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# NOVEL MOLECULAR INSIGHTS IN THE INHIBITORY POTENTIAL OF ANTIFUNGAL DRUGS ON ATP-BINDING CASSETTE TRANSPORTERS MRP1, MRP2, MRP3, MRP4, MRP5, P-GP, BCRP AND BSEP.

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OBJECTIVES

Over the past decades it has become increasingly apparent that drug-efflux pumps play a key role in drug disposition. Although antifungal drugs have great potential for drug interactions mainly based on inhibition of CYP P450 enzymes, knowledge of contribution of efflux transporters in drug-drug interactions is limited. In this study, we set out to explore the inhibitory potential of fluconazole (FLZ), itraconazole (ITZ), hydroxyitraconazole (hITZ), posaconazole (PSZ), voriconazole (VCZ), isavuconazole (ISAV), anidulafungin (ANF), caspofungin (CAS), micafungin (MCF) and amphotericin B deoxycholate (AMB) on the ATP-binding cassette transporters MRP1-5, P-gp, BCRP and BSEP *in vitro*.

METHODS

After transduction of HEK293 cells with recombinant baculoviruses containing MRP1-5, P-gp, BCRP and BSEP genes, membrane vesicles were isolated and verified for overexpression and functionality. The vesicular transport assay was used to study the inhibitory action of antifungal drugs on the transport of model substrates ([$^3$H]-$E_1$S, [$^3$H]-$E_2$17βG, [$^3$H]-MTX, [$^3$H]-NMQ and [$^3$H]-TCA) by the efflux transporter.

RESULTS

FLZ and VCZ were incapable of inhibiting ATP-dependent uptake >50% for all studied efflux transporters. P-gp, BCRP and BSEP were all inhibited by the triazoles ITZ (IC50 = 2, 0.4 and 0.4 x 10-6M, respectively), hITZ (IC50 = 9, 8 and 17 x 10-6M), PSZ (IC50 = 9, 7 and 34 x 10-6M) and ISAV (IC50 = 9, 15 and 94 x 10-6M). ANF (inhibiting MRP4, P-gp and BCRP with IC50 = 4, 4 and 1 x 10-6M) and ITZ were incapable to fully inhibit transporters, probably due to poor solubility. MCF was unique in inhibiting MRP1-5, P-gp, BCRP and BSEP with an IC50 of 21, 148, 42, 3, 22, 45, 21 and 85 x 10-6M. CAS inhibited MRP1, 3 and 5, P-gp, BCRP and BSEP (IC50 = 112, 158, >200, 34, 11 and 182 x 10-6M). Only BCRP was inhibited by AMB (IC50 = 127 x 10-6M).

CONCLUSIONS

These results provide important new insights into the inhibitory potential of antifungal drugs on ATP-binding cassette efflux transporters. Although echinocandins demonstrate poor capability for clinically relevant drug-drug interactions, they seem to be an appreciable inhibitor of efflux transporters. Interestingly, despite the wide range and variability of drug-drug interactions with azole antifungals, they exhibit limited inhibition on efflux transporters. This study will contribute to the further understanding of molecular mechanisms involved in drug-drug interactions. It will assist in explaining unresolved toxicity, thereby optimizing patient care.