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Antibiotic penetration into lung tissues

Effective antibiotic treatment for lung infections requires an amount of drug at the site of infection sufficient to achieve or exceed the minimum inhibitory concentration (MIC) for that antibiotic against the pathogen. Recent developments in methodology have enabled concentrations of many antibiotics to be measured in small samples of tissue. The two main assay techniques are either a microbiological assay system where inhibition of growth of an indicator organism exposed to a sample of tissue is quantified, or high performance liquid chromatography. The sensitivity and reproducibility of these assay systems are remarkably high. The bioassay technique has the advantage of only measuring active amounts of the antibiotic, but has the disadvantage with some antibiotics such as clarithromycin of not differentiating between parent compound and active metabolites.[1]

As well as sputum, other sites in the lung that have been investigated for concentrations of antibiotic include the bronchial mucosa, alveolar macrophages, and epithelial lining fluid.[2] Mucosal concentrations have been measured by taking several biopsies during bronchoscopy; the samples are then ultrasonicated and assayed. Using the technique of bronchoalveolar lavage macrophages and epithelial lining fluid may be obtained. The epithelial lining fluid often requires freeze drying to concentrate the samples about 10 times before assay. Rapid separation of cells and epithelial lining fluid is achieved by immediate centrifugation of the lavage aspirate to prevent efflux of some antibiotics such as quinolones or macrolides from macrophages. These techniques are extensively reviewed elsewhere.[3] Quantification of concentrations in the epithelial lining fluid remains problematical because of movement of solute and solvent across the alveolar-capillary barrier during the lavage procedure.[4]

Mechanisms of penetration of antibiotics into the lung

Physiochemical properties of antimicrobial agents are important in determining their concentrations in various lung tissues. High protein binding may make passage of the antimicrobial from the blood into tissue more difficult.[5] Lipophilicity, however, usually enhances penetration compared with relatively lipid insoluble antimicrobials such as some penicillins and cephalosporins.[5] The concentrations of antibiotics in lung tissues result from a dynamic process of penetration and clearance. If a single dose of antibiotic is given, the peak tissue level will lag behind the peak serum level. However, after several doses of an antibiotic with a long half life have been administered, steady state kinetics will be achieved both in the serum and in the tissues.[6] Impaired renal or hepatic function may also cause elevated concentrations of antibiotic in lung tissues. Mechanisms of antibiotic penetration into lung tissue include passive diffusion, permeation,[7] active transport,[8 9] and bulk flow; it is likely that other mechanisms also exist[10] (table 1). Metabolism of drugs may occur in the lung – for example, by Clara cells – and this could theoretically affect tissue concentrations.[11]

Some antibiotics such as β-lactams remain mainly extracellular and their concentration in the extracellular space equals that of serum.[6] In a tissue sample such as a bronchial mucosal biopsy the overall concentration of such an antibiotic will depend on the relative distribution of water between the intracellular and extracellular compartments of bronchial biopsy samples. Radiolabelled markers have shown extracellular water to be about 40% of total biopsy weight.[12]

Aminoglycosides are too polar to pass across membranes and appear to enter cells very slowly by endocytosis.[13] Interestingly, within phagocytes there may be preferential distribution of antibiotic. Quinolones appear to accumulate in the cytosol[14] whereas macrolides are distributed both in the cytosol and within lysosomes[15]; aminoglycosides accumulate almost exclusively in the lysosomes. Similarly, alveolar macrophages obtained at lavage and then incubated with various antibiotics show poor uptake of penicillins or cephalosporins, but up to fivefold concentrations with rifampicin or tetracycline, and considerable concentrations of erythromycin, clindamycin, or ethambutol are achieved.[16] Peripheral blood polymorphonuclear leucocytes also concentrate certain antibiotics to a similar extent.[17] The pulmonary endothelium is non-fenestrated[18] unlike, for example, the bronchial capillary endothelium,[19] and therefore provides more of a barrier to the passage of some antibiotics into the epithelial lining fluid.

Concentrations found in lung sites

Concentrations of antibiotics in the sputum have been studied extensively, but few antibiotics penetrate well into the secretions. The concentrations of β-lactam antibiotics are usually around 5–20% of those in the serum.[20] Macrolides such as erythromycin also achieve relatively low sputum concentrations after oral dosing.[21] Gentamicin concentrations in sputum are about 25% of those of serum.[22] Trimethoprim appears to penetrate into sputum relatively well, with concentrations sometimes exceeding serum levels.[23] Quinolones also penetrate into sputum relatively well.[24] Unfortunately the measurement of sputum concentrations of antibiotics is subject to many variables such as dilution with saliva (which often has a lower concentration of antibiotic than sputum[20]), instability related to changes of temperature, pH, or protein content,[25] and pooling of secretions over many hours making it difficult to relate peak sputum to peak serum concentrations.

Table 2 shows examples of tissue concentrations of antibiotics within the lung. Concentrations of β-lactams such as amoxycillin or cephalosporins[26] in bronchial mucosa are around 40% of simultaneous serum concentrations, regardless of dose. This is consistent with the theory that β-lactams remain mainly extracellular. However, other antibiotics accumulate within cells including those in the bronchial mucosa – for example, quinolones and macrolides. Levels of such antibiotics in mucosal tissue

Table 1 Possible mechanisms of antibiotic penetration into the lung

Method	*Examples*	*Comments*
Passive diffusion	Beta-lactams	Low molecular weight molecules, cannot be saturated hence close serum:tissue relation. Helped by large surface area in pulmonary bed. Impaired if high protein binding in blood
Permeation	Chloramphenicol, macrolides, rifampicin	Rate limited by the degree of liposolubility
Active transport	Quinolones, clindamycin	Energy dependent and hence can be saturated leading to discrepancy between serum and tissue levels
Bulk flow	Unknown	Ultrafiltration of drug through capillary pores across a pressure gradient

Table 2 Examples of mean (SD) tissue concentrations (mg/l or mg/kg) of antibiotics

Drug	*Dose*	*Serum*	*Bronchial biopsy*	*ELF*	*Macrophage*
Cefuroxime axetil[26]	500 mg single oral dose (fasting)	3·9 (1·9)	1·8 (0·7)	0·7 (0·6)	Very low levels only in 9/14 patients
Ciprofloxacin[28]	250 mg twice daily orally for 4 days	1·2 (0·6)	1·9 (1·0)	3·0 (2·8)	13·4 (12·7)
Azithromycin[29]	500 mg orally single dose	0·1 (0·05)	3·9 (1·2)	2·2 (0·9)	23·4 (5·1)
Clarithromycin[42]	250 mg twice daily orally for 2 days	1·2 (0·04)	Not measured	10·4 (0·7)	86·5 (3·6)

ELF = epithelial lining fluid.

exceed serum levels; for example, quinolone levels in tissue are often 1·5–2·0 times higher than serum levels.[27 28] Concentrations of antibiotics in bronchial mucosal tissue compared with serum concentrations are much more variable between different types of macrolides – for example, azithromycin levels are extremely high in tissue in the presence of very low serum levels,[29] but roxithromycin levels are less so.[30] The pulmonary capillary endothelium is a more difficult barrier for drugs such as some antibiotics to penetrate by passive diffusion. This has been shown for β-lactams where the concentrations in epithelial lining fluid are lower than bronchial biopsy concentrations.[26] However, other antibiotics, notably quinolones, have been found to have higher concentrations in epithelial lining fluid than in bronchial biopsy samples,[31] raising the likelihood of a different mechanism of penetration across the pulmonary capillary endothelium.

Clinical significance of tissue levels

If the concentration of an antibiotic at the site of infection exceeds the MIC required to inhibit or kill a particular bacterial strain, it is reasonable to assume that clinical efficacy is likely to be high. However, the peak concentrations of some antibiotics such as quinolones may be more important than the area under the concentration-time curve which seems crucial with β-lactams.[32] The concentration of antibiotic refers to that which remains active at the site and which has not been rendered inactive by enzyme degradation or other means. Site concentrations of antibiotic are known to be important in other disorders such as urinary tract infection where drugs with very low serum concentrations are concentrated in the urine and are effective when serum concentrations alone would predict clinical failure.[33] Where there is bacteraemia – for example, in some cases of pneumococcal pneumonia – the serum concentration of antibiotic is likely to be crucial. However, in other infections involving the lung the concentration of antibiotic in extravascular sites such as alveoli, mucosa, and sputum is likely to be very relevant to efficacy. With exacerbations of chronic bronchitis sputum concentrations of an antibiotic may be the most important.[34] With infectious exacerbations of chronic bronchitis a good clinical response was seen if ampicillin concentrations in the sputum exceeded the MIC of the infecting organism.[35] However, with tissue invasion by bacteria the concentrations in the mucosa may then become relevant. In pneumonia the concentrations of antibiotic within the epithelial lining fluid, macrophages, and neutrophils are likely to be crucial.[36]

Many quinolones have borderline activity against the pneumococcus – for example, the MIC_{90} of ciprofloxacin to this organism is 2 mg/l and concentrations of about 3 mg/l in epithelial lining fluid have been reported.[28] Several newer quinolones such as temafloxacin (now withdrawn) and sparfloxacin have a lower MIC_{90} against pneumococcus (0·25 mg/l for sparfloxacin)[37] with epithelial lining fluid concentrations that predict better efficacy,[31] for which there is some support from clinical trials.[38] Experiments with animal models of pneumococcal lung infections also show that tissue concentrations of quinolones[39] and macrolides[40] such as azithromycin and clarithromycin correlate with therapeutic success. Clarithromycin combines good serum concentrations with high tissue concentrations[41 42]; efficacy has been shown in bronchitis[43] and pneumonia.[44] Azithromycin has very low serum concentrations but very high tissue concentrations even 96 hours after a single dose[29]; clinical studies have shown its effectiveness in exacerbations of chronic bronchitis and some pneumonias[45] but the low serum concentrations may be a disadvantage with more severe pneumococcal infections.

Intracellular concentrations of antibiotics are of particular clinical interest when considering infections such as *Legionella pneumophila*, *Chlamydia pneumoniae*, and atypical mycobacteria. Clinical studies of some quinolones[46 47] or macrolides[45] have shown their effectiveness in atypical pneumonias. With its high macrophage concentration clarithromycin has been found to be effective in the treatment of *Mycobacterium avium intracellulare* in patients with AIDS[48] (usually in combination with other drugs to prevent resistance). Good penetration of antibiotics into lung tissue including abscesses may explain clinical efficacy in difficult infections such as *Mycobacterium fortuitum*.[49]

Concentrations of antibiotic achieved in the bronchial tree either by nebulisation or injection through an endotracheal tube have been assessed only to a limited extent. Distribution of nebulised pentamidine has been measured with radiolabelled markers and is critically dependent on nebuliser type, volume of fill, and nebuliser dose.[50] Less efficient distribution of pentamidine to the upper lobes than to the lower lobes may lead to a reduced site concentration and risk relapse of *Pneumocystis carinii* in the upper lobes.[51 52] Quantitative deposition of nebulised gentamicin has also been assessed in patients with cystic fibrosis and relatively higher levels found in those with a lower FEV_1 and central deposition of aerosol in the presence of undetectable serum concentrations.[53] Clinical efficacy of antimicrobial treatment in patients with cystic fibrosis is directly correlated with concentrations of drug achieved in bronchial secretions.[54] Endotracheal instillation of gentamicin in patients with Gram negative bronchopneumonia resulted in concentrations in bronchial secretions that correlated with good clinical outcome and lower mortality.[55 56] High concentrations of tobramycin have recently been reported after nebulisation[57] in lung tissue with very low serum levels.

In conclusion, the ability to measure accurately the concentration of an antibiotic at specific sites within the lung has enabled the mechanisms of penetration and accumulation to be studied further. Inflammation itself is known sometimes to affect these mechanisms, usually leading to enhancement of levels of some antibiotics in affected tissues. It is increasingly recognised that antibiotics have other effects at the site of infection apart from their direct bacteriocidal or bacteriostatic effects. Immunomodulating effects and airway epithelial ion transport have been described with some macrolides.[58] Further research is required to investigate the relevance of site concentrations of antimicrobial agents to these effects.

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