3-compartment pharmacokinetic model for estimation of
talaporfin sodium concentration in interstitial space

Yuko UNO, Emiyu OGAWA, Tsunenori ARAI
1School of Fundamental Science and Technology, Graduate School of Science and Technology, Keio University
2Department of Applied Physics and Physico-Informatics, Faculty of Science and Technology, Keio University

Abstract: We constructed a 3-compartment pharmacokinetic model for canine consisted of three compartments including plasma, interstitial space, and cell to estimate talaporfin sodium concentration change in interstitial space. Photosensitization reaction is performed when talaporfin sodium distributes in the interstitial space employing a short drug-light interval in our arrhythmia ablation. We studied interstitial concentration constructing the 3-compartment numerical model using talaporfin sodium concentration in canine plasma, and in addition, other measured relative concentrations of canine tissue, including plasma, interstitial space and cell information. We represented differential rate equation of the drug concentration in each compartment. Fitting the measured data set to the calculated concentration in each compartment, the rate constants in the constructed 3-compartment model were determined with $R^2=0.98$. Using the 3-compartment model, the interstitial talaporfin sodium concentration and the available condition in our arrhythmia ablation could be estimated.

Keywords: talaporfin sodium, pharmacokinetics, 3-compartment model, interstitial space

1. Introduction

The aim of this study is to estimate talaporfin sodium concentration in the interstitial space constructing 3-compartment model in silico. We have applied extra-cellular photosensitization reaction using talaporfin sodium to less heating myocardial arrhythmia ablation therapy [1-3]. In our proposed ablation, photosensitization reaction is performed when talaporfin sodium distributes in the interstitial space due to a short drug-light interval. However talaporfin sodium concentration change in the interstitial space has never been reported. After intravenous injection, the distribution of talaporfin sodium changes from plasma, to the interstitial space, then into the cell. In our proposed methodology, the interstitial space being our targeting photosensitization reaction area, talaporfin sodium concentration change in the interstitial space should be investigated.

Using the pharmacokinetic numerical model, we could estimate the time change of talaporfin sodium concentration in the interstitial space. Despite 2-compartment model consisted of plasma and tissue [4, 5] has been used as the conventional pharmacokinetic model, the concentration in the interstitial can not be estimated. Therefore, we proposed a 3-compartment pharmacokinetic model for canine consisted of three compartments including plasma, interstitial space, and cell to estimate the concentration in the interstitial space and the effective clinical condition.

2. Materials and Methods

2.1 Plasma concentration and tissue fluorescence measurement of talaporfin sodium in canine

Talaporfin sodium (2.5 mg/kg) was intravenously administrated to an adult male dog. Talaporfin sodium concentration in plasma was measured by a spectrophotometer. Talaporfin sodium fluorescence in skin and myocardium were measured in vivo canine model by our developed fluorescence measurement system [6, 7]. The skin fluorescence excited by 409 ± 16 nm light to match talaporfin sodium Soret-band was measured by a spectrometer. The myocardial fluorescence excited by 663 ± 2 nm light to match talaporfin sodium Q-band was measured by a femtowatt photoreceiver.

2.2 3-compartment model

The proposed 3-compartment pharmacokinetic model consisted of plasma, interstitial space, and cell compartments is shown in fig. 1. The drug quantity of each compartment is described by the series of equation (1), (2), and (3).

![Fig. 1 Structure of 3-compartment model](image)

where, $V_i$, $C_i$, and $k_{ij}$ indicate the volume of each compartment, talaporfin sodium concentration in each compartment, and rate constant, respectively.

In optimization procedure, $V_i$ and initial value of $k_{ij}$ were given. The square sums of the difference between the measured plasma concentration and $C_1$ (the calculated plasma), the measured myocardial concentration and $C_2$ (the calculated myocardium), and the measured skin concentration and $C_3$ (the calculated skin) were calculated. Output parameters, $k_{ij}$ were optimized to minimize the square sums of the difference between the measured data set and calculated data by conjugate gradient method corresponding “fmincon” in MATLAB. The limitation of $k_{ij}$ was greater than or equal to zero.
3. Results and Discussion

Time history of the estimated talaporfin sodium concentration in each compartment is presented in fig. 2 (the solid line: concentration in plasma, the dashed line: concentration in interstitial space, and the dotted line: concentration in cell). The measured talaporfin sodium concentrations are also plotted in fig. 2 (circle plot: plasma, triangle plot: myocardium, and square plot: skin). Fitting to minimize the square sums of the difference between the measured data set and calculated data, the rate constants in the 3-compartment pharmacokinetic model were obtained. The fitting operation was confirmed with coefficient of determination, 0.98.

![Fig. 2 The estimated time history of talaporfin sodium concentration](image)

In fig. 2, the estimated talaporfin sodium concentration peak in the interstitial space is found at 20 μg/ml equal to 30% of the initial talaporfin sodium concentration in plasma at 7 minutes after injection. Assuming that the interstitial concentration within its peak value -20% is the therapeutic effective range, the available drug-light interval is estimated from 3 to 17 minutes. Using the 3-compartment pharmacokinetic model, the available clinical condition could be estimated.

There are two hypotheses in this model. First of all, the measured myocardial fluorescence comes only from myocardial interstitial space. Second of all, the measured skin fluorescence comes only from skin cells. This compartment model should be modified because myocardial and skin fluorescence include plasma, interstitial, and cell concentration in a certain distribution ratio.

4. Conclusion

In the constructed 3-compartment pharmacokinetic model for canine consisted of three compartments including plasma, interstitial space, and cell, the fitting operation was confirmed with coefficient of determination, 0.98. Using the 3-compartment model, the interstitial talaporfin sodium concentration could be estimated.

Reference


