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Preparation, characterization and in-vitro studies of [68Ga]NODAGA-Pamidronic acid for PET bone imaging

Background
For years, bisphosphonates (BP) were known for its role in reducing the risk of skeletal related event in patients with bone metastases by accumulating and inhibiting the osteoclastic activity. Hence, since the emergence of germanium-68/gallium-68 generator for positron emission tomography (PET) imaging, developments in gallium-68 labeled BP for bone imaging have been looked into. Through the conjugation of a stable bifunctional chelator to a BP namely 2,2′-(7-(1-carboxy-4-((2,5-dioxopyrrolidin-1-yl)oxy)-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (NODAGA) and Pamidronic acid, this research aims to study the preparation, characterization, and in-vitro studies of [68Ga]NODAGA-Pamidronic acid ([68Ga]NODPAM) for PET bone imaging.

Methodology
NODAGA was conjugated to Pamidronic acid via NHS ester strategy. The conjugated precursor was characterized using tandem mass spectrometry (MS/MS) and purified using high performance liquid chromatography (HPLC). The conjugated NODAGA-Pamidronic acid was radiolabeled with gallium-68 in acetate buffer forming [68Ga]NODPAM complex. The percentage radiochemical purity (%RCP) was assessed using radio-thin layer chromatography scanner (stationary phase: TLC-SG 60; mobile phase: acetonitrile:0.4M Phosphate (7:3)). The human plasma stability was studied 0.5 hourly for 2.5 hours. The bone binding assay of [68Ga]NODPAM was performed using synthetic hydroxyapatite (HA) and was compared with [99mTc]MDP. To visualize the retention of [68Ga]NODPAM on bone, a preliminary PET image of fresh bone incubated in [68Ga]NODPAM was performed.

Results/Discussion
The MS/MS analysis of conjugated NODAGA-Pamidronic acid produced expected mass-to-charge ratio (calculated [M-H]- m/z: 591, obtained [M-H]- m/z: 591). Based on the fragments produced, the structure of NODAGA-Pamidronic acid was confirmed ([M-H-H2O]- m/z: 573, [M-H-H2O-HPO2]- m/z: 509). The %RCP of radiolabeled [68Ga]NODPAM was above 90% within 15 minutes at pH 4-4.5. The [68Ga]NODPAM proves to be stable in human plasma throughout the study. The in-vitro percentage HA bone binding assay performed showed significant difference between [68Ga]NODPAM 82.25%±1.72% and [99mTc]MDP of 53.21%±0.28% (p-value <0.05). The superiority of [68Ga]NODPAM in bone binding assay may be due to its indirect chelation ([68Ga]-chelate-BP) effect as compared to direct chelation ([99mTc]-BP) which may hinder its affinity of BP towards HA. Preliminary assessment using animal PET proves good bone uptake.

Conclusion
[68Ga]NODPAM was prepared and characterized accordingly and the in vitro bone binding assay was assessed. From previous studies, radiolabeled gallium-68 bisphosphonates showed convincing animal biodistribution results. Though the data obtained may not reflect overall clinical potential, preliminary data suggests that further [68Ga]NODPAM experiments on animal model especially to determine the biodistribution and bone-to-blood ratio must be performed in order to prove its clinical indication.

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