Pharmacokinetics, Dosimetry, and Histopathology to Enable Phase-I Clinical Trial in Patients with Neuroendocrine Tumors

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Abstract

**Objective:** Evaluate pharmacokinetics of 225Ac-DOTATOC with and without kidney protection (KP) to compare 225AcNO3 and “free” 225Ac derived from accelerator production versus stockpile extraction; to estimate predicted radiation absorbed dose (RADD) to humans receiving 225Ac-DOTATOC, and to evaluate histopathology of 10 days post-administration.

**Methods:** 225AcNO3-accelerator, and 225AcNO3-stockpile, as 225Ac-DOTATOC prepared using 225AcNO3-stockpile was administered IV to male Sprague-Dawley rats, n= 5 per cohort per time point, with and without KP 1, 2 hours to 90 days post-administration, rats were euthanized. Bone marrow aspirates were collected for histological examination. Organs were collected, weighed, evaluated for radiolucency using a gamma counter and processed for histopathological examination. Cumulative organ radioactivity was used as the input function to estimate mean radiation absorbed tissue dose in humans (OLINDA / EGS 4.1). Mean Residence Times (MBq-h/MBq) were determined to allow estimation of RADD in mSv/MBq.

**Results:** 225Ac-DOTATOC (1μCi + KP 3μCi 10μCi +KP 10μCi) Accelerator. Stockpile: Accelerator- 9.21E8, 8.53E-1, 1.60E+01 -10.34 1.66E+02 1.45E+02 14.48 8.85E-3, 1.00E-3, 3.62E+00 9.57E-3, 3.62 6.73E+01 5.64E-5, 5.29E-02 17.47 4.21E-01 3.93E-01 7.12 1.515 5.156 28.15 -11.88 4.46E-03 3.50E-03 27.43 2.94E-3, 3.23 1.69 4.645 9.40E-6, 6.41E-10.94 2.86E-02 1.96E-02 45.92 1.09E+02 6.22E-7, 7.72E+00 -21.57 6.80E+01 4.45E+01 52.81 0.596 1.314 157.68 2606.94 3.12 9.988 -21.48 5.93E+02 3.88E+02 52.84 7.05E+00 6.902 14.47 6.35E+00

**Specific aims in healthy rats:**
1. PK: 1. MRT: a radiation absorbed dose (RADD) following IV 225Ac-DOTATOC.
2. Estimate radiation absorbed dose in human subjects following IV 225Ac-DOTATOC.
3. Evaluate histopathology to determine the effects of dosage and kidney protection in normal rats up to 90 days PA.

**225Ac:Stockpile vs Accelerator Production**

**Dosimetry**
- 225AcNO3: 6.13 2.107 2.849 % 225 Ac/227 Ac
- 225Ac-DOTATOC: 2.45 ± 0.002 % 225 Ac/227 Ac

**Histopathological Findings**
- Bone marrow changes were more severe in the 225AcNO3-accelerator and 225AcNO3-Stockpile groups that died before the end of the study, suggesting that some bone marrow regeneration was taking place in rats that survived for the entire study. There was mild to moderate bone marrow hypoplasia in the 3 μCi KP DOT225AcNO3, 10 μCi KP DOT225AcNO3, and 10 μCi KP DOT225Ac NO3 groups.
- Cardiac necrosis and subendocardial fibrosis were seen in all groups except the vehicle control, DOT225AcNO3 control, and the 3 μCi KP DOT225Ac NO3 groups.
- All groups except the two control groups showed evidence of tubulointerstitial nephritis, but the pattern of nephropathy in each group varied.

**Histological Findings**
- Bone lesions were seen only in 225AcNO3-accelerator treated rats. These changes included mineralization of individual myofibers (a degenerative change) and expanded myofibers.

**Conclusion:**
- 3 μCi 225Ac-DOTATOC was administered IV to male Sprague Dawley rats, n= 5 per cohort per time point, with and without KP 1, 2 hours to 90 days post-administration. Blood was collected for CBC and metabolic profile. Organs were collected, weighed, evaluated for radiolucency using a gamma counter and processed for histopathological examination. Cumulative organ radioactivity was used as the input function to estimate mean radiation absorbed tissue dose in humans (OLINDA / EGS 4.1). Mean Residence Times (MBq-h/MBq) were determined to allow estimation of radiation absorbed dose in mSv/MBq. Reference source was 227Ac in all experiments. Rats receiving 3 μCi KP DOT225Ac NO3 or 10 μCi KP DOT225Ac NO3 developed mild to moderate bone marrow hypoplasia. All DOT225AcNO3 groups showed normal pattern of fat replacement in bone marrow consistent with mild to moderate bone marrow hypoplasia. There were no cardiac lesions seen in any of the groups except those receiving 225AcNO3-accelerator. Leukocytes were not affected in 225AcNO3- and accelerator groups and accelerated accumulation of 225AcNO3 was the same as in all other organs. Cardiac production 225Ac NO3 and 225Ac NO3 + KP were both similar to 225AcNO3-accelerator group. Cardiac lesions in control and 225Ac-DOTATOC groups were negligible at all timepoints. The estimated radiation absorbed dose data from 225Ac-DOTATOC was low in all critical organs. Accelerator produced 225Ac NO3 contains 225Ac NO3 group. In all cases, the absorbed doses did not result in any effect.

**Future**
- 227Ac reference source to determine intrinsic efficiency
- Data normalized using Osiris 2.0

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**Results**

**Results cont.**