Summary and keywords

Amphotericin B (AmB) as the only antibiotic available for many decades for the treatment of life-threatening invasive candidiasis is known for its broad spectrum of fungicidal activity with very rare resistance among clinical isolates. However, the use of AmB is limited due to serious adverse effects. One of the many strategies to reduce the toxicity of AmB is to reduce the antibiotic dose by combining therapy with antifungal drugs that demonstrate synergistic interactions.

For this purpose, in this work, studies were carried out on a group of 1,3,4-thiadiazole derivatives, which allowed the selection of a compound called 4-(5-methyl-1,3,4-thiadiazol-2-yl)benzene-1,3-diol (abbreviated C1), which in combination therapy with AmB demonstrates strong synergistic activity, low cytotoxic activity while maintaining antifungal activity. Cell viability studies using the MTT test showed that compound C1 does not increase the cytotoxicity of AmB against mammalian cell lines: NHDF, COS-7, CHO-K1. Analyses performed using fluorescence microscopy, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) suggested different mechanisms of action of both compounds. Changes in the morphology and ultrastructure of *C. albicans* after treatment with compound C1 were different than after the action of AmB used alone. The antifungal activity of C1 is associated with the disruption of cell wall biogenesis, which may make cells more sensitive to the antibiotic. In addition, studies have shown that C1 induces stronger oxidative stress in *C. albicans* cells than AmB. In order to confirm the hypothesis regarding the different mechanisms of action of AmB and C1, FTIR spectroscopic analysis of isolated *C. albicans* cell walls was performed, which showed that the main mechanism of synergistic antifungal activity of the compounds is associated with disruption of the integrity of the cell wall. The results of the conducted experiments give hope for the possibility of using combined therapy AmB-C1 in the treatment of fungal infections.

Keywords: amphotericin B, 1,3,4 - thiadiazole derivatives, synergism, cytotoxicity, antifungal activity.

Katarzyna Futera