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Review article

Antifungal pharmacodynamics: Latin America's perspective

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ABSTRACT

The current increment of invasive fungal infections and the availability of new broad-spectrum antifungal agents has increased the use of these agents by non-expert practitioners, without an impact on mortality. To improve efficacy while minimizing prescription errors and to reduce the high monetary cost to the health systems, the principles of pharmacokinetics (PK) and pharmacodynamics (PD) are necessary. A systematic review of the PD of antifungals agents was performed aiming at the practicing physician without expertise in this field. The initial section of this review focuses on the general concepts of antimicrobial PD. *In vitro* studies, fungal susceptibility and antifungal serum concentrations are related with different doses and dosing schedules, determining the PD indices and the magnitude required to obtain a specific outcome. Herein the PD of the most used antifungal drug classes in Latin America (polyenes, azoles, and echinocandins) is discussed.

Introduction

Invasive fungal infections are currently an important cause of morbidity and mortality, especially in immunosuppressed patients and those admitted in intensive care units.[1,2] *Candida* spp. are the most frequent etiological agent of fungal infections in humans, ranking fourth among the etiologic agents of bloodstream infections in the United States, with a mortality similar to septic shock. In Latin America, a higher incidence of candidemia has been reported compared to countries of the northern hemisphere.[3] Additionally, the diversity of climates and habitats in Latin America leads to a higher incidence of endemic mycoses, including histoplasmosis, paracoccidioidomycosis, and coccidioidomycosis.[4]

In the last years, the incidence of healthcare-associated fungal infections has been rising, mainly of invasive candidiasis and aspergillosis.[5] There has also been an increased report of non-albicans *Candida* infections, which display reduced susceptibility to antifungal drugs.[6] Finally, the number of patients

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with profound immunosuppression secondary to the treatment of hematologic malignancies and organ transplantation is growing, and it has been associated with the increase of invasive fungal infections due to several genera of molds that represent formidable diagnostic and therapeutic challenges.[7] Despite the availability of effective antifungal drugs, mortality due to fungal infections remains high,[8] a fact that has prompted the search for new products and a better understanding of the pharmacology of these agents to optimize therapy.

There are additional components in Latin America to the "host-fungi-drug" triad that may alter the pharmacodynamics (PD) with unknown impact on resistance. For economic and political reasons, generics are extensively used despite their unproven therapeutic equivalence and, in some cases, the treatment must be stopped due to shortage in supply. Moreover, the pharmacokinetics (PK)/PD knowledge has not been extensively introduced in the curriculum of medical schools and related clinical medical education activities are limited, mainly because PK and PD integrations may be seen as complex and not practical. In consequence, the advancements on the PD of antifungal have not been implemented as in other regions of the world.

Methods

A literature search was performed in the PubMed/MEDLINE database looking for clinical trials, journal articles or reviews available in full-text, written in Spanish or English languages, published from January 1962 to July 2015, including the keywords: pharmacodynamics (PD), pharmacokinetics (PK), antifungals, candidiasis, and aspergillosis. Papers about antifungal therapy co-authored by the expert in the field David R. Andes, were also searched. Out of 140 papers identified the authors selected the relevant papers about *in vitro*, *in vivo*, and clinical PD of antifungal agents, mainly emphasizing on the PK/PD concepts; to build a practical review for general physicians, especially in developing countries. The references of the selected papers were also used if the authors considered them relevant for the review.

Review

General concepts of antimicrobial pharmacodynamics

The study of the PK and PD properties of any antimicrobial is based on the exposure-response relationship of the drug and the infecting pathogen.[9] This relationship can be modeled (Fig. 1) by integrating a PK parameter (*e.g.*, maximal concentration or C_{max}, and area under the curve or AUC) and a PD parameter related with the response expected against the infecting microorganism (*i.e.*, minimal inhibitory concentration or MIC). The knowledge derived from these integrations has facilitated the design of optimal drug regimens and potentially reduce toxicity and the development of resistance.[10]

Classically, PK studies are about assessing absorption, distribution, metabolism, and elimination of drugs. The aim of

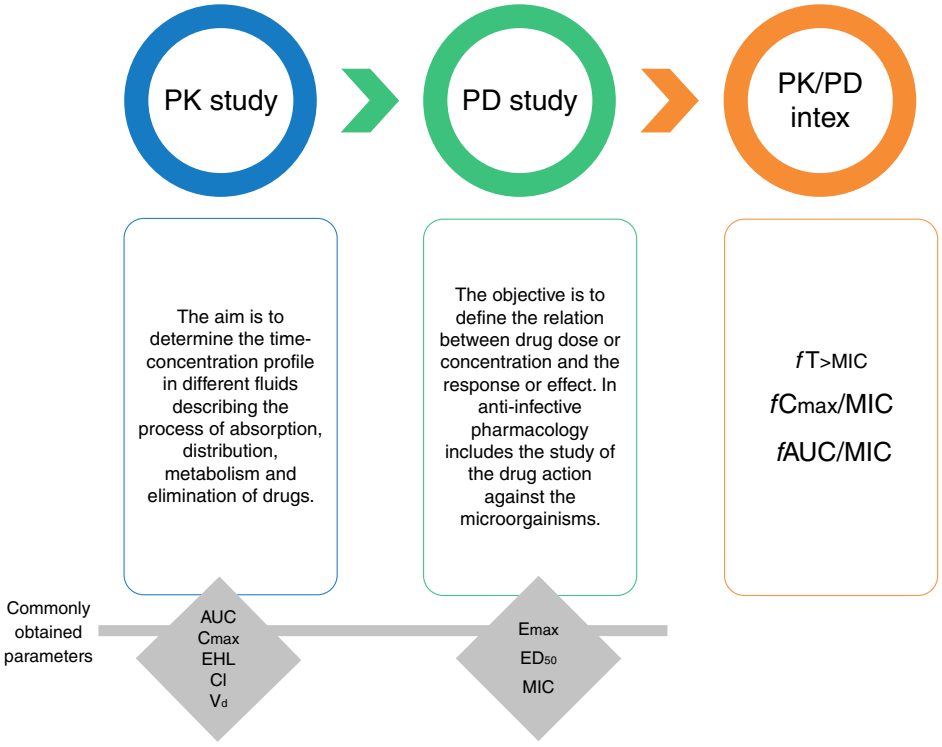

Fig. 1 – Pharmacokinetics (PK), pharmacodynamics (PD) and PK/PD integration. *Pharmacokinetic parameters*. AUC, area under the concentration-time curve; C_{max}, maximal concentration or peak; EHL, elimination half-life; Cl, clearance; V_d, volume of distribution. *Pharmacodynamic parameters*. E_{max}, maximum effect, a measure of efficacy. ED_{50}, effective dose to achieve 50% of the E_{max}, a measure of potency. MIC, minimal inhibitory concentration.