Wulkersdorfer *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A6.1
http://www.intrinsicactivity.org/2015/3/S2/A6.1
published online: 9 September 2015

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

A6.1

Non-linear dose-dependent distribution of tariquidar to the human liver measured with PET

Beatrix WULKERSDORFER[1], Martin BAUER[1], Markus ZEITLINGER[1], Maria WEBER[1], Cécile PHILIPPE[2], Johann STANEK[1,3], Sabine STROMMER[1], Wolfgang WADSAK[2], Markus MÜLLER[1] and Oliver LANGER[1,3,*]

[1]Department of Clinical Pharmacology, Medical University of Vienna, Austria; [2]Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria; [3]Health and Environment Department, AIT Austrian Institute of Technology GmbH, Seibersdorf, Austria

Background: The investigational third-generation P-glycoprotein (ABCB1) inhibitor tariquidar (XR9576) has been used in clinical trials in tumour patients in combination with anticancer drugs, such as vinorelbine, paclitaxel, docetaxel and doxorubicin, in order to overcome multidrug resistance of tumours [1]. In these clinical trials increased systemic exposure to anticancer drugs was observed in patients receiving tariquidar leading to dose-limiting toxicities, which has been attributed to inhibition of ABCB1 in tissues other than the tumour tissue. In the present study we used positron emission tomography (PET) imaging to study the *in vivo* distribution of [^{11}C]tariquidar to the liver of healthy volunteers.

Methods: Four healthy male volunteers underwent two consecutive 60-min dynamic abdominal PET scans with [^{11}C]tariquidar, a first scan after administration of only a microdose of [^{11}C]tariquidar (< 20 µg) and a second scan during continuous i.v. infusion of unlabelled tariquidar (3.75 mg/min). In parallel to PET imaging arterial blood sampling was performed and radioactivity in plasma was measured in a gamma counter. The liver was delineated as a region of interest on MR-co-registered PET images and distribution of [^{11}C]tariquidar to the liver was expressed as the liver-to-plasma area under the time-activity curve ratio (AUC_{liver}/AUC_{plasma}) and as uptake clearance from blood into liver ($CL_{uptake,liver}$), which was estimated by a previously described graphical analysis approach (integration plot) [2].

Results: Following i.v. injection of [^{11}C]tariquidar, high radioactivity uptake was observed in the liver. In PET scan 2, which was performed during infusion of unlabelled tariquidar, AUC_{plasma} was 44.7 ± 21.1% higher than in PET scan 1, in which only a microdose of [^{11}C]tariquidar was administered (scan 1: 13.3 ± 3.1, scan 2: 18.9 ± 4.0, $p = 0.012$, paired *t*-test). AUC_{liver}/AUC_{plasma} was reduced by 32.0 ± 8.7% (scan 1: 25.7 ± 5.1, scan 2: 18.3 ± 4.0, $p = 0.01$) and $CL_{uptake,liver}$ was reduced by 27.1 ± 9.0% in scan 2 as compared to scan 1 (scan 1: 0.49 ± 0.08 ml/min/g, scan 2: 0.36 ± 0.09 ml/min/g, $p = 0.002$).

Discussion: We observed non-linearity in [^{11}C]tariquidar distribution to the human liver. Liver distribution was lower and plasma exposure was higher for a pharmacological dose as compared with a microdose of [^{11}C]tariquidar pointing to dose-dependent inhibition by tariquidar of basolateral uptake transporters in hepatocytes, *i.e.* organic anion transporting polypeptides (OATPs). This suggests that tariquidar is substrate and inhibitor of human OATPs. Inhibition of OATPs in the liver may have also contributed to increased plasma concentrations of anticancer drugs observed in previous clinical trials with tariquidar.

Acknowledgements: Funded by the Austrian Science Fund FWF, grant F3513-B20.

References

1. Fox E, Bates SE: **Tariquidar (XR9576): a P-glycoprotein drug efflux pump inhibitor.** *Expert Rev Anticancer Ther,* 2007; 7(4):447–459. doi:10.1586/14737140.7.4.447
2. Takashima T, Wu C, Takashima-Hirano M, Katayama Y, Wada Y, Suzuki M, Kusuhara H, Sugiyama Y, Watanabe Y: **Evaluation of breast cancer resistance protein function in hepatobiliary and renal excretion using PET with ^{11}C-SC-62807.** *J Nucl Med,* 2013; 54(2):267–273. doi:10.2967/jnumed.112.110254

*Corresponding author e-mail: *oliver.langer@meduniwien.ac.at*