

## K5

### **A pilot study to assess the efficacy of tariquidar to inhibit cerebral P-glycoprotein in humans with (R)-[<sup>11</sup>C]verapamil and PET**

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#### **Background**

Tariquidar (TQD), a potent, nontoxic, third-generation P-glycoprotein (P-gp) inhibitor, is a possible reversal agent for central nervous system drug resistance. In animal studies, TQD has been shown to increase delivery of P-gp substrates into brain by several-fold. Our aim was to measure P-gp function at the human blood-brain barrier (BBB) after TQD administration using PET and the model P-gp substrate (R)-[<sup>11</sup>C]verapamil (VPM).

#### **Methods**

Five healthy volunteers underwent paired VPM PET scans and arterial blood sampling, before and at 3h after i.v. administration of TQD (2 mg/kg). VPM distribution volumes (DV) before and after TQD administration were estimated for 44 brain regions using a 4-rate-constant-2-tissue-compartment model. Parametric images depicting DV differences between the two PET scans were generated using the pixel-wise Logan plot and analyzed by statistical parametric mapping (SPM5).

#### **Results**

TQD administration resulted in significant increases (Wilcoxon test for paired samples) in DV (+24 ± 15%, p = 0.043) and the influx rate constant ( $K_1$ , +49 ± 36%, p = 0.043) of VPM across the BBB (whole brain grey matter). Strong correlation was observed between change in brain DV after TQD and TQD exposure in plasma (r = 0.90, p = 0.037). SPM analysis revealed significantly smaller DV increases in cerebellum, mediotemporal lobe and brain stem as compared to other brain regions.

#### **Conclusions**

TQD significantly increased brain distribution of VPM, due to increased influx. Regional differences in VPM DV changes in response to TQD treatment suggest regional variability of cerebral P-gp function, which might make some brain areas more resistant and others more vulnerable to the accumulation of P-gp substrates.