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Suggested pathway to assess radiation safety of ^{11}C-labeled PET tracers for first-in-human studies

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Dear Sir,

Before a new radioactive tracer can be used in humans, many national as well as local Institutional Radiation Safety Committees often require that a biodistribution study be conducted in animals. The aim of these time-consuming and expensive studies is to assess the dose of absorbed radiation in animals so that the human dose can be extrapolated. Because of their physical similarity to humans (organ size and body weight), monkeys are arguably the best animal species to estimate radiation burden in human subjects. The extrapolation can be performed with different methods [1], for example by converting the percent administered activity in the monkey organ to percent administered activity in the same human organ. Basically, the human residence time for a given organ is derived by performing the animal to human organ mass ratio multiplication for each time point and then by integrating that time-activity curve to derive a hypothetical area under the curve for that human organ. This process is then repeated for each major source organ. The resulting residence times are then used in conjunction with an anthropomorphic human phantom to calculate the human dose. This method assumes that the metabolism of radiopharmaceuticals is similar between the two species and varies only as a function of organ mass. However, as we will describe below, it is our contention that results obtained in this manner from monkeys are misleading. This commentary will suggest a more accurate alternative that nevertheless maintains a wide safety margin.

To investigate this issue, we identified a total of nine ^{11}C-labeled tracers for which both monkey and human absorbed doses were reported. We compared the absorbed doses extrapolated from monkeys for that particular radioligand and the mean dose from human biodistribution data for all nine radiotracers.

The results of these studies showed that, in general, doses extrapolated from monkeys overestimated the human effective dose (Table 1). Looking at all nine tracers, we found that the mean dose extrapolated from monkeys was 7.3±1.6 μSv/MBq, while the mean dose measured in actual human studies for the same tracers was 5.7±1.2 μSv/MBq (paired *t* test: $p<0.001$). Furthermore, such overestimates were not constant, but showed unpredictable variations; indeed, the percentage difference ranged from −72 to +11%. The most likely reason for such discrepancies is metabolic differences between different species. For instance, for ^{11}C-(*R*)-rolipram, biodistribution in monkey poorly estimated biodistribution in humans [2]. Compared to humans, monkeys had a higher liver uptake, no hepatobiliary excretion, and higher urinary elimination. This led to an approximately 40% overestimate of

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the effective dose [2]. For ^{11}C-PBR28, monkey data overestimated the effective human dose by 60%, with exposures to individual organs both over- and underestimated [3].

Moreover, the doses measured in human studies were quite constant across the different tracers (range 4.3–7.8 μSv/MBq) (Table 1). This suggests that when predicting the human dose for a given tracer, a simple mean human value from all published studies is a better predictor of the effective dose than the value derived from monkeys for that specific tracer.

We also searched the literature and found 21 other ^{11}C-labeled tracers for which dosimetry in human scans had been calculated. With the exception of ^{11}C-WAY-100635, whose effective dose was about 12–16 μSv/MBq, all other tracers had very similar, low estimates (range 3.0–6.8 μSv/MBq, mean 5.1 μSv/MBq) that closely agree with the average dose of 5.8 μSv/MBq found in the first nine tracers (Table 2).

Based on the findings reviewed here we conservatively recommend that the upper limit of injected activity can be derived from the maximum reported effective dose in humans. For ^{11}C ligands, the maximum effective dose (16 μSv/MBq) was found for ^{11}C-WAY-100635 (Table 2). Although to our knowledge the International Commission on Radiological Protection (ICRP) has not proposed any radiation dose limits for volunteer subjects in human radiation experiments, including radionuclide metabolism studies and testing of new diagnostic agents, Institutional Radiation Safety Committees usually do establish upper limits. For instance, at the National Institutes of Health (NIH), the upper limit of effective dose for subjects participating in research radiation studies is 50 mSv [4]. Thus, the maximum injectable activity of ^{11}C-WAY-100635 would be 3,125 MBq (84 mCi). It should be noted that even an activity more than 8 times lower (370 MBq or 10 mCi) would be sufficient to perform a study with an acceptable imaging quality. That is, we think that 370 MBq of any ^{11}C-labeled radiopharmaceutical can be safely used for first-in-human studies without needing to conduct prior animal biodistribution studies.

Nevertheless, it is possible that even when the effective dose is low, a given tracer may deliver an excessive absorbed dose to a specific organ. To address this issue, Gatley [5] performed simulation studies to estimate an intravenously injected quantity of several ^{11}C-labeled compounds that could not exceed a regulatory limit of 50 mSv on absorbed doses for individual organs. Upper limits on organ cumulative activities were estimated by assuming that ^{11}C-Iabeled compounds are instantaneously distributed in the plasma and then transferred solely and irreversibly to a single organ. This approach would allow the assessment of the “worst case” estimate (although such an estimate would be obviously unrealistic), in order to conservatively plan initial human positron emission tomography (PET) imaging studies. Using an organ limit of 50 mSv, Gatley showed that a preliminary study with up to 130 MBq of ^{11}C could be performed in humans without reaching this limit. This preliminary study would yield ^{11}C arterial plasma data, which could in turn be used to give a refined upper limit on radiation absorbed doses [5].

In the case of ^{11}C-WAY-100635, the limiting organ is the bladder, with an estimated dose of 0.167 mGy/MBq in men and 0.220 mGy/MBq in women [6]. Even for this tracer, an activity of up to 300 MBq in men and 227 MBq in women can be administered in a single injection before reaching 50 mSv, an organ limit established by the US Food and Drug Administration for radioligands studied under a Radioactive Drug Research Committee (21CFR361.1).

To safely perform first-in-human studies of new ^{11}C-labeled tracers, we suggest the following design:

1. Begin with whole-body scanning in a single human subject using 370 MBq (10 mCi). If we confirm that the radioactivity is fairly widely distributed in the body, we would know that no organ is likely to receive the theoretical maximal irradiation hypothesized by Gatley; therefore, higher activities may be injected.
2. To determine whether the radioligand is worth pursuing, then do five to ten kinetic scans centered on the organ of interest (e.g., brain) using doses up to 740 MBq (20 mCi).
3. If the radioligand looks promising, complete the human dosimetry study by acquiring a total of six to ten wholebody scans at 370 MBq (10 mCi) each.

Please note that 10 mCi is adequate for whole-body imaging because we quantify large regions, i.e., the whole organ. Higher injected activities (e.g., 20 mCi) are necessary for brain imaging because we measure subregions of brain and, more importantly, because we seek to measure rapidly declining concentrations of the parent radioligand in plasma.

Taken together, these data suggest that monkey dosimetric studies with ^{11}C-labeled tracers are not only unreliable, but also unnecessary, as such studies can be safely performed in humans. We suggest that the very first human subject have a whole-body scan to confirm a fairly broad distribution in the body. Subsequent subjects may have dedicated imaging of the target organ as well as arterial blood sampling for rigorous compartmental modeling. Only after the tracer is deemed to be reasonably useful would additional whole-body studies be performed to estimate radiation doses from a larger sample size (five to ten subjects). One advantage of this pathway is that the radiation exposure to the larger sample of five to ten subjects would be avoided if the tracer is thought to lack utility based on rigorous compartmental analyses. Finally, our recommendation is made for ^{11}C-labeled tracers because we had dosimetry data from biodistribution data in monkeys for many radioligands (i.e., nine). Nevertheless, similar arguments might also be made for ^{18}F-labeled tracers.

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Table 1

Comparison between the effective dose extrapolated from monkeys for nine different tracers and the actual effective dose measured in humans

Tracer	Dose from monkeys (μSv/MBq)	Reference	Dose from humans (μSv/MBq)	Reference	% difference as compared to monkey estimates[a]	% difference as compared to the human mean[b]
^{11}C-BTA-1	7.4	Parsey et al. (2005) [7]	4.3	Thees et al. (2007) [8]	−72.1	−25.1
^{11}C-(*R*)-Rolipram	6.6	Sprague et al. (2008) [2]	4.8	Sprague et al. (2008) [2]	−37.5	−16.4
^{11}C-DASB	6.2	Tipre et al. (2004) [9]	7.0	Lu et al. (2004) [10]	11.4	21.9
^{11}C-PBR28	10.3	Brown et al. (2007) [3]	6.6	Brown et al. (2007) [3]	−56.1	14.9
^{11}C-CUMI-101	6.9	Parsey (unpubl.)	5.3	Hines et al. (2011) [11]	−30.2	−7.7
^{11}C-MePPEP	6.6	NIMH/SNIDD [12]	4.6	Terry et al. (2010) [13]	−43.5	−19.9
^{11}C-dLop	9.4	Liow et al. (2009) [14]	7.8	Seneca et al. (2009) [15]	−20.5	35.8
^{11}C-(*R*)-PK11195	5.3	Our unpubl. data	5.0	Hirvonen et al. (2010) [16]	−6.0	−13.0
			4.6	Kumar et al. (2010) [17]	−13	−19.9
^{11}C-raclopride	6.7	Herscovitch et al. (1997) [18]	6.3	Slifstein et al. (2006) [19]	−6.3	9.7
			6.7	Ribeiro et al. (2005) [20]	0	16.6
Mean±SD	7.3±1.6		5.7±1.2		−29.0±26.5	0±21.7

[a] Obtained for each tracer *j* by: (human dose$_j$ − monkey dose$_j$)*100/human dose$_j$

[b] Obtained for each tracer *j* by: (human dose$_j$ − mean human dose)*100/mean human dose

Table 2

Effective dose measured in humans for 21 different ^{11}C-labeled tracers

Radiopharmaceutical	Target	Effective dose (μSv/MBq)	Reference
^{11}C-Glucose	Cell metabolism	3.0[a]	Graham et al. (1998) [21]
		3.8[b]	
^{11}C-NPA	Dopamine $D_{2/3}$ receptor	3.2	Laymon et al. (2009) [22]
^{11}C-ABP688	Metabotropic glutamate receptor subtype 5 (mGluR5)	3.7	Treyer et al. (2008) [23]
Methyl-^{11}C-thymidine	Cancer imaging	3.8	Thierens et al. (1994) [24]
^{11}C-GSK931145	Glycine transporter 1	4.0[a]	Bullich et al. (2011) [25]
		4.9[b]	
^{11}C-MeAIB	Amino acid transport	4.0	Tolvanen et al. (2006) [26]
^{11}C-PD153035	Epidermal growth factor receptor	4.0[a]	Liu et al. (2009) [27]
		5.2[b]	
^{11}C-MP4B	Butyrylcholinesterase	4.2	Virta et al. (2008) [28]
^{11}C-Choline	Tumors and proliferative disorders	4.4	Tolvanen et al. (2010) [29]
^{11}C-Carfentanil	μ-Opiate receptor	4.6	Newberg et al. (2009) [30]
^{11}C-Docetaxel	Cancer imaging	4.7	van der Veldt et al. (2010) [31]
^{11}C-PIB	β-Amyloid plaque	4.7	Scheinin et al. (2007) [32]
^{11}C-MPGA	GABA receptor	4.8	Santens et al. (1998) [33]
^{11}C-Acetate	Cancer imaging	4.9	Seltzer et al. (2004) [34]
^{11}C-Flumazenil	$GABA_A$ receptor complex	5.0	Nugent et al. (2004) [35]
^{11}C-Methionine	Cancer imaging	5.2[c]	Deloar et al. (1998) [36]
		5.0[d]	
^{11}C-PIB	β-Amyloid plaque	5.3	O'Keefe et al. (2009) [37]
^{11}C-NNC112	Dopamine D_1 receptor	5.7	Cropley et al. (2006) [38]
^{11}C-PE2I	Dopamine transporter	6.4	Ribeiro et al. (2007) [39]
^{11}C-Mirtazapine	Central adrenoceptor	6.8	Marthi et al. (2003) [40]
^{11}C-WAY-100635	$Serotonin_{1A}$ receptor	12.2[a]	Parsey et al. (2005) [6]
		16.0[b]	
Mean±SD		5.1±2.2	
Range		3.0–16.0	
Median		4.7	

GABA γ-aminobutyric acid

[a]Male

[b]Female

[c]Caucasian

[d]Japanese