Dosimetry for 6-[18F]Fluoro-L-DOPA in humans based on in vivo microPET scans and ex vivo tissue distribution in mice

F. Bretin¹, G. Warnock¹, M.A. Bahri¹, L. Libert¹, C. Lemaire¹, C. Phillips¹, A. Seret¹, A. Luxen¹ and A. Plenevaux¹

¹ Cyclotron Research Centre, University of Liège, Belgium

Introduction

Radiation dosimetry of new radiopharmaceuticals generally starts with studies in small animals such as mice and rats. The traditional technique has long been ex vivo measurement of the biodistribution over time using harvested organs at different times post administration of the radiopharmaceutical. Since this approach requires a significant amount of animals, dynamic microPET studies, where the complete biodistribution of the tracer over time can be determined in vivo in a single scan, are an invaluable alternative. Due to known imaging artifacts and limitations, such as partial volume effect, a hybrid technique combining harvesting organs (post-scan) and dynamic imaging was introduced to achieve a cross-calibration to account for these limitations.

Materials & Methods

The tissue distribution over time of 6-[18F]Fluoro-L-DOPA was determined by:

1) Radioassay of harvested organs in isoﬂurane-anesthetized mice:
   - Brain, heart, kidneys, liver, lung, spleen and testes
   - At 2, 5, 10, 30, 60, 120 minutes post injection, n=4 at each time point
   - Average bodyweight 23.5 ± 1.75 g; Average injected activity 8.47 ± 1.45 MBq

2) Dynamic PET imaging acquired using a FOCUS 120 microPET over 120 minutes after injection of 6-[18F]fluorodeoxyglucose followed by radioassay of harvested organs in isoﬂurane-anesthetized mice (n=4). CT images were obtained using a GE eXplore 120 micro-CT prior to dynamic PET imaging:
   - Time frames: 6x5s, 6x10s, 3x20s, 5x30s, 5x60s, 8x150s, 6x300s, 6x600s.
   - Average bodyweight 22.1 ± 1.21 g; Average injected activity 7.66 ± 1.62 MBq

Clearly identifiable organs were manually segmented in the reconstructed co-registered PET/CT images and organ time-activity-curves (TACs) were obtained. TACs from PET were multiplied with the cross-calibration factor between PET activity and Gamma counter activity levels.

TACs from both methods were extrapolated from a simulated 35 g standard mouse to a 70 kg standard male human using a technique based on organ to bodyweight ratios (Kirschner et al., 1975):

\[
\frac{c_O}{c_{B} \times \text{bodyweight}} = \left( \frac{k_{O}}{k_{B \times \text{bodyweight}}} \right)_{\text{human}}
\]

A bladder voiding scenario was used to simulate excretion every 2 h. The absorbed doses in major human organs were calculated using the extrapolated TACs with the commercially available human dosimetry software OLINDA/EXM (Version 1.1).

Results

- TACs were derived using the tissue distribution and the hybrid technique, average correlation coefficient between TACs r = 0.94 ± 0.05, p < 0.001
- Differences at high activity levels were revealed in Bland-Altman plots for TACs with a correlation below r = 0.94 (lung 0.91 and heart 0.85)
- Residence times and doses were calculated for a standard 70kg male human using both methods
- The highest doses were received by organs in excretion pathways comprising bladder (0.142 mGy/MBq both methods), kidneys and liver (see Figure 4)
- The effective total body dose was 0.0193 mSv/MBq for hybrid and 0.0189 mSv/MBq for pure harvesting based method

Conclusions

Scaling errors in the PET TACs are likely caused by quantification errors such as partial volume effects and image artifacts, which caused an underestimation in activities measured by microPET imaging only in brain, heart and lung (mean: 30%, 10% and 28%, respectively) and an overestimation in kidney and liver (mean: 21% and 30%). The use of the hybrid imaging technique to cross-calibrate the TACs improved the accuracy of the imaging-based dosimetry estimates. Therefore the hybrid technique combining dynamic imaging and harvesting organs (post-scan) is a suitable alternative to the gold standard ex vivo radioassay method using harvested organs at different time points. It yields comparable results yet reduces significantly the amount of animals needed in the study and can accelerate data acquisition.

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• M. Bahri is a “collaborateur logistique” from FRS-FNRS Belgium
• A. Plenevaux is senior research associate from FRS-FNRS Belgium