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MEETING ABSTRACT

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Positron-emission tomography imaging reveals a functional interplay between ABCB1 and ABCG2 in the hepatobiliary excretion of dual substrate drugs

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Background: ABCB1 and ABCG2 are two efflux transporters located at the canalicular membrane of hepatocytes. Among other transporters, ABCB1 and ABCG2 mediate the secretion of drugs or drug metabolites from the liver into bile. Changes in hepatic ABCB1 and ABCG2 transport activity (caused by ***e.g.*** disease, drug–drug interactions or genetic polymorphisms) may lead to alterations in the plasma clearance of drugs, which can affect the pharmacological and/or toxicological effect of their substrate drugs. In order to assess tissue pharmacokinetic (PK) changes caused by alteration of hepatic transport activity, non-invasive quantification methods such as positron-emission tomography (PET) can be implemented. In this study, we evaluated the suitability of PET imaging in combination with the model ABCB1/ABCG2 substrate [^{11}C]tariquidar to measure hepatic ABCB1/ABCG2 transport activity in humans and mice.

Methods: [^{11}C]Tariquidar PET scans were carried out in 5 healthy volunteers without and with co-infusion of a pharmacological dose of tariquidar (225 mg/h). In addition, FVB wild-type, *Abcb1a/b*$^{-/-}$, *Abcg2*$^{-/-}$ and *Abcb1a/b*$^{-/-}$*Abcg2*$^{-/-}$ mice underwent PET scans without and with pre-treatment with unlabelled tariquidar (15 mg/kg). A three-compartment PK model was used to determine the rate constants defining the hepatic kinetics of the radiotracer. Moreover, to assess potential involvement of basolateral hepatic transporters in the uptake of tariquidar from blood into hepatocytes, *in vitro* uptake experiments were performed with [^{11}C]tariquidar or [^{3}H]tariquidar in different cell lines overexpressing major hepatic uptake transporters (SLCO1B1, SLCO1B3, SLCO2B1, SLC22A1 and SCL22A3).

Results: In humans, no radiolabelled metabolites of [^{11}C]tariquidar could be detected in plasma during the PET scan. The co-administration of unlabelled tariquidar caused a significant ($p < 0.05$) reduction in the rate constant describing the transfer of radioactivity from liver into bile (k_3) suggesting saturation of ABCB1/ABCG2 transport activity. In mice, 30 min after radiotracer injection, the percentage of unchanged [^{11}C]tariquidar in plasma, liver, bile and kidneys was higher than 78%, indicating that little metabolism of the radiotracer was occurring during the duration of the PET scan. Treatment with unlabelled tariquidar in mice significantly reduced k_3 in wild-type, *Abcb1a/b*$^{-/-}$ and *Abcg2*$^{-/-}$ mice, but not in *Abcb1a/b*$^{-/-}$*Abcg2*$^{-/-}$ mice. Furthermore, in baseline scans, the value of k_3 was significantly lower in *Abcb1a/b*$^{-/-}$*Abcg2*$^{-/-}$ mice as compared to wild-type and single knockout mice. *In vitro* uptake experiments indicated that tariquidar is not transported in the basolateral membrane of hepatocytes by any of the studied major uptake transporters.

Discussion: These results suggest that [^{11}C]tariquidar is a metabolically stable PET tracer which can be used in humans and mice to measure hepatic ABCB1 and ABCG2 transport activity without a confounding effect of basolateral uptake transporters. Our data point to a mutual functional redundancy between ABCB1 and ABCG2 in the hepatobiliary excretion of dual substrate drugs.

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Keywords: [^{11}C]tariquidar – ABCB1/ABCG2 – liver – positron-emission tomography

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