PET Physiological Measurements Using Constant Infusion

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ABSTRACT. A wide range of study designs can be used with positron emission tomography methods to provide quantitative measurements of physiological parameters. While bolus injection of tracer is the conventional approach, use of combined bolus plus constant infusion provides a number of advantages for receptor-binding tracers. Of recent interest is the use of this approach to dynamically follow the displacement of tracer during in vivo changes in neurotransmitter concentrations. This paper provides an overview of the tradeoffs in using bolus/infusion methods versus conventional bolus injection for receptor binding studies.

KEY WORDS. Constant infusion, Equilibrium, Receptors, Modeling, Volume of distribution

PHYSIOLOGICAL IMAGING METHODS

Radioactive tracers have been used to measure in vivo physiological parameters for decades (22). Successful use of a tracer for this purpose depends upon an in-depth understanding of the underlying physiological factors that control the tissue radioactivity levels. Mathemtical rigor can be applied to tracer studies with appropriate modeling techniques. Initially, tracer kinetic modeling studies can be quite complex. However, this methodology can be used to develop a simple and practical model-based measurement protocol to yield a quantitative physiological assay. With a good understanding of the tracer’s characteristics, the method can properly account for the effects of the input function, the time course of tracer available to the target organ. Also, the method can be tuned to be maximally sensitive to the parameter of interest and minimally influenced by extraneous physiological factors. For example, an assay for receptors should be only minimally influenced by changes in blood flow. Application of a model-based method ideally should reduce intersubject variability and increase the accuracy of the resultant measurements. However, in some cases, model-based methods can be overly complex to implement. Thus, errors in the models and their application can increase noise in the data. In many cases, the signal-to-noise improvement from a full, complex modeling approach is small or nonexistent. Thus, careful selection of the best method is difficult and requires careful assessment of the biological question of interest and the physiological characteristics of the tracer (2).

RECEPTOR METHODS

In the positron emission tomography (PET) literature, a large number of studies have focused on measurements of receptors and neurotransmitters. A wide variety of methodology has been used, including ratios of tissue concentrations between regions with and without specific binding made at various times postinjection; graphical analysis using plasma or reference region input functions; compartment modeling methods with a single administration of high specific activity ligand; and complex multiple-injection studies using competitors, displacement, or high and low specific activity tracer (6, 11–18, 24, 28). For many of these bolus injection studies with reversible ligands (i.e., those that reach or approach equilibrium during the time course of the study), the analysis method directly or indirectly determines the binding potential (BP) (25), the equilibrium ratio of bound to free (or free plus nonspecifically bound) tracer. Calculation of the binding potential is often made using the difference or ratio of volume of distribution (V) measurements from regions with specific and nonspecific uptake, under the assumption of uniform nonspecific binding.

V is the ratio at true equilibrium of total tissue concentration to a reference concentration (e.g., free metabolite-corrected plasma concentration). Although equilibrium is not reached in a bolus injection experiment, V can be determined by the compartment model parameters e.g., \( K_i/k_i \) or \( K_i/k_i(1 + k_i/k_i) \) for one- or two-tissue compartment models, respectively) or the slope of a Logan graphical analysis (24). V is linearly related to the free receptor concentration, but also includes factors such as the level of nonspecific binding, although it is not sensitive to blood flow or capillary extraction. V is typically the parameter that is best determined in these type of experiments. In other words, although individual rate parameters can be estimated by certain analyses, they typically have larger uncertainties and are often more affected by errors in the assumptions of the model or measurements of the input function or reference region than is V.

CONSTANT INFUSION

Bolus injection studies can provide estimates of BP and V with the use of an appropriate analysis method. A different approach is to deliver the radioactive tracer as an infusion to achieve constant radioactivity levels in the regions of interest and in the blood (3, 19, 20). Multiple short scans can be acquired to demonstrate that constant radioactivity levels have been reached. Once equilibrium is achieved, V can then be measured directly from the concentration ratio of tissue to plasma. If the binding potential is calculated with respect to a region with nonspecific binding, no blood measurements are necessary since the calculation only involves...
tissue concentration ratios; this has the significant advantage of avoiding measurements in blood, which are often complicated by the presence of radioactive metabolites. This simple analysis of a constant infusion experiment also has the advantage of being quite “model-independent” compared to the analysis techniques applied to dynamic bolus studies.

To produce equilibrium more rapidly, the tracer is typically delivered as a bolus followed by a continuous infusion (B/I). Although ideally the infusion protocol would be optimized for every individual (26), this would require a preliminary bolus study in each subject. Based on population values from bolus experiments, a fixed bolus fraction of the dose can be determined in advance by an optimization procedure (3).

EQUILIBRIUM FOLLOWING A BOLUS INJECTION?

$V$ is the ratio at true equilibrium between the tissue concentration and that of a reference fluid. For tracers that bind reversibly to tissue, the tissue:plasma ratio and the ratio of tissue concentration values between regions often become constant over time following a bolus injection (3). The ratios achieved in this period are different from those achieved during true equilibrium. When a constant tissue:plasma ratio is achieved following a bolus injection, this ratio is called the apparent volume of distribution ($V_{\text{app}}$) and this condition is termed “transient equilibrium” following the nomenclature of parent:daughter radioactive decay (10).

The disagreement between the apparent and true volumes of distribution can be shown with a brief derivation. Consider the differential equation describing the tissue uptake rate of a reversible tracer with a single tissue compartment, shown in Eq. (1):

$$\frac{dC}{dt} = K_1C_p - k_2C$$

where $C$ is the tissue concentration, $C_p(t)$ is the plasma input function, and $K_1$ and $k_2$ are the influx and efflux rate constants, respectively. At true equilibrium (derivatives equal 0), Eq. (1) shows that $V = C/C_p = K_1/k_2$. Following a bolus injection, eventually the plasma tracer activity begins a monoexponential clearance phase with rate $\beta$ [i.e., the fractional rate of change $(dC_p/dt)/C_p \rightarrow -\beta$]. For reversible tracers, eventually all the tissue radioactivity levels also clear at this same fractional rate [i.e., see Eq. (2)].

$$\frac{dC}{dt} \rightarrow -\beta C$$

At this point in time, since plasma and tissue are both clearing at the same fractional rate, constant concentration ratios between them have been achieved (i.e., transient equilibrium). Inserting Eq. (2) into Eq. (1) and solving for the tissue:plasma ratio yields Eq. (3):

$$V_{\text{app}} = \frac{C}{C_p} \rightarrow K_1 \frac{C}{k_2 - \beta} = \frac{V}{1 - \frac{\beta}{k_2}}$$

Thus, the terminal plasma clearance rate $\beta$ produces an increase in the measured tissue:plasma ratios so that $V_{\text{app}} > V$. If $\beta$ is small with respect to the tissue clearance ($\beta << k_2$), then this overestimation is small. There is no overestimation under equilibrium conditions ($\beta = 0$). For regions with slower tissue clearance (e.g., due to specific receptor binding) or for tracers with faster terminal plasma clearance rates, this effect can be large, producing overestimates of 100% or more. In a manner similar to that derived above, the ratios between different tissue regions are also affected by plasma clearance (3).

BOLUS VERSUS INFUSION FOR TISSUE RATIO ANALYSIS

The above analysis showed that in bolus studies, tissue concentration data alone does not provide accurate physiological information since the plasma clearance rate affects the results. Thus some form of modeling or graphical analysis is required to remove these plasma clearance effects from the data. If such analysis is not performed to correct the bolus data, there will be three effects. First, the measured indices will be biased, as shown above. Second, if there is significant within-group variation in plasma clearance, there will be additional variability in group data. Third, if the plasma clearance rates are different between subject groups (e.g., due to different liver function causing different rates of peripheral metabolism), $V_{\text{app}}$ and tissue concentration ratios will differ between the groups; this could lead to an incorrect conclusion if the only between-group difference is in fact peripheral metabolism. This suggests that if a simple ratio analysis is to be performed, the B/I protocol would be better. On the other hand, intersubject variation in plasma clearance rates would also contribute to lack of equilibrium in the infusion case, thus producing bias and/or variability in the data.

To assess whether intersubject variability may be a significant problem for bolus and B/I protocols, a simulation of a receptor model was performed. An arterial input function from a human $\left[{\text{18F}}\right]$FP-TZTP study (4) was used in the simulation ($\left[{\text{18F}}\right]$FP-TZTP is an $M_2$ muscarinic agonist). A two-tissue compartment model was used for the region of interest (ROI) with specific binding and a one-tissue compartment model was used for the background (BKG) region without specific binding. For both ROI and BKG, the tracer uptake rate ($K_1$) was 0.5 mL/min/mL, and the volume of distribution of free plus nonspecific binding ($V_e = K_1/k_2$) was set to 3 mL/mL. The ROI was simulated with a binding potential ($k_3/k_4$) of 5 and a dissociation rate ($k_4$) of 0.1 min$^{-1}$. Based on simulation of the bolus response, the B/I protocol was designed with the bolus fraction ($K_{\text{bolus}}$) of 75 min (i.e., the bolus dose was equal to 75 min of infusate), and the B/I input function was calculated (3).

Time-activity curves for ROI and BKG were simulated for the bolus and B/I cases with a 25% standard deviation in each of the following parameters: $K_1$, $V_e$, BP, $k_4$, and the terminal plasma clearance rate $\beta$. The apparent binding potential was calculated from simulated tissue concentration values (ROI/BKG – 1) from 60–120 min, and the bias and percent SD in this value were tabulated (Table 1). As shown above, for the bolus case the bias in binding potential is large (i.e., the estimates of BP are more than twice as large as the true value), while the infusion results are unbiased. However, it is important to realize that the absolute value of the binding potential may be of limited importance, particularly where BP is the ratio of bound tracer to free plus nonspecifically bound tracer at equilibrium. Thus, it may be more important to determine the effect on intersubject variability in the binding potential estimates. For variability in $K_1$, BP, or $k_4$, the variabilities of the BP estimates by either the bolus or B/I methods are small and similar. However, for variation in the free plus nonspecific volume of distribution $V_e$ or the plasma clearance rate, the variability in the bolus case is much larger than the B/I case. This is not surprising because these two parameters control the tissue and plasma clear-
second measurement of binding is made with a second tracer by determining In the first scan, control levels of binding are measured, for example, formed, each with a bolus injection of high specific activity tracer. intervention paradigm. In the first approach, two scans are per-

have been used to estimate receptor binding changes in such an model for the PET and a tracer kinetic model that accounted for the measurements was substantial, particularly because of the short time periods for pre- and poststimulus measurements were optimized. The magnitude of this difference in physiological parameters is also larger for the bolus case, particularly due to intersubject variability in $V_e$ and $\beta$. See text for simulation details.

MEASUREMENT OF IN VIVO CHANGES IN NEUROTRANSMITTERS WITH INFUSIONS

Since PET neuroreceptor studies are sensitive to the concentration of free receptor, they can be used to indirectly assess changes in synaptic neurotransmitter concentration. With appropriate modeling techniques, the change in radiotracer binding can be attributed to changes in the level of synaptic neurotransmitter that competes with the radiotracer for receptor binding. Two experimental designs have been used to estimate receptor binding changes in such an intervention paradigm. In the first approach, two scans are performed, each with a bolus injection of high specific activity tracer. In the first scan, control levels of binding are measured, for example, by determining $V_i$; then, after the pharmacological intervention, a second measurement of binding is made with a second tracer injection. This approach has been used successfully with the D2 ligand $[^{11}C]$raclopride (11) as well as with several other tracers. For example, Dewey et al. (7, 8) demonstrated the effects of changes in synaptic dopamine induced by direct manipulation of the dopamine system and by indirect pharmacological interventions.

The second study design is to use the B/I technique. First, the B/I administration of tracer is performed to achieve equilibrium, and control binding levels are determined from tissue:plasma or tissue:background region ratios. Then, a stimulus is administered while the infusion of radiotracer continues, and the change in specific binding of the tracer is monitored. This approach has been used to measure the difference in amphetamine-induced dopamine release between healthy controls and patients with schizophrenia using iodobenzamide ($[^{123}I]$IBZM) (21) and $[^{11}C]$raclopride (1). Analysis of the $[^{11}C]$raclopride human data suggested that statistical noise in the measurements was substantial, particularly because of the short half-life of $^{11}$C (20.4 min). To improve the quality of B/I results while maintaining the simple clinical utility of the method, the time periods for pre- and poststimulus measurements were optimized. This optimization was performed based on a statistical noise model for the PET and a tracer kinetic model that accounted for the displacement of $[^{11}C]$raclopride by dopamine (9). As a result of the optimized timings, the statistical significance of the difference in specific binding between patients with schizophrenia and normal subjects was increased (27). This type of optimization analysis may be highly useful to maximize the sensitivity of a variety of simple analytic schemes.

BOLUS VERSUS INFUSION

The B/I methodology has a number of advantages over bolus techniques. First, the data analysis is very simple and often can be accomplished without measurements in blood. If blood is to be used, at equilibrium the arterial venous differences may be quite small, so venous sampling may be adequate instead of the more invasive arterial sampling. For studies of changes in neurotransmitter concentrations, control and stimulus binding levels can be measured with one tracer synthesis and the total patient study time is shorter. However, the choice of bolus or infusion paradigms is not simple. Bolus studies can also be analyzed without blood measurements by use of various graphical and reference region analyses (15, 18, 23). Also, complete dynamic acquisition of data permits the estimation of more than one parameter (e.g., $K_i$ images as a measure of blood flow) (5, 16, 18); for B/I studies, if scanning is only performed at equilibrium, only $V_i$ can be estimated. The optimal time and duration for scanning must be determined in a B/I study. This generally results in a trade-off between achieving equilibrium and maximizing statistical counts. Thus, the statistical quality of bolus studies may be better than B/I scans, particularly for short-lived PET tracers. A B/I scan is also more technically complex due to the prolonged tracer infusion.

In summary, for a given tracer, there is a very wide choice of methodology. If the goal is a clinically practical protocol, involving short scans with little or no blood analysis and straightforward data and image processing, there are still many possible designs with simple methodology. The best choice depends upon the biological question, the magnitude of the signal of interest, and the variability of the “extraneous” physiological factors that affect the tracer’s uptake. The use of a well-validated tracer kinetic model can greatly improve the design of the simple protocol for a particular biological question. However, even with a complete understanding of the tracer, the choice of the optimal protocol may still be an educated guess based on many assumptions. Thus, practical logistical issues that affect patient throughput can also play a role in the definition of the final methodology.

References


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<th>Parameter</th>
<th>Bolus</th>
<th>Infusion</th>
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<tr>
<td>$K_i$</td>
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</tr>
<tr>
<td>$V_e$</td>
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<tr>
<td>$\beta$</td>
<td>138</td>
<td>–2</td>
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Mean and percent SD of the percent bias in binding potential calculated from concentration ratios of region of interest to background region. Bolus injection shows positive biases due to transient equilibrium, which are eliminated by use of infusion protocol. Intersubject variability in the parameters is also larger for the bolus case, particularly due to intersubject variability in $V_e$ and $\beta$. See text for simulation details.


