Preclinical evaluation of the alpha-particle generator nuclide 225Ac for somatostatin receptor radiotherapy of neuroendocrine tumors.

PURPOSE: Peptide receptor radionuclide therapy (PRRT) using somatostatin analogues labeled with beta-particle-emitting isotopes such as 90Y or 177Lu has been a promising treatment strategy for metastasized neuroendocrine tumors. Although remission can be accomplished in a high percentage of neuroendocrine tumors, some tumors do not respond to this treatment. alpha-Emitting isotopes such as the 10-day half-life alpha-emitting generator nuclide Actinum-225 (225Ac)-are characterized by extremely high cytotoxic activity on the cellular level, and may be superior in the treatment of neuroendocrine tumors not responding to PRRT using beta-emitting isotopes.

EXPERIMENTAL DESIGN: Radiolabeling of 225Ac 1,4,7,10-tetra-azacyclododecane N,N',N'',N'''-tetraacetic acid-Tyr3-octreotide (DOTATOC) was done at pH 5 (60 minutes at 70 degrees C) without further purification. Biodistribution in nude mice bearing AR42J rat pancreas neuroendocrine tumor xenografts were measured for up to 24 hours. Toxicity was tested by weight changes, retention variables (blood urea nitrogen and creatine), and histopathology in mice 7 months after treatment with 10 to 130 kBq (n = 4-5). Therapeutic efficacy was assessed by tumor weighing in animals treated 4 days after
xenotransplantation and compared with 177Lu-DOTATOC as a reference. RESULTS: Activities up to 20 kBq had no significant toxic effects in mice. In contrast, activities higher than 30 kBq induced tubular necrosis. Biodistribution studies revealed that 225Ac-DOTATOC effectively accumulated in neuroendocrine xenograft tumors. 225Ac-DOTATOC activities were shown to be nontoxic (12-20 kBq), reduced the growth of neuroendocrine tumors, and showed improved efficacy compared with 177Lu-DOTATOC. CONCLUSIONS: 225Ac might be suitable to improve PRRT in neuroendocrine tumors.