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Meeting abstract

In vivo dose finding of tariquidar using (*R*)-[^{11}C]verapamil μPET

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Introduction

Tariquidar (TQD, Xenova, UK) is a third-generation inhibitor of the multidrug efflux transporter P-glycoprotein (P-gp) with potential applications in neurology and oncology in order to increase drug exposure of tissues targeted for treatment. We used small-animal positron emission tomography (μPET) with the P-gp substrate (*R*)-[^{11}C]verapamil (VPM) in order to measure in vivo the degree of P-gp inhibition at the rat blood-brain barrier (BBB) after administration of different doses of TQD.

Methods

Wistar Unilever rats received intravenous doses of 0, 1, 3, 5, 7.5 and 15 mg/kg of TQD followed by a 1-hour VPM μPET scan recorded at 2 hours after TQD administration. Brain-to-plasma radioactivity ratios were fitted to a sigmoidal dose-response curve.

Results

TQD inhibited P-gp-mediated efflux of VPM across the BBB with an apparent half-maximum effective dose (ED_{50}) of 6.6 mg/kg (95% confidence interval: 4.9–8.2 mg/kg) which was in good agreement with previous data reported in mice for another P-gp substrate (loperamide, ED_{50}: 5.7 mg/kg) [1]. Brain-to-plasma radioactivity ratios after 0 and 15 mg/kg of TQD were 0.23 and 3.15, respectively.

Conclusion

Our data suggest that TQD is a potent inhibitor of P-gp at the rat BBB. Moreover, VPM PET appears to be a useful tool for in vivo dose finding of novel P-gp inhibitors in animals and humans.

References

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