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Considerations for effect site pharmacokinetics to estimate drug exposure: concentrations of antibiotics in the lung

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Bronchoalveolar lavage (BAL) and microdialysis have become the most reliable and relevant methods for measuring lung concentrations of antibiotics, with the majority of BAL studies involving either healthy adult subjects or patients undergoing diagnostic bronchoscopy. Emphasis on the amount of drug that reaches the site of infection is increasingly recognized as necessary to determine whether a dose selection will translate to good clinical outcomes in the treatment of patients with pneumonia. Observed concentrations and/or parameters of exposure (e.g. area-under-the-curve) need to be incorporated with pharmacokinetic–pharmacodynamic indices so that rational dose selection can be identified for specific pathogens and types of pneumonic infection (community-acquired vs hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia). Although having measured plasma or lung concentration–time data from critically ill patients to incorporate into pharmacokinetic–pharmacodynamic models is very unlikely during drug development, it is essential that altered distribution, augmented renal clearance, and renal or hepatic dysfunction should be considered. Notably, the number of published studies involving microdialysis and intrapulmonary penetration of antibiotics has been limited and mainly involve beta-lactam agents, levofloxacin, and fosfomycin. Opportunities to measure in high-resolution effect site spatial pharmacokinetics (e.g. with MALDI-MSI or PET imaging) and *in vivo* continuous drug concentrations (e.g. with aptamer-based probes) now exist. Going forward these studies could be incorporated into antibiotic development programs for pneumonia in order to further increase the probability of candidate success.

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Introduction

An adequate drug concentration at the site of an infection continues to have an important role in our ability to understand the pharmacokinetic–pharmacodynamic (PK–PD) relationships of antibiotics [1]. During the past 50 years, numerous studies have been conducted to measure tissue, cell or fluid concentrations of antibiotics in the lung [2,3,4••,5,6••,7•,8••]. Various methods and sampling sites have been used. Nevertheless, no clear consensus exists on the optimal approach for measuring the concentrations of antibiotics in the lung [3,4••,5,6••,7•,9]. Methods that involve measuring the concentrations of antibiotics within specific subcompartments of the lung provide important insights into antimicrobial efficacy. Bronchoalveolar lavage (BAL) and microdialysis are currently the most reliable and relevant methods for measuring lung concentrations of antibiotics [4••,5,7•,8••]. This review will focus on human studies that have used these two techniques to measure intrapulmonary concentrations of antibiotics.

Intrapulmonary penetration

A variety of methodologies have been used for measuring concentrations of antibiotics and determining their distribution patterns in the lungs [6••,8••]. Each has its advantages, potential limitations, and methodological issues. Historically, anti-infective drug concentrations were measured by obtaining lung tissue during a surgical procedure. Although this is one of the oldest methods for measuring drug concentrations in the lung, whole-tissue concentrations may be difficult to interpret [9]. The major drawback of drug concentrations reported from whole lung tissue, bronchial tissues and/or secretions is the assumption that antibiotics are uniformly distributed within all lung compartments (e.g. extracellular, intracellular, interstitium). The measured drug concentration will therefore represent a mixture from all compartments instead of the drug concentration at the clinically relevant site of infection. Currently, the two preferred methods for measuring antibiotic concentrations in the lung are BAL and microdialysis. Bronchoscopy with BAL can determine concentrations in both the epithelial lining fluid (ELF) and alveolar macrophages (AM), whereas microdialysis measures concentrations in the interstitial fluid of the lung [4••,8••]. The ELF is the relevant site for the extracellular respiratory pathogens that are causative in acute bacterial pneumonia and infective exacerbation of

chronic bronchitis. These lower respiratory tract infections may progress to involve the interstitial fluid of the lung. By contrast, infections caused by intracellular pathogens such as *Legionella pneumophila* and *Chlamydophila pneumoniae* exist within AM.

Assessment of antimicrobial drug concentrations in lungs

Most studies that measure drug concentrations at an infection site often place too much emphasis on the value of the penetration ratio. Unfortunately, ratios are used to claim that specific antibiotics may be better for treating pneumonia. The ratio of site-to-plasma concentrations provides an important pharmacological characteristic. However, in isolation it is not adequate to determine whether an agent will be effective at treating pulmonary infection and also does not identify how much drug needs to be administered.

Penetration ratios change as a function of time because concentrations in plasma and at the site of infection demonstrate system hysteresis (e.g. increases and decreases at different rates from each other). Such time-dependency limits the interpretability of measures from a single sampling time and the true penetration of a drug into the lung. To overcome this limitation, samples should be collected from a population of patients (or subjects) throughout the dosing interval (even though an individual patient only contributes a single lung concentration). In addition, an overall measure of drug exposure (i.e. the area-under-the-curve [AUC]) in each compartment should be calculated and used to determine the penetration ratio.

The amount of drug that reaches the site of infection is an important determinant of dose selection. Observed concentrations and/or measures of drug exposure (e.g. area-under-the-curve, AUC) are fundamental to rational dose selection for specific pathogens and pneumonic diseases (e.g. community-acquired [CABP] vs hospital-acquired [HABP] bacterial pneumonia, including ventilator-associated bacterial pneumonia [VABP]).

The following aspects in study design are critical for a precise estimate of drug exposure and to support clinical dose and candidate regimen selection for new agents: (i) investigating regimens that are most likely to be progressed to subsequent clinical trials; (ii) ensuring serial sampling from plasma throughout the dosing interval in individual patients; (iii) sampling from the lung that covers the dosing interval at a population level (because each patient can only contribute a single lung concentration); (iv) determining concentration ratios from robust estimates of AUC in plasma and the relevant pulmonary subcompartment; (v) considering plasma protein binding with both unbound and total drug concentrations in plasma and using these data to better understand penetration characteristics; (vi) using analytical procedures that are both sensitive and specific for plasma and effect site concentrations; (vii) correcting for dilution from sampling (i.e. BAL) with urea estimation being the most commonly used procedure; (viii) translating effect site exposures using non-clinical PK–PD targets, for example relating human ELF exposure to ELF PK–PD targets from highly predictive murine models of pneumonia; and (ix) performing PK–PD modelling and simulation to assess and predict the performance of various candidate regimens.

Bronchoalveolar lavage (BAL) studies

Bronchoscopy with BAL has become a reliable technique for measuring concentrations of antibiotics in ELF. During the past two decades, several groups of investigators have used this method to determine drug penetration into ELF and to compare plasma and ELF concentrations of antibiotics [4••,10]. Using BAL studies to assess ELF concentrations has become an important component of antibacterial drug development programs since the majority of pneumonic infections are caused by extracellular pathogens [11••,12]. Table 1 provides an update on published studies evaluating plasma and ELF exposures of antibiotics that have recently been approved or are currently in development [13–25]. We direct the reader to our previous review publications regarding data for other anti-infective agents as well as a detailed description of using bronchoscopy and BAL for measuring ELF drug concentrations and determining intrapulmonary penetration [4••,5].

Healthy subjects

The majority of BAL studies have involved either healthy adult subjects or patients undergoing diagnostic bronchoscopy (Table 1) [4••,13–25]. A few studies have targeted older outpatients or patients with a clinical diagnosis of mild to moderate chronic bronchitis, chronic obstructive pulmonary disease, or community-acquired bacterial pneumonia [4••]. A comparison of these patients with mild to moderate respiratory tract infections and/or inflammatory processes has suggested that ELF concentrations were similar in magnitude and time course to those observed in healthy subjects. Thus, antibacterial concentrations in ELF from healthy subjects tend to serve as an estimate of the average drug exposure at extracellular sites of lung infection.

Pharmacokinetics and pharmacodynamics are increasingly recognized to be essential tools in the development of new antibiotics in order to maximize the probability that the right dose for infected patients will be studied during clinical trials [1,11••]. An intrapulmonary penetration study in healthy subjects can assist a drug development program by determining whether or not an antibiotic penetrates into lung, and if it does, whether concentrations of the antibiotic can be adequately