



Tariquidar-induced P-glycoprotein inhibition at the rat blood-brain barrier studied by positron emission tomography with (R)-[¹¹C]verapamil

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Purpose

- ~30% of patients with epilepsy are pharmacoresistant
- Overexpression of the drug efflux transporter P-glycoprotein (Pgp) at the blood-brain barrier is found in resistant patients and rat models of epilepsy and may be one reason for pharmacoresistance.
- Modulation of Pgp at the blood-brain barrier by the highly selective inhibitor tariquidar may be a promising strategy to overcome drug resistance.
- In the present study it was evaluated whether μ PET-imaging with the Pgp substrate (R)-[¹¹C]-verapamil and the Pgp inhibitor tariquidar could be used to quantify Pgp-function in the brain.

Methods



- Naïve female Wistar rats
- Focus 220 μ PET-Scanner, 350-750 keV, 6 ns timing
- Tracer: (R)-[¹¹C]-verapamil
- Paired Scans
- Pgp-inhibitor: tariquidar IV
- Blood-sampling: A. carotis catheter
- Application: V. jugularis catheter
- Activity: 1-2 mCi (37-74 MBq) in 500 μ L

Results

Administration of tariquidar results in an up to 11-fold increase of (R)-[¹¹C]-verapamil brain uptake

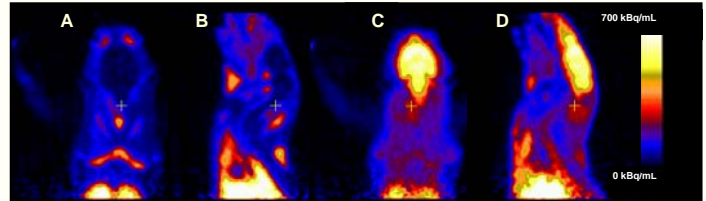


Fig.: Transversal (A and C) and sagittal (B and D) PET summation images (0–60 min) recorded before (A and B, scan 1) and after (C and D, scan 3) administration of tariquidar (15 mg/kg).

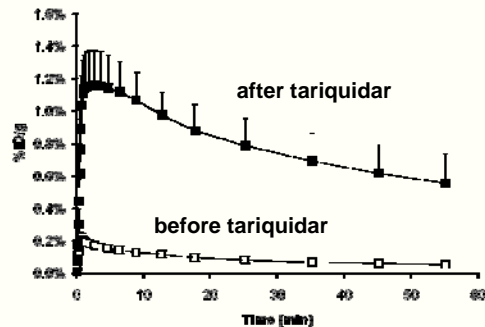


Fig.: Time-activity curves in rat brain for (R)-[¹¹C]-verapamil PET scans recorded before (\square , n = 5, scan 1) and after (\blacksquare , n = 5, scan 3) administration of tariquidar (15 mg/kg). Activity concentration is expressed as mean percentage injected dose per gram (\pm SD for n = 5).

Results

Dose-response assessment of tariquidar

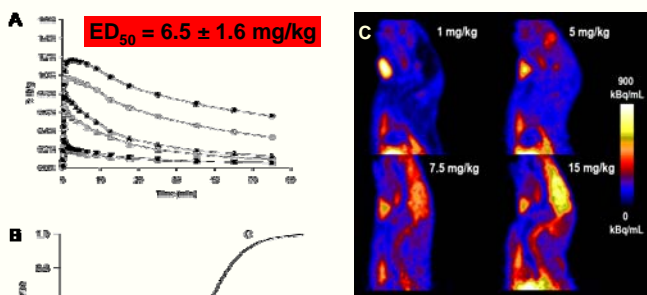


Fig.: (A) Time-activity curves in rat brain for (R)-[¹¹C]-verapamil PET scans recorded after administration of tariquidar (1, 3, 5, 7.5, 15 mg/kg). Activity concentration is expressed as mean percentage injected dose per gram. (B) Preliminary dose-response curve after administration of tariquidar. (C) Transversal PET summation images (0–60 min) recorded after administration of tariquidar.

Time course of tariquidar function

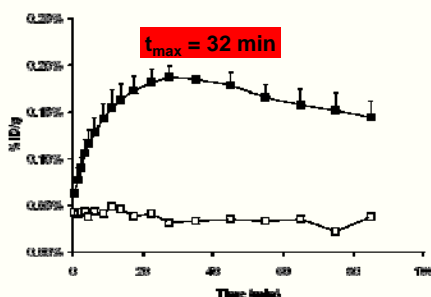


Fig.: Brain time-activity curves for PET scan 2 recorded from 0 to 90 min after administration of vehicle (\square , n = 2) or tariquidar, 15 mg/kg (\blacksquare , n = 5). PET scan 2 measured remainder of circulating activity from scan 1. Activity concentration is expressed as mean percentage injected dose per gram (\pm SD for n = 5).

Outcome parameters for 2T4K-model

Parameter	Before TQD	After TQD	% Δ
K_1 (mL·mL ⁻¹ ·min ⁻¹)	0.07 \pm 0.03	0.58 \pm 0.20	+711 [†]
k_2 (min ⁻¹)	0.34 \pm 0.06	0.27 \pm 0.07	-23
k_3 (min ⁻¹)	0.29 \pm 0.22	0.37 \pm 0.17	+27
k_4 (min ⁻¹)	0.73 \pm 0.29	0.66 \pm 0.49	-9
DV (mL·mL ⁻¹)	0.30 \pm 0.08	3.68 \pm 0.81	+1,137 [†]

[†] indicates significant differences, paired t-test (p < 0.05)

Conclusion / Outlook

❖ (R)-[¹¹C]-verapamil μ PET is a promising tool for quantifying Pgp function at the BBB.

Next steps:

- ❖ This setup will be used to quantify Pgp expression in rat models of drug resistant epilepsy.
- ❖ In parallel to the animal studies this approach will be translated to healthy volunteers and epileptic patients.

Acknowledgements

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