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MEETING ABSTRACT Open Access

Dose-response assessment of tariquidar for inhibition of P-glycoprotein at the human blood-brain barrier using (*R*)-[^{11}C]verapamil PET

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Background

Positron emission tomography (PET) with the radiolabelled substrate of the multidrug efflux transporter P-glycoprotein (P-gp) (*R*)-[^{11}C]verapamil (VPM) can be used to assess P-gp function at the blood-brain barrier (BBB). We have shown in rats that performing VPM PET scans after half-maximum inhibition of P-gp with the third-generation P-gp inhibitor tariquidar (TQD) is more sensitive for detecting regional differences in cerebral P-gp function than VPM baseline scans [1]. In order to translate this concept to humans a detailed understanding of the dose-response relationship of TQD for inhibition of P-gp at the human BBB is required.

Materials and methods

Healthy male subjects (n = 3 per dose group) underwent VPM PET scans and arterial blood sampling at 1 h after infusion of TQD at doses of 3, 4, 6 and 8 mg per kg body weight. Brain uptake of radioactivity was quantified as the ratio of the area under the time-activity curve (AUC) in whole brain and in arterial plasma (AUC_{brain}/AUC_{plasma}). Radiometabolites of VPM in plasma were assessed with a previously described solid-phase extraction protocol [2]. Data were pooled with data from a previous pilot study in 5 healthy male subjects, who underwent paired VPM PET scans before and after administration of 2 mg/kg TQD [2].

Results

TQD was well tolerated in all but 1 subject, who belonged to the 8 mg/kg dose group and experienced mild hypotension and bradycardia as adverse events. Administration of TQD at different doses exerted no effect on the fraction of polar radiometabolites of VPM in plasma. AUC_{brain}/AUC_{plasma} increased with increasing doses of TQD from 0.30 ± 0.06 for baseline scans to 0.74 ± 0.18 for the 4 mg/kg dose, but did not further increase at doses >4 mg/kg.

Conclusions

Our data suggest that the half-maximum effect dose (ED_{50}) of TQD to enhance VPM-derived brain activity uptake in humans is similar to the value previously determined in rats using an identical study protocol (3.0 ± 0.2 mg/kg) [1]. In humans complete inhibition of P-gp at the BBB seemed to occur at TQD doses ≥4 mg/kg. The maximum increase in brain activity uptake was several-fold lower in humans as compared to rats (2.5 and 10-fold maximum increases relative to baseline in rats and humans, respectively).

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