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Amphotericin A21: New Antifungal-Effective and Safe

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Short Communication

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INTRODUCTION

AmB has not only been the "gold standard" of antifungal medications from its first introduction in 1959, but it has also been the only option for treating acute systemic mycoses in many cases. This is confirmed by current studies that explain AmB's therapeutic applications. We have, for example, the case of the global emergence of resistance to azoles in *Aspergillus fumigatus* infections. For more than 50 years, an intrathecal application of AmB-deoxycholate has been employed to treat *Coccidioidal meningitis* and there is no present alternative. In the cases of Aspergillosis and facial Murcomycosis, the attention of pathogenesis due to murcomycosis or blastomycosis can

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only be treated with AmB, with azoles reserved for drug intolerance. AmB continues to be the option for moderate, severe, or disseminated cases of histoplasmosis, as well as for pulmonary Cryptococcus's. It is in new therapies such as stem cell transplantation, where the nephrotoxicity of liposomal AmB is frequent, as are the obstruction of the renal elimination of other drugs, antifungal prophylaxis in lung transplantation or other infections. Despite AmB's great efficacy, its use has been highly restricted given its strong toxicity, which causes renal failure, damage to the distal renal tubes, alteration of blood flow and smooth muscle function. This is the reason why, since the appearance of AmB, there has been a search for derivatives or formulations that reduce this collateral toxicity. The most effective formulation in this regard is the liposomal one, which is already in its third decade of application. Furthermore, as recently highlighted, all antifungal agents, including the various formulations of AmB, echinocandins, and new generation azoles, have a liver toxicity that ranges from mild and asymptomatic to severe and fulminant liver failure. However, the expensive liposomal is not accessible to all to patients suffering from invasive mycosis, which limits the treatment of a large group of patients. Therefore, there is an urgent need for therapeutic alternatives with antifungal activity and specific mechanisms of action to treat fungi.

Amphotericin-A21 is a semi-synthetic compound derived from Amphotericin B (L-histidine methyl ester of Amphotericin B) [1,2]. It has been shown to have fungal activity like AmB, but much less collateral mammalian cell toxicity. This analog displays selective action toward the fungal membrane, which increases its effectiveness while reducing its toxicity. Collateral toxicity has been the great therapeutic problem when using AmB. The effectiveness of AmB-A21 has been demonstrated in *in vitro* models with different strains of candida and in an animal model of candidiasis, showing the same antifungal potency as AmB. A detailed description of preclinical safety studies was published in Basic Clinical Pharmacology and Toxicology and The FASEB Journal, where it's lethal dose 50 (LD50) in mice was shown to be 7-fold higher compared to that of AmB [3-5]. Preclinical *in vitro* studies performed on normal human kidney cells have shown that the AmB-A21 derivative has less nephrotoxic effects, and studies on human erythrocytes have shown less hemolytic effect than the parent molecule. Additionally, it has been shown AmB-A21 is not genotoxic, nor does it produce teratogenic effects in chicken embryos. Long-term studies have shown that oral administration of repeated doses for 6 months did not produce biochemical or blood cell changes; also, no alterations were observed in the brain, thymus, spleen, lungs, liver, kidney, intestine or spleen in experimental animals. The only toxicity data was found in testies; however, the effect was reversible 8 weeks after stopping treatment. The results of the toxicological investigation confirm the safety profile of amphotericin A21. Current antifungal therapies based on polyenes, flucytosine, azoles and echinocandins are employed either as monotherapies or in combination for prophylaxis, and as empiric, preventive, or specific therapies. The effectiveness, however, has stalled. Although these drugs are clinically useful, they have several limitations: high toxicity, ineffectiveness due to the presence of drug-resistant strains, or the high-cost of liposome formulations on the market that, while effective, are not accessible to the general population. Therefore, we urgently require new, more effective, safer, and lower-cost antifungals. Amphotericin A21 has an excellent margin of safety and the potential to move ahead into exploratory Phase I clinical trial. Amphotericin A21 could potentially enable safe long-term antifungal treatment given its reduced side effects and could be accessible to a much larger population.

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