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# Tissue penetration of antibacterial agents: how should this be incorporated into pharmacodynamic analyses?

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Despite the accepted knowledge that the activity of antibiotics depends on the unbound concentration at the site of infection, current pharmacodynamic analysis mostly relies on published total blood concentrations. Such concentrations do not necessarily correlate with concentrations at the site of infection. Methodological problems and separation of bound and unbound fractions, however, limit the applicability of most measured 'tissue concentrations' as adequate pharmacokinetic input into pharmacodynamic analyses. Recently, research on using free blood concentrations as surrogate concentrations has received more attention and may be useful for infection sites such as soft tissue infections. Although our understanding of antibiotic pharmacodynamics in tissues has become much more advanced, we are still lacking appropriate and accurate pharmacokinetic data derived from the site of infection.

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## Introduction

*In vitro* pharmacodynamic (PD) models relate the antibacterial activity to the concentration of the drug. They are designed to assess the antibacterial effect, the emergence of resistance, and to establish the pharmacodynamic parameter and the magnitude of that parameter best related to outcome [1]. These models play a key role in the investigation of new antimicrobial agents in the early and late phases of clinical development as well as in the optimization of antibiotic effectiveness once used widely [2••]. Typically the pharmacodynamics of antibiotics are studied *in vitro* by exposing bacteria to a fixed concentration or preferably fluctuating concentrations in a pattern that should ideally mimic *in vivo* pharmacokinetics (PK) as closely as possible. The data may be analyzed with an integrated PK–PD model to link antibiotic concentrations

to bacterial killing rates by using a maximum effect ( $E_{max}$ ) model that may be used to predict drug effects at the target site (Figure 1) [3].

In most pharmacodynamic analyses, the pharmacokinetics generally used are those in the blood (plasma or serum) because they are easily accessible and available. Such an approach does not take into account that most infections do not occur in the plasma but rather occur in tissue sites and that antibiotics do not distribute evenly throughout the body [4]. We know the fact that to be effective both the bacteria and the drug need to be in the same place at the same time. It seems to be intuitive to consider the active drug concentrations that are measured at the actual site of infection and use this data for simulating the pharmacokinetics of antibiotics in the *in vitro* models [5]. Since there is less reliable information available about extravascular concentrations of antibiotics over time, it would be beneficial to find a surrogate marker that is readily available and relates to the concentration at the site of the infection, begging the question if blood concentrations could be used as surrogate markers.

## Tissue penetration of antibacterial agents

The definition of tissue drug concentration is highly variable and historically burdened. In the past it was used to characterize the concentration in a homogenized biopsy sample, which assumes that the tissue is homogeneous, that antibiotics as well as bacteria are evenly distributed through it, and that both the bound and unbound fractions of antibiotics are active. Each of these basic assumptions is incorrect. Using homogenized whole tissue drug concentrations would underestimate the effective site concentrations of drugs that equilibrate with the extracellular space, such as  $\beta$ -lactams and aminoglycosides and, in turn, would lead to an overestimation of intracellularly accumulating drugs, such as quinolones or macrolides. Concentrations of antimicrobials obtained from homogenized tissues or by other techniques that do not discriminate between pharmacological compartments are not only an average of intracellular and extracellular concentrations but also include those fractions of an antibiotic that is bound to interstitial proteins or intracellular and intercellular membrane structures. Only the free concentrations of antibiotics at the target site are, however, responsible for the therapeutic effect. Pharmacodynamic models that are based on the concentrations of antimicrobials obtained from homogenized tissues or other similar techniques are of limited value for the interpretation of drug exposure/efficacy relationships in tissues.