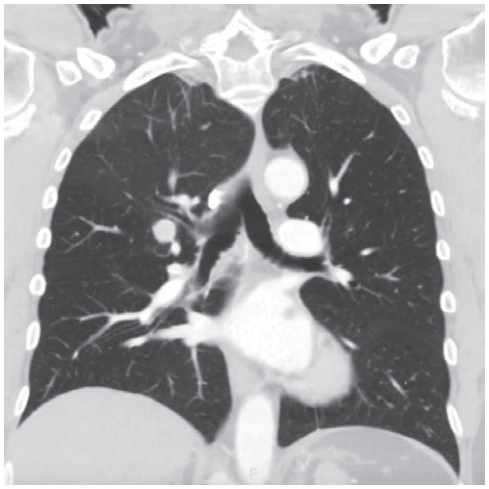
In this issue of Anesthesiology, Dhanani *et al.*[1] provide evidence that the tobramycin lung interstitial space fluid concentrations measured after a single 400-mg aerosol dose are twice those measured after the equivalent intravenous dose. Tobramycin interstitial space fluid concentrations were measured using samples obtained by microdialysis catheters surgically inserted in anesthetized and mechanically ventilated ewes with normal lungs. The study confirms the results of a number of previous experiments that demonstrated high antibiotic lung tissue concentrations after nebulization compared with the intravenous route.[2] In these studies, the antibiotic lung tissue concentrations were measured using high-performance liquid chromatography performed on postmortem tissue samples after they were cryomixed in nitrogen, weighed, and homogenized in buffer solution.[3] Despite of some limitations—a small number of animals, the lack of optimization of the nebulization procedure, the inclusion of animals with normal lungs—the study is of great interest because it assesses concomitantly tobramycin lung concentrations by two independent methods: microdialysis for measuring lung interstitial space fluid concentrations and bronchoalveolar lavage for measuring epithelial lining fluid concentrations.[4] The former is the reference method, but it cannot be used routinely in clinical practice because of its invasiveness. The latter, despite numerous methodologic issues, is widely used in clinical practice to assess pharmacokinetic profiles after antibiotic nebulization.[5–7] As expected, epithelial lining fluid and lung interstitial space fluid concentrations were much higher after tobramycin nebulization than after intravenous administration. However, the 100-fold overestimation of lung interstitial space fluid concentrations by epithelial lining fluid concentrations was not anticipated and appears to be a result of primary importance with a direct clinical relevance.



"…measuring [lung] epithelial lining fluid antibiotic concentrations in patients receiving inhaled antibiotics is not an appropriate method for assessing lung tissue concentrations."

The observation of Dhanani *et al.* that epithelial lining fluid concentrations overestimate lung interstitial space fluid concentrations leads to the understanding that the high epithelial lining fluid concentrations observed in the experimental and clinical literature are an artifact rather than a benefit of aerosolized antibiotic administration. In animals and critically ill patients receiving a single aerosol dose of polymyxin or aminoglycoside,[5,8,9] the epithelial lining fluid antibiotic concentrations measured 1 h after nebulization were found to be extremely high: between 700 and 4,000 μg/ml in sheep receiving 4 to 8 mg/kg of nebulized colistin methanesulfonate,[9] between 1,000 and 3,000 μg/ml in critically ill patients with ventilator-associated pneumonia receiving 2 to 3 mg/kg of nebulized colistin methanesulfonate,[7] and between 135 and 16,127 μg/ml in critically ill patients with ventilator-associated pneumonia receiving 3 mg/kg of nebulized amikacin.[5] Ignoring the absolute values that were largely above 1,000 μg/ml and hardly compatible with increased antibiotic parenchymal deposition, all authors considered the very high epithelial lining fluid concentrations as a direct benefit of the inhalation route. Dhanani *et al.* showed that the epithelial lining fluid concentrations were 100-fold higher than the interstitial space fluid concentrations[1]: 1 h after a 400-mg aerosol dose, epithelial lining fluid tobramycin concentrations ranged from 650 to 1,781 μg/ml (interquartile range), values very close to those reported in

Image: J. P. Rathmell.

This editorial accompanies the article on p. 344.

Accepted for publication May 1, 2019. From the Sorbonne University of Paris, Multidisciplinary Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, La Pitié-Salpêtrière hospital, Assistance Publique Hôpitaux de Paris, Paris, France.

 Anesthesiology 2019; 131:229–32. DOI: 10.1097/ALN.0000000000002824

<zdoi;. DOI: 10.1097/ALN.0000000000002824>

rats after the administration of an equivalent aerosol, 250 to 2,500 μg/ml.[8] That epithelial lining fluid concentrations overestimate lung interstitial space fluid concentrations should not diminish the observation that the measured peak interstitial space fluid concentrations after aerosol administration were more than twice those observed after intravenous administration of the same dose.

To understand why antibiotic epithelial lining fluid concentrations overestimate lung tissue concentrations, a few basic elements should be considered. The bronchoalveolar lavage procedure implies positioning the distal tip of the fiberscope as far as possible in the bronchial tree, to get distal samples representative of epithelial lining fluid. Three to five aliquots of 20 to 60 ml saline are administered by the biopsy channel of the fiberscope, the aspirates from the first two aliquots are discarded, and the later aliquots are used for epithelial lining fluid analysis. As illustrated in figure 1A, the aspirate in which epithelial lining fluid concentrations are measured, lavages a large segmental area.[10] During the fiberoptic bronchoscopy, the fiberscope is contaminated by tracheal and proximal airway secretions during its passage through the tracheobronchial tree. In

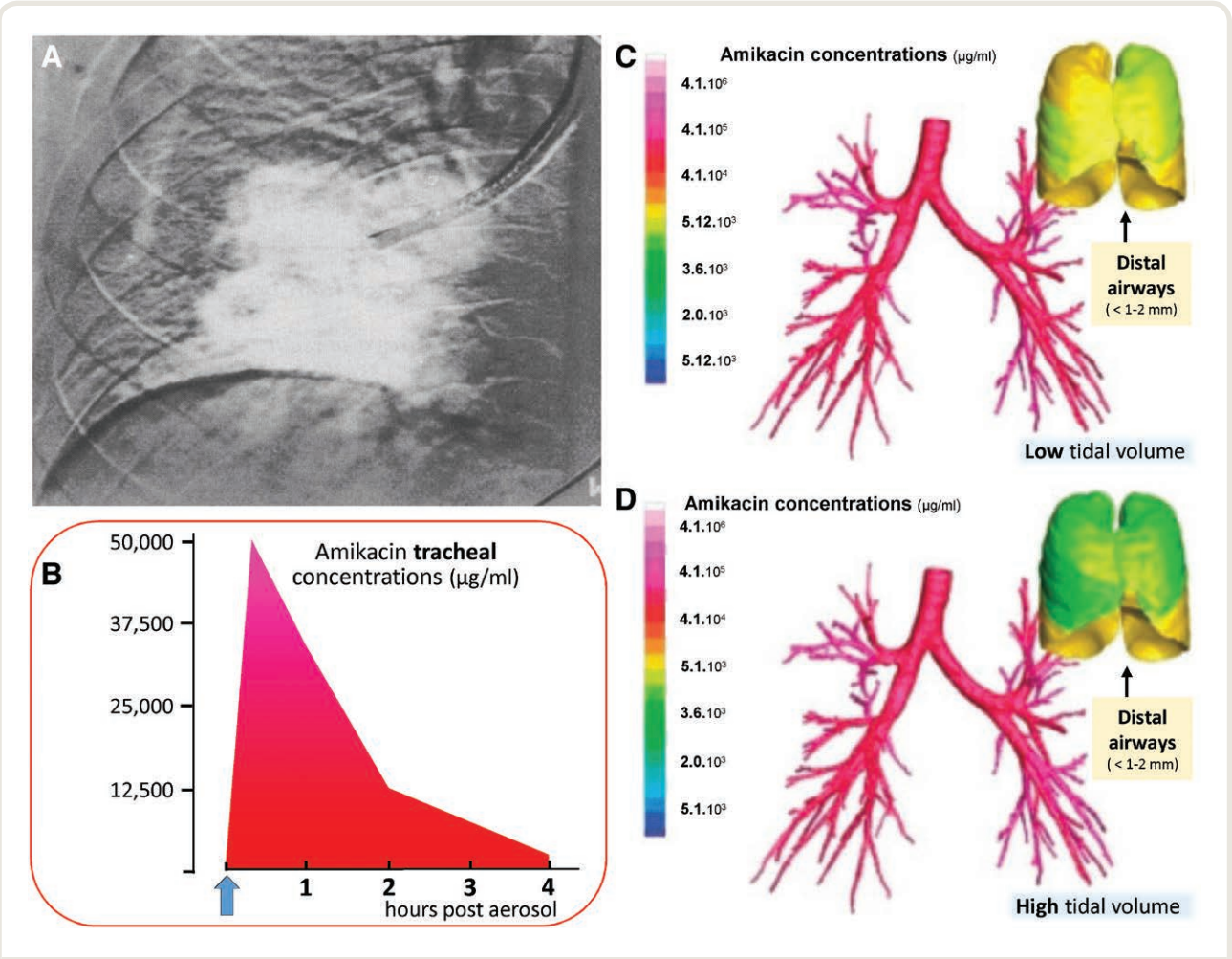


Fig. 1. Anatomical and time-dependent distribution of antibiotic tracheobronchial concentrations after inhaled amikacin. (*A*) Distribution of bronchoalveolar lavage fluid as assessed by digital subtraction radiography. The aspirate from the third 60-ml aliquot is issued from the entire volume of the medial segment of the middle lobe. Reproduced from Kelly *et al.*[10] with the permission of the publisher. (*B*) Amikacin tracheal concentrations over time after a single aerosol administration of amikacin 300 mg in five pigs. Measurements were performed at predose, 10 min, 2 h, and 4 h after administration of the dose. Reproduced and adapted from Li Bassi *et al.*[11] with the permission of the publisher. (*C* and *D*) Influence of tidal volume on the distribution of tobramycin concentrations between proximal and distal airways immediately after the nebulization of 600 mg in patients with cystic fibrosis. Aerosol concentrations in the central and more distal airways were computed using airway models reconstructed from computed tomography scans of patients with cystic fibrosis, in combination with computational fluid dynamic simulations. Proximal airways defined as bronchi with an internal diameter greater than 1 mm are represented as the tracheal bronchial tree, whereas distal airways are represented as lung parenchyma. Nebulization was simulated using a PARI-LC^R Plus nebulizer (Midlothian, USA; aerosolized particle mass median aerodynamic diameter = 3.4 μ) using either a low (*C*) or large tidal volume (*D*). Reproduced and adapted from Bos *et al.*[12] with the permission of the publisher.

addition, aspirates of bronchoalveolar lavage not only reflect epithelial lining fluid but are also contaminated by distal airways secretions. The first two aliquots are discarded in the hope of getting rid of the distal airway contamination. However, contamination cannot be completely avoided, explaining why quantitative thresholds are required for bacteriologic diagnosis of ventilator associated pneumonia. During the nebulization procedure, the tracheobronchial tree is coated with aerosolized particles and, as shown in figure 1B, the high tobramycin tracheobronchial concentrations peak within the first hour and then progressively decrease as a result of systemic resorption.[11] In addition, for a given tobramycin dose, the proximal and distal bronchial concentrations depend on ventilator settings. As shown in figure 1, C and D, large tidal volumes increase the proximal and decrease the distal bronchial concentrations.[12] It is therefore recommended that the ventilator settings be modified during the nebulization phase to limit the inspiratory flow turbulences, reduce the bronchial deposition, and increase the distal lung penetration of the aerosolized antibiotic.[13] Volume-controlled ventilation with constant inspiratory flow should be selected with an inspiratory to expiratory ratio of 50%, a respiratory frequency of 12 to 15 bpm, a tidal volume of 6 to 8 ml/kg, and an inspiratory pause of 20%. In addition, specific ventilator circuits avoiding sharp angles should be used.[13] In the study by Dhanani *et al.*, the lack of optimization of ventilator settings likely contributed to the high tobramycin tracheobronchial concentrations by promoting inspiratory turbulences.[1]

The hypothesis that the epithelial lining fluid samples are falsely elevated as a result of a heavy bronchial contamination is supported by a study performed in patients with ventilator-associated pneumonia treated by two daily aerosol doses of amikacin 400 mg.[5] On the third day of treatment, the epithelial lining fluid and tracheal amikacin concentrations were concomitantly measured and found to be elevated in similar proportions. As shown in figure 2, A and B, the tracheal amikacin concentrations measured in the 6 h after the aerosol dose administration were very close to the epithelial lining fluid concentrations, ranging between 135 and 16,128 μg/ml for the former and between 136 and 16,128 μg/ml for the latter. The tracheal concentrations measured in the 6 h preceding the second aerosol dose significantly decreased, ranging between 100 and 1,826 μg/ml, likely as a result of the amikacin systemic diffusion through the bronchial mucosa. Immediately after completion of the nebulization, the fiberscope and the bronchoalveolar lavage lavage fluid were heavily contaminated by very high tracheobronchial antibiotic concentrations (fig. 2C), whereas 12 h later the contamination was significantly reduced (fig. 2D). By analogy, the interpretation of quantitative bacteriology of distal lung samples obtained from a bronchoalveolar lavage performed in patients receiving inhaled antibiotics should be interpreted with caution.

There are now enough data to consider that measuring epithelial lining fluid antibiotic concentrations in patients receiving inhaled antibiotics is not an appropriate method for assessing lung tissue concentrations. The tracheobronchial contamination of the fiberscope during the bronchoalveolar lavage procedure and the fact that the aspirates of aliquots reflect predominantly distal airways antibiotic concentrations explain the overestimation of true epithelial lining fluid concentrations. Unfortunately, microdialysis catheters cannot be inserted routinely in patients, except in the context of thoracic surgery. As a consequence, pharmacokinetic–pharmacodynamic studies concerning antibiotic nebulization should be restricted to animal studies until new tools, like microneedles and aptamer-based probes,[14] become available in clinical practice.

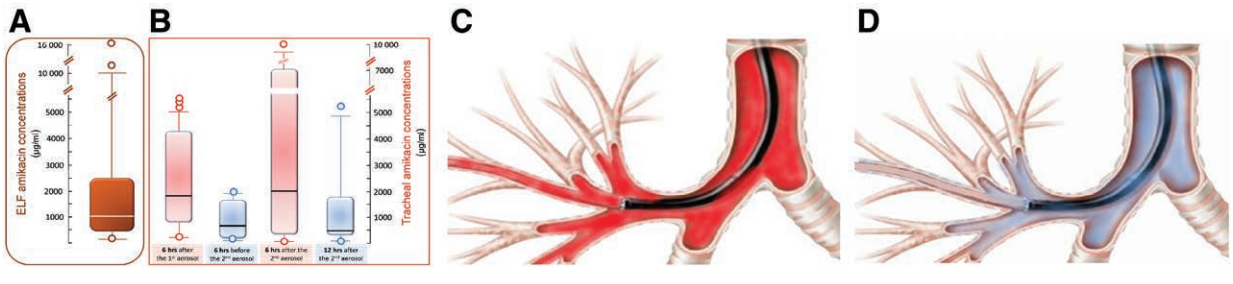


Fig. 2. Amikacin concentrations in the tracheal aspirates and epithelial lining fluid (ELF) of patients with ventilator-associated pneumonia treated by two daily aerosol doses of 400 mg. (*A*) ELF amikacin concentrations measured on day 3 of treatment in 28 patients. (*B*) Amikacin tracheal concentrations measured in 19 patients, in the 6 h after the first and second aerosol dose of day 3 (*light red boxplots*) and in the 6 h preceding the second aerosol dose of day 3 and the first aerosol dose of day 4 (*light blue boxplots*). Reproduced and adapted from Luyt *et al.*[5] with the permission of the publisher. (*C*) The image illustrates the position of the fiberscope within the tracheobronchial tree immediately after amikacin nebulization. The high local antibiotic concentration is indicated in red according to the color scale of figure 1, C and D. (*D*) The image illustrates the position of the fiberscope within the tracheobronchial tree 12 h after amikacin nebulization. The lower local antibiotic concentration is indicated in blue according to the color scale of figure 1, C and D.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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