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Title: Human Radiation Dosimetry of Orally or Intravenously Administered ^{18}F-Fluorodeoxyglucose

Running Title: Oral Administration of ^{18}F-FDG

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ABSTRACT

Purpose: Intravenous access is difficult in some patients referred for ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging. Extravasation at the injection site and accumulation in central catheters can lead to limited tumor ^{18}F-FDG uptake, erroneous quantitation, and significant image artifacts. In this study, we compare the human biodistribution and dosimetry of ^{18}F-FDG for oral and intravenous administrations sequentially in the same subjects to ascertain the dosimetry and potential suitability of orally administered ^{18}F-FDG as an alternative to intravenous administration. We also compared our detailed intravenous ^{18}F-FDG dosimetry with older dosimetry data. **Methods**: Nine healthy volunteers (6 male and 3 female; ages 19-32 years) underwent PET combined with computed tomography (PET/CT) imaging after oral and intravenous administration of ^{18}F-FDG. Identical preparation and imaging protocols (except administration route) were used for oral and intravenous studies. During each imaging session 9 whole body PET scans were obtained at 5, 10, 20, 30, 40, 50, 60, 120 and 240 minutes (min) after ^{18}F-FDG administration (370 ± 16 MBq). Source organ contours drawn using CT were overlaid onto registered PET images to extract time-activity curves. Time-integrated activity coefficients derived from time-activity curves were given as input to OLINDA/EXM for dose calculations. **Results**: Peak blood uptake following orally administered ^{18}F-FDG was observed at 45-50 min after ingestion. The oral-to-intravenous ratios of ^{18}F-FDG uptake for major organs at 45 min were: blood (1.07 ± 0.24), heart wall (0.94 ± 0.39), brain (0.47 ± 0.12), liver (1.25 ± 0.18) and kidneys (0.84 ± 0.24). The highest organ absorbed doses (μGy/MBq) for oral ^{18}F-FDG administration were observed for urinary bladder (75.9 ± 17.2), stomach (48.4 ± 14.3) and brain (29.4 ± 5.1) and the effective dose was significantly higher (20%) than for

intravenous administration (P = 0.002). **Conclusions**: FDG has excellent bioavailability following oral administration but peak organ activities occur later than post-intravenous injection. These data suggest PET at 2 h following oral ^{18}F-FDG administration should yield images that are comparable in biodistribution to conventional clinical images acquired 1 h post-injection. Oral ^{18}F-FDG is a palatable alternative to intravenous ^{18}F-FDG when venous access is problematic.

Key Words: FDG, dosimetry, oral ^{18}F-FDG

INTRODUCTION

Fluorodeoxyglucose (^{18}F-FDG) is a widely used radiotracer of glucose metabolism. While originally developed for brain imaging, ^{18}F-FDG is most commonly used to image cancers, which generally have higher rates of glucose metabolism than most normal tissues (1). ^{18}F-FDG is also used to image infections, inflammation and myocardium viability (2-4). In virtually all of these applications, ^{18}F-FDG is given intravenously.

^{18}F-FDG uptake typically rises in untreated tumors, while most normal tissues have gradually declining tracer uptake over time (5). For tumors, ^{18}F-FDG positron emission tomography (PET) imaging is commonly performed at 1 hour (h) post-intravenous injection. The 1 h delayed static imaging with quantitation using standardized uptake value (SUV) has played a significant role in the dissemination of PET technology. However, accurate quantitation assumes the entire injected dose has reached the bloodstream and can be distributed throughout the body.

Although intravenous access is clearly simple and useful for routine ^{18}F-FDG administration, many patients present with veins too poor or fragile for an intravenous line. This is a common occurrence in cancer patients undergoing extensive chemotherapy, because of venous inflammation or thrombosis, but poor venous access can occur in any patient (6-8). While central venous catheters can be used, they are associated with thrombotic and infectious complications and can often have radiotracer stick to their walls or tip, confounding interpretation and quantitation (9,10). In addition, many pediatric patients have a fear of injection. The pain and anxiety associated with injections can potentially result in activation of the brain that could alter tracer distribution.

Extravasation of ^{18}F-FDG at the injection site can also lead to poor uptake and major artifacts. Multiple attempts to gain intravenous access may not be successful, resulting in an inability to scan some patients. In such scenarios, there is a need for an alternative ^{18}F-FDG administration route. Oral administration of ^{18}F-FDG is an attractive alternative, provided it does not result in significant loss of information from scans or unfavorable dosimetry.

Existing Knowledge in Oral ^{18}F-FDG imaging

Martinez *et al* first used oral ^{18}F-FDG administration in primates and humans (11). They observed that the blood curve for oral administration had a longer uptake time, with a peak of about 60 minutes (min) which continued for 120 min compared with intravenous injection. They did not find much difference in the oral and intravenous route in human brain images. They suggested performing radiation dosimetry studies especially for gut and liver before use in humans. Masud *et al* compared brain images of intravenous and oral ^{18}F-FDG administration in healthy humans (12). It was observed that the blood activity curve build-up phase was slow and continued up to around 110 to 120 min when administered orally. They did not find a significant difference in the brain images between the intravenous and oral methods except for later accumulation of ^{18}F-FDG. Higashi *et al* studied the oral administration of ^{18}F-FDG in normal rodents (13). They concluded that the fasting condition and ^{18}F-FDG diluents and osmolality play a major role in ^{18}F-FDG absorption from the gut. It was shown that in a rodent model, 48 h fasting and a hypotonic solution as diluent for ^{18}F-FDG yielded better absorption of 18F-FDG from the gut.

Franc *et al* reported a case of a lung cancer patient who had to undergo oral ^{18}F-FDG due to non-palpable veins (14). They observed high uptake in the mouth, esophagus, stomach and bowel. Nair *et al* compared oral and intravenous ^{18}F-FDG administration methods in two healthy humans and seven cancer patients (15). They claimed that all lesions were seen on both oral and intravenous images. The SUV on images from orally administered patients were 30-60 % lower than the SUV measured on images from patients undergoing intravenous administration. It was also observed that a larger amount of activity was retained in the gut. It was presumed that activity from the gut was eventually absorbed, but the uptake in normal organs was delayed following oral delivery compared to intravenous delivery.

The aim of the current study was to systematically compare the human biodistribution and dosimetry of ^{18}F-FDG for oral and intravenous administrations in the same subjects to ascertain the potential applicability of orally administered ^{18}F-FDG as an alternative to intravenous delivery.

MATERIALS AND METHODS

Subjects

This prospective study was approved by the Johns Hopkins Medicine Institutional Review Board (approval designation NA_00068464) and all subjects signed a written informed consent. Healthy volunteers over 18 years of age were eligible to participate in this study. Volunteers were recruited using flyers placed at various locations on the Johns Hopkins medical campus and modest financial compensation was provided for participation. Pregnant women and

anyone taking a medication known to influence glucose metabolism (e.g. insulin or metformin) were excluded.

^{18}F-FDG Preparation

^{18}F-FDG was obtained from PETNET Solutions (Knoxville, TN). Oral ^{18}F-FDG was prepared by dissolving the targeted 370 MBq dose in approximately 500 ml of sugar-free fruit punch. This solution was given to participants in a sealed container with a straw so as to avoid spills. Participants were instructed to drink the entire volume within five min followed by an additional 500 ml of water. Intravenous ^{18}F-FDG was given in a 370 MBq dose per the standard clinical protocol.

Study Protocol

Eligible participants were asked to undergo two imaging sessions separated by at least 24 h and by no more than 14 days (d). Oral administration of ^{18}F-FDG was always performed during the first visit and intravenous administration during the second. For both visits, participants were instructed to fast for at least 6 h prior to the planned time of ^{18}F-FDG administration. After reporting to the imaging center, participants underwent a brief, routine history and physical and were then asked to change into a hospital gown. During both imaging sessions, the same dose of ^{18}F-FDG (targeted 370 MBq) was used and the same imaging procedure performed with the only difference being the route of ^{18}F-FDG administration.

Imaging Parameters

PET and computed tomography (PET/CT) images were acquired using a Discovery RX VCT (GE Healthcare) PET/CT scanner. Whole-body PET/CT images were acquired 5, 10, 20, 30, 40, 50, 60, 120 and 240 min after both oral and intravenous administration of ^{18}F-FDG. During each imaging session, the first six PET scans were acquired for 45 sec per bed position and the last three scans were acquired for 255 sec per bed position. Low-dose CT scans (120 kVp, 45 mA, 0.984 pitch, and 0.5 sec tube rotation) were acquired prior to the start of the 5, 60, 120, and 240 min PET scans, for a total of 8 CTs per volunteer. Images were obtained from vertex through the mid-thighs. Attenuation and scatter-corrected PET images were reconstructed using three-dimensional ordered-subsets expectation-maximization (OSEM) with 2 iterations, 21 subsets and a 3 mm Gaussian filter. The scanner was calibrated with respect to the same dose calibrator used for the ^{18}F-FDG subject measurements, which was itself calibrated using a ^{68}Ge reference source traceable to a national metrology institute. Routine phantom quality control studies confirmed the quantitative accuracy of the PET images, at least for objects greater than around 22 mm in size.

Dosimetry

The PET/CT images from both imaging sessions were used to extract biodistribution data for oral and intravenous methods of ^{18}F-FDG delivery, respectively. Low-dose CT was used to guide the manual delineation of each organ of interest using MIMvista (version 5.1; MIM vista Corp). Volumes-of-interest were applied to the corresponding whole-body PET series to extract the mean source activity concentrations. Gastrointestinal organs were delineated into stomach contents, small intestine (SI) contents, upper large intestine (ULI) contents and lower large intestine (LLI) contents. Whenever a source organ could not be drawn completely, the average

activity concentration was multiplied by a standard phantom–based organ volume-density product (16). Activity concentration, normalized to administered activity, was plotted against time for each organ. Curve fitting was done using SAAM-II (version 1.2.1). Time-integrated activity coefficients were calculated per MIRD Committee formalism (17). The OLINDA/EXM 1.0 dosimetric software was used to obtain absorbed dose estimates and effective doses for each subject. Dynamic bladder model in the OLINDA/EXM was used to obtain urinary bladder time-integrated activity coefficient with a voiding interval of 1.5 h and biological half-time obtained from whole body time-activity curve for each study subject.

Statistical Methods

Differences in estimated absorbed dose between orally and intravenously administered ^{18}F-FDG were assessed using paired t-tests. All data analyses were performed using Excel (Microsoft Corporation) and in all cases, a P-value less than 0.05 was considered statistically significant.

RESULTS

Nine healthy participants were included in this study (Table 1). Eight participants completed both oral and intravenous ^{18}F-FDG imaging studies and one participant completed oral ^{18}F-FDG imaging, but not intravenous ^{18}F-FDG imaging. Figures 1 and 2 show images of a single volunteer following both routes of ^{18}F-FDG administration at selected time points. A clear difference exists in abdominal imaging (with more tracer in the bowel after oral administration and less in the brain) at early time points. Figure 3 shows ^{18}F-FDG biodistribution in seven selected tissues, in Becquerels (Bq) per Megabecquerel (MBq) of

administered activity per gram of tissue. In most organs (excluding the brain and bladder), the activity per gram of tissue was about the same approximately 70 min following oral or intravenous administration. Peak blood uptake following orally administered ^{18}F-FDG was observed at 45-50 min.

The mean oral-to-intravenous ratios of ^{18}F-FDG uptake for major organs at 45 min were: blood (1.07 ± 0.24), heart wall (0.94 ± 0.39), brain (0.47 ± 0.l2), liver (1.25 ± 0.18) and kidneys (0.84 ± 0.24). Absorbed dose estimates for both routes of administration are shown in Table 2. Of the major organs, the highest absorbed dose following the oral administration was observed in the urinary bladder wall, followed by stomach wall and then brain. The highest absorbed dose following intravenous administration was to the urinary bladder wall, followed by the brain and then the heart wall. The total effective dose was 20% higher for oral than for intravenous administration (0.018 ± 0.003 mSv/MBq versus 0.015 ± 0.002 mSv/MBq, respectively; P = 0.002). High gastric and small bowel uptake was visually identified through 1.5 h into the study.

Figure 4 compares the mean estimated absorbed dose to each organ for all participants following both methods of ^{18}F-FDG administration. For most organs, the mean estimated absorbed dose was similar for intravenous versus oral administration, with the exception of the stomach wall, small intestine, heart wall, kidneys, and brain. Following oral administration, mean activity in the stomach wall and small intestine was 3.4 and 1.7 times higher than following intravenous administration, respectively. Following intravenous administration, mean activity in the heart wall, kidneys, and brain was 2.1, 1.6, and 1.4 times higher than following oral administration, respectively.

DISCUSSION

^{18}F-FDG is a critically important tracer for PET imaging with a wide and growing range of indications. While intravenous delivery of ^{18}F-FDG is normally very effective, difficult venous access, especially in cancer patients, is common. Indeed, standards have been developed which limit the number of attempted intravenous insertions by a single nurse to two in chemotherapy patients and to a total of four attempts using different individuals (7). Using an infusion catheter can be helpful, but catheters carry with the risk of complications including superior vena cava obstruction, infection, and occlusion, among others (9). Thus, intravenous access can sometimes be problematic and the availability of an additional tracer delivery route, e.g. orally, can be logistically attractive when the time for the patient to complete the study is critical.

Given the importance of quantitative imaging, the ability to measure relative tracer uptake is highly dependent on knowing the amount of activity that was successfully administered. Patients with extravasated injections can have obvious alterations in SUV, either due to less tracer reaching the blood stream, or due to slowed absorption of tracer to the blood stream. Both may affect quantitation. Oral ^{18}F-FDG has the potential to allow for delivery and quantitation in cases where it might otherwise be impossible to scan the patient with ^{18}F-FDG. However, the repeatability of oral ^{18}F-FDG uptake in humans has not been studied.

While catheter infusion systems are attractive, ^{18}F-FDG can stick to catheters or to the tip of a catheter or port, confounding imaging and quantitation. Indeed, ^{18}F-FDG uptake in clots at

the ends of catheters can cause confusion in some cases. Misdiagnosis of active lymphoma has occurred when tracer has actually been accumulated in the tip of a catheter/clot (18). In other situations, ^{18}F-FDG uptake in a catheter tip has been considered a normal variant. Oral ^{18}F-FDG potentially could provide advantages in such situations by limiting infusion related ^{18}F-FDG uptake. Oral administration potentially can avoid such confounding uptake and may be particularly relevant for attempts to assess infections in infusion catheters and ports, separating infused from accumulated activity, the latter much more relevant.

In tumor imaging, clinical studies suggest many tumors, at least outside of the immediate proximity of the bowel, can be imaged using ^{18}F-FDG PET. Clearly, an orally administered ^{18}F-FDG dose followed by PET /CT imaging has a higher probability of imaging tumor foci than does a scan which was cancelled due to lack of venous access. Indeed, oral ^{18}F-FDG might be considered as “any port in a storm”, even if there is not a port.

A review of the literature (Table 3) shows that our intravenous dosimetry results are generally consistent with other ^{18}F-FDG dosimetry reports, but are perhaps more robust as they include a longer duration of imaging acquisition to determine biodistribution over time. Thus, they are probably somewhat more reliable than measurements using a more limited number of imaging data points. Interestingly, our data show somewhat lower dosimetry than, for example, the FDA-approved package insert.

Our dosimetry data support a somewhat higher total body residence time for ^{18}F-FDG given orally than intravenously, likely because excretion is slower and later as there is activity remaining in the bowel for some time post-injection that cannot be rapidly excreted. Other

limited dosimetry exists for ^{18}F-FDG given orally, but it is not strictly comparable. Shingaki et al constructed ^{18}F-FDG laden capsules which were designed to dissolve in the gut (19). This variable clearance from the stomach and variable dissolution of the capsules makes comparisons to our data difficult.

Oral ^{18}F-FDG avoids the need to sedate or cause pain with an intravenous injection. Pain or stress may have effects on ^{18}F-FDG biodistribution which could be confounding. Masud et al showed quantitative differences in brain glucose metabolism in subjects who received ^{18}F-FDG by the oral or intravenous route (12). They observed glucose metabolism to be significantly higher in the superior frontal gyrus, superior parietal lobule, lingual gyrus and left cerebellar hemisphere in the intravenous group than in the oral group. Metabolically active areas were found in the superior, middle and inferior temporal gyrus, parahippocampal gyrus, amygdaloid nucleus, pons and cerebellum in the oral group when compared with the intravenous group, perhaps due to pain in the latter group.

Our study did not evaluate the diagnostic accuracy of ^{18}F-FDG PET given orally. However, our dosimetry data support a higher total body effective dose, by about 20%, for oral ^{18}F-FDG. Our studies were conducted in normal volunteers. Patients may indeed differ somewhat from the normal volunteers. For example, profoundly delayed gastric emptying might be expected to delay the absorption of FDG given orally and require later imaging times. The delayed absorption of ^{18}F-FDG from the bowel suggests that the optimal time for brain or tumor imaging after oral ^{18}F-FDG is likely to be about 2 h post-ingestion. Zhang et al determined the optimal uptake time for imaging all organs but the brain to be 50 – 60 minutes, though this was

based on a case report of one healthy volunteer (20). It is also probable that oral dosing would not be optimal for patients with tumors located in the upper abdomen or in the bowel wall. Such lesions might be more difficult to detect with oral as compared with intravenous dosing. Additional systematic studies of oral ^{18}F-FDG in patients with difficult venous access, or in need of evaluation of tissues or devices through which ^{18}F-FDG is commonly injected, are warranted.

CONCLUSION

Oral ^{18}F-FDG administration is feasible and results in excellent absorption and delivery of the radiotracer throughout the body. Peak uptake in normal tissues is somewhat delayed and the overall radiation absorbed dose following oral administration is about 20% higher than for intravenous delivery. Oral ^{18}F-FDG delivery should be considered if intravenous access is not feasible or desirable. Our data suggest a 2 h uptake to be optimal for oral ^{18}F-FDG and provide additional data on intravenous ^{18}F-FDG dosimetry.

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Key Points

Question: Is orally administered ^{18}F-FDG a suitable alternative to intravenously administered ^{18}F-FDG?

Pertinent Findings: In a prospective study, nine healthy participants underwent separate PET/CT imaging following oral and intravenous administrations of ^{18}F-FDG. The total effective dose was significantly higher by 20% from orally administered ^{18}F-FDG than from intravenously administered ^{18}F-FDG.

Implications for Patient Care: Oral administration of ^{18}F-FDG is a reasonable option when venous access is difficult or impossible.

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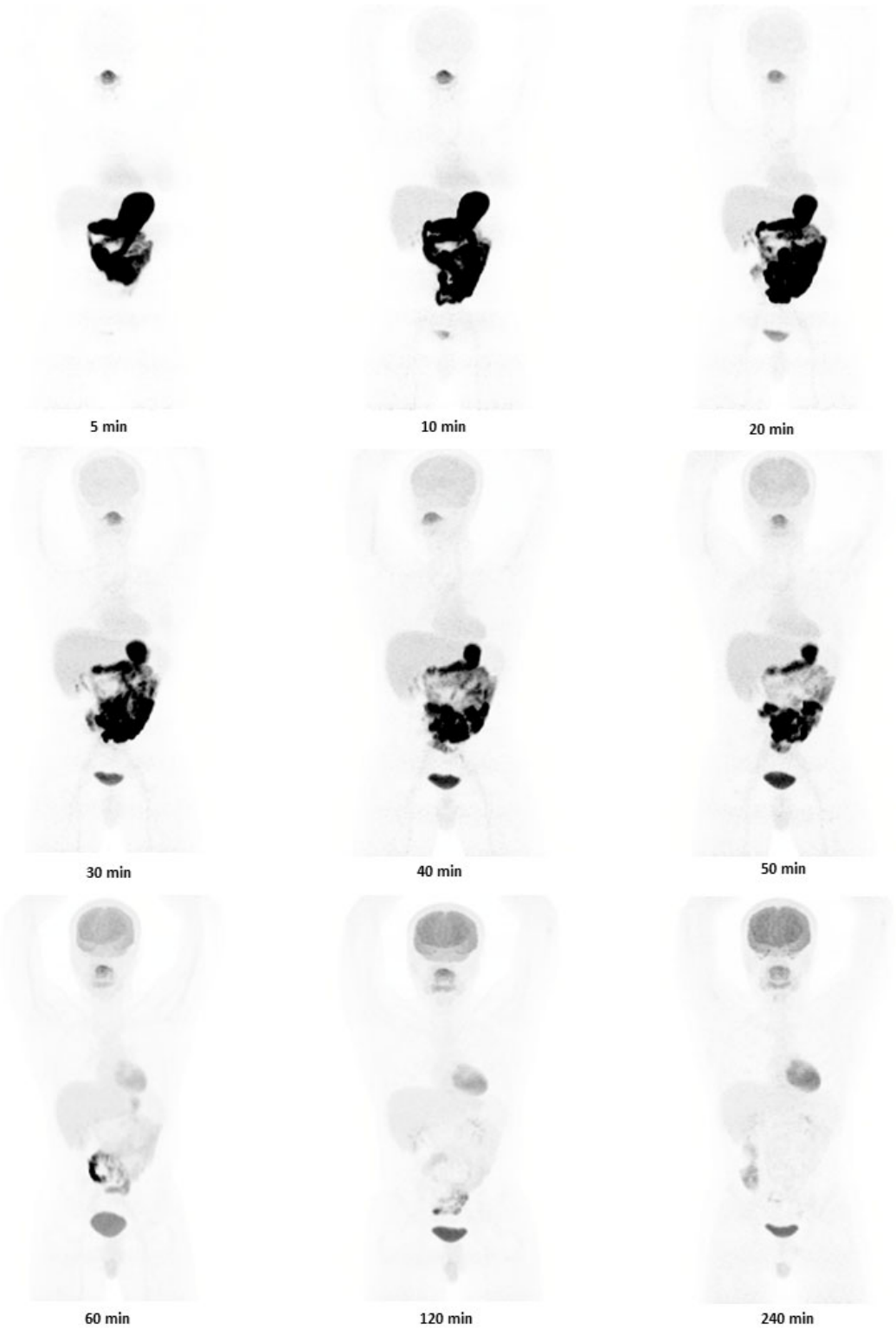
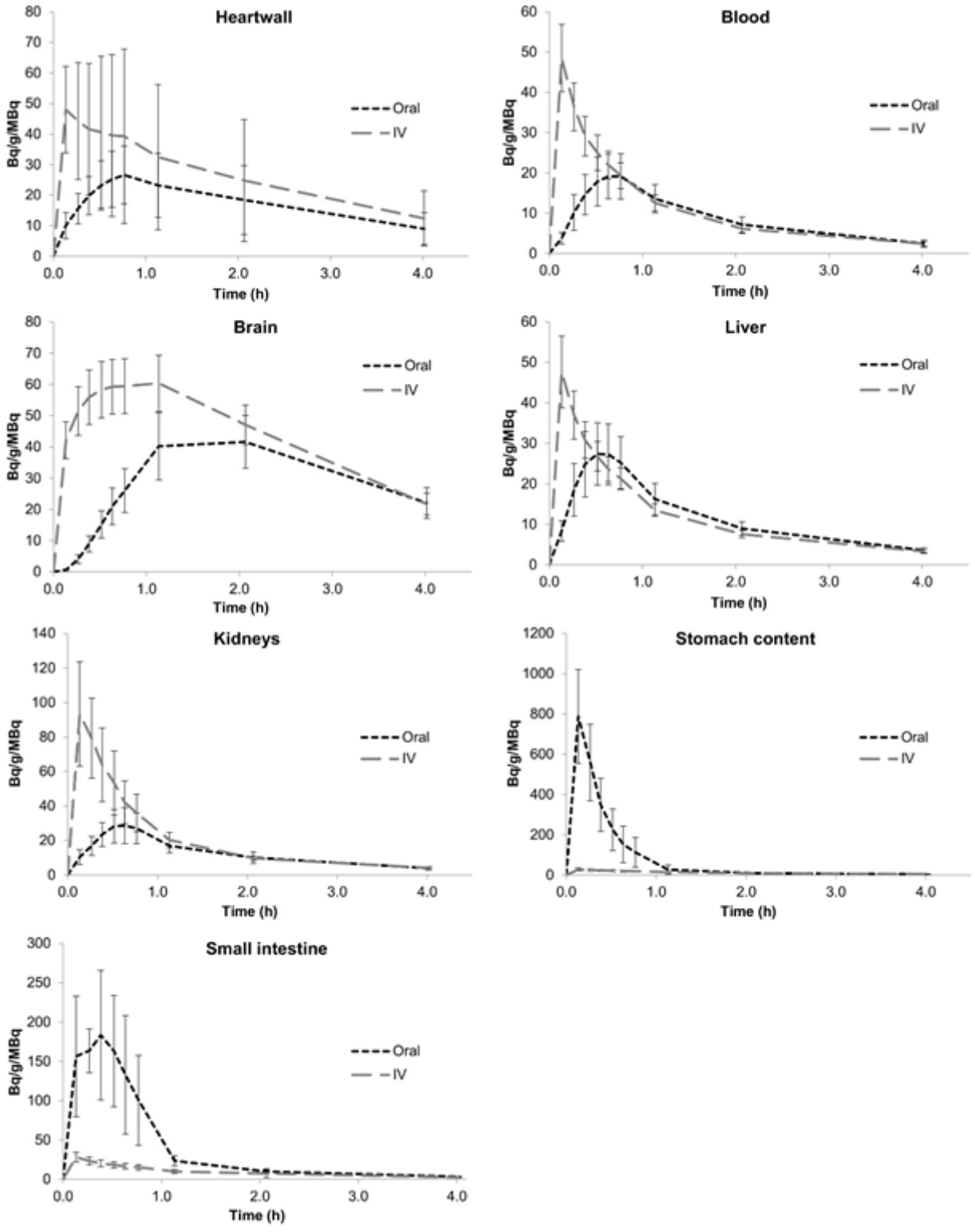
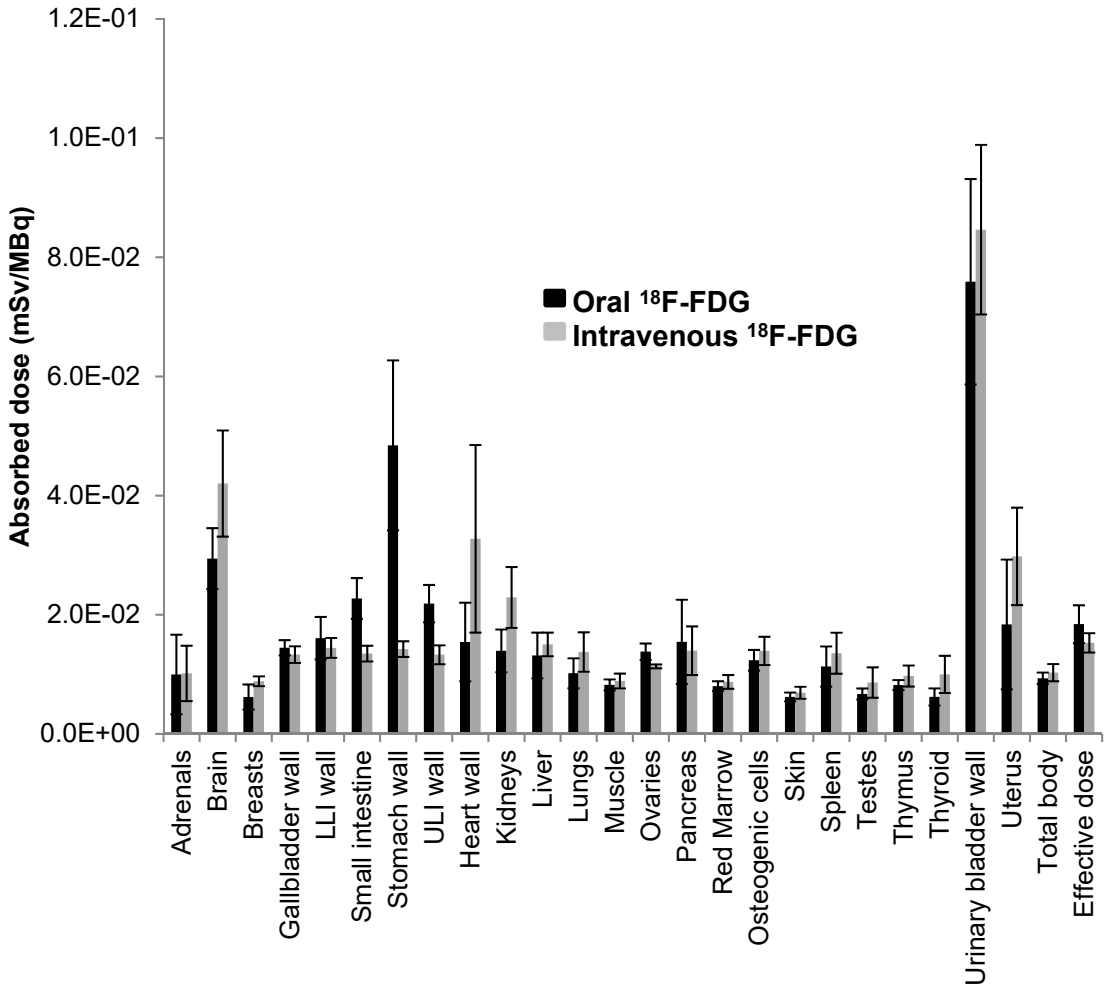
[FIGURE 1. Images of one participant (subject #4 in Table 1) from specified time points following intravenous administration of 18F-FDG. The same color scale was used for all images.]



[FIGURE 2. Images of one participant (subject #4 in Table 1) from specified time points following oral administration of 18F-FDG. The same color scale was used for all images.]



[FIGURE 3. 18F-FDG time-activity curves for selected source organs plotted as activity concentration normalized to administered activity.]



[FIGURE 4. Estimated radiation dose to each organ for both orally and intravenously administered ^{18}F-FDG.]