Human Brain Dosimetry in Disrupted Blood Brain Barrier Using [Sn-117m]-DOTA-Annexin V (SnDAV): A Model for Targeting Aged Microglia in Alzheimer's Disease

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BACKGROUND

Microglia, the macrophages of the brain,[1,2] are a potential target for treatment based on the neuroinflammatory hypothesis of Alzheimer's Disease (AD). Annexin V binds to the outer leaflet of the cell membrane of cells undergoing apoptosis. Previous studies[3,4] utilizing Sn-117m chelated to annexin V [SnDAV] demonstrated localization in atheroma-containing macrophages. Human stroke subjects were injected intravenously with SnDAV in order to target apoptosis in carotid artery macrophages. The dose of radiation delivered to the macrophages can itself induce apoptosis.

Sn-117m ($t_{1/2}$=14 d) is a unique radionuclide that decays by isomeric transition, producing both gamma rays at 159 keV, 86% abundance as well as monoenergetic conversion electrons (CE) (~140 keV; >110%) with a range of about 300 μm in tissue.

METHODS

In the CAROTID 1 (0.5 mCi safety study) and CAROTID 2 (3 mCi imaging study) trials, Sn-117m was coupled to aminobenzyl-DOTA and purified using HPLC (Figure 1). Conjugation of the chelate to annexin V-128 was accomplished by

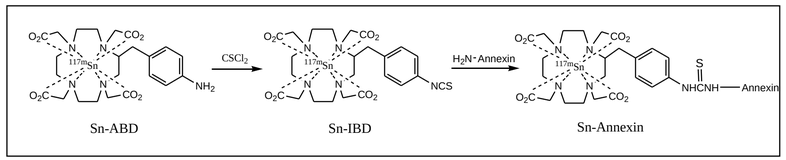

Figure 1. Production of [Sn-117m]-DOTA-annexin V (SnDAV)

preparing the isothiocyanate version of the chelate and then reacting it with lysine residues on the annexin for 90 minutes at 37C. Analytical methods used to evaluate the cGMP SnDAV that was produced demonstrated >95% monomer, cell binding, typically pK=23-25, overall chelation yields were ~95%, and ~40% for conjugation to the annexin V. Subjects with symptomatic carotid stenosis and ischemic signs who were scheduled to undergo carotid endarterectomy were given an intravenous dose of SnDAV prior to surgery. Brain dosimetry was determined by employing HERMES image analysis software to calculate the organ activity at various time points (Table 1 and Figure 2). Patients were imaged with scintigraphy (CAROTID 1 and 2) as well as SPECT (CAROTID 2) (Figures 3 and 4).

Residence time in brains of patients from CAROTID 1					
	Patient 002	Patient 003	Patient 004	Patient 005	Patient 006
time (d)	9.4	4.5	4.1	4.6	6.6

Table 1. Residency time in the brain is a surrogate for the biological half-life. Note patient 002 has a residency time of SnDAV which is substantially longer than that of the remainder of the cohort, suggesting a greater disruption of the BBB in this patient. In addition, although the biological half-life of 9.4 days is shorter than the physical half-life of 13.6 days, it suggests that SnDAV is well retained in the tissue.

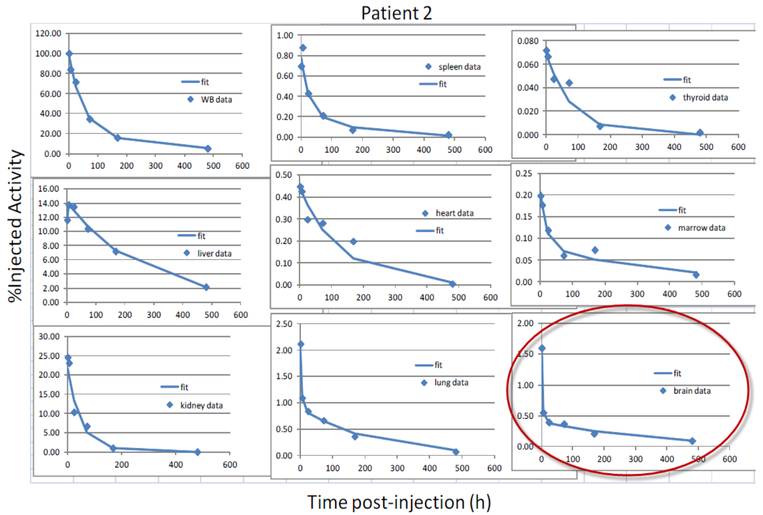

Figure 2. The nine measured tissues in patient 002 (CAROTID 1, 0.5 mCi), show variability in SnDAV retention. The brain and lung demonstrate rapid washout of SnDAV plateauing to a near steady-state. This data suggests longer term retention in these tissues

RESULTS

SnDAV resided in the brain of human post-stroke subjects, delivering gamma photons and therapeutic CE for up to 500 hours. We were able to determine that SnDAV was bound to and slowly released from the brain, and resided in the brain long enough to provide a potential therapeutic effect for at least 21 days.

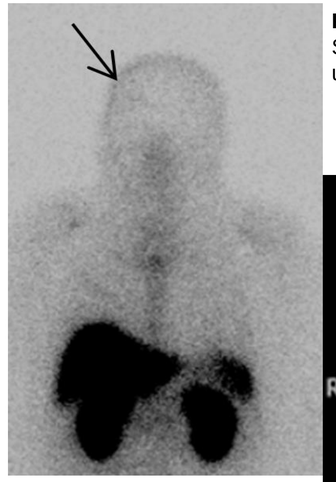

Figure 3: Patient #7 from CAROTID 2 (3mCi SnDAV) has scintigraphy suggesting increased uptake of SnDAV in the right parietal region.

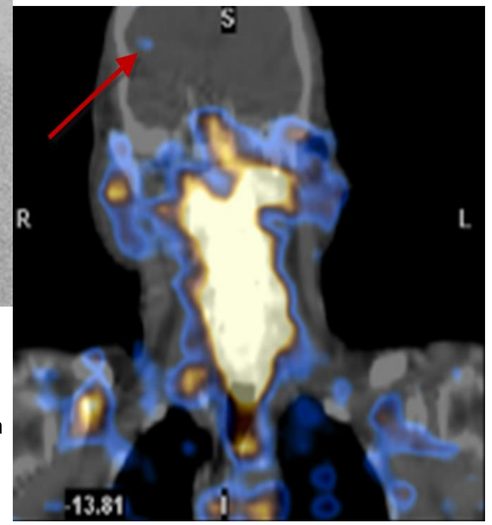

Figure 4: Patient #10 from CAROTID 2 (3mCi SnDAV) with a SPECT image demonstrating a focal abnormailty in the right parietal area.

CONCLUSIONS

We have demonstrated that systemically delivered SnDAV resides in the brain of subjects with ischemia-disrupted BBB. We hypothesize that SnDAV may be used to suppress aged microglia[5,6] as a novel AD amyloid and tau[7] therapeutic.

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