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MEETING ABSTRACT Open Access

A PET microdosing study with the P-glycoprotein inhibitor tariquidar

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Background

The adenosine triphosphate-binding cassette transporters P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) restrict absorption and body distribution and promote excretion of several clinically used drugs. Tariquidar (XR9576) is a potent third-generation dual Pgp and BCRP inhibitor, which is currently tested in clinical trials to overcome chemoresistance of tumors and to enhance brain distribution of Pgp/BCRP substrate drugs. We performed a positron emission tomography (PET) microdosing study with carbon-11-labelled tariquidar ([^{11}C]tariquidar) which aimed at assessing the brain distribution of [^{11}C]tariquidar in healthy volunteers.

Methods

Six healthy subjects received an i.v. bolus injection of approximately 400 MBq of [^{11}C]tariquidar containing less than 30 μg of unlabelled tariquidar. Then, dynamic brain PET scans and arterial blood sampling were performed. Radiolabelled metabolites of [^{11}C]tariquidar in plasma were measured with a solid-phase extraction/HPLC assay. Brain activity uptake was expressed as the ratio of the area under the whole brain grey matter time-activity curve to the area under the plasma time-activity curve from time 0 to 60 min ($AUC_{0-60\ brain}/AUC_{0-60\ plasma}$).

Results

Brain activity uptake was low after injection of [^{11}C]tariquidar with a mean $AUC_{0-60\ brain}/AUC_{0-60\ plasma}$ of 0.14 ± 0.03. At 60 min after radiotracer injection, 78 ± 12% of total radioactivity in plasma was in the form of unchanged parent radiotracer. Less than 1% of the total injected dose excreted in urine over 90 min.

Conclusions

Low brain uptake of radioactivity is consistent with tariquidar being, at microdoses, a dual substrate of Pgp and BCRP. [^{11}C]Tariquidar PET after inhibition of Pgp with unlabelled tariquidar may be a promising approach to selectively assess BCRP function at the human blood-brain barrier.

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