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Suggested pathway to assess radiation safety of ^{18}F -labeled PET tracers for first-in-human studies

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Dear Sir,

Labeling new radioligands with ^{18}F has several advantages because of the longer half-life of ^{18}F (about 110 min) compared to that of ^{11}C (about 20 min). This longer half-life makes an on-site cyclotron unnecessary. Furthermore, measurements of radioactivity concentrations in the brain with PET as well as in plasma with liquid chromatography are more robust. However, a longer half-life also yields a higher radiation burden.

Before testing a new radioligand in humans, dosimetry studies are customarily performed in animals, and dose estimates are extrapolated to humans. These studies, especially in monkeys, are labor-intensive, expensive, and not feasible in some institutions. Moreover, several authors have shown that animal data, even those derived from monkeys, poorly predict human data [1–3]. For these reasons, we previously proposed a practical pathway to test new ^{11}C radioligands directly in humans [1]. Here, we propose a similarly novel pathway to test ^{18}F -labeled tracers.

After an extensive search using PubMed and appropriate dosimetry-related keywords, we identified 54 studies reporting the effective dose (ED) and/or the effective dose equivalent (EDE) of ^{18}F tracers in humans (Supplementary Table 1). We included only studies done in humans (rather than those done in animals with extrapolation of the data to humans) and those published after 1995; prior to that date, substantial differences existed in both dosimetry methodology and in the performance of the machines used. The average ED across studies was $20.6 \pm 6.8 \mu\text{Sv/MBq}$ (range 8.6 – 39.6 $\mu\text{Sv/MBq}$; with the vast majority in the range 15 – 30 $\mu\text{Sv/MBq}$).

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Conflicts of interest None.

Reliability of dosimetry estimates

Comparing results published by different institutions performing human dosimetry studies for the same tracer showed that absorbed dose values are poorly reproducible. Notably:

- The dosimetry of [^{18}F]-A85380 was measured in three different studies, yielding an ED of 19.4, 23.7, and 39 $\mu\text{Sv}/\text{MBq}$, respectively [4–6].
- The ED of [^{18}F]-AV-45 was estimated at 13, 16, and 19.7 $\mu\text{Sv}/\text{MBq}$ [7–9].
- The dosimetry of [^{18}F]-choline was estimated at 18 $\mu\text{Sv}/\text{MBq}$ (risk-weighted absorbed dose coefficient) [10] and 34.1 $\mu\text{Sv}/\text{MBq}$ (EDE) [11].
- ED estimates for [^{18}F]-FDG recently published by Staff and colleagues (15 $\mu\text{Sv}/\text{MBq}$) were 21 % lower than values reported in the ICRP 106 publication (19 $\mu\text{Sv}/\text{MBq}$) [12], and half the value calculated by Deloar et al. (29 $\mu\text{Sv}/\text{MBq}$) [13].

These discrepancies can likely be explained by different methodological approaches between the studies and by simple intersubject variability. If the absolute values of the absorbed dose are very low, as in the case of positron emitting radioligands, small methodological differences may cause large percentage variations. Although the final ED generally always falls in the 10 – 40 $\mu\text{Sv}/\text{MBq}$ range, the precise value of each tracer may not be very meaningful.

Several authors have pointed out that human dosimetry values extrapolated from animals poorly predict actual human values [1–3]. The present analysis of the literature further suggests that human values obtained in one institution poorly predict human values acquired in a different institution.

Regulatory limits

Under routine use conditions for ^{18}F -labeled radiotracers (about 185 MBq or 5 mCi), it is unlikely that the resulting absorbed dose would exceed the dose constraints recommended by regulatory bodies.

Several European countries generally follow an ED limit of 10 mSv, as per the ICRP recommendations [14]. Although the US Food and Drug Administration has no strict ED limit for radiotracers studied under Investigational New Drug applications, many institutions—including the National Institutes of Health—limit ED to 50 mSv, which is five times the limit allowed in Europe. However, for those radiotracers studied in the US under the auspices of a Radioactive Drug Research Committee (RDRC), limits are applied to both individual organs and the “whole body.” Under these guidelines, the limit for radiation-sensitive organs (gonads, red marrow, spleen, and eye lens) is 30 mSv, and for all other organs 50 mSv. In addition to these individual organ limits, according to the RDRC criteria the limit for the “whole body” (now defined as ED) is 30 mSv.

Thus, the strictest limit of radiation exposure to the whole body (ED) is 10 mSv, practiced in Europe. The strictest limits for individual organs are 30 mSv for sensitive organs and 50 mSv for all others, as required by US RDRC regulations. For each of these three limits, we calculated the maximal allowable injected activities for the ^{18}F radiotracers (Supplementary Table 1). The radiotracer with the highest ED was [^{18}F]-FPPRGD2, for which an ED limit of 10 mSv would restrict the injected activity to 253 MBq. [^{18}F]-FPPRGD2 also had the highest exposure to the sensitive organs (defined by RDRC): 67.5 $\mu\text{Sv}/\text{MBq}$ to the spleen; a limit of 30 mSv would restrict the injected activity to 444 MBq. The radiotracer with the highest exposure to other organs (defined by RDRC) was 4FMFES (about 800 $\mu\text{Sv}/\text{MBq}$ to the gallbladder); a limit of 50 mSv would restrict the injected activity to 63 MBq. Thus, by

the strictest of all three limits applied in Europe or the US, the maximal injected activity would be 63 MBq.

Methods to reduce radiation exposure

The organs with the highest radiation exposure from ^{18}F radiotracers are almost always the urinary bladder (26 of 53 radiotracers for which information about the critical organ was available) or the gallbladder (16/53). The few exceptions are the kidneys (5 of 53), liver (3 of 53), pancreas (2 of 53), and lungs (1 of 53; Supplementary Table 1). Notably, the dose to the bladder and the gallbladder may be reduced by stimulating voiding. For example, in those studies in which different voiding models were simulated, the equivalent dose to the bladder was reduced by a factor of two to four [4, 15–19]. Voiding of the bladder can be induced by diuretics or simple hydration, while voiding of the gallbladder can be stimulated with cholecystokinin or fatty foods. Indeed, the high gallbladder dose from 4FMFES can be partially attributed to the fact that the subjects fasted before tracer injection [20].

Taken together, the evidence reviewed above shows: (a) that the dose from positron emitters is generally low, and that no published ^{18}F tracer has ever exceeded the ED constraints with a standard 5 mCi activity; (b) dosimetry from animals is notoriously unreliable; and (c) while dosimetric estimates in humans tend to be rather constant and fall into a predictable range of values, they are not otherwise very reproducible.

Proposed pathway

Because dosimetry estimates from animals provide inaccurate data for humans, we recommend that dosimetry in animals not be required prior to human imaging. In addition, the published dosimetry values for humans—though often not reproducible—fall with a relatively narrow range, which allows us to estimate the exposure from a novel radiotracer. It should also be noted that, based on the highest exposures to the whole body or individual organs for all published radiotracers, maximal injected activities can be calculated that would fulfill the strictest European or US limits. Based on these principles, we propose the following for first-in-human studies of ^{18}F radiotracers:

1. Begin with whole-body scanning in a single human subject using about 74 MBq, which is less than one-third of the safe activity of the most irradiating ^{18}F -tracer in terms of ED (^{18}F -FPPRGD2; see Supplementary Table 1). The aim of this first scan would be to detect a tracer that disproportionately accumulates in a single radiosensitive organ, such as the gonads. If this first scan confirms that the radioactivity is fairly widely distributed in the body, higher activities may be injected. To increase the count rates from this low injected activity, a slower whole-body scan may be acquired.
2. Do up to ten kinetic scans centered on the organ of interest using doses up to 5 mCi to determine whether the radioligand is worth pursuing.
3. If the radioligand looks promising, perform whole-body dosimetry studies in humans. Retest variability can be studied after the dosimetry study.

Some institutions in Europe and the US require that the first studies of perhaps five to ten subjects be whole-body scans to estimate dosimetry. One important advantage of the pathway we propose is that all subjects (with the exception of the very first subject) would be spared exposure if the radioligand was discontinued after the kinetic analysis (step 2). Most institutions require that the consent form numerically estimate radiation exposure to the subject. Before completing the dosimetry study in step 3, we recommend that an average ED value of 20 $\mu\text{Sv}/\text{MBq}$ be used. Finally, because the urinary bladder commonly receives

the highest doses, we recommend that subjects be encouraged to void as soon after the injection as practicable, and frequently in the hours following. Consideration should also be given to stimulating emptying of the gallbladder with a fatty meal if the initial human scan (step 1) shows high uptake in the liver and/or gallbladder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Zanotti-Fregonara P, Innis RB. Suggested pathway to assess radiation safety of (11)C-labeled PET tracers for first-in-human studies. *Eur J Nucl Med Mol Imaging*. 2012; 39:544–547. [PubMed: 22160195]
2. van der Aart J, Hallett WA, Rabiner EA, Passchier J, Comley RA. Radiation dose estimates for carbon-11-labelled PET tracers. *Nucl Med Biol*. 2012; 39:305–314. [PubMed: 22033023]
3. Sakata M, Oda K, Toyohara J, Ishii K, Nariai T, Ishiwata K. Direct comparison of radiation dosimetry of six PET tracers using human whole-body imaging and murine biodistribution studies. *Ann Nucl Med*. 2013; 27:285–296. [PubMed: 23404061]
4. Obrzut SL, Koren AO, Mandelkern MA, Brody AL, Hoh CK, London ED. Whole-body radiation dosimetry of 2-[18F]Fluoro-A-85380 in human PET imaging studies. *Nucl Med Biol*. 2005; 32:869–874. [PubMed: 16253812]
5. Bottlaender M, Valette H, Roumenov D, Dolle F, Coulon C, Ottaviani M, et al. Biodistribution and radiation dosimetry of 18F-fluoro-A-85380 in healthy volunteers. *J Nucl Med*. 2003; 44:596–601. [PubMed: 12679405]
6. Kimes AS, Horti AG, London ED, Chefer SI, Contoreggi C, Ernst M, et al. 2-[18F]F-A-85380: PET imaging of brain nicotinic acetylcholine receptors and whole body distribution in humans. *FASEB J*. 2003; 17:1331–1333. [PubMed: 12759330]
7. Adler L, Wolodsko J, Stabin M, McNelis T, Gammage L, Joshi A. Radiation dosimetry of F18-AV-45 measured by PET/CT in humans. *J Nucl Med*. 2008; 49(Suppl 1):283.
8. Lin KJ, Hsu WC, Hsiao IT, Wey SP, Jin LW, Skovronsky D, et al. Whole-body biodistribution and brain PET imaging with [18F]AV-45, a novel amyloid imaging agent - a pilot study. *Nucl Med Biol*. 2010; 37:497–508. [PubMed: 20447562]
9. Wong DF, Rosenberg PB, Zhou Y, Kumar A, Raymont V, Ravert HT, et al. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected]) F-18. *J Nucl Med*. 2010; 51:913–920. [PubMed: 20501908]
10. Giussani A, Janzen T, Uusijarvi-Lizana H, Tavola F, Zankl M, Sydoff M, et al. A compartmental model for biokinetics and dosimetry of 18F-choline in prostate cancer patients. *J Nucl Med*. 2012; 53:985–993. [PubMed: 22570328]
11. DeGrado TR, Reiman RE, Price DT, Wang S, Coleman RE. Pharmacokinetics and radiation dosimetry of 18F-fluorocholine. *J Nucl Med*. 2002; 43:92–96. [PubMed: 11801711]
12. International Commission on Radiological Protection (ICRP). ICRP Publication 106: radiation dose to patients from radiopharmaceuticals—addendum 3 to ICRP publication 53. *Ann ICRP*. 2008; 38(1–2)
13. Deloar HM, Fujiwara T, Shidahara M, Nakamura T, Watabe H, Narita Y, et al. Estimation of absorbed dose for 2-[F-18]fluoro-2-deoxy-D-glucose using whole-body positron emission tomography and magnetic resonance imaging. *Eur J Nucl Med*. 1998; 25:565–574. [PubMed: 9618570]

14. International Commission on Radiological Protection (ICRP). ICRP Publication 62: radiological protection in biomedical research. Ann ICRP. 1992; 22
15. Yaghoubi S, Barrio JR, Dahlbom M, Iyer M, Namavari M, Satyamurthy N, et al. Human pharmacokinetic and dosimetry studies of [(18)F]FHBG: a reporter probe for imaging herpes simplex virus type-1 thymidine kinase reporter gene expression. J Nucl Med. 2001; 42:1225–1234. [PubMed: 11483684]
16. Tolvanen T, Lehtio K, Kulmala J, Oikonen V, Eskola O, Bergman J, et al. 18F-Fluoroerythronitroimidazole radiation dosimetry in cancer studies. J Nucl Med. 2002; 43:1674–1680. [PubMed: 12468519]
17. Doss M, Kolb HC, Zhang JJ, Belanger MJ, Stubbs JB, Stabin MG, et al. Biodistribution and radiation dosimetry of the integrin marker 18F-RGD-K5 determined from whole-body PET/CT in monkeys and humans. J Nucl Med. 2012; 53:787–795. [PubMed: 22499613]
18. Vesselle H, Grierson J, Peterson LM, Muzi M, Mankoff DA, Krohn KA. 18F-Fluorothymidine radiation dosimetry in human PET imaging studies. J Nucl Med. 2003; 44:1482–1488. [PubMed: 12960196]
19. Smolarz K, Krause BJ, Graner FP, Wagner FM, Hultsch C, Bacher- Stier C, et al. (S)-4-(3-18F-Fluoropropyl)-L-glutamic acid: an 18F-labeled tumor-specific probe for PET/CT imaging - dosimetry. J Nucl Med. 2013; 54:861–866. [PubMed: 23568366]
20. Beauregard JM, Croteau E, Ahmed N, van Lier JE, Benard F. Assessment of human biodistribution and dosimetry of 4-fluoro-11beta-methoxy-16alpha-18F-fluoroestradiol using serial whole-body PET/CT. J Nucl Med. 2009; 50:100–107. [PubMed: 19091905]