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Review

Therapeutic drug monitoring of intracellular anti-infective agents☆

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ABSTRACT

Many microorganisms, including viruses, some bacteria and fungi, replicate within the cells. Therefore, the efficacy of therapy and the selection of resistances could be related to intracellular concentration of the drugs and to their ability to cross biological membranes and penetrate into various tissue compartments.

The efficacy of treatment may be limited by pharmacological factors. Dose–response relationship exists for many agents, and failure to maintain adequate concentrations may allow the development of viral or bacterial resistance, thereby decreasing the probability of response of current and subsequent therapies.

The major target of antivirals and many other anti-infective agents is within infected cells. Therefore, clinical outcome ultimately should be related to intracellular drug concentrations. Intracellular pharmacokinetics provides information regarding drug disposition in a compartment where microorganism replication occurs and combined with plasma data may be useful in understanding therapeutic failure in relation to cellular resistance.

With a focus on possible methodological biases, this review reports the current state of the art in intracellular, particularly in peripheral blood mononuclear cells, therapeutic drug monitoring of the following anti-infective drugs: antivirals, antifungals and antibiotics.

Although measurement of intracellular concentrations needs to be still standardized focusing on each single drug, this review showed some relationships between intracellular concentrations of few anti-infective drugs and their efficacy and/or toxicity. Such relationships should be interpreted with caution, as intracellular concentrations reflect the total amount of drug within the cell and not the effective unbound fraction. The number of clinical studies in that area is, however, rather limited, and not always adequately designed. Then, intracellular drug determination has to be considered a test for research only and not to be carried out as routine.

Contents

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1. Introduction

Many microorganisms, including viruses, some bacteria and fungi, replicates within the cells. Therefore, the efficacy of therapy and the selection of resistance could be then related to intracellular concentration of the drugs and to their ability to cross biological membranes and penetrate into various tissue compartments. Actually, therapeutic drug monitoring (TDM) is usually performed in plasma. The use of TDM to quantify drugs in plasma probably needs to be supplemented, and possibly supplanted, in some case, by information about intracellular concentrations and intracellular distribution [1]. These issues are particularly important, for example, for antiretroviral drugs used in anti-HIV therapy.

In fact, morbidity and mortality related to HIV infection have dramatically decreased in countries in which highly active antiretroviral therapy (HAART) has been made available, turning HIV infection into a manageable chronic disease. However, HAART regimens have shown some limitations, the major one is the failure to eradicate HIV even after several years of therapy. One of the reasons is that, despite potent antiviral treatment, in some compartments the virus persists, suggesting that antiretrovirals do not reach all of the infected cells: however, there are no data to support this theoretical assumption [2].

The efficacy of treatment may be limited by pharmacological factors. Dose–response relationship exists for many agents, and failure to maintain adequate concentrations may allow the development of viral or bacterial resistance, thereby decreasing the probability of response of current and subsequent therapies. Fixed dosage of agents may result in different systemic and intracellular concentrations of drugs (interindividual variability).

TDM consists in individualizing dosages with the aim of maximizing the efficacy of treatment and minimizing toxicity. The combination of pharmacokinetic–pharmacodynamic relationships, for example, in the antiretroviral therapy and the presence of a wide interpatient variability in drug exposure support the application of TDM in HIV-infected individuals [3].

Antituberculars TDM offers an opportunity to optimize and individualize medical treatment and prevent adverse outcomes, in particular in patients with comorbidities, such as HIV, diabetes, malnutrition, renal and hepatic impairment. The same could be applied to other anti-infective therapies.

Therefore clinical outcome ultimately should be related to intracellular drug concentrations. Intracellular pharmacokinetics provides information regarding drug disposition in a compartment where microorganism replication occurs and, combined with plasma data, may be useful in understanding therapeutic failure in relation to cellular resistance. In order to improve therapeutic efficacy, it is therefore important that the intracellular pharmacokinetics of drugs, such as protease inhibitors in HIV, is studied in association to plasma pharmacokinetics.

In this review we reported previous studies on intracellular TDM for antivirals, antifungals and antibiotics, with a focus on the description of possible methodological biases.

2. Mechanisms influencing intracellular drug accumulation

2.1. General principles and transporters

Most of anti-infective agents as antifungals and antibiotics act by binding to their targets into the cells. Generally, the xenobiotics pass from the systemic circulation to the extravascular compartment by passive diffusion or by active transport. Passive diffusion is usually the most common mechanism for trans-membranal transport of xenobiotics in the body. Small, lipophilic, un-ionized and unbound molecules easily diffuse, and diffusion between plasma and peripheral blood mononuclear cells (PBMC) could be influenced by differences in the pH that alters the membrane potential [14]. The active transport is mediated by binding proteins, which may slow the diffusion rate. Basic drugs, that have a greater affinity for cells or tissue proteins than for plasma proteins, very rapidly leave the bloodstream, and protein binding is not a limiting factor; for these drugs, the volume of distribution is high, the amount of the drug in plasma is small compared with the amount in tissues and cells, and small changes in plasma protein binding will not affect the drug level in the extravascular compartments [4]. Membrane transporters (efflux and influx) have an important role in drug absorption and disposition, and they explain, at least in part, the broad inter-individual variability in intracellular concentrations of drugs [5–12]. The main type of efflux transporters are: ATP-binding cassette (ABC)-type transport proteins [7], P-glycoprotein (P-gp), Breast cancer resistance protein (BCRP) [12,13] and multidrug resistance proteins (MRPs) expressed in the apical