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Publication date:
2015

Document Version
Early version, also known as pre-print

Link to publication from Aalborg University

Citation for published version (APA):
Modeling PET tracer uptake kinetics in inflammation and infection imaging using a porcine osteomyelitis model – preliminary results

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Introduction
Bone marrow infection (osteomyelitis) is a severe condition that can result in degradation of the affected bone and disability, as well as systemic infection originating from the osteomyelitic focus. Osteomyelitis is often hard to treat with antibiotics, and surgery is frequently needed.

The present study investigates PET scanning (Positron Emission Tomography) of pigs with experimental osteomyelitis, modeling the human condition, and permitting testing of new diagnostic tracers. PET uses short-lived radioactive tracers to reveal physiological and pathophysiological events in the living body. Using dynamic (rather than static) PET scans allows kinetic analysis of the results. This can reveal details of the uptake process, thereby giving more information about the advantages and disadvantages of the studied tracers.

Kinetic modeling
To study the uptake and release of the tracers, kinetic modeling was performed.

Volumes-of-interest (VOI) were drawn on lesion sites in the right hind limb. To compare with non-infected sites, similar VOIs were drawn at the same anatomical position in the non-infected left hind limb. In this preliminary analysis, all considered volumes were spheres of approximately the same size as the lesions as seen on the CT scans.

For a given VOI, the mean PET signal (Bq/mL) over time was analyzed as follows:

\[ \text{Water} = \frac{\text{blood}}{\text{plasma}} = \frac{\text{uptake of blood}}{\text{uptake of plasma}} \]

To determine the irreversible uptake of the tracer, the Patlak plot will be used.

The possible infection/inflammation tracers were analyzed with the compartment model shown in Figure 2b. This model has a second tissue compartment allowing modeling of irreversible tracer uptake.

To test if uptake was indeed irreversible, a Patlak plot was created for the time-dependent signal. If uptake is irreversible then the Patlak plot will be a straight line with a positive slope. The slope of the Patlak plot will be the “irreversible uptake rate” (net influx rate), K, describing the irreversible uptake.

Briefly, the Patlak plot assumes that after some time, blood and tissue will be at equilibrium. The rate K describes the irreversible uptake from this combined blood/non-inferior compartment, see Figure 2c. For further explanation, see Jødal (2015).

Porcine model and scannings
Osteomyelitis in the right hind limb was induced in four 40 kg female juvenile pigs (Danish Landrace) by intra-articular inoculation of Staphylococcus aureus (right femoral artery). The pigs were administered pain killers. On day 7 the pigs were scanned with a series of scans, along with arterial blood sampling. Dynamic PET scans were performed on the hind part of the pig using 18F-water for studying blood flow, and four other tracers as possible infection markers: 11C-methionine, 11C-PK11195, 18Ga-chloride, and 18F-FDG. The pigs were sacrificed and necropsied after scanning, and the combined results of scans and necropsies were used to determine the location of osteomyelitic lesions.

For further details and overall results, see Nielsen et al. (2015). Figure 1 shows examples of PET/CT scanning.

Results
One osteomyelitic lesion in the femoral head/neck of the first pig, and one in the metatarsus II bone of the fourth pig was studied.

Water: For both lesions, the kinetic modeling showed blood flow to be similar in the infected and non-infected side. Infected (right) and non-infected (left) sides are compared in Table I.

Possible infection/inflammation tracers: In both lesions, all four tracers showed linear kinetic analysis, implying reversible uptake. An example of a Patlak plot is shown in Figure 3. The ratio between the right (infected) and left (non-infected) side was highest for FDG and lowest for PK11195. Infected (right) and non-infected (left) sides are compared in Table II.

In Table I, the 11C-O-water is used to determine the blooduptake of the tracer, while in Table II, the 11C-methionine is used to determine the tracer uptake of the lesion.

Observations of these lesion sites, including uptake and comparison to normal tissue, were used to create a model of the lesion.

Discussion and outlook
Inflammation and infection usually results in increased blood flow, at least in the acute state, and it is therefore surprising that these two lesions had low uptake of blood flow (blood flow) at the same level as the corresponding non-infected positions in the opposite leg. Further analysis of these and other lesions are to be made to see if this finding is general for osteomyelitis lesions, which could be a part of the inability of systemic antibiotic therapy.

Of the possible infection/inflammation tracers, FDG uptake was found to have the highest uptake ratio relative to the non-infected side. A high ratio means it should be distinguished from the non-infected tissue, although uptake in other tissue (e.g. muscle uptake) should also be taken into account. In the case of PET scans, we did not show high ratios in any of the two lesions, and furthermore showed strange results giving suspicion of sticking to tubing, which makes the tracer harder to work with.

The series of pig scans continues, but without PK11195 as a tracer. Knowledge of which tracers are taken up by osteomyelitis lesions can hopefully lead to improved scanning of patients with suspicion of osteomyelitic infections.

References

Jødal. Interpretation of the Patlak plot, Tinkus PET Centre web site (2015).

www.tukspetcentre.net/petanalysis/model_patlak_interpretation.html