Phosphonate-complexes of Gallium-68 for bone tumour imaging

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Objectives

As ^{99m}Tc-phosphonates are well established tracers for the diagnoses of bone metastases using SPECT, analogue attempts for PET using the ^{68}Ge/^{68}Ga generator based ^{68}Ga tracers would be potentially useful. Therefore molecules containing phosphonate structure with binding affinities to apatite and being adequate complexing agents for trivalent Gallium could be considered as interesting vectors for the synthesis of generator-based PET-tracers for skeletal imaging. EDTMP, different triazacyclononane- (n=1-3 phosphonates) and DOTA-derivatives (tetraphosphonate) as well as new phosphonate structures were investigated.

Methods

Germanium-68 provides the positron emitter Gallium-68 as an easily available and inexpensive source of a PET nuclide. With the published concentration and purification method by Zhernosekov et al. [1] ^{68}Ga is obtained in 400 µL acetone/HCl mixture.

The first series of phosphonates (EDTMP, DOTP [2], NOTA-derivatives [3] and DO3AP-ABn [4]) were labelled in 400 µL 0.12 M Na-HEPES buffer by adding the ^{68}Ga fraction. Through variation of reaction time, temperature, pH and different amounts of the ligands, optimum reaction parameters for complex formation were tested. Analyses of radiochemical yield were carried out by TLC on cellulose. Binding studies on synthetic apatite were applied to simulate the binding of the ^{68}Ga-phosphonates to bone structures. A second generation of bis-phosphonates (BPAMD, BPAPD and BPPED) was labelled, assayed concerning binding to apatite and investigated *in vivo* as well.

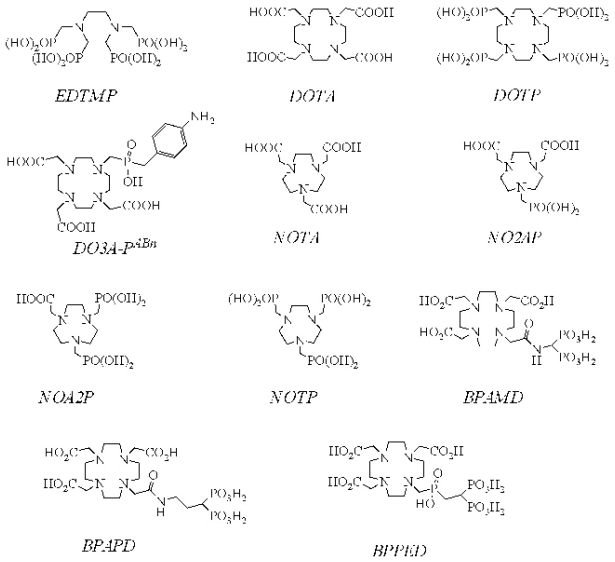

Fig. 1: ligands investigated in this study

Results

Labelling proceeds at temperatures between 25 and 75°C within 2 to 10 min in a total volume of 800 µL. Ligands are used in nanomole amounts only and the radiochemical yields are 50 to 95%. Strong and fast binding was observed for DOTP & EDTMP. Within the series of ^{68}Ga-triazacyclononanes with n=1-3 phosphonates, an increasing binding to apatite was observed.

The radiochemical yield of ^{68}Ga-DOTP was only 50%. *In vivo* experiments showed a relatively low stability of ^{68}Ga-EDTMP whereby large amounts of the ligand (>1.5 mg/kg body weight) has to be used. The bis-phosphonates showed also high binding to apatite and furthermore high stability *in vivo* in rats. Only nanomole amounts of these ligands are necessary for bone imaging.

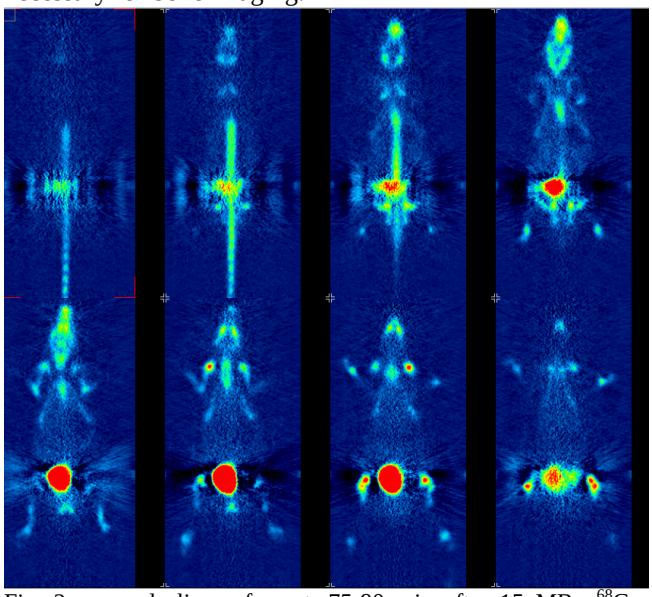

Fig. 2: coronal slices of a rat, 75-90 min after 15 MBq ^{68}Ga-BPAMD was injected

Conclusions

Syntheses of ^{68}Ga complexes are performed within 20 min after elution of the generator. Evaluations with synthetic apatite show high binding in a short time for ^{68}Ga-EDTMP and the ^{68}Ga-DOTP as well as the three new DOTA-derivatives BPAMD, BPAPD and BPPED. Preliminary µ-PET imaging on rats demonstrated bone uptake *in vivo* for ^{68}Ga-EDTMP and ^{68}Ga-DOTP. Due to the low stability of Ga-EDTMP and the low labelling yield of ^{68}Ga-DOTP the new ligands BPAMD, BPAPD and BPPED seem to be of more interest. µ-PET imaging of ^{68}Ga-BPAMD showed significant uptake in bone and high *in vivo* stability.

References

[1] Zhernosekov et al, J Nucl Med 48: 1741-8
[2] Sherry et al, Inorg Chem 35: 4604–12
[3] Geraldes et al, Magn Reson Med 9: 94–104
[4] Rudovsky et al, Org Biomol Chem 3: 112–7