Journal of Labelled Compounds and Radiopharmaceuticals

Published online 13 May 2010 in Wiley Interscience (www.interscience.wiley.com) DOI: 10.1002/jlcr.1764

10th International Symposium on the Synthesis and Applications of Isotopes and Isotopically Labelled Compounds—WBA–New Methods and Applications and WBA–Instrumentation and Regulatory

Sessions 5 & 6: Monday, June 15, 2009

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Abstract: Predicting human radiation Dosimetry for clinical radiolabelled drug development studies was discussed.

Keywords: Carbon-14; Dosimetry; Whole-Body Autoradiography

PREDICTING HUMAN RADIATION DOSIMETRY FOR CLINICAL RADIOLABELED DRUG DEVELOPMENT STUDIES: A COMPARISON OF METHODS

A COMPARISON OF HUMAN ^{14}C DOSIMETRY METHODS FOR DRUG DEVELOPMENT

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Abstract: Human ^{14}C-and ^{3}H-radiolabeled drug studies are performed as part of drug development to determine human metabolism. Sponsors conducting the study must assure that human volunteers will not be subjected to dangerous radiation exposure from the radiolabeled drug. Several different mathematical methods to determine human dosimetry have been developed and are used by different pharmaceutical companies. Most often these studies have utilized organ homogenate data from animal studies. However, rodent quantitative whole-body autoradiography (QWBA) data, which provides true tissue concentrations, is now being used for dosimetry predictions. Anecdotal evidence suggested that different dosimetry methods provide different estimates. This study tested that hypothesis. Methods: rat tissue distribution data obtained from a QWBA ^{14}C-drug study was utilized to estimate human ^{14}C dosimetry using 3 different equations suggested by the FDA and the International Commission on Radiological Protection (ICRP)]. The results of the study showed that each method produced different dosimetry predictions. Moreover it demonstrated a need to revise the methods to utilize tissue concentration data, which is more precise than organ homogenate data. The benefits of a proper rodent study design and using tissue distribution data provided by QWBA vs. organ homogenate assays will also be discussed.

Keywords: Human; 14-Carbon; Dosimetry; MIRD; ICRP; FDA CRF Title 21

Introduction and Background: Human ^{14}C-and ^{3}H-radiolabeled drug studies are performed as part of drug development to determine human metabolism. The sponsor must prove to the clinic conducting the study that human volunteers will not be subjected to dangerous radiation exposure after internal administration of the radiolabeled drug by submitting a prediction of the exposure which is most often based on animal tissue distribution data. Several different mathematical methods to determine human dosimetry have been developed and used by different pharmaceutical companies over the years. Most often these studies have utilized organ homogenate data from animal studies. However, quantitative whole-body autoradiography

(QWBA) data, which provides true tissue concentrations, is now being used for dosimetry predictions and companies have used these data in combination with established dosimetry methods. Anecdotal evidence suggested that there are misunderstandings about dosimetry and that different dosimetry methods provide different estimates. This study tested that hypothesis.
Methods: A rodent tissue distribution study, which was designed to provide reliable tissue PK parameters, was conducted and tissue concentration data, as opposed to organ homogenate concentrations, were determined (see Table 1 for Study Design).
The following three sets of recommended calculations were chosen for the comparison:

1. 'Hendee-Marinelli' Equation (Dain et al. 1996).
2. Medical Internal Radiation Dose Committee (MIRD Equation), (4th International Radiopharmaceutical Dosimetry Symposium, Nov 1985).
3. ICRP recommendations (weighting factors for whole body exposure taken from 2009 guideline).

The proposed human dose was 100 μCi/70,000 g human.

For the purposes of comparison and to eliminate confusion, rad = rem and rem will be used to better match the US regulatory terminology.

The following describes the 'Hendee-Marinelli' equation.

$D_{tissue} = (73.8)\ (E\beta)\ (Cmax)\ (t1/2)$

where: D_{tissue} = radioactive dose (rem)
$E\beta = \beta$ particle energy for ^{14}C (using maximum E of 0.156 MeV and average E of 0.0493 MeV)
$t1/2$ = Biological effective half-life (days) from rat PK data
Cmax = Maximum human concentration (μCi/g organ)
= Cmax in rat (μg equiv/g) x human dose (μCi/g)/Dose in rat (mg/kg)

Human Whole-Body Radiation exposure was estimated as the summation of the individual tissue exposures.

The following describes the MIRD Equation.

1.1. Cumulated Radioactivity in the Body (Ã)

$\tilde{A}_{man} = A_{man} \times (T_{t.s.} \div \ln 2)$

Where: $\tilde{A}_{man}$ (μCi · h) is the cumulated radioactivity predicted in humans,
A_{man} (μCi) is the proposed ^{14}C dose to man (typically = 100 μCi), and
$T_{t.s.}$ (h) is the longest terminal ^{14}C half-life determined in each test species (Half lives calculated by linear regression of concentration-time data from QWBA study).
T_{rat} = typically the longest time (hrs) observed for a tissue in a QWBA study.

Therefore, based on data from rats:

$\tilde{A}_{man} = 100\ \mu Ci \times (h \div \mu \ln 2) = \mu Ci \cdot h$

1.2. Mean Absorbed Body Dose (D)

$D_{man} = \tilde{A}_{man} \times S_{man} \times RBE$

Table 1. Rodent study design and tissue pharmacokinetic parameters

Animal Model	Numbers of Animals	Doses: Radioactivity Drug	Dose Route	Post-Dose Sampling Times
Male Pigmented Rats	1 per time point; total of 8	100 μCi/kg 15 mg/kg	Oral Gavage	0.5, 1, 4, 8, 24, 72, 96, and 168 h post-dose

Tissue Concentration data for the following tissues and biological fluids and organ contents were determined using QWBA for each rat: adipose (brown and white), adrenal gland, bile (in duct), blood (cardiac), bone, bone marrow, brain (cerebrum, cerebellum, medulla), cecum (and contents), epididymis, eye (uveal tract and lens), Harderian gland, heart (myocardium), kidney (renal cortex and medulla), large intestine (and contents), liver, lung, lymph node, mammary gland, pancreas, pituitary gland, prostate gland, salivary gland, seminal vesicles, skeletal muscle, skin (pigmented and non-pigmented), stomach (gastric mucosa and contents), small intestine (and contents), spleen, spinal cord, testis, thymus, thyroid, and urinary bladder (and contents).
Tissue concentrations were determined as μCi/g of tissue or sample at each
Tissue pharmacokinetic (PK) parameters were determined for each tissue using WinNonlin, Non-compartmental analysis: Area under the concentration-time curve from time 0 to infinity (AUCinf), Area under the concentration-time curve from time 0 and including all time points (AUCall), time where the maximal concentration was reached (Tmax); the maximal tissue concentration reached (Cmax), the terminal in vivo half-life of radioactivity (t1/2), and the number of time points used to determine the t1/2 and the r^2 values for the line determining t1/2. The last 2 parameters were used to determine the reliability of the t1/2, where 3 or more time points must have been used and the r^2 value must be >0.85 for the t1/2 to be considered valid.

Where: D_{man} (rem) is the mean absorbed whole body dose in man,
$\tilde{A}_{man}$ (μCi · h) is the cumulated radioactivity predicted in humans,
S_{man} (rad/μCi · h) is the absorbed dose per unit of cumulated radioactivity in man ($=1.5 \times 10^{-6}$)
RBE (rem/rad) is the relative biological effectiveness (= 1 for ^{14}C).
Therefore, based on pharmacokinetic data from rats (Ref. 1), the predicted human whole body exposure to radioactivity (mean absorbed body dose) is:
$D_{man} = \mu Ci \cdot h \times 1.5 \times 10^{-6}$ rad/μCi · h × 1 rem/rad = rem

1.3. Cumulated Radioactivity per Gram Tissue ($\tilde{A}$/m)

$\tilde{A}/m = AUCINF$
Where: $\tilde{A}/m$ (μCi · h/g) is the cumulated radioactivity per gram of tissue,
AUCINF (μCi · h/g) is the total area under curve for each tissue determined from QWBA study data.

1.4. Mean Absorbed Tissue Dose (D)

$D_{rat} = \tilde{A}/m \times \Delta \times \Phi \times RBE$
Where: D_{rat} (rem) is the tissue exposure or mean absorbed tissue dose in rats,
$\tilde{A}/m$ (μCi · h/g) is the cumulated radioactivity per gram of tissue,
Δ(g · rad/μCi · h) is the equilibrium dose constant (= 0.105 for ^{14}C),
Φ is the absorbed fraction of energy (= 1 for ^{14}C), and
RBE (rem/rad) is the relative biological effectiveness (= 1 for ^{14}C).
D_{rat} values (in rem) for each tissue are shown in Table 1.
The mean absorbed tissue dose predicted in man (D_{man}) is:
$D_{man} = D_{rat}$ × (^{14}C dose to man ÷ ^{14}C dose to rats)
Where: the proposed ^{14}C dose to man = 100 μCi/70 kg = 1.43 μCi/kg,
and the ^{14}C dose to rats = 100 μCi/kg for pigmented rats as determined from QWBA study.
Therefore, $D_{man} = (D_{rat} \times 1.43\ \mu Ci/kg \div 100\ \mu Ci/kg)$
$D_{man} = D_{rat} \times 0.0143$

The following describes the ICRP equation.

Organ/Tissue Exposure Calculations

The fundamental equation for calculation of the radiation dose H_T, which was taken up in a given organ or tissue is:
H_T [mSv] = C [μCi × d/g] × E_p [MeV] × f
C : time integral of concentration of radioactivity in target organ
E_p : mean particle energy = 0.050 MeV for ^{14}C
f : conversion factor = 512 [mSv × g/μCi × d × MeV]
The equation for the radiation dose H_T for any organ or tissue, after inclusion of the radiation energy, for practical use, was:

$$H_T[mSv] = k[mSv \times g/\mu Ci \times d] \times \int_0^{\infty} c_t\, dt[\mu Ci \times d/g]$$

k :dose constant for ^{14}C ($= Ep \times f$) = 25.6 [mSv × g/μCi × d]
c_t: ^{14}C-concentration in the organ at time t
The integral of the ^{14}C-concentration-time function for the period 0 - infinity was equal to the area under the concentration-time curve $AUC_{(0-\infty)}$ of the ^{14}C-concentration multiplied by the specific radioactivity:

$$\int_0^{\infty} c_t \times dt[\mu Ci \times d/g] = s[\mu Ci/mg] \times AUG_{(0-\infty)}[mg \times d/g]$$

Thus, the radiation dose H_T in any organ was:

$$H_T = k \times s \times AUC_{(0-\infty)(organ)}\ [mSv]$$

The radiation dose H_T for any other organ or tissue was calculated according to general equation (1). For the reference organ plasma, the radiation dose H_{plasma} was:

$$H_{plasma} = k \times s \times AUC_{(0-\infty)(plasma)}\ [mSv]$$

For individual organs and tissues in man, the radiation doses H_T were calculated based on the radiation dose in plasma multiplied with the organ factor R_T, which was the ratio of AUC_T to AUC_{plasma} of ^{14}C in rats.

$$H_{T(man)} = H_{plasma(man)} \times R_T\ [mSv]$$

Whole Body Dose Calculation

The whole body burden D_{wb} (for stochastic effects), which was in accordance to the ICRP, was determined from the individual organ and tissue doses H_T. In this study, only a standard list of mandatory organs with defined weighting factors was taken into account. This list included the 5 organs that had the highest H_T value, and the 5 most sensitive organs, for a total of 10 organs. All other organs were considered as remainder organs on average.

$$D_{wb} = \Sigma w_T \times H_T \text{ [mSv]}$$

H_T : dose taken up in an individual organ or tissue
w_T : weighting factor for that organ or tissue

Results & Discussion: Table 2 presents a summary of the resulting tissue and whole body exposure estimates provided by each dosimetry method. The results show that each method produces a different prediction of tissue and whole body exposure. During the course of this comparison it was also observed that the equations (e.g. MIRD) are best designed for organ homogenate data, which are obtained from organ dissection/homogenate analyses, and do not readily account for the use of actual tissue concentrations. The equations also do not adequately consider allometric scaling from rodents to humans considering recent developments in the field. Furthermore the use of weighting is not appropriate for use on individual tissues but instead of determining the contribution of tissues to whole body exposure. A common practice among labs is also to use PK parameters that have been obtained from studies where reliable parameters cannot be obtained due to study designs that do not adequately capture time points resulting in unrealistic t1/2 and AUC values that can grossly over or underestimate exposures. QWBA results have repeatedly shown that tissue concentrations often vary considerably within organs and thus from organ homogenate data and that organ homogenate analysis can greatly underestimate the actual tissue exposure to radioactivity (e.g. concentration found in the cortex and medulla of the kidney). This finding suggest that the current dosimetry methods may need to be revised to better

Table 2. Individual tissue and whole body exposure values determined by 3 different dosimetry methods

Tissue	Hendee Method		MIRD Committee		ICRP w/out Weighting		ICRP w/Weighting		Whole Body Exposures	
	D (rem)	D (mSv)	Dman (rem)	Dman (mSv)	HT (rem)	HT (mSv)	HT (rem)	HT (mSv)	rem	mSv
Adipose (brown)	0.012	0.121	0.214	2.145	ND	ND	ND	ND		
Adipose (white)	0.004	0.040	0.166	1.660	ND	ND	ND	ND		
Adrenal Gland	0.039	0.387	0.284	2.839	0.01234	0.12335	0.00011	0.00113		
Blood (cardiac)	0.009	0.090	0.061	0.614	0.00000	0.00003	0.00000	0.00000		
Bone (femur)	0.003	0.027	0.175	1.754	0.00762	0.07620	0.00008	0.00076		
Bone Marrow	0.011	0.106	0.094	0.935	0.00406	0.04063	0.00049	0.00488		
Brain	0.001	0.012	0.063	0.632	0.00275	0.02745	0.00003	0.00027		
Cecum	0.014	0.135	0.385	3.851	0.01673	0.16731	ND	ND		
Epididymis	0.028	0.278	0.222	2.223	0.00966	0.09659	0.00077	0.00773		
Eye Lens	0.003	0.028	0.048	0.483	ND	ND	ND	ND		
Eye Uveal Tract	0.011	0.105	0.352	3.520	ND	ND	ND	ND		
Heart	0.034	0.343	0.199	1.993	0.00866	0.08660	0.00008	0.00080		
Large Intestine	0.057	0.569	0.592	5.920	0.02572	0.25724	0.00309	0.03087		
Liver	0.090	0.901	0.179	1.790	0.00778	0.07777	0.00031	0.00311		
Lung	3.408	34.082	20.631	206.314	0.89646	8.96459	0.10758	1.07575		
Lymph Node	0.018	0.175	0.196	1.962	0.00853	0.08525	0.00008	0.00078		
Pancreas	0.025	0.245	0.194	1.939	0.00842	0.08423	0.00008	0.00077		
Pituitary Gland	0.032	0.317	0.203	2.028	ND	ND	ND	ND		
Prostate Gland	0.016	0.164	0.247	2.470	0.01073	0.10733	0.00010	0.00099		
Renal Cortex	0.202	2.022	0.541	5.412	0.02352	0.23518	0.00022	0.00216		
Renal Medulla	0.082	0.820	0.436	4.363	0.01896	0.18960	0.00076	0.00758		
Salivary Gland	0.011	0.110	0.106	1.061	0.00461	0.04612	0.00005	0.00046		
Seminal Vesicles	0.012	0.120	0.192	1.924	0.00836	0.08361	0.00008	0.00077		
Skeletal Muscle	0.010	0.098	0.202	2.023	0.00879	0.08788	0.00008	0.00081		
Skin	0.014	0.136	0.254	2.540	0.01104	0.11037	0.00011	0.00110		
Small Intestine	0.010	0.098	0.301	3.014	0.01310	0.13097	0.00012	0.00120		
Spinal Cord	0.009	0.090	0.318	3.180	ND	ND	ND	ND		
Spleen	0.056	0.561	0.265	2.649	0.01151	0.11510	0.00011	0.00106		
Stomach	1.507	15.074	6.733	67.332	0.29257	2.92567	0.03511	0.35108		
Testis	0.004	0.037	0.069	0.687	0.00298	0.02985	0.00024	0.00239		
Thymus	0.005	0.046	0.072	0.718	0.00312	0.03119	0.00003	0.00029		
Thyroid	0.013	0.135	0.214	2.140	0.00930	0.09298	0.00037	0.00372		
Urinary Bladder	0.182	1.819	0.731	7.311	0.03177	0.31765	0.00127	0.01271		
Hendee Method									5.929	59.29
MIRD Method									0.272	2.718
ICRP Method									0.153	1.528

utilize true 'tissue' concentration data from QWBA studies for determining the tissue level exposure. This preliminary study shows the need to re-examine in detail the guidelines and methods being used to determine human ^{14}C dosimetry from administered radiolabeled drugs for human studies.

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