

Tariquidar Inhibition of P-glycoprotein Function In Patients With Mesial Temporal Lobe Epilepsy Measured With PET And (R)-[¹¹C]Verapamil

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Background and Hypotheses

- Overexpression of drug transporter P-glycoprotein (Pgp) is thought to be involved in pharmacoresistant mesial temporal lobe epilepsy (mTLE) by extrusion of antiepileptic drugs (AEDs) [1, 2]
- We hypothesise that:
 - In drug-resistant mTLE, uptake of the Pgp substrate (R)-[¹¹C]verapamil (VPM) is reduced in the epileptogenic relative to contralateral regions and compared to healthy controls
 - The 3rd-generation Pgp inhibitor tariquidar (TQD) increases VPM uptake, but this increase is attenuated in epileptogenic regions compared to contralateral regions of mTLE patients and to healthy controls

Methods

Patients

- To date 4 healthy controls (1 male, age 35-55 y) and 6 drug-resistant mTLE patients with unilateral hippocampal sclerosis (3 males, age 30-56 y) (Table 1)

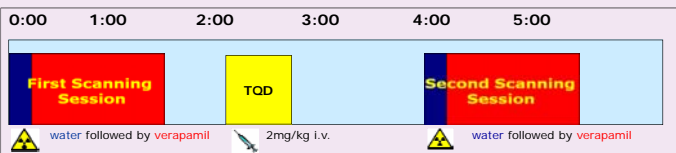
Table 1 Clinical EEG and MRI data of 6 drug-resistant mTLE patients

Patient	Gender/Age (years)	Syndrome	MRI	EEG	Age at onset of Epilepsy (years)	Interval last CPS to PET (days)	Current AEDs (dose: mg/day)
1	M/43	L mTLE	L HS	LT	5	21	PHT (325) CLOB (20) SVP (1500) LVT (2000) CBZ (1000) ZON (150) CLOB (10)
2	F/38	R mTLE	R HS	RT	18	12	LTG (200) PRG (300)
3	F/56	R mTLE	R HS	RT	11	3	LEV (750) OXC (600) CLOB (20)
4	M/30	L mTLE	L HS	LT	19	6	VPA (1600) CBZ (1200) TPM (150)
5	M/56	L mTLE	L HS	LT	0.83	3	CBZ (400) PHT (350) LTG (100)
6	F/50	R mTLE	R HS	RT	12	4	

M, male; F, female; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; CBZ, carbamazepine; VPA, valproic acid; PHT, phenytoin; CLOB, clobazam; PGB, progabalin; EEG, electroencephalography; R, right; L, left; T, temporal; HS, hippocampus sclerosis.

PET data acquisition

- [¹⁵O]H₂O scan to measure regional cerebral blood flow (rCBF), followed by (R)-[¹¹C]verapamil scan to assess Pgp function with arterial blood sampling
- 60min after a 30min infusion of TQD (2mg/kg i.v.) to inhibit Pgp, second set of water and VPM scans acquired



PET data processing

- Regional VPM data quantified by K₁ from single-tissue compartment model with VPM plasma input function and analysis performed on first 10min of dynamic data containing limited radiolabeled metabolites [3]
- Asymmetry index calculated as: $AI(\%) = \frac{ipsi - contra}{contra} \times 100$
- rCBF estimated from dynamic data using single-tissue compartment model with variable dispersion and fixed delay
- Statistical analysis performed using Mann-Whitney U-test (between groups) and Wilcoxon signed-rank test (for asymmetry index within groups); statistical significance p < 0.05

References
[1] Sisodiya et al., Brain 2002; 125: 22-31.
[2] Loscher and Potschka, J Pharmacol Exp Ther 2002; 301: 7-14.
[3] Muzi et al., J Nucl Med. 2009; 50: 1267-75.
[4] Abraham et al., Eur J Nucl Med Mol Imaging. 2008; 35: 116-23.

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Conclusion

- In support of the hypothesis of Pgp overexpression in mTLE:
 - VPM K₁ increases globally by 2-fold in healthy controls compared to mTLE patients after TQD
 - Less pronounced increase in VPM K₁ after TQD in some temporal lobe regions ipsilaterally to the epileptogenic focus compared to contralaterally
- Open questions are:
 - Does epilepsy, uncontrolled seizures or chronic treatment with AEDs stimulate a global response of Pgp function?
 - Do mTLE patients have increased metabolism of TQD from AEDs (similar to increased metabolism in VPM [4])? TQD plasma levels currently awaiting measurements

Results

- At baseline, no difference in VPM K₁ (mL/min/cm³) values for temporal lobe regions between healthy controls (0.031 ± 0.01) and mTLE patients (0.039 ± 0.01).
- After TQD, significant increase in VPM K₁ for temporal lobe regions in healthy controls (60%) compared to mTLE patients (26%) (p < 0.05) (Figure 1)

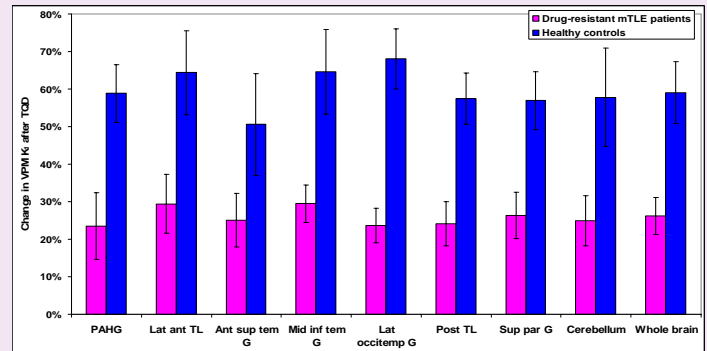


FIG 1. Mean % change in VPM K₁ following TQD (2mg/kg i.v.) for 4 healthy controls and 6 mTLE patients in 6 different temporal lobe regions of interests (ROI) and the extratemporal control ROI (superior parietal gyrus) as well as cerebellum and whole brain. PAHG, parahippocampal and ambient gyrus; Lat ant TL, lateral anterior temporal lobe; Ant sup tem G, anterior superior temporal gyrus; Mid inf tem G, middle and inferior temporal gyrus; Lat occitemp G, lateral occipitotemporal gyrus; Post TL, posterior temporal lobe; Sup par G, superior parietal gyrus. Error bars represent standard error of the mean (SEM).

- No effect of TQD on rCBF (mL/min/cm³) in temporal lobe regions of healthy controls (0.38 ± 0.02 versus 0.37 ± 0.02 at baseline) and mTLE patients (0.36 ± 0.02 versus 0.36 ± 0.02 at baseline)
- After TQD, asymmetry index decreases (i.e. increases of VPM K₁ contralateral > ipsilateral) in anterior superior temporal gyrus and posterior temporal lobe (p < 0.05) in mTLE patients compared to baseline (Figure 2). No significant changes measured in healthy controls

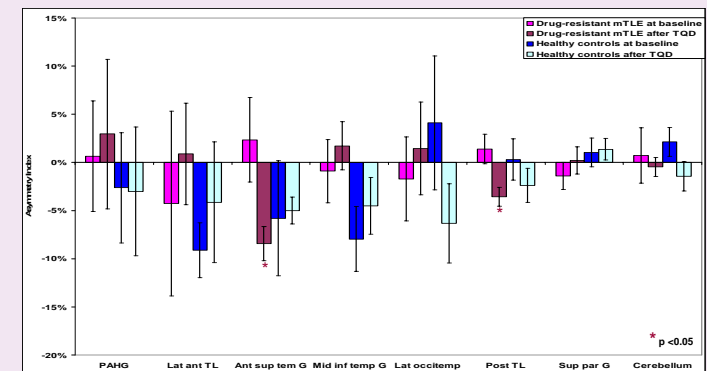


FIG 2. Mean asymmetry index (%) in VPM K₁ at baseline and after TQD (2mg/kg i.v.) for 4 healthy controls and 6 mTLE patients in 6 different temporal lobe ROIs and the extratemporal control ROI (superior parietal gyrus) as well as cerebellum. (See Fig 1 for region abbreviations). Error bars represent SEM.