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Voriconazole-Based Salts Are Active against Multidrug-Resistant Human Pathogenic Yeasts

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Abstract: Voriconazole (VOR) hydrochloride is unequivocally converted into VOR lactates and valinates upon reaction with silver salts of organic acids. This study found that the anticandidal in vitro activity of these compounds was comparable or slightly better than that of VOR. The *Candida albicans* clinical isolate overexpressing *CaCDR1/CaCDR2* genes, highly resistant to VOR, was apparently more susceptible to VOR salts. On the other hand, the susceptibility of another *C. albicans* clinical isolate (demonstrating multidrug resistance due to the overexpression of *CaMDR1*) to VOR salts was comparable to that to VOR. Comparative studies on the influence of VOR and its salts on Rhodamine 6G efflux from susceptible and multidrug-resistant *C. albicans* cells revealed that VOR salts are poorer substrates for the CaCdr1p drug efflux pump than VOR.

Keywords: voriconazole; *Candida albicans*; multidrug resistance

1. Introduction

The emergence of human pathogenic fungi that are resistant to commonly used antifungal drugs is a great challenge for antimicrobial chemotherapy [1]. Another problem is the limited repertoire of effective low-toxic antifungals for humans [2]. One such drug, voriconazole (VOR), is a second generation triazole antifungal agent, demonstrating high in vitro and in vivo activity against human pathogenic yeasts and molds. It is used in clinics to treat invasive aspergillosis and candidiasis, and fungal infections caused by *Scedosporium* and *Fusarium* species in immunocompromised patients [3]. It is a relatively safe drug and has a small number of side-effects with oral or intravenous administration [4]. Unfortunately, fungal resistance to VOR is not rare. The molecular basis of this resistance is most often a point mutation (especially in *Aspergillus* spp. Molds) in the *CYP51A* gene encoding lanosterol demethylase, which is an intracellular target for VOR [5]. However, resistance of *Candida* spp. yeast to VOR may also be due to the multidrug (MDR) type, owing to the overexpression of genes encoding drug efflux proteins belonging to the ABC or MFS subfamily. Evidence for participation of ABC transporters, CaCdr1p and CaCdr2p, in VOR resistance in *Candida albicans* were previously presented [6].

Earlier reports indicated that the conversion of azole and triazole antifungals—ketoconazole, fluconazole, tebuconazole and propiconazole—into respective ionic forms upon protonation of the nitrogen atoms in the azole or triazole ring and combination with the appropriate anion may result in improvement of the antifungal properties of the obtained salts, in comparison with the mother compounds [7–9]. Some of these salts exhibit physicochemical properties that are attributed to ionic liquids, especially the liquid state of matter at room temperature [7,8]. It is worth mentioning, therefore,