LEAKAGE FORM BLOOD BRAIN BARRIER: EFFECT OF INJECTION PROFILE ON PLASMA AND EXTRAVASCULAR CONCENTRATIONS

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ABSTRACT

This work describes a method for studying the effect of injection profile on the concentration of contrast agent in plasma and lesion leakage spaces. The proposed method is based on Tofts and Kermode (TK) compartmental model and Monte Carlo simulation. Analytical methods for solving compartmental equations considering injection effects are complicated. We treat passing of the contrast agent through the compartments as intrinsically statistical processes. Therefore, it is simulated by the Monte Carlo method. The amount of contrast agent that leaks out of a vessel depends on its permeability, lesion volume of Blood Brain Barrier (BBB), and injection function. Variation in injection profile produces different arterial input functions (AIFs) and extravascular curves. Calculation of summary parameters (in contrast to deconvolution) takes no account of the variation in these two functions. In our approach, the coefficients of TK model equations are used for calculating the fraction of contrast agent in each compartment. Gamma, box, and trapezoidal functions are used for the plasma input. Concentrations of the contrast agent in plasma, extravascular, and lesion leakage spaces as functions of time are found without solving any equations. To validate our approach, it is shown that it generates similar results to Weinmann data and analytical methods for TK model with a bolus injection and gamma function. The proposed method can be used for studying injection effects on the permeability estimation results.

INTRODUCTION

Any injury to the brain, whether due to direct trauma, inflammatory, or chemical toxins, causes a breakdown of the BBB, allowing free diffusion of large molecules into the nervous tissue. It is believed that this is brought about by actual destruction of the vascular endothelial cells or disruption of their tight junctions [1]- [3]. Use of contrast agents like Gd-DTPA (gadolinium diethylenetriamine pentaacetic acid) in magnetic resonance imaging (MRI) or radioactive materials in nuclear medicine imaging identifies regions of Blood Brain Barrier (BBB) breakdown in neurological diseases [4]. MRI is the ideal imaging technique for evaluating brain tumors and other abnormalities because of its high tissue contrast and ability to show injury of BBB. Several physiological models have been proposed to allow MRI-based quantification of the capillary permeability. Nowadays, the dynamic contrast enhancement (DSC) MRI is increasingly used for the measurement of cerebral perfusion, cerebral blood volume, and mean transit time. There are two commonly used methods for the quantification of DSC data.

The first method, requires measurement of the arterial input function (AIF) and principles of contrast agent dynamics in the tissue. The physiological parameters *CBF*, cerebral blood volume *(CBV)*, and mean transit time (MTT) are estimated by this method through a time-consuming decovolution process. The second method uses summary parameters calculated from the tissue concentration or *C(t)* curve e.g., time to peak (TTP) and maximum peak concentration (MPC). This method is fast and straightforward and does not require the measurement of AIF. However, the results

depend on the injection profile [5]. Despite frequent use of the above methods in the analysis of perfusion data, there is no reported study to assess effects of variations in the injection profile on AIF, *C(t),* and the summary parameters.

In this paper, effects of the injection profile on the summary parameters are studied. For this purpose, Tofts and Kermode (TK) model is an analyzed using statistical method to avoid complexity and difficulty of dealing with the analytical methods. The results of the analytical methods and the statistical method (Monte Carlo simulation) are compared with the published data by Wienmann et al (see ref. [2]) for the TK model. In this case, the bolus injection (input to the plasma compartment) is assumed to be a Gamma function and the analytical results are compared to the statistical results (Monte Carlo simulation). In addition, for the box and trapezoidal input functions, Monte Carlo simulation is conducted and the effects of the injection profile on the summary parameters are found.

MATERIALS AND METHODS

The Tofts and Kermode's compartmental consists of four compartments, the plasma space, kidneys, extracellular space, and lesion leakage space [2]. By solving compartmental equations, the concentrations of the contrast agent in plasma, extracellular space, and leakage space as function of time are derived. For Monte Carlo simulation, crossing of particles from a compartment to the other ones can be considered as a simple weighted summation of exponential decays by independent models [6]. The number of particles in each compartment follows the exponential function:

$$C_i(t) = A_i \exp(-\lambda_i t) \qquad (1)$$

where *i* refers to plasma, extracellular space or lesion leakage space and λ_i is the rate constant of each compartment and A_i is the amplitude component. The probability of exiting from a compartment and entering to another compartment in time interval *dt* is:

$$P(t)dt = \lambda_i \exp(-\lambda_i t)dt \qquad (2)$$

The distribution function is:

$$R(t) = \int_0^t P(t)dt = 1 - \exp(-\lambda_i t) \qquad (3)$$

The inverted function is obtained as:

$$R^{-1}(t) = t_t = \frac{-\ln(\xi)}{\lambda_i}, \quad 0 \le \xi < 1 \qquad (4)$$

where *i* refers to plasma, extracellular space or lesion leakage space, t_t is time of transit from a compartment to another compartment, λ_i is rate constant of i-th space, and ξ is a uniform random variable distributed between *(0-1)*[7].This simulation is based on the movements of the contrast agent particles between the four compartments[8].

Our procedure is as follows. Particles enter plasma with a bolus or another profile injection. A random number; ξ is produced uniformly between *zero* and *1*. The time of transit or t_t of the plasma is calculated by equation (4). If t_t is larger than time interval (*dt),* the particle will move out of the plasma compartment, otherwise, it stays in the compartment. For a fixed number of particles, the ratio of the particles exited (N_{exited}) to the initial particles $(N_{initial})$ is calculated for the plasma and another compartments in a time interval. The concentration of particles is given by:

$$C_p(t_i) = (1 - \frac{N_{exited-p}}{N_{initial-p}})C_p(t_{i-1}) + \frac{N_{exited-e}}{N_{initial-e}} C_e(t_i) + r(t_i) \qquad (6)$$

where $r(t_i)$ is the input to the model and is zero at time $t=0^-$. $C_p(t)$ is the contrast agent concentration in the plasma space, and $C_e(t)$ is the contrast agent concentration in extracellular space. Other parameters are explained previously. According to this equation, concentration of the plasma compartment in a time interval is the sum of the remained particles and those came from the extracellular space. Likewise, the concentration in extracellular space and leakage space or $C_l(t)$ are obtained as:

$$C_e(t_i) = (1 - \frac{N_{exited-e}}{N_{initial-e}})C_e(t_{i-1}) + \frac{N_{exited-p}}{N_{initial-p}} C_p(t_i) \qquad (7)$$

$$C_l(t_i) = (1 - \frac{N_{exited-l}}{N_{initial-l}})C_l(t_{i-1}) + \frac{N_{exited-p}}{N_{initial-p}}C_p(t_i)$$

These compartments do not have input. For calculating of the contrast agent concentration in each compartment, the ratio of N_{exited} to $N_{initial}$ is evaluated for each compartment. Then the concentrations are obtained in plasma and extracellular and leakage spaces in a time interval.

RESULTS

For evaluating the proposed approach, at the first, TK model and a bolus of Gd-DTPA as input of plasma are considered. For this case analytical method and Monte Carlo simulation are used for calculating $C_p(t)$, $C_e(t)$, and $C_l(t)$. The results were compared with the Weinmann data (see to ref [2]). Then, a Gamma function is considered as the input of the plasma space. Analytical method and Monte Carlo simulation are showing the same results.

Finally, the box and trapezoidal functions are considered as input of the plasma space. Each of the box and trapezoidal functions enters the plasma compartment and particles enter to the other compartments proportional to rate transfer plasma or K_1, rate transfer kidneys or $K2$ and rate transfer leakage or k. The $C_p(t)$, $C_e(t)$, and $C_l(t)$ are obtained over time. The mean values of the relative statistical errors of $C_p(t)$ and $C_e(t)$ are 4.8% and 5.1%, respectively. For each of simulated concentration curve, the commonly used summary parameters were calculated [5], [9] (see Fig. 1): 1) MPC; 2) TTP; 3) full with half maximum (FWHM); 4) integral to peak $\mathrm{ITP} = \frac{\int_0^{TTP} C(t)dt}{\int C_a(t)dt}$; 5) normalized first moment; $\mathrm{MTT} = \frac{\int^{T} tC(t)dt}{\int C(t)dt}$ and 6) the perfusion index $\mathrm{CBF} = \frac{\mathrm{CBV}}{\mathrm{MTT}}$, $CBV = \frac{\int C(t)dt}{\int C_a(t)dt}$.

The result of simulation and calculated summary parameters over the range of different box and trapezoidal functions are shown in Table 1. The changing of function width is between 1-10s. The table shows that some parameters vary with the width of the injection function. For example, MTT variations are between 61.9-64.4 s for the box functions and between 61.8-64.5 s for the trapezoidal functions.

The parameters with negligible variations can be used in practice, as they are independent of the injection profile. Other parameters, on the other hand, like TTP of plasma and tissue and FWHM of tissue vary significantly with the injection profile and thus are not useful in practice.

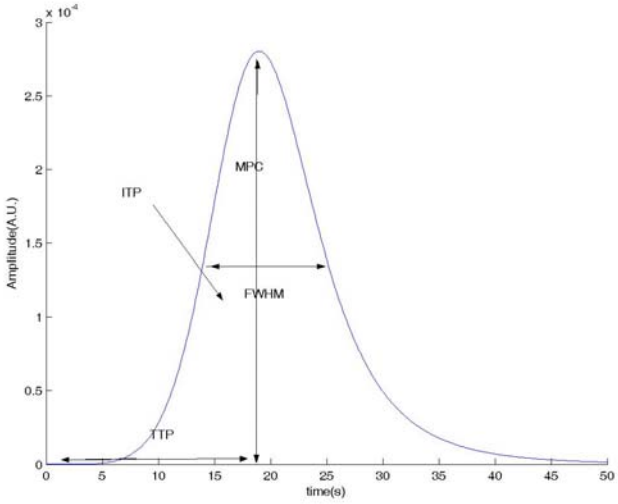

Fig. 1. Schematic tissue concentration-time curve illustrating summary parameters

CONCLUSIONS

This work estimates summary parameters of tissue in injured tissue by compartmental model. Analytical and statistical methods (Monte Carlo simulation) are used for these purposes. Following the injection of the contrast agent, the shape of resulting AIF can vary between subjects, presumably due to the influence of patient physiology (cardiac output vascular structure, etc.) and injection condition (cannula size, injection rate, etc.). Effects of injection profiles on the quantification results have not been studied in the past because of the unknown bolus shape and inexact time of bolus injection. As some approaches have used

Table (1). Variations of the summary parameters with the variations of the injection profile.

	Box function $k=0.005(s^{-1})$ $v_l=50\%$		Trapezoidal function $k=0.005(s^{-1})$ $v_l=50\%$	
	$C_p(t)$	$C(t)$	$C_p(t)$	$C(t)$
MPC(A..U.)	*0.0029-0.0037*	*0.00056-0.00059*	*0.0023-0.0027*	*0.000430-0.00044*
TTP(s)	*1-10*	*45.9-50.2*	*0.9-9.4*	*45.8--50.5*
FWHM(s)	*9.1-12.1*	*89.1-89.9*	*9.1-12.2*	*89-89.8*
ITP	*0.019-0.155*	*0.184-0.196*	*0.011-0.110*	*0.145-0.147*
MTT(s)	*61.9-64.4*	-	*61.8-64.5*	-
CBF(ml/g/s)	*0.0093-0.0097*	-	*0.0092-0.0098*	-

summary parameters for the quantification of dynamic susceptibility contrast data, it is necessary to study effects of injection profile on these parameters

In our approach, we use Monte Carlo simulation because:

- Without solving complicated equations, desired results are obtained.
- New parameters can be considered in the models by probability density functions.
- Arbitrary nonlinear functions and injection effects can be simulated by this method.

A disadvantage of the method is its long execution time, especially when a large number of particles are used for reducing the error. However, these calculations are usually done off-line and thus the execution speed is not critical.

In conclusion, this study has shown that the summary parameters of the perfusion studies should be interpreted with caution. All of the summary parameters depend on the injection profile but their variations are not the same. Use of a standard injection profile (an injection with specific width) and the parameters with minimal effect from the injection profile improve the accuracy of the quantification of the DSC data.

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