Modelling PET tracer uptake kinetics in inflammation and infection imaging using a porcine osteomyelitis model - preliminary results

Jødal, Lars; Hansen, Søren Baarsgaard ; Jensen, Svend Borup; Bender, Dirk; Alstrup, Aage Kristian Olsen; Afzelius, Pia; Nielsen, Ole Lerberg

Publication date:
2015

Document Version
Early version, also known as pre-print

DEPARTMENT OF VETERINARY DISEASE BIOLOGY
UNIVERSITY OF COPENHAGEN

Modeling PET tracer uptake kinetics in inflammation and infection imaging using a porcine osteomyelitis model
– preliminary results

Lars Jødal[1,2,3], Søren Baarsgaard Hansen[2], Svend Borup Jensen[3,4], Dirk Bender[2], Aage Kristian Olsen Alstrup[2], Pia Afzelius[5], Ole Lerberg Nielsen[1]

[1] Dept. of Veterinary Disease Biology, University of Copenhagen
[2] Dept. of Nuclear Medicine & PET Center, Aarhus University Hospital
[3] Dept. of Nuclear Medicine, Aalborg University Hospital
[4] Dept. of Chemistry and Biochemistry, Aalborg University
[5] Dept. of Diagnostic Imaging, North Zealand Hospital, Copenhagen University Hospital

Introduction

Bone marrow infection (osteomyelitis) is a severe condition that can result in degradation of the affected bone and disablement, 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 on the advantages and disadvantages of the studied tracers.

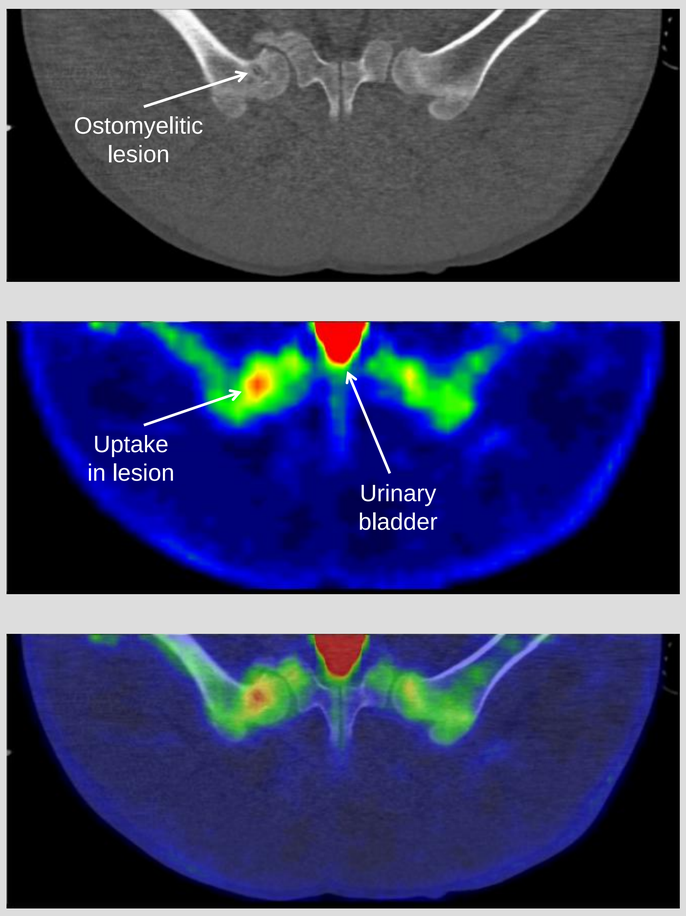

Figure 1. Example images from PET/CT scanning

Upper: CT-scanning of pig with osteomyelitic lesion in right femoral head/neck. Middle: PET-scanning with ^{18}F-FDG. Lower: Fused PET/CT image.

Porcine model and scannings

Osteomyelitis in the right hind limb was induced in four 40 kg female juvenile pigs (Danish Landrace) by intra-arterial inoculation of *Staphylococcus aureus* (right femoral artery). The pigs were administered pain killers. On day 7 the pigs were scanned with a series of tracers, along with arterial blood sampling. Dynamic PET scans were performed on the hind part of the pig using ^{15}O-water for studying blood flow, and four other tracers as possible infection markers: ^{11}C-methione, ^{11}C-PK11195, ^{68}Ga-citrate, and ^{18}F-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.

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 limb. To compare with non-infected sites, similar VOIs were drawn at the same anatomical position in the non-infected left 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:

Water flows freely with the blood plasma, and its initial uptake will be a measure of blood flow in the tissue. More precisely, the kinetics of the ^{15}O-water was analyzed with the compartment model shown in Figure 2a. The K_1 uptake rate constant was taken as measure of blood flow.

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 made for the time-dependent signal. If uptake is irreversible then the Patlak plot will become a straight line with positive slope. The slope of the Patlak plot will be the "irreversible uptake rate" (net influx rate), K_i, describing the irreversible uptake.
Briefly, the Patlak plot assumes that after some time, blood and the "reversible" compartment are in equilibrium. The rate K_i describes the irreversible uptake from this combined blood/reversible compartment, see Figure 2c. For further explanation, see Jødal (2015).
The plasma measurements for ^{11}C-methionine and ^{11}C-PK11195 were metabolite-corrected, while the other tracers did not show significant metabolization.

Figure 2 . Models for kinetic analysis

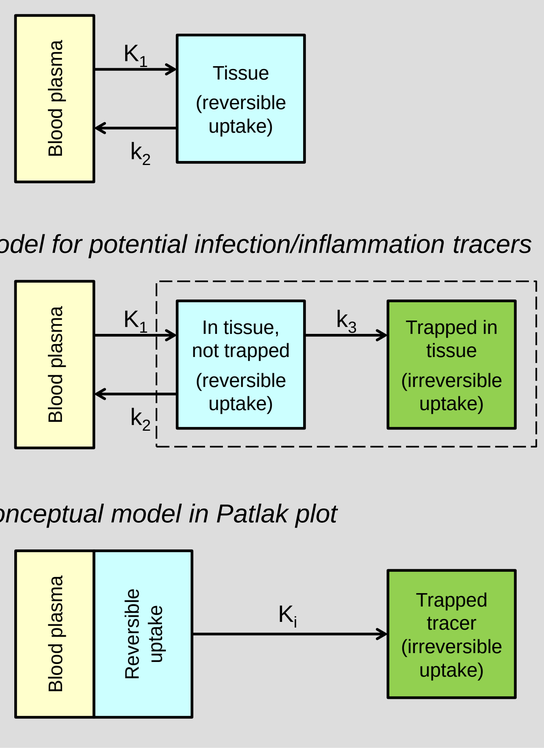

Figure 3. Example Patlak plot

Patlak plot for ^{11}C-methionine uptake in femoral head/neck lesion

Results

One osteomyelitic lesion in 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 Patlak plot, signifying irreversible 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.
PK11195 showed surprisingly low values of the plasma input curve. Other researchers have found this tracer to be sticking to tubing, which could give erroneously low values in the plasma curve initially while making later values unreliable.

Table I. Model results for water (measure of blood flow)

Lesion	Tracer	K_1		ratio infected/ non-infected
		infected	non-infected	
Femoral head/neck	^{15}O-water	0.30 min^{-1}	0.27 min^{-1}	**1,1**
Metatarsus II	^{15}O-water	0.10 min^{-}	0.11 min^{-1}	**0.9**

Table II. Model results for infection/inflammation tracers

Lesion	Tracer	K_i		ratio infected/ non-infected
		infected side	non-infected	
Femoral head/neck	^{11}C-methionine	0.068 min^{-1}	0.048 min^{-1}	**1.4**
	^{11}C-PK11195	0.54 min^{-1} (*)	0.39 min^{-1} (*)	**1.4**
	^{68}Ga-citrate	0.008 min^{-1}	0.006 min^{-1}	**1.2**
	^{18}F-FDG	0.012 min^{-1}	0.006 min^{-1}	**2.0**
Metatarsus II	^{11}C-methionine	0.078 min^{-1}	0.023 min^{-1}	**3.7**
	^{11}C-PK11195	0.47 min^{-1} (*)	0.31 min^{-1} (*)	**1.6**
	^{68}Ga-citrate	0.0059 min^{-1}	0.0016 min^{-1}	**3.8**
	^{18}F-FDG	0.046 min^{-1}	0.010 min^{-1}	**4.9**

(*) Plasma curve for PK11195 may be unreliable, which could lead to too high values of K_i while ratio of K_i values would be more stable.

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 water uptake (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 osteomyelitic 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 will make it easier to distinguish infection from non-infection, although uptake in other tissue (e.g. muscle uptake) should also be taken into account. PK11195 did not show high ratio 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 scannings continues, but without PK11195 as a tracer. Knowledge of which tracers are taken up by osteomyelitic lesions can hopefully lead to improved scanning of patients with suspicion of osteomyelitic infections.

References

Nielsen, Afzelius, Bender, Schønheyder, Leifsson, Nielsen, Larsen, Jensen, Alstrup. Comparison of autologous ^{111}In-leukocytes, ^{18}F-FDG, ^{11}C-methionine, ^{11}C-PK11195, ^{68}Ga-citrate for diagnostic nuclear imaging in a juvenile porcine haematogenous *staphylococcus aureus* osteomyelitis model, *Am J Nucl Med Mol Imaging* (2015); **5**:169-182. www.ajnmmi.us/files/ajnmmi0002237.pdf

Jødal. Interpretation of the Patlak plot, *Turku PET Centre web site* (2015). www.turkupetcentre.net/petanalysis/model_patlak_interpretation.html