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Combination interaction of fluconazole with efflux pump inhibitors against antifungal resistant Candida parapsilosis

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ABSTRACT

Introduction

C. parapsilosis is the most common fungal pathogen recovered in neonatal intensive care units and is associated with a higher mortality rate due to its multidrug resistance. This study investigated the virulence factors and reversal of efflux activity by using a well-known antifungal drug (fluconazole) in combination with two efflux pump inhibitors (pantoprazole and omeprazole). In addition the effect of most active combination on pathogenicity markers of *C. parapsilosis* has studied.

Materials and methods

The microbroth dilution method was used to obtain antifungal susceptibility tests of conventional antifungal drugs (fluconazole and amphotericin B) against twelve clinical isolates of *C. parapsilosis*, as well as antifungal susceptibility tests of two efflux pump inhibitors (EPI). In addition, the combination of efflux pump inhibitors (pantoprazole and omeprazole) with fluconazole, an antifungal drug, was determined by calculating the fractional inhibitory concentration index (FICI) based on zero-interaction theory of Loewe additivity. a time-kill kinetics assay was used to study the antimicrobial activity of fluconazole and efflux pump inhibitors against *C. parapsilosis*. The virulence factors in *C. parapsilosis* isolates were determined using in vitro virulence assays. The effects of the efflux pump inhibitors on virulence factors were also studied, and comparison of percent reduction of virulence factors was determined in both fluconazole-resistant and susceptible *C. parapsilosis*. The effects of Pantoprazole and Omeprazole on efflux pump were also investigated using two assays (Rhodamine 6G accumulation and Hoechst 33342 accumulation).

Results

The efflux pump inhibitors showed enhanced antifungal activity in combination with antifungal agents against *C. parapsilosis*. When pantoprazole was combined with fluconazole, the median Minimum inhibitory concentration for fluconazole and pantoprazole decreased from 125 to 31.25 µg/ml and from 620 to 310 µg/ml respectively. In the time-kill kinetics assay, fungistatic activity of Fluconazole was changed to fungicidal by addition of efflux pump inhibitors (pantoprazole and omeprazole) at their ½MIC values. On the other hand, this study demonstrated that *C. parapsilosis* had a variety of virulence characteristics, including the ability to adhere to epithelial cells and secretion of proteinase hydrolytic enzyme. Pantoprazole and omeprazole reduced the ability of *C. parapsilosis* cells to adhere to epithelial cells. Adhesion was reduced in a concentration-dependent manner. The reduction was significant ($p < 0.001$) at all the test concentration. Proteinase synthesis in *C. parapsilosis* strains, was also significantly reduced at test concentrations. The reduction was significant $P = < 0.01$ However, the results also showed that pantoprazole and omeprazole and their combinations was significantly reduced efflux pump activity.

Conclusion

Candida resistance has increased, particularly to azoles, and advent of *C. parapsilosis* as most prevalent non *albicans Candida* species poses a significant threat to the future. Combination therapy is shown to be therapeutically efficacious, and MIC values of fluconazole decreased when it was combined with omeprazole and pantoprazole.

Further study is needed to understand the epidemiology, microbiology, genetics, and antibiotic susceptibility of this pathogen. The ability to express different virulence factors, such as adherence, proteinase, and phospholipase production, is strain-dependent and the widespread use of antifungal agents leads to drug resistance in *C. parapsilosis*.