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REVIEW

Pharmacokinetics of antibiotics in the lungs

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ABSTRACT: This paper reviews current knowledge on the relationship between local penetration or antibiotics and therapeutic efficacy in pulmonary and bronchial infections. The antimicrobial drug concentration at the site of infection is supposedly determinative for the efficacy of the antibiotic treatment but the number of studies in respiratory infections supporting this hypothesis is limited. The mechanisms responsible for the pulmonary deposition or orally or systemically administered antibiotics include passive diffusion, active transport, bulk flow and permeation. The penetration of antimicrobial drugs into the respiratory tract is influenced by both host-related factors, such as inflammation or mechanical injury, and drug-related factors, such as molecular weight. In addition, local bio-inactivation can occur. The final bioactive antibiotic concentration at the site of the respiratory infection is, therefore, the result or a very complex dynamic process. Different sampling and measuring methods have been used for the assessment of antibiotic concentrations at the site of respiratory infections. Concentrations in sputum, bronchial secretions and biopsy specimens have been correlated with serum concentrations and clinical outcome. Bronchoalveolar lavage could be a promising technique for evaluating antibiotic drug concentrations in alveolar lining fluid. For many antibiotics, data concerning penetration and pharmacokinetic behaviour in the respiratory tract are lacking.

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The aim of this paper is to review the current knowledge about the assessment and clinical relevance of the local concentration of antimicrobial drugs at the site of infection in the treatment of bronchopulmonary infections. The clinical importance of the concentration of antibacterial agents at the foci of infection, the pharmacokinetic behaviour of antibiotics in the respiratory tract, the specimen collections and methods of measurement of antibiotic concentration and the degree of penetration of several antibiotics will be discussed.

Infections of the lower respiratory tract are common problems in clinical practice and are a major medical problem throughout the world. Lower respiratory tract infections remain an important cause of morbidity, mortality and economic loss all over the world. The ultimate clinical outcome of a bacterial bronchopulmonary infection is a function of two main variables: the efficacy of the natural defence mechanisms and the institution of an appropriate antimicrobial therapy.

Both pharmacodynamic and pharmacokinetic factors determine the efficacy of antimicrobial therapy. The pharmacodynamic determinants of an effective antimicrobial therapy include:

1. Intrinsic antimicrobial activity of the drug against the infecting respiratory pathogen.
2. Bactericidal activity of the drug.
3. Stability of drug activity in the presence of common bacterial resistance mechanisms.
4. Absence of major organ toxicity.

Pharmacokinetic studies of antimicrobial therapy relate the administration of the drug to the concentration-time profile within body fluids and include its absorption, distribution, metabolism and excretion properties. Pharmacokinetic properties of antimicrobial drugs determine the dosage, the dosing frequency and the concentration of the antibiotic at the site of infection.

Importance of local antimicrobial drug concentration

The rational goal of an effective antimicrobial drug therapy is to produce, at the site of the infection, a concentration-time profile such that free drug concentrations equal or exceed the minimal inhibitory concentrations (MIC) for the infecting pathogen, as determined *in vitro*. The measurement of the antibiotic concentration in body fluids and tissue samples makes it possible to determine whether the drug concentration at the site of infection is high enough when compared with the MIC value and, thus, to predict the therapeutic effect.

Time profile

Data from animal models and human studies have shown that the clinical outcome of Gram-negative bacteraemia in granulocytopenic subjects and nosocomial pneumonia treated with betalactam antibiotics is significantly better when the serum drug levels of these classes of antibiotics remains above the MIC of the infecting pathogen for the whole dosing interval rather than for only a fraction of the dosing interval. This would favour administration of betalactam antibiotics by constant infusion or by frequent intermittent administration [1–3].

Aminoglycosides differ markedly from betalactams in that their killing rate of bacilli is more rapid and that they tend to induce a prolonged post-antibiotic effect [1, 4, 5]. Therefore, it is less important for aminoglycosides to maintain serum concentrations above the MIC during the whole dosing interval. Indeed, the best predictors of a favourable clinical outcome after treatment with aminoglycosides are high peak concentrations achieved in serum and high peak-serum-concentration to MIC-ratio [1, 6, 7]. Hence, aminoglycosides need not be given in a frequent dosing schedule or as a constant infusion to keep serum levels always above the MIC, as is the case with betalactams. Twice daily or even once a day administration of aminoglycosides provides an adequate pharmacokinetic profile, diminishing toxicity and the need for therapeutic monitoring.

Local concentration

The bronchial mucosa and bronchial wall are the sites of acute bacterial infection in patients with an infectious exacerbation of chronic obstructive lung disease (COPD), bronchiectasis and cystic fibrosis. In patients with bacterial pneumonia, the site of infection is in the alveolar spaces with its alveolar lining fluid and in the interstitium of the lung [8]. It seems, therefore, logical to hypothesize that the efficacy of antibiotic treatment of lower respiratory tract infections will greatly depend upon the level of antimicrobial drug at these sites. A positive correlation between clinical outcome of a bacterial lower respiratory tract infection and the local concentration of an antibiotic in relation to its MIC has been shown in only a few studies. STEWART *et al.* [9] showed that a clinical response to treatment with amoxycillin in patients with lower respiratory tract disease occurred more rapidly in patients with sputum levels of ≥ 0.25 $\mu g \cdot ml^{-1}$. MAY and DELVES [10], INGOLD [11] and MAESEN and co-workers [12, 13] also demonstrated that a satisfactory clinical response to treatment of infectious exacerbations of COPD with either ampicillin or bacampicillin correlated with the presence of sputum levels in excess of the MIC of the isolated sputum pathogen.

KLASTERSKY and co-workers [14, 15], in patients with Gram-negative bronchopneumonia, showed that endotracheally administered aminoglycosides resulted in higher levels of this drug in bronchial secretions. These high levels correlated with a statistically significant improvement in clinical outcome and a lower mortality. These studies suggest that the level of antimicrobial drug in sputum and bronchial secretions is of clinical importance; poor clinical response being correlated with levels lower than the MIC of the specific pathogen [12–15]. We are not aware of any prospective studies, correlating the concentration of antimicrobial drugs at the site of infection to the clinical outcome of parenchymal lung infection.

Factors influencing the pharmacokinetics of antibodies in the lung

Following systemic administration, the antimicrobial drug has to penetrate into the site of infection. For endobronchial infections (cystic fibrosis, bronchiectasis, infectious exacerbation of COPD) the circulating antibiotic must cross the blood-bronchus barrier. In parenchymal consolidation the antibiotic has to cross the alveolar-capillary membrane to reach the alveolar lining fluid and interstitium. The mechanisms of drug transport across these biological barriers may vary [16–20]. Most tissues, including the bronchial wall and lung parenchyma, contain capillary beds with pores large enough to admit the passage of substances of a molecular weight of up to 1000. The alveolar-capillary membrane can be regarded as a double layer porous capillary (fig. 1).

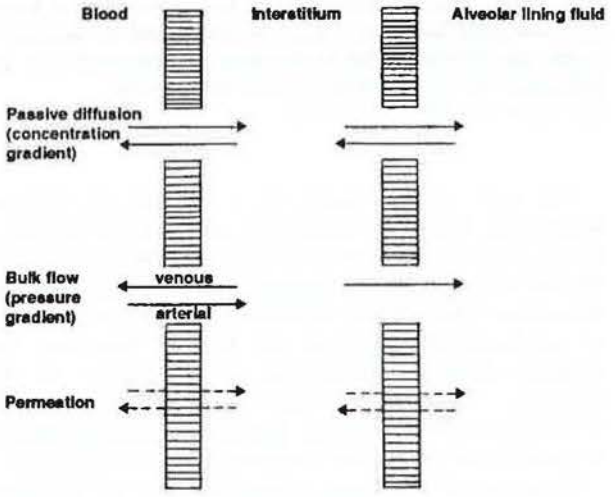

Fig. 1. – Mechanisms of transport through a porous membrane.

Passive diffusion along a concentration gradient seems to be the most important mode of transport from the vascular space into tissue fluids [16, 18, 21]. The rate of concentration changes during the process of passive diffusion is highly dependent upon the surface area. Given the enormous surface of the alveolar-capillary membrane in contrast to the blood-bronchus barrier, one could assume that antibiotic concentrations in interstitium and alveolar lining fluid are closely approximating concentrations in serum. These local concentrations should parallel closely the fluctuating concentration in serum, higher serum levels being accompanied by higher local concentrations [16, 18].

Only for a few antibiotics is there evidence to support the presence of energy consuming, active transport of drugs across the pulmonary vascular membranes analogous to the transport across the blood-brain barrier [16, 22].

Bulk flow is a mechanism whereby the drug is ultrafiltrated along a pressure gradient through capillary pores. This mode of transport contributes significantly to the transport of large, lipid soluble molecules. For relatively small molecules like antibiotics, however, bulk flow plays only a minor role [18].

Permeation, a passive transport through the cells of the capillary membranes, is an important method of drug transport across nonporous membranes, such as the blood-brain barrier, but only to a lesser extent across porous capillary membranes such as the pulmonary capillary bed [18].

Host-related and drug-related factors may influence the penetration of antimicrobial drugs across the blood-bronchus barrier and alveolar capillary membrane. The most important host-related factor is the integrity of the anatomic barriers which may be damaged by inflammation or mechanical injury. Inflammation causes vasodilation and increased capillary permeability, enhancing tissue penetration of antibiotics [16, 22, 23]. For betalactam antibiotics clindamycin, oleandomycin and erythromycin, a clear relationship between the degree of inflammation and the degree of penetration in the airways has been shown, with a decrease of, penetration when the inflammation subsides [9, 10, 12, 21–27, 30] When, during treatment, the inflammation diminishes, the penetration of these antibiotics will decrease and the local drug concentration can drop below the bactericidal concentration, increasing the likelihood of relapse [10, 11].

A relationship between the degree of inflammation and the local antimicrobial drug concentrations has not been shown for tetracyclines [21, 28, 29]. The studies concerning aminoglycosides are controversial. For gentamicin, no relationship has been found [17, 31]. With tobramycin and amikacin a correlation between the local level of drug and the protein content of bronchial secretions was shown. Mechanical injury to the barriers caused by fibreoptic bronchoscopy, excessive coughing *etc.* can cause leakage of blood with an increasing amount of antibiotics penetrating into the site of infection [16].

The penetration of antibiotics into pulmonary tissue and bronchial secretions also depends on different drug-related characteristics [16, 22]. Antibiotics of a larger molecular weight seem to penetrate more easily than smaller antibiotics, probably because the smaller ones are trapped in mucin pores [32]. Some structural features of the antibiotic, such as the presence of multiple benzene rings, seem to favour penetration. Also lipid soluble agents penetrate to a greater extent [16]. A major factor influencing penetration is the serum protein binding of the antimicrobial drug. Serum protein binding determines the level of free drug available to diffuse across membranes [1, 16, 18, 22]. Antibiotics with higher protein binding penetrate to a lesser extent into the interstitial fluids. Dose, route and mode (continuous infusion *versus* intermittent) of administration will all affect the profile of the concentration-time curve [18, 33].

Once the antibiotic has arrived at the site of infection, its antimicrobial activity can be changed by several factors. ALEXANDER *et al.* [34] showed that a given concentration of tobramycin in bronchial secretions produced, *in vitro*, a smaller inhibition of bacterial growth (measured as the diameter of the inhibition zone) than an identical concentration of the antibiotic, dissolved in serum. The rule that only the free, nonprotein-bound portion of the antimicrobial drug is biologically active applies not only in serum but also at the site of pulmonary infection. The exact percentage of drug bound to proteins or other endobronchial or intra-alveolar macromolecules is unknown.

In addition, the antibiotic can undergo bioinactivation by enzymes of bacterial origin (*e.g.* betalactamase) or by enzymes originating from leucocytes. The latter has been studied extensively by THIJS [35], showing increasing inactivation of aminoglycosides with increasing purulence of bronchial secretions. The local pH, the presence of cations with an antagonistic effect such as calcium and magnesium and local oxygen tension (Po_2) and carbon dioxide tension (Pco_2) are other factors influencing the antimicrobial activity of a given local level of antimicrobial drug [36].

Furthermore, the local antibiotic concentration is a dynamic rather than a static phenomenon. Antibiotics may be eliminated from the endobronchial and intraparenchymal area by lymphatic drainage, mucociliary transport mechanism, coughing or reabsorption and back diffusion to the circulation [16, 18, 22]. Accumulation of antibiotics can occur at the site of infection. Accumulation in the airways may be caused by a diminished clearance from the bronchial lumen, as has been shown in COPD patients with a decreased efficiency of the mucociliary transport system [16]. The local concentration can also increase due to pooling in the secretions, *e.g.* when selective absorption or evaporation of water occurs [16]. For some antibiotics such as doxycycline, trimethoprim and enoxacin, a lack of correlation between serum levels and levels in bronchial secretions has been observed. For these antimicrobial drugs increasing concentrations in bronchial secretions during therapy or even a local concentration above the serum concentration were found. These findings suggest accumulation at the site of infection [29, 37, 38].

In conclusion, the final bioactive concentration of an antimicrobial drug at the site of a bronchial or pulmonary infection is the result of a very complex dynamic process which explains the intra- and interindividual variability of the results of published studies.

Specimen collections and methods of measurement of antibiotic concentration

The penetration of antibiotics has been evaluated by the determination of drug concentration in different respiratory fluids and in tissue samples. Sputum samples can be collected during a given period of time after

administration of the antimicrobial drug. Before assay, the sputum samples are liquefied and homogenized. However, the sputum may be diluted by saliva during collection, resulting in false low levels. Conversely, there may be secretion of antimicrobial drug in the saliva, producing false high levels in the collected sputum specimens. Furthermore, the sample obtained is a pooled specimen of bronchial secretions. This pooling effect increases with decreasing efficiency of mucociliary clearance and cough reflex and can cause an apparent lack of correlation between serum and sputum levels [16, 19]. The degree of purulence of sputum can be determined and related to the drug concentration. Comparing the sputum levels with simultaneously obtained serum level allows calculation of the percentage of penetration and production of concentration-time profile [22]. Bronchial secretions can be obtained by transtracheal aspiration in endotracheally intubated and tracheotomized patients or by fibrebronchoscopic aspiration. This procedure avoids contamination by saliva. The bronchial secretions are handled in the same way as sputum specimens. The antibiotic concentration in these secretions are supposed to approximate to the local mucosal levels of antimicrobial drugs, although the pooling effect remains. Reproducible results have been obtained with regard to the determination of antibiotic concentration in bronchial secretions [16, 22, 23]. As with sputum samples concentration-time profiles, ratio of endobronchial level to serum level and correlation with degree of purulence were determined.

Tissue samples of bronchial mucosa and lung parenchyma can be obtained by fibrebronchoscopy, transcutaneous needle biopsy or during thoracotomy [19]. The tissue samples are weighed, homogenized and centrifuged before assay [37–41]. There are, however, two major drawbacks using tissue samples. Firstly, it is difficult to obtain a lung or bronchial mucosa specimen completely free from blood. The blood concentration of the drug is bound to influence the measured tissue concentration. To overcome this problem KROENING *et al.* [41] determined the haemoglobin concentration of the supernatant fluid after centrifugation of the tissue and applied a formula to assess tissue concentration without blood admixture. Secondly, the value of drug concentration in tissue samples for predicting therapeutic efficacy is limited, because the measured concentration averages the contribution of the different compartments of the tissue, such as extracellular and intracellular fluid. Indeed, the distribution of the antimicrobial drug within the tissue cannot be expected to be uniform (*e.g.* it can be limited to the extracellular compartment, dependent upon the lipid solubility of the antibiotic). Also, since it is believed that most infections occur in the interstitial fluid, levels of antibiotic in the extracellular fluid are more relevant than those in whole tissues [18].

Bronchoalveolar lavage is another, relatively recent, technique by which the cells and fluid lining the alveolar walls can be examined [42]. Bronchoalveolar lavage (BAL) can be an important diagnostic tool and has given us insight into the pathogenesis of a lot of (mainly interstitial) pulmonary diseases [42]. Only a few authors have used the technique of bronchoalveolar lavage to determine the concentrations of medications, including antibiotics in the alveolar lining fluid [43, 44]. The great difficulty of such determinations is the unpredictable dilutional factor caused by the instilled saline solution, which makes it difficult to compare the concentration of the antibiotic level in the aspirated lavage fluid and serum.

However, the variability of the dilutional effect can be avoided to a great extent, if the concentration of the antibiotic in serum and BAL fluid is compared to the concentration of a reference substance, with a molecular weight in the same order as the investigated antimicrobial drug. Urea and/or creatinine are mainly used as reference substances [43, 44]. By comparing the ratio of the antibiotic concentration to the reference substance concentration in bronchoalveolar lavage fluid, with the same ratio in serum, we can determine the relative coefficient of penetration (RCP) of the antibiotic into the alveolar lining fluid.

The ratio between the measured concentration of the antimicrobial drug in the bronchoalveolar lavage fluid and the real concentration of the drug in the alveolar lining fluid (ALF) is equal to the same ratio for the reference molecule and in fact represents the dilution factor:

$$\frac{(\text{Antibiotic})_{BAL}}{(\text{Reference substance})_{BAL}} = \frac{(\text{Antibiotic})_{ALF}}{(\text{Reference substance})_{ALF}}$$

Urea and creatinine are small molecular weight substances which diffuse readily through the alveolar-capillary membrane. One can assume that in steady-state conditions serum urea concentration equals the urea concentration in the alveolar lining fluid giving:

$$(\text{Antibiotic})_{ALF} = \frac{(\text{Antibiotic})_{BAL} \times (\text{Urea})_{serum}}{(\text{Urea})_{BAL}}$$

Comparing the concentration of the antibiotic in serum and in the alveolar lining fluid determines the degree of penetration across the blood-air barrier at any given time.

Another problem of the dilutional effect caused by the instilled lavage fluid is the very low concentration of both the investigated molecule and the reference substance in the BAL fluid that is recovered. Therefore, highly sensitive techniques, such as high pressure liquid chromatography (HPLC), radio-immunoassay (RIA), fluorescence immunoassay or concentration procedures, such as lyophylisation, are needed. The microbiological agar disc diffusion assay as described by BENNET *et al.* [45] is less accurate but is frequently used for the measurement of antibiotic concentrations in respiratory fluids and tissue samples. In this assay, the concentration of the antibiotic in the investigated specimen is calculated indirectly by comparing the inhibition zone on the agar disc with the inhibition zone caused by a known concentration of the antibiotic. The zones of inhibition for known concentrations of the antibiotic are used to make a standard curve. This bioassay is, however, less

sensitive than the currently available highly sensitive techniques mentioned above.

Concentration of antimicrobial drugs in respiratory fluids and tissues

The importance of the concentration of a particular antimicrobial drug in respiratory fluids and tissue samples (table 1) has already been stressed. Comparing the local concentration-time profile of antibiotic with its minimal inhibitory concentration (MIC) will allow us to predict therapeutic efficacy. It is clear from the complexity of the pharmacokinetics of antibiotics at the level of the lung, that the rate and extent of penetration will vary for different antibiotics. Moreover, methodological problems and difficulties with standardization will inevitably lead to conflicting results. The penetration of an antimicrobial drug is often expressed as the percentage ratio between the concentration in the investigated specimen and the concentration in a simultaneously obtained serum sample. However, the penetration of some antibiotics into respiratory fluids or tissues lags behind the serum concentration profile where the antibiotic can already be in the elimination phase [22]. It is, therefore, more meaningful to calculate, if possible, the ratio between the peak level in the investigated specimen and the peak level in serum or to calculate the ratio between the area under the concentration-time curve for the specimen to the same area for serum.

Most studies conclude that higher serum levels of antimicrobial drugs are reflected by higher levels in the respiratory fluids and tissues. This suggests passive diffusion as the most important mode of transport [16].

Table 1. – Concentration of antimicrobial drugs in respiratory fluids and tissues

	Ratio sputum/serum %	Ref.
Amikacin	24	[49, 57]
Amoxycillin	3–6	[9, 11, 20, 26, 27]
Ampicillin	3–10	[16, 20–22, 24]
Bacampicillin	13–20	[12, 20, 27]
Carbenicillin	11–20	[47, 60]
Cefaclor	8–10	[39, 59]
Cefotaxime	25	[58]
Cefoxitin	20–25	[20, 23]
Cefuroxime	18	[20, 57]
Doxycycline	20–35	[29, 51]
Enoxacin	100	[54–56]
Erythromycin	5	[30]
Gentamicin	27–40	[15, 31, 47, 48, 60, 63]
Minocycline	28–60	[28, 50, 57]
Netilmicin	14–20	[33]
Ofloxacin	78–103	[62]
Piperacillin	4–15	[22, 40]
Sulphamethoxazole	13–18	[57, 61]
Tobramycin	65–67	[34, 41, 43]
Tricarcillin	2	[22]
Trimethoprim	>100	[38, 53, 57, 61]

Betalactam antibiotics

It has been shown that penicillin G, administered intramuscularly, penetrates into sputum with a good correlation between sputum and serum concentration. Sputum levels ranged between 0.3 and 3.1 $U \cdot ml^{-1}$ [16, 46]. The penetration of ampicillin into sputum and bronchial secretions after oral and parenteral administration is low, being 2–5% of serum concentrations. A great interindividual variation is observed and the relationship between serum concentration and sputum concentration is rather poor. For any given serum concentration the corresponding concentration in sputum or bronchial secretions varies widely [10, 21–24]. The local concentrations of amoxycillin in respiratory secretions are somewhat higher and the correlation between serum and sputum levels is better than for ampicillin, the ratio being 6% [9, 21–23, 26]. The oral dose of amoxycillin needed to obtain comparable concentrations in bronchial secretions as of ampicillin is half the oral dose of ampicillin but this is largely due to a better absorption from the gastrointestinal tract [26]. For bacampicillin there is a clear correlation between serum levels and level in bronchial secretions with a ratio of 13–22% [12, 13, 27]. The concentration of carboxypenicillins (carbenicillin and ticarcillin) in bronchial secretions is rather low with a mean ratio between serum level and level in bronchial secretions of 3.5%. The airway concentrations were inadequate to inhibit most strains of *Pseudomonas* [21, 22, 27].

With regard to the ureido penicillins, a penetration ratio of 4% was found for mezlocillin [22]. The penetration of piperacillin in sputum and bronchial mucosa was variable but showed a significant dose-response relationship. The concentration attained was adequate to eradicate *Haemophilus influenzae* and *Streptococcus pneumoniae*, but was borderline effective for *Pseudomonas aeruginosa* [40].

The concentration of cephalosporins in sputum and bronchial secretions are in the range of 5–10% of the peak serum concentration. Most agents reach a concentration adequate to treat *S. pneumoniae*. The second generation and the third generation cephalosporins reach a local concentration high enough to eradicate *H. influenzae*. The concentrations of cefaclor in bronchial mucosa are effective against *S. pneumoniae*, but some strains of *H. influenzae* will not be inhibited by the concentration attained [39]. The local concentration of third generation cephalosporins is adequate to treat non-pseudomonal Gram-negative bacilli [22]. The concentration of moxalactam at the alveolar lining fluid was studied by bronchoalveolar lavage. Increasing serum concentrations of moxalactam were significantly correlated with increasing concentrations at the alveolar level ranging from <1–6 $\mu g \cdot ml^{-1}$ in the bronchoalveolar lining fluid [44].

Aminoglycosides

The studies concerning the penetration of aminoglycosides in sputum and bronchial secretions showed a ratio of bronchial to serum peak concentrations between 10 and 30%. There was no significant difference between the different aminoglycosides concerning penetration in bronchial secretions. The aminoglycoside level attained is often lower than the MIC for most of the Enterobacteriaceae and for *P. aeruginosa* [17, 21–23, 31, 33–35, 47–49]. The penetration of tobramycin in lung parenchyma has been evaluated by the determination of concentrations in pulmonary tissue and in bronchoalveolar lavage fluid [41, 43]. It seems, from both studies, that the penetration of tobramycin in bronchial secretions differs from its penetration in lung interstitium and alveolar lining fluid. Indeed, both studies showed a ratio of 50% between lung and blood concentrations. The ratio between the concentration in bronchial secretions and blood averaged only 20%.

Tetracyclines

There is a good correlation between the sputum and serum concentrations of tetracyclines after oral administration, the ratio being 10–30%. The concentrations attained exceed the MIC of all *S. pneumoniae* strains and most *H. influenzae* strains [28, 29, 50, 51]. The sputum concentration of doxycycline has no relationship to the degree of inflammation and increases progressively over a number of days with increasing sputum-serum ratios [29]. Concentrations of doxycycline in bronchial wall homogenates and in lung tissue exceed the MIC for *H. influenzae* and *S. pneumoniae* strains [52].

Other antibiotics

Oral administration of trimethoprim yields concentrations in lung tissue and bronchial secretions which are higher than corresponding serum concentrations, suggesting accumulation [38, 53]. For erthromycin the sputum concentrations were approximately 10% of the serum concentrations [22, 30]. Within the group of quinolones, the ratio of the concentration of enoxacin in the bronchial mucosa to the concentration in serum averaged 47% [37]. The degree of penetration of enoxacin into sputum reached 90–100% of the serum concentration [52], suggesting accumulation. In lung tissue the concentration of enoxacin and ofloxacin were significantly higher than the plasma concentration [55, 56].

Conclusion

The determination of the concentration of antimicrobial drugs in respiratory fluids and pulmonary tissues could be important for prediction of the therapeutic efficacy of an antibiotic treatment in bacterial lower respiratory tract infections. The disposition of antibiotics in the bronchial tree and pulmonary tissue is the result of a very complex and dynamic pharmacokinetic process. The penetration into bronchial secretions and sputum has been investigated for many antimicrobial drugs and has been correlated with the minimal inhibitory capacity of respiratory pathogens. However, for many antibiotics, data concerning penetration and pharmacokinetic behaviour in the respiratory tract are lacking. The concentrations of antibiotics in pulmonary interstitium and alveolar lining fluid have been studied using tissue samples. Contamination with blood is the main methodological problem. The time-concentration profile of antibiotics in the bronchial tree and in the alveolar lining fluid has not been studied until now. Also the influence of inflammation or concomitant medications on the penetration of antibiotics has not been evaluated. Bronchoalveolar lavage may be a promising technique for evaluating antibiotic drug concentrations in alveolar lining fluid and may allow us to answer some of the many remaining questions about the pharmacokinetics and pharmacodynamics of antibiotics in the airways and the lung parenchyma.

References

1. Dursano GL. – Minireview: role of pharmacokinetics in the outcome of infections. *Antimicrob Agents Chemother*, 1988, 32, 289–297.
2. Bodey GP, Ketchel SJ, Rodriguez V. – A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. *Am J Med*, 1979, 67, 608–616.
3. Schentag JJ, Smith IL, Swanson DJ, DeAngelis JF, Fracasso JE, Vari A, Vance JW. – Role of dual individualization with cefmonoxine. *Am J Med*, 1984, 77 (Suppl. 6a), 43–50.
4. Bustamante CI, Drusano GL Tatem BA, Standiford HC. – Postantibiotic effect of imipenem on *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*, 1984, 26, 678–682.
5. Vogelman DS, Craig WA. – Postantibiotic effects. *J Antimicrob Chemother*, 1985, 15, 37–46.
6. Moore RD, Lietman PS, Smith CR. – Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis*, 1987, 155, 93–99.
7. Moore RD, Smith CR, Lietman PS. – Association of aminoglycoside plasma levels with therapeutic outcome in Gram-negative pneumonia. *Am J Med*, 1984, 77, 657–662.
8. Spencer H. – The bacterial pneumonias. *In:* Pathology of the Lung. Pergamon Press, 1985, pp. 167–213.
9. Stewart SM, Anderson IM, Jones JR, Calder MA. – Amoxycillin levels in sputum, serum and saliva. *Thorax*, 1974, 29, 110–114.
10. May JR, Delves DM. – Treatment of chronic bronchitis with ampicillin. Some pharmacological observations. *Lancet*, 1965, i, 929–933.
11. Ingold A. – Sputum and serum levels of amoxicillin in chronic bronchial infections. *Br J Dis Chest*, 1975, 69, 211–216.
12. Maesen FPV, Beeuwkes H, Davies BI, Bujtendijk HJ, Brombacher PJ, Wessman J. – Bacampicillin in acute exacerbations of chronic bronchitis - a dose-range study. *J Antimicrob Chemother*, 1976, 2, 279–285.

13. Davies BI Maesen FPV, Brombacher PJ, Sjovall J. – Twice daily dosage of becampicillin in chronic bronchitis: a double blind study. *Scand J Respir Dis*, 1978, 59, 249–256.
14. Klastersky J, Geunig C, Mouawad E, Daneau D. – Endotracheal gentamicin in bronchial infections in patients with tracheostomy. *Chest*, 1972, 61, 117–120.
15. Klastersky J, Carpentier-Meunier F, Kahan-Coppens L, Thijs JP. – Endotracheally administered antibiotics for Gram-negative bronchopneumonia. *Chest*, 1979, 75, 586–591.
16. Pennington JE. – Penetration of antibiotics into respiratory secretions. *Rev Infect Dis*, 1981, 3, 67–73.
17. Wong GA, Peirce TH, Goldstein F, Hoeprich PD. – Penetration of antimicrobial agents into bronchial secretions. *Am J Med*, 1975, 59, 219–223.
18. Barza M, Cuchural G. – General principles of antibiotic tissue penetration. *Antimicrob Agents Chemother*, 1985, 15 (Suppl. A), 59–75.
19. Rebuck AS, Braude AC. – Assessment of drug disposition in the lung. *Drugs*, 1984, 28, 544–553.
20. Bergogne-Berezin E. – *In:* Respiratory infections: diagnosis and management. 2nd Edition. Pennington ed., Raven Press, 1988, pp. 608–631.
21. Lambert HP. – Clinical significance of tissue penetration of antibiotics in the respiratory tract. *Scand J Infect Dis*, 1978, 14 (Suppl.), 262–266.
22. Smith BR, LeFrocq JL. – Bronchial tree penetration of antibiotics. *Chest*, 1983, 6, 904–908.
23. Bergogne-Berezin E, Morel C, Even P, Benard Y, Kafe H, Berthelot G, Pierre J, Lambert-Zechovsky N. – Pharmacocinétique des antibiotiques dans les voies respiratoires. *Nouv Presse Méd*, 1978, 7, 2831–2836.
24. Stewart SM, Fisher M, Young JE, Lutz W. – Ampicillin levels in sputum, serum and saliva. *Thorax*, 1970, 25, 304–311.
25. Halprin GM, McMahon SM. – Cephalexin concentration in sputum during acute respiratory infections. *Antimicrob Agents Chemother*, 1973, 3, 703–707.
26. May JR, Ingold A. – Amoxicillin in the treatment of infections of the lower respiratory tract. *J Infect Dis*, 1974, 129, 189–193.
27. Bergogne-Berezin E, Morel C, Benard Y, Berthelot J, Kafe H. – Pharmacokinetic study of betalactam antibiotics in bronchial secretions. *Scand J Infect Dis*, 1978, Suppl. 14, 267–272.
28. Brogan TD, Neale L, Ryley HC, Davies BH, Charles J. – The secretion of minocycline in sputum during therapy of bronchopulmonary infection in chronic chest disease. *J Antimicrob Chemother*, 1977, 3, 247–251.
29. Hartnett BJS, Marlin GE. – Doxycycline in serum and bronchial secretions. *Thorax*, 1976, 31, 144–148.
30. Marlin GE, Davies PR, Rutland J, Berend H. – Plasma and sputum erythromycin concentrations in chronic bronchitis. *Thorax*, 1980, 35, 441–445.
31. Wieser O, Regula H, Wundt W. – Die Ausscheidung von Gentamicin über den Bronchialbaum. *Dtsch Med Wochenschr*, 1972, 96, 870–872.
32. Saggers BA, Lawson D. – *In vivo* penetration of antibiotics into sputum in cystic fibrosis. *Arch Dis Child*, 1968, 43, 404–409.
33. Thijs JP, Klastersky J. – Concentration of netilmicin in bronchial secretions and in serum during intermittent *versus* continuous infusion: a cross-over study in humans. *J Infect Dis*, 1979, 140, 634.
34. Alexander MR, Berglund EM, Kasik JE, Fox A, Chinn WM. – The concentration of tobramycin in bronchial secretion. *Chest*, 1979, 75, 675–677.
35. Thijs JP. – Penetration et bioactivité des aminoglycosides dans les secretions bronchiques. Thèse, 1980.
36. Reynolds HY, Levine AS, Wood RE. – Diminished effect of gentamicin under anaerobic or hypercapnia conditions. *Lancet*, 1976, i, 447–449.
37. Marlin GE, Braude PD, Whelan AJ, Somogyi AA. – Penetration of enoxacin into human bronchial mucosa. *Am Rev Respir Dis*, 1986, 134, 1209–1212.
38. Hansen I, Lykkegaard-Nielsen M, Heerfordt L, Henriksen B, Bertelsen S. – Trimethoprim in normal and pathological human lung tissue. *Chemotherapy*, 1973, 19, 221–234.
39. Marlin GE, Nicholls AJ, Funnell GM, Bradbury R. – Penetration of cefaclor into bronchial mucosa. *Thorax*, 1984, 39, 813–817.
40. Marlin GE, Burgess KR, Burgoyne J, Funnell GR, Guinness MDG. – Penetration of piperacillin into bronchial mucosa and sputum. *Thorax*, 1981, 36, 774–780.
41. Kroening U, Liebig S, Wundschock M. – Tobramycin-Spiegel in menschlichen Lungengewbe. *Infection*, 1978, 6, 231–235.
42. Hunninghake GW, Gadek JE, Kawanimi O, Ferrans VJ Crystal RG. – Inflammatory and immune processes in human lung in health and disease: evaluation by bronchoalveolar lavage. *Am J Pathol*, 1979, 97, 149–206.
43. Braude AC, Hornstein A, Klein M, Vas S, Rebuck AS. – Pulmonary disposition of tobramycin. *Am Rev Respir Dis*, 1983, 127, 563–565.
44. Braude AC, Cohen RD, Penner JL, Preston MA, Rebuck AS. – Pulmonary disposition of moxalactam. *Chest*, 1984, 86/6, 881–883.
45. Bennett JC, Brodie JL, Benner EJ, Kirby WMM. – Simplified, accurate method for antibiotic assay of clinical specimens. *Appl Microbiol*, 1966, 14, 170–177.
46. Hafez FF, Stewart SM, Burnet ME. – Penicillin levels in sputum. *Thorax*, 1965, 20, 219–225.
47. Pennington JE, Reynolds HY. – Concentrations of gentamicin and carbenicillin in bronchial secretions. *J Infect Dis*, 1973, 128, 63–68.
48. Pennington JE, Reynolds HY. – Pharmacokinetics of gentamicin sulfate in bronchial secretions. *J Infect Dis*, 1975 131, 158–162.
49. Dull WC, Alexander MR, Kasik JE. – Bronchial secretion levels of amikacin. *Antimicrob Agents Chemother*, 1979, 16, 767–771.
50. Clauzel AM, Bonnet D, Allegrini J, Simeon de Buochberg M. – Concentrations de minocylcine dans les sécrétions bronchiques. *Nouv Presse Méd*, 1978, 7, 4236.
51. Campbell MJ. – Tetracycline levels in bronchial secretions. *J Clin Pathol*, 1980, 23, 427–434.
52. Gartmann J. – Doxyziklinkonzentrationen im Lungengewebe in der Bronchialwand und im Bronchialsekret. *Schweiz Med Wochenschr*, 1972, 102, 1484.
53. Hansen IB, Lykkegaard Nielsen M, Bertelsen S. – Trimethoprim in human saliva, bronchial secretion and lung tissue. *Acta Pharmacol Toxicol*, 1973, 32, 337–344.
54. Davies BI, Maesen FPV, Teengs JP. – Serum and sputum concentrations of enoxacin after single oral dosing in a clinical and bacteriological study. *J Antimicrob Chemother*, 1984, 14 (Suppl.), 83–89.
55. Wijnands WJA, Vree TB, Baars AM, Van Herwaarden CLA. – Pharmacokinetics of enoxacin and its penetration into bronchial secretions and lung tissue. *J Antimicrob Chemother*, 1988, Suppl. B, 21, 67–77.
56. Wijnands WJA, Vree TB, Baars AM, Halfkenscheid JCM, Kohler BEM, Van Herwaarden CLA. – The penetration of enoxacin into lung tissue. *J Antimicrob Chemother*, 1988, Suppl. C, 22, 85–89.
57. Bergogne-Berezin E. – Penetration of antibiotics into the respiratory tree. *J Antimicrob Chemother*, 1981, 8, 171–174.

58. Bergogne-Berezin E, Morel C, Pierre J, Monrocq N, Dournovo P, Bernard Y. – The penetration of cefotaxime into bronchial secretions. *Rev Inf Dis,* 1982, 4, 5392–5395.
59. Simon C, Gatzemeier U. – Serum and sputum levels of cefaclor. *Postgrad Med J,* 1979, 55 (Suppl. 4), 30–34.
60. Marks MI, Prentice R, Swarson R, Cotton EK, Eichkoff TC. – Carbenicillin and gentamicin: pharmacologic studies in patients with cystic fibrosis and pseudomonas pulmonary infections. *J Pediatr,* 1971, 79, 822–828.
61. Hughes DTD. – Use of combinations of trimethoprim and sulfamethoxazole in the treatment of chest infections. *J Infect Dis,* 1973, 128, 701–705.
62. Davies BI, Maesen FPV, Geraedts WH, Bour C. – Penetration of ofloxacin from blood to sputum. *Drugs,* 1987, 34 (Suppl. 1), 26–32.
63. Odio W, Vanlaer E, Klastersky J. – Concentrations of gentamicin in bronchial secretions after intramuscular and endotracheal administration. J *Clin Pharmacol,* 1975, 15, 518–524.

Pharmacocinétiques des antibiotiques au niveau pulmonaire. Y. Valcke, R. Pauwels, M. Van Der Straeten.

RÉSUMÉ: Dans cet article sont passées en revue les connaissances actuelles concernant la corrélation entre la pénétration locale des antibiotiques et l'efficacité thérapeutique dans les infections bactériennes des voies respiratoires inférieures. La concentration des drogues antimicrobienees au niveau du site infectieux est supposée être déterminante pour l'efficacité du traitment antibiotique, mais le nombre d'études consacrées aux infections respiratoires, qui supportent cette hypothèse, est limité. Les mécanismes, responsables de la pénétration pulmonaire des antbiotiques administrés par voie orale ou parentérale incluent la diffusion passive, le transport actif, le bulk flow et la perméabilité. La pénétration des médicaments antibactériens au niveau des voies respiratoires est influencée par des caractéristiques de l'hôte, telles que l'inflammation ou les traumatismes mécaniques, et par des facteurs propres aux médicaments, comme le poids moléculaire. De plus, une inactivation locale peut se produire. La concentration finale et biologiquement active des antibiotiques au site de l'infection est donc le résultat d'un processus dynamique très complexe. Plusieurs méthodes ont été employées afin de déterminer la concentration des antibiotiques dans les expectorations, les différentes sécrétions respiratoires et les biopsies tissulaires. Les valeurs obtenues ont été corrélées avec les taux sériques et l'efficacité clinique. Le lavage bronchoalvéolaire semble être une technique fiable pour évaluer les concentrations des antibiotiques au niveau de l'alvéole. Pour plusieurs antibiotiques nous ne disposons pas encore de données concernant la pénétration et la pharmacocinétique dans les voies respiratoires.
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