

EFFECTS OF DP7 ON HUMAN AND RAT LIVER CYP-DEPENDENT ACTIVITIES: A KINETIC STUDY

D'Elia Paolo, Dragoni S., De Matteis F., Valoti M., Kawase M., Shah A., Motohashi N., Molnar J., Sgaragli G.

Dipartimento Scienze Biomediche, Università degli Studi di Siena, via A. Moro 2, 53100 Siena

The overexpression of permeability-glycoprotein (P-gp) and other drug transporters (ATP-binding cassette) confers a multidrug resistance (MDR) phenotype on cells in various diseases, including many forms of cancer. A lower cell concentration of cytotoxic drugs due to their accelerated efflux is a consequence of the overexpression of P-gp. Endeavouring to find MDR-inhibitors is a crucial task for exploring new anti-cancer therapeutic interventions. Many cytotoxic agents and MDR inhibitors are both substrates of P-gp and cytochrome P450 (CYP) 3A4. This results in unpredictable pharmacokinetic interactions. The ideal MDR-reverter should inhibit P-gp leaving unaffected CYP [1]. Differently substituted 1,4-dihydropyridines were investigated for their activity as MDR reverters and the new 3,5-dibenzoyl-4-(3-phenoxy-phenyl)-1,4-dihydro-2,6-dimethylpyridine (DP7) was reported as a powerful P-gp inhibitor, almost devoid of cardiovascular effects [2,3]. The aim of the present study was to investigate the effects of DP7 on CYP-activities by human and rat liver microsomes. When rat microsomes were incubated with DP7, concentration-inhibition curves were obtained with use of selective substrates markers of CYP activities (ethoxy-resorufin (ETR) for CYP1A1, pentoxy-resorufin (PTR) for 2B, methoxy-resorufin (MTR) for 1A2 and benzyloxy-resorufin (BZR) for 1A1/2, 2B and 3A. Inhibitions gave IC₅₀ values of 3.8 μM for PTR, 3.8 μM for ETR and 10.4 μM for BZR and were not competitive in nature. Moreover, these inhibitions were reversible and not dependent on time, NADPH concentration nor on the formation of possible metabolites of DP7. DP7 inhibition of CYP3A4 enzyme activities by rat and human liver microsomes was assessed fluorimetrically using 7-benzyloxy-quinoline (BQ) and [3-[3(3,4-difluorobenzyl)oxy]-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5H)-one] (DFB). The DP7 concentration-inhibition relationship curve with rat liver microsomes gave an IC₅₀ value of 4.17 μM for BQ and with human microsomes an IC₅₀ value of 34.67 μM for DFB. In the latter case, it was not possible to achieve a 50% inhibition even at 75 μM DP7-concentration using BQ as a substrate. In conclusion, the moderate inhibition of CYP isoforms in rat liver microsomes and the weak inhibition of human CYP3A4 enzyme activities operated by DP7, suggest that it represents a lead compound for the development of novel MDR reverting dihydropyridines of therapeutic interest.

(Supported by a grant from Ministero degli Affari Esteri, Roma)

References:

1. Fusi F. et al., (2006), *Current Drug Targets*, 7(8):949-959.
2. Saponara S. et al., (2004), *Br. J. Pharmacol.*, 141(3):415-22.
3. Saponara S. et al., (2007), *Eur. J. Pharmacol.*, doi:10.1016