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Modeling of ^{18}F-^{10}B-FBPA

Specificity

As an amino acid analog, boronophenylalanine is actively taken up by tissue. In rapidly proliferating tissue, such as tumors, uptake is accelerated. Thus it is possible to achieve good contrast in ^{10}B concentration between malignant and normal tissue by using BPA as carrier. Imahori *et al.* detected tumor-to-normal ratios of around 3 for glioma patients (1). Chadha *et al.* achieved an average tumor-to-blood ratio of 3,5 with BPA-Fr; the ^{10}B concentration in normal brain was smaller than that in blood (2). Mallesch et al. detected average T/B ratios of 4,4±3,2 in metastatic melanoma (n=12) and 2,2±1,2 in glioma (n=6) (BPA-Fr) (3). Tumor-to-normal ratio reaches equilibrium after 20 min (1).

Similarity in pharmacokinetics between fluorine-18-labeled L-fluoroboronophenylalanine and L-^{10}B-BPA has been demonstrated by Imahori *et al* (4).

The accumulation of ^{18}F-^{10}B-FBPA has been found to correlate with the degree of malignancy (1). The L form of the tracer is taken up better than the DL form (1).

Compartmental modeling

Imahori et al. used a three-compartment model for the evaluation of kinetics of ^{18}F-^{10}B-FBPA (1). They fitted k4 first but omitted it later because of its minimal significance.

Kabalka *et al.* used a four-compartment model for kinetic analysis of ^{18}F-BPA-Fr (5). This model differs from the three-compartment model by an additional blood-pool compartment that represents protein and RBC binding of ^{18}F-BPA-Fr in whole blood as well as the appearance of possible metabolites in whole blood. This compartment corrects for the whole-blood part of the total activity detected by PET, a problem often addressed by arterial blood sampling. The rate constants k1-k4 are the same as for the three-compartment model described by Huang *et al.* for ^{18}F-2-fluoro-2-deoxyglucose (6).

Non-compartmental modeling

Patlak analysis

Imahori *et al.* found, that when the data were represented as Gjedde-Patlak plots, there was a positive slope, suggesting the involvement of one-way transfer and accumulation of the tracer (1). The initial K1, k2 and k3 values obtained from the Gjedde-Patlak plots correlated well with the real rate constants yielded from fitting (1).

^{18}F-^{10}B-FBPA data

Original data

Ten patients with glioma were examined in Turku PET Centre using ^{18}F-^{10}B-FBPA as tracer. The acquired data for each patient comprise dynamic PET images collected during 51 minutes after intravenous injection of ^{18}F-FBPA, time-activity points for arterial plasma from the corresponding time interval, dynamic PET images collected after inhalation of tracer amount of [O-15] carbon monoxide, and three time-activity points of venous blood from the imaging period. Activities are in units kBq/ml.

FBPA scans were interpreted to regional TACs in dft files using program `img2dft 3.0` and files containing determinations of regions of interest (ROIs).

Corrections to data

Metabolite correction: Based on results of Imahori *et al.* (7) and Ishiwata *et al.* (8), any metabolic correction was considered unnecessary.

Delay correction: Based on visual inspection of plasma and tissue TACs, delay correction was also considered unnecessary.

Weighting: Data were not weighted.

Blood volume correction: PET data were corrected for blood volume activity by subtracting the contribution of vascular radioactivity from regional PET TACs. This was accomplished using program `dftcbv 0.2.` For calculation, vascular volume fractions and blood TACs were needed.

Vascular volume fraction in each case was determined by means of an [O-15] CO-study. This fraction (Vb) was calculated by multiplying the PET image of the CO-study by factor $\frac{1}{0{,}85 \cdot b} \cdot 100\%$, where *b* is the average activity of blood samples collected during imaging. The program used to perform this was `ecatcalc 1.4.` The output image was interpreted to a dft file using program `img2dft 3.0.`

Plasma TACs measured from samples collected during PET scanning were converted to blood TACs based on the ratio of activities in red blood cells and plasma. The ratio had been determined from ten separate patients earlier (unpublished). The ratio for FBPA is assumed to rise from zero with a slope of 0,00888. Real values of hematocrites of individual patients were included in calculation. The program used was `p2blood 1.3.`

Modeling of ^{18}F-^{10}B-FBPA

Compartmental modeling

Having corrected the data for blood background activity, we used a three-compartment model for kinetic analysis. For comparison, we performed the calculatios both with k4 and without it, assuming it equal to zero. In normal tissue, fitting K1, k2 and k3 yielded curves comparing well to the blood-corrected time-activity points in most regions. However, in tumor this model seemed insufficient, as evaluated by visual inspection. Including fitting k4 in the procedure gave curves that matched better with the measured time-activity points. The fitting procedure was accomplished by programs `fitk3 2.1` and `fitk4 2.1.` The fitted curve of a specific region and the

corresponding blood-corrected measured TAC were drawn into the same picture and converted to .ps form for visual inspection by program `dft2ps 0.3.1`.

We evaluated the fitted curves using AIC analysis. Bootstrap method was used to evaluate the SD's for each of the fitted parameters.

We also calculated K1 and k2 using the two-compartment model, but the resulting fitted curves failed to depict the measured data satisfactorily. We concluded that this model was insufficient for these data.

Non-compartmental modeling

We drew Patlak and Logan plots from the data to determine if the uptake of FBPA was reversible or irreversible. The original data not subjected to blood volume correction was used.

Patlak analysis

There was a distinctive positive slope on the following regions (as coded by Katja Havu-Aurén): tum, pai, and pari. A slight positive slope was detected in most cases on par, scal, lac, pal, and sel. No unambiguous positive slope was found on nen. Five last frames were used in the fit (25-60 min). Ki values obtained by Patlak analysis were usually smaller than those yielded from the three-compartment model (fitting K1-k3) by 35 % on average.

Logan analysis

DV values derived from logan analysis and three-compartment reversible fitting were in agreement. They usually differed from each other 20 % or less in either direction. Six last frames were used in the fit (20-60 min).

References

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