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TISSUE DISTRIBUTIONS OF RADIOPHARMACEUTICALS LABELED WITH
POSITRON EMITTERS AND PROBLEMS IN RELATING THEM TO HUMAN STUDIES

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INTRODUCTION

As far as organ distribution is concerned, for a given element or compound it of course makes no difference what the decay characteristics of the labeling nuclide may be. The only unusual but general problem in this area, when dealing with positron emitters, is that very few of the commonly-used nuclides have half-lives greater than 1-2 hours. Therefore, unless the compound can be prepared with a different but longer lived nuclide, in an equally stable position chemically and metabolically, one is forced to do the necessary dissections and counting of samples in a short period of time, keeping accurate track of elapsed time. This problem is exacerbated, in many cases, since more often than not the organ distributions themselves are distinctly time dependent. Therefore a time-averaged distribution must be worked out for purposes of dose calculations. None of this need be of surpassing difficulty, but it usually does require more than normal attention to detail.

In addition the calibration of gamma counters for positron emitters is not generally as simple as is that of longer-lived nuclides. Accurately calibrated, pure positron emitting, standards are not commercially available due to their short-half lives. Furthermore, the settings given for the positron emitters on many commercial dose calibrators are generally not more reliable than about $\pm 20\%$ (1).

It is possible to obtain reasonable organ distributions from carefully calibrated positron cameras capable of whole-body scanning, but one must be very careful to correlate organ distributions measured directly with the results obtained from such cameras, and to take into account varying body weights and attenuation factors in interpreting such data. An example of such an approach for $^{13}\text{NH}_3$, can be cited here (2).

However, assuming that such considerations are understood properly and that correct results are obtainable, we can discuss some results and generalizations in this area without further concern with the technical aspects of the needed data collection.

There is one major difference between positron emitters and pure photon emitting nuclides with respect to the effect on doses to the various organs. Pure photon emitters deposit relatively little energy in the organ in which they are located, especially at higher energies. However, with positron emitting nuclides essentially all of the energy related to the particle itself is deposited in that organ. The average range of the commonly used positron emitters is 1-4 mm before annihilation takes place, and thus

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virtually none of them escape from the organ in which the decay event takes place (3). The energy deposited by the annihilation photons is distributed exactly like that of any 511 keV photon. But the result is that a very high fraction of the organ dose, with positron emitters, comes from the particle itself (typically 90% of the total). Thus, while the organ distribution itself does not differ from that which would obtain with any other label, the effect of the distribution with respect to dose is very different with these nuclides as compared to those labeled with pure photon-emitters.

Rather than attempting a complete review of published organ distributions involving positron-emitting nuclides, this paper will discuss a few specific examples intended to illustrate some specific points in this area. In particular, work with 2-fluoro-2-deoxyglucose will be discussed in some detail, and its distribution in the body compared with the closely related (chemically but not biologically) 3-fluoro-3-deoxyglucose and 1-¹¹C-2-deoxyglucose. Other compounds labeled with these two nuclides, and with ¹³N and ¹⁵O will also be discussed.

GLUCOSE AND ITS MIMICS

It has been known for some time that 2-deoxyglucose mimics the biological behavior of glucose itself, but only through the first step in normal glucose metabolism, phosphorylation at the 6 position. Since the next step in glucose metabolism normally involves a rearrangement at the 2 position, a reaction which is blocked by the absence of the hydroxy group at the position in 2-deoxyglucose, it was expected that this compound might be useful in studying glucose metabolic rates in vivo because it would be trapped in situ at the sites where glucose metabolism is taking place. This was confirmed by the use of ¹⁴C-2-deoxyglucose in animals, and the organ distribution of this compound was determined directly by that means (4). The synthesis of ¹¹C-2-deoxyglucose several years ago was found to be quite difficult, so the ¹⁸F labeled analog was investigated as a possible substitute. The synthesis of ¹⁴C labeled 2-fluoro-2-deoxyglucose was accomplished (5) and the organ distribution of the compound was determined in animals by the same method. It was indeed found to behave similarly to 2-deoxyglucose itself at the sites where glucose metabolism was taking place, and it was also found to be blocked at those sites after the first metabolic step. After the preparation of the ¹⁸F compound was accomplished (6), its distribution in mice and dogs was also confirmed directly since the half life of 110 minutes allowed ample time for dissection and counting of the needed samples.

The organ distributions for 2-¹⁸F-deoxyglucose (2-FDG) (7) are given in Table 1 and those for 1-¹¹C-2-deoxyglucose (2-DG) in Table 2. Both of these are based on work done at Brookhaven. It can be seen that, at 30 and 60 minutes there is a great deal of similarity in the distribution of these two compounds, as would be expected in this specific case. There is considerably higher uptake in the kidneys and liver with 2-DG than with 2-FDG, but otherwise the behavior is comparable.

These compounds represent a rather unusual situation with regard to tissue distribution, however, because they are trapped metabolically and tend to remain where they are distributed throughout the body, chiefly in organs having high hexokinase activity. They tend to clear rather rapidly from those organs with low hexokinase activity. It is more usual for the organ distribution to change with time, as the compound administered is distributed and metabolized, and therefore it is usually necessary to obtain distributions at various times in order to make appropriate dose calculations. Such is the case, for example, with ¹¹C-glucose itself and

Table 1

2-¹⁸F-2-deoxyglucose
Organ distribution (dog), at 60 min and 135 min

<u>ORGAN</u>	<u>%/organ (60)</u>	<u>%/organ (135)</u>
Brain	2.1	2.8
Heart	3.5	2.4
Kidneys	0.8	0.5
Liver	3.2	2.2
Lungs	2.4	1.3
Ovaries	0.01	0.003
Pancreas	0.20	0.3
Spleen	1.15	0.9
Urine	13.3	50.0

Table 2

1-¹¹C-2-deoxyglucose
Distribution (% of injected dose) at 30 min (dog)

<u>ORGAN</u>	<u>%</u>	<u>Dose (mR)/mCi</u>
Bladder	20.0	270
Brain	1.4	8
Heart	4.3	48
Kidney	2.1	59
Liver	5.7	26
Lung	2.2	17
Ovaries	0	85
Pancreas	0.2	16
Spleen	1.0	34
Testes	0.3	67
Whole Body	62.8	11

with 3-¹⁸F-3-deoxyglucose (3-FDG) (8), a compound which behaves similarly to glucose in many ways but has some very interesting differences from it. The 3-FDG is phosphorylated at the 6-position much more slowly than is glucose itself, but its metabolism is not stopped at that point. However, some fluorine-containing metabolites are trapped in tissues to an extent comparable to 2-FDG (8). The distributions of these two compounds are given in Table 3, and it can be seen that their behavior is very different from that of the 2-deoxy compounds. The actual metabolic behavior of each compound must be understood in order to make meaningful extrapolations of organ distributions even with compounds which are not very different chemically.

The behavior of 2-FDG also points up the problem in relating animal tissue distributions to those in humans. In the dog, an appreciable amount of the compound is taken up by the heart, and excellent images of the dog heart can be obtained using it. However, in the human a more variable proportion of 2-FDG is taken up by the heart, normally, and it has been more difficult to obtain consistently good human heart images with it (9). Its lack of appreciable concentration in organs other than brain and heart is practically unique, and is an advantage from the dosimetry standpoint. It is probably the most useful positron emitting compound available today, and is certainly so for the study of brain glucose metabolism.

The behavior of 2-FDG with respect to the kidneys and the bladder dose deriving from it is worthy of comment. Glucose itself can be actively

Table 3

3-¹⁸F-3-deoxyglucose¹
and ¹¹C-glucose
% of injected dose, dog, 1 hour

<u>ORGAN</u>	<u>3-FDG</u>	<u>GLUCOSE</u>
Brain	2.65	0.9
Heart	5.8	0.8
Liver	11.2	3.8
Lung	2.2	0.6
Kidney	1.8	0.7
Spleen	0.5	—
Blood	~ 30	—

¹Welch, M., Private Communication

transported by kidney tissue and is resorbed by it, so that in non-diabetics very little glucose is found in the urine. This is an active transport process, presumably requiring the presence of a hydroxy group at position 2 of the glucose molecule (10,17), and this is of course not present with either 2-DG or 2-FDG. The transport also does not occur with 3-FDG, however, even though the 2-OH group is still present in that case (8). These compounds do accumulate in the urine to a great extent, with a result that the bladder becomes the organ receiving by far the highest dose from administration of these three compounds. Studies have been done with a collimated probe placed directly over the bladder during brain scans done with 2-FDG on the PETT III at Brookhaven, and the range of percent of injected dose for 10 subjects was from 8 to 41%, with an average of about 22% being present one hour after injection (11). If one assumes that the activity remains in the bladder throughout its decay, this results in a calculated dose of $435 + 76 \text{ mR/mCi}$ (for injections of 5-10 mCi), assuming a 200 cc bladder and 50% of the particles reaching the bladder wall. These are the assumptions upon which the currently published S values are based. However, it is obvious that if, two hours after injection, the subjects eliminate the accumulated urine, this dose will be cut in half since there is very little additional washout into the urine after about one hour.

EFFECT OF SPECIFIC ACTIVITY

There are many applications in which the specific activity of the compound used has a great effect on the tissue distribution, and therefore metabolic behavior, of the material used. For example, the earliest work with ¹⁸F labeled analogs of phenylalanine (12) used material with a considerable amount of carrier present, and it showed relatively poor liver/pancreas ratios in animals. Since it was hoped that it might be useful for pancreas scanning, this result was disappointing. However, improvements in the synthetic methods used for the compounds finally led to products with considerably higher specific activity, and their use improved the liver/pancreas ratio by a factor of two to three. That this is not always the case, however, can be seen by the similar behavior of glucose itself and 3-deoxyglucose, where the former compound is in plentiful supply in the body and the latter is not present at all.

Another general caution in relating animal distributions to those in the human is illustrated by ¹¹C-2DG, where it was found that assuming the same percent per organ in mouse ovaries and in the human led to a very high calculated dose to the human ovary with this compound. However, the mouse ovary is a much larger fraction of total body weight than is that of the

human, and when this was taken into account the reasonable dose indicated in Table 2 is calculated. This problem has been discussed in the literature before (13), and it is one which should be kept in mind when such extrapolations are being made.

THE OCTYLAMINES

Another example of the importance of understanding the biochemistry involved can be shown by the different behavior of the same compound labeled with a different nuclide at a different position. Octylamine labeled with ^{13}N and with ^{11}C in the 1-position has been studied at Brookhaven with mice (14) and, in the ^{11}C case, with human subjects (15). The compound is taken up very rapidly by the lungs and may be of some use in studying aberrations in metabolism in various disease states. It is known to be deaminated in the lung tissue almost immediately, by monoamine oxidase, but the metabolites are retained by the lung tissue reasonably well (in the ^{11}C case) over a sufficient period of time to obtain good images of the area. The metabolism to $^{11}\text{CO}_2$ builds up rapidly for about 5 minutes, then follows a slowly declining rate until insufficient activity is present to continue the measurements. In the ^{13}N case the activity apparently enters the ammonia pool in the body and eventually shows a distribution similar to that of $^{13}\text{NH}_3$ itself, with a reasonable amount still appearing in the lung tissue. The tissue distributions of both labeled octylamines and of ammonia in mice at 5 minutes post injection are shown in Table 4.

Table 4

^{13}N and 1- ^{11}C -octylamine distribution (mice, 5 min)
(% dose/organ)

ORGAN	^{11}C	^{13}N	$^{13}\text{NH}_3$
Blood	2.31	—	—
Brain	1.89	—	—
Heart	0.35	0.8	1.4
Kidneys	9.34	6.2	7.0
Liver	6.25	6.5	14.0
Lungs	3.78	1.5	1.4
Spleen	0.74	0.7	0.9
Whole Body	75.50	84.2	72.8

Table 5

$^{13}\text{NH}_3$ Distribution
(% of injected dose, at equilibrium)

ORGAN	% ¹	% ²	% ³
Blood	6.4 ± 0.3	—	—
Brain	6.9 ± 0.5	0.5 ± 0.2	—
Liver	7.1 ± 0.7	11.9 ± 1.7	14.0
Bladder (urine)	6.4 ± 1.1	8.7 ± 3.3	7.0
Whole Body	73.2	75.3	72.8
Heart	—	3.6 ± 0.5	1.4

¹Lockwood et al., J. Clin. Invest. 63, 449 (1979)

²Gelbard et al., Radiology 116, 127 (1975)

³BNL (mice)

The variability of tissue distribution measurements with the same compound, $^{13}\text{NH}_3$, at different times and places is indicated in Table 5. Generally speaking, this is a fair example of the effects of different techniques, diets, and other variables on the data obtained in such work. It is common practice to lump all of the injected activity which cannot be accounted for specifically in the "whole body" category, and the most consistent thing about this particular data is that three different groups each did not account for approximately 75% of the activity in this case. This is not really a totally unfair approach, since in most cases the activity not accounted for is largely in the circulating blood pool.

NUCLIDES OF VERY SHORT HALF-LIFE

Another commonly used positron emitting nuclide is ^{15}O . Since its half life is roughly 2 minutes it is not practical to synthesize any very esoteric compounds with it, and its chief uses have been with $^{15}\text{O}_2$ (to measure metabolic rates), C^{15}O (to label blood) and C^{15}O_2 (to measure flow rates in blood pools). Under these circumstances it is impractical to try to measure concentrations in tissue, and doses are best calculated based on whole body distribution of the nuclide.

SOLUBILITY PROBLEMS

Another problem in finding tissue distributions has occurred when a compound of limited solubility in neutral aqueous media is encountered (16). Clearly this situation should be avoided but it has occurred and results in most of the injected material never leaving the injection site, or at least doing so at a very slow rate. A comparable situation occurs occasionally when an accidental intramuscular injection is made of a compound which does not have any solubility problem. Again the material is distributed at a greatly reduced rate and may follow an abnormal distribution pattern as well. In determining tissue distributions one should be aware of such pitfalls and take pains to avoid them. With positron emitters this can result in a very high local radiation dose from the particles themselves; the photons are of such high energy that they need not be considered a problem in this case. The effects of such an occurrence have been considered by the Radioactive Drug Research Committee at Brookhaven, and it was concluded that the increased risk was not a serious one because there is no known documentation of radiation-induced tumors being formed in muscle tissue.

In summary, from the standpoint of tissue distribution there is nothing unusual about positron emitters as such. The measurements may be more difficult than normal because of the short half-lives of most of them, but the data can be collected in the same way as for any other compounds. The most important thing is to know something about the biochemistry involved in order to understand the time course of the tissue distribution patterns as they evolve.

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