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Pulmonary Disposition of Antimicrobial Agents: In Vivo Observations and Clinical Relevance

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INTRODUCTION

The rationale for measuring the concentrations of antimicrobial agents at potential sites of infection other than serum is that pathogens may be confined to sites which are separated from the blood by significant barriers to antimicrobial agent movement. Thus, the concentrations within these sites may differ markedly from those observed in serum, and clinical efficacy may be more directly related to the concentrations of drugs local to the pathogen. In the lung, the relationship between concentrations of drug at the site of infection and clinical efficacy is not clear because of difficulties with studies designed to measure efficacy. First, there are problems with defining end points in respiratory infections. Resolution of a chest infection may be indicated by normalization of the body temperature, clearing of purulent sputum, time for bacterial eradication from sputum, and absence of reinfection during a follow-up period (13, 19, 33, 40). All of these measures do not necessarily equate with clinical response. For example, normalization of temperature may even indicate a lack of host response to infection and herald a deterioration as a result of the disease. Bacterial eradication is not always associated with a response. Many patients must be admitted to the hospital even though their general practitioner has given them antibiotics. Culture of sputum samples is often negative and does not mean that the pathogens have been eradicated but, rather, that they will not grow in vitro after having been exposed to antibiotic. Second, the multifactorial nature of the clinical response means that antimicrobial chemotherapy may be only one of many factors which may play a role in recovery (48).

Concentrations observed in vivo. (i) Sputum and whole lung tissue. Extensive reviews of sputum and bronchial secretion concentrations have appeared (14, 45, 52), and general trends can be derived from these reviews. The penetration of most drugs into these sites is low so that concentrations in sputum are usually lower than the simultaneous concentrations in serum. For the penicillins and cephalosporins, the ratio of the concentration of drug in sputum or bronchial secretions to that in serum is between 0.05 and 0.25. The fluoroquinolones have better penetration characteristics, and concentrations in bronchial secretions are between 0.80 and 2.0 times those in serum. As for the β-lactam antimicrobial agents, wide variations in the concentrations of individual agents have been noted; these variations probably reflect the methodological difficulties outlined in part one of this minireview (1). The macrolides have penetration ratios of 5 to >500%. Unfortunately, data are very variable for the most commonly used macrolide erythromycin, with one study (14) reporting a level of erythromycin in sputum that was 5% of that in serum, and others (36) have reported levels of erythromycin in sputum that were from 25 to 85% those in serum. This, again, likely reflects methodological problems. Logically, a lipophilic drug such as erythromycin should reach higher ratios than the β-lactams. The newer agents have been shown to have higher ratios of the concentration of drug in sputum or bronchial secretions to that in serum (oleandomycin, 80 to 100%; azithromycin, 500%). Aminoglycosides and tetracyclines have ratios of 20 to 60%. The methodological difficulties with determination of concentrations in sputum are such that precise values are not available and the ratios given here may serve only as a crude guide to the concentrations of drug at this important site of infection.

Table 1 provides site of infection-to-serum ratios for whole lung tissue. Concentrations of drug in whole lung tissue quantify the penetration of antibiotics in a crude way because lung tissue consists of many different components. However, it is likely that concentrations of antimicrobial agents in interstitial fluid equate with those in serum, because the capillary endothelium is relatively permeable (12). It follows that the principal determinant of the value of the site of infection-to-serum ratio is the degree to which the antimicrobial agent concentrates in the cellular component. Those antimicrobial agents which are known to accumulate in cells have ratios of greater than 1 (e.g., tetracyclines and macrolides), while those which do not readily penetrate cell membranes have ratios of less than 1 (e.g., penicillins and cephalosporins).

(ii) Bronchial mucosal biopsy specimens. There are surprisingly few published data on the concentrations of antimicrobial agents in bronchial biopsy specimens (2–5, 7, 26, 34, 35, 37). This is despite the relative ease of obtaining these samples compared with that of obtaining lung tissue and also the potential advantage that there are less constituent tissue types. The ratios of concentrations in bronchial biopsy specimens to those in serum (BB/S ratio) show much greater consistency. Clear differences can be demonstrated between classes of antimicrobial agents, and the similarity of the ratios, particularly for the β-lactams, is probably sufficient to allow prediction of levels of drug in biopsy specimens from the concentrations in serum. This is somewhat surprising, since one might expect differences in half-lives of drug in tissue and serum to influence the ratio when, in single-dose studies, the time from the dose is varied (2, 7, 37). This is not the case for β-lactams; whether they are administered as single or multiple doses, the BB/S ratio is between 0.35 and 0.55. We have studied several other β-lactams, and all of the mean BB/S ratios have fallen in the range of 0.35 to 0.55 (3, 7, 8, 26). Indeed, the individual ratios do not vary greatly (they are usually from 0.3 to 0.8). Because of the consistency of these values, it is now possible to dispense with the relatively time-consuming task of measuring concentrations of β-lactams in bronchial biopsy specimens and, instead, assume that the concentration is between the values given above. This assumes that the physicochemical properties of new β-lactams are similar to those of existing agents. This

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TABLE 1. Selected site of infection-to-serum ratios for whole lung tissue[a]

Antimicrobial agent	Site of infection-to-serum ratio
Amoxicillin	0.40–0.49
Clavulanate	0.23
Floxacillin	0.16–0.36
Cefamandole	0.39–0.52
Doxycycline	2.3
Amikacin	0.5
Tobramycin	0.5
Erythromycin	1.7–5
Spiramycin	2.2–38

[a] Data were obtained from previously published reports (14, 45, 52).

may not be a safe assumption, however, because conversion of β-lactams to basic derivatives can lead to better intracellular penetration (15, 47). A useful approach would be to develop methods to measure the relative concentrations in the interstitial fluid and the cellular component of the bronchial biopsy specimen to define the distribution more precisely.

If the situation is clear for the β-lactams, it is by no means so for the fluoroquinolones and the macrolides. The fluoroquinolones have different ratios. Ciprofloxacin, temafloxacin, and lomefloxacin have mean ratios of between 1.7 and 1.9 (4, 5, 26), while enoxacin has been reported to achieved ratios of over 100 (34), although the latter observation is not readily explicable and requires confirmation. Similarly, for the macrolides a ratio of over 50 is found for azithromycin (2) which is greatly in excess of the ratios found for erythromycin. Data on the concentrations of other classes of antimicrobial agents in bronchial biopsy specimens are too limited to allow conclusions to be drawn, and further work done by standard methods should be encouraged.

The very limited data and the lack of standardized methods mean that it is difficult to make any conclusions about the more recently studied epithelial lining fluid (ELF) and alveolar macrophages (AMs). Published data on the concentrations of antimicrobials agents in human AMs and ELF in vivo are given in Table 2. In addition, the concentrations of moxalactam and tobramycin in lavage aspirates have been investigated, but the results were not expressed as concentrations in ELF and various dosages were used (16, 21). The problem of efflux of antimicrobial agents from AM during bronchoalveolar lavage was addressed in only two studies (11, 20). In vitro efflux of azithromycin was found to be very slow and, therefore, was not a significant source of error. The concentrations given for the other drugs which are known to concentrate in AMs may be a gross underestimate, depending on the degree of efflux that occurs during bronchoalveolar lavage and immediately before centrifugation. The concentrations of the agents studied observed in vivo in AMs so far broadly agree with what is known about the in vitro uptake of different classes of antimicrobial agents (18, 23, 31).

Published data on the concentrations in ELF exist for azithromycin, cefuroxime, clavulanic acid, amoxicillin, and cefpirome (2, 7, 8). It is likely that the other concentrations given are minimum values, since other methods overestimate the volume of ELF. The level of roxithromycin of only 2 mg/liter after a regimen of 300 mg twice daily for 3 days is lower than might be expected for a macrolide, and indeed, in this study (18) the volume of ELF recovered by bronchalveolar lavage was over double that estimated by using newer methods (9, 40). We have investigated the concentrations of ciprofloxacin, lomefloxacin, sparfloxacin, and temafloxacin in ELF and have found concentrations two- to threefold those in serum (6, 10, 11, 27). These data will be reported separately.

The time course of pulmonary antimicrobial agents in the bronchoalveolar space has not been studied by many workers, but the new azalide azithromycin yielded some interesting results when it was administered as a single 500-mg oral dose (2). The concentrations of azithromycin in serum were found to be low at 12 h (0.5 mg/liter) and were subsequently lower, so that at 96 h the concentrations were only just measurable (0.01 mg/liter). The concentrations in bronchial biopsy specimens and ELF rose to levels well above those in serum, and at 96 h they were 50 to 100 times greater than those in serum. The concentrations of azithromycin in AMs were much higher than those in ELF or bronchial biopsy specimens, and there was a sudden rise in concentrations at 48 h. A method of delivery of drug to the site of infection is suggested by this finding. In vitro studies of the uptake of azithromycin by phagocytes have shown that uptake is completed after 24 h of incubation with the antibiotic. We can therefore postulate that penetration of azithromycin into the epithelial lining occurs in two ways. First, direct diffusion may occur, and second, azithromycin may be taken up by blood monocytes while there are relatively high concentrations in serum. The majority of monocytes undergo margination into tissues, including the lung, after 48 h, thus increasing the concentrations in AMs.

TABLE 2. Antimicrobial agent concentrations in human AMs in vivo[a]

Antimicrobial agent	Dosage regimen	Route of administration	Concn	
			AM (mg/kg)	ELF (mg/liter)
Azithromycin	500 mg statim	Oral	23	1.4
Spiramycin	500–1,000 mg, 1 day	Intravenous	17–20	
Roxithromycin	300 mg twice daily, 5 days	Oral	21	2.0
Josamycin	1 g twice daily, 3 days	Intravenous	44	
Cefuroxime axetil	500 mg statim	Oral	1.2	0.7
Amoxicillin	500 mg statim	Oral	2.0	2.6
Clavulanic acid	250 mg statim	Oral	ND[b]	1.3
Cefpirome	1 g statim	Intravenous	—[c]	7.2
Temafloxacin	600 mg twice daily, 3 days	Oral	79.2	26.3

[a] Data were obtained from previously published reports (2, 7, 8, 11, 18, 44).
[b] ND, not detected.
[c] —, mostly undetectable, although in two patients levels of 3.1 and 2.2 mg/liter were found.

Unfortunately, there is only one full report of the concentrations of the fluoroquinolone temafloxacin in human AMs in vivo (11) (Table 2). However, concentrations of three other fluoroquinolones (lomefloxacin, ciprofloxacin, and sparfloxacin) in AMs have been investigated, including their efflux characteristics both in vivo and in vitro (6, 10, 27). These data will be reported in detail separately, but they show that concentrations in AMs are six to eight times those in ELF, which corresponds to the intracellular to extracellular concentration ratio observed in vitro (20).

The influence of inflammation on the integrity of the barriers to antimicrobial agent movement. Host-related as well as drug-related factors may influence the penetration of antimicrobial drugs across the blood-bronchus and alveolar-capillary barriers. The most important host-related factor is the integrity of the anatomical barriers which may be damaged by inflammation and mechanical injury. In the presence of inflammation, the partitioning of antimicrobial agents in tissue compartments may be altered because of increases in membrane permeability (14, 45). Thus, for drugs such as the β-lactams, which do not cross membranes readily, the penetration might increase in the presence of inflammation. For the β-lactam antibiotics clindamycin, oleandomycin, and erythromycin, increased levels in bronchial secretions have been shown in more inflamed airways, with a corresponding decrease in levels when the inflammation subsides (14, 20, 28, 33, 36, 39, 50). It has been suggested that the concentrations at sites of infection may fall sufficiently to allow relapse of infection, because of reestablishment of normal barriers to movement (45).

Tetracyclines do not show a similar relationship between concentrations in bronchial secretions and the degree of inflammation (25, 32, 36). There is some controversy for the aminoglycosides, with gentamicin levels apparently not correlating with inflammation while tobramycin and amikacin do show correlations (14, 53). The reason for this discrepancy might, again, be due to the methodological problems associated with the measurement of antimicrobial agents in sputum and bronchial secretions described in part one of this minireview (1).

The relevance of assessing drug concentrations in healthy lung has rightly been questioned, because it is argued that the concentrations in inflamed tissues may be different and that these may be more appropriate as predictors of clinical efficacy. However, in any infection there is healthy tissue bordering the inflamed area, where antimicrobial agent levels may be important for the prevention of microbial spread. In addition, the barriers to antimicrobial agent movement may regain their integrity during the stages of resolution of the infection, so that poor penetration of an antimicrobial agent into healthy tissue might lead to a relapse. Measurement of antimicrobial agent concentrations at inflamed sites of infection in the lung poses further methodological and ethical problems. There are no methods available to estimate the volume of ELF in an inflamed lung, and the differential cell count in the lung may be markedly different, with neutrophils predominating in bacterial infections. Fiberoptic bronchoscopy and bronchoalveolar lavage may be unethical in cases of pneumonia, for which the procedure is not clinically indicated.

Clinical relevance. If concentrations of antimicrobial agents at sites of infection are to be clinically relevant, it is necessary that they be related to MIC v. For some sites of infection this relationship is clear. For example, drugs which achieve very low concentrations in serum but are concentrated in the urine are effective in lower urinary tract infections. Furthermore, concentrations in renal tissue are good predictors of efficacy in ascending urinary tract infections (29, 41, 49). In the lung, the relationship is less clear, but early work by May (38) first suggested that concentrations in sputum were better predictors of efficacy than concentrations in serum were, and other investigators have confirmed this finding (24, 30, 38, 51). For bronchial biopsy specimens, the concept of relating MICs for 90% of isolates tested to the measured total drug concentration is flawed by the fact that there are at least two clear-cut compartments, intracellular and extracellular. For bronchial mucosal infections, we have no clinical evidence to suggest whether drug in the intracellular or the extracellular drug compartment is the most important. However, it is useful to consider the possible reasons why one or the other may be important. Where the pathogens exist in the lumen, it will be important that antimicrobial agents penetrate cell membranes or tight intercellular junctions. Such antibiotics usually penetrate into cells well, and therefore, there are relatively high concentrations in bronchial biopsy specimens. Thus, in this case the total concentration in the bronchial biopsy specimen in relation to the MIC might best relate to clinical efficacy. When epithelial cell invasion occurs, the pathogens are in contact with both the antimicrobial agent that is released from disrupted cells and that which is within the interstitial fluid. Again, in this situation the total antimicrobial agent concentration should relate directly to the MIC. However, this assumes, as with all sites of infection, that the activity of the antimicrobial agent is unaffected by the local environment, in which conditions are very different from those in vitro. From the model of bronchial infection given above, it is reasonable to suppose that concentrations of antimicrobial agents in the bronchial interstitium are only of value when tissue invasion has occurred, because there needs to be a breach of the bronchial epithelium before bacteria may be present in the interstitium.

The concentrations of antimicrobial agents in AMs are likely only a predictor of the clinical response to intracellular pathogens in relation to the MICs for 90% of isolates tested, provided that the drug is active within the cell. In vitro methods enable the determination of intracellular killing by antimicrobial agents and have shown that intracellular concentrations do not necessarily relate to intracellular activity (22). Further work is needed to investigate the effect of antimicrobial agents on specific intracellular pathogens in vitro, such as *Legionella pneumophila*.

The relation of the MICs for 90% of isolates tested to the concentrations achieved in the respiratory tract is perhaps most applicable to the ELF, where there is a single compartment. However, like other sites, the composition of ELF is very different from in vitro conditions (17, 42, 43, 46).

In theory, measurement of concentrations at sites of infection in the lung and application of these to MICs appears to be a promising way of predicting clinical efficacy. What is clear from the published data is that there is as yet no proof that these measurements are useful. There are two reasons for this. First, there are insufficient data on the concentrations achieved by different classes of antimicrobial agents at the more recently investigated sites of infection; and second, studies of clinical efficacy in relation to concentrations at pulmonary sites are needed. The latter could be approached by comparing the efficacies of two different antimicrobial agents with the same MIC for a particular organism but with markedly different tissue penetrations, such as a β-lactam agent and a fluoroquinolone. Large numbers of patients would be required, and with any clinical

study the outcome measures would need to be clearly defined.

CONCLUSION

Assessment of the efficacies of antimicrobial agents may be facilitated by the measurement of the concentrations achieved at potential sites of infection. In the lung the relationship between concentrations at sites of infection and clinical efficacy is not clearly established because of methodological difficulties which have only recently been addressed, insufficient data on concentrations at the newer sites such as ELF and AMs, and a lack of properly controlled clinical studies designed to investigate this relationship. From published data, broad trends can be derived for some classes of antimicrobial agents. Those agents which can be shown to accumulate in cells in vitro have higher concentrations in bronchial mucosa than in serum and tend to penetrate more effectively into bronchial secretions than do agents which do not penetrate cells. This observation is consistent with the barriers to antimicrobial agent movement described in part one of this minireview (1). The limited data on concentrations in ELF and AMs are also consistent with these trends. The concentrations of β-lactams in bronchial biopsy specimens have been shown to be a consistent fraction of the simultaneous concentrations in serum. Therefore, concentrations in biopsy specimens can now be predicted from those in serum, thus obviating the need for further time-consuming measurement of concentrations in biopsy specimens, in which the physicochemical properties of new agents are known to be similar to those of existing agents. Unfortunately, there are insufficient data to allow the same conclusions to be made for other agents and for other sites, and further work is needed. Finally, the clinical value of measuring antimicrobial agent concentrations at sites of infection in the lung must be investigated by making direct comparisons of antimicrobial agents with markedly different concentrations at sites of infection.

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