Regulatory Toxicology and Pharmacology 97 (2018) 57–62

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Prediction of tissue concentrations of monoclonal antibodies in mice from plasma concentrations☆

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ARTICLE INFO

Keywords:
Allometry
Antibody biodistribution coefficient
Monoclonal antibodies
Tissue-to-plasma partition coefficients
Volume of distribution at steady state

ABSTRACT

The objectives of this study were to develop and evaluate allometric methods for predicting tissue-to-plasma partition coefficients (Kp) in mice from experimentally determined in-vivo volume of distribution at steady state (Vss) for monoclonal antibodies (mAbs). The Vss was allometrically predicted (using a fixed exponent 1.0 or 0.9) in a given tissue of the mice. The Kp was predicted using Vss and tissue specific physiological parameters. In total, Kp values were predicted for 20 mAbs, 121 tissues, and 665 tissue concentrations. The predicted Kp values and tissue concentrations were compared with the experimental results as well as an empirically predicted antibody biodistribution coefficient (ABC). Comparison of the predicted Kp values by the two proposed methods with experimentally determined Kp values indicated that 64–75% of the predicted Kp values were within two-fold prediction error. For 665 tissue concentrations, 63%, 74%, and 48% tissue concentration ratio were within 0.5–2 fold prediction error by exponent 1.0, exponent 0.9, and ABC, respectively. The proposed allometric methods are better than ABC method for the prediction of tissue Kp values and tissue concentrations. The proposed methods can reasonably predict tissue concentrations of mAbs using plasma concentration gathered at early stage of biologics development.

1. Introduction

Physiologically based pharmacokinetic (PBPK) modeling is becoming popular in drug discovery and development (Björkman, 2005; Edginton et al., 2006a, 2006b, 2008; Grass and Sinko, 2002; Nestorov, 2007). For small molecules, tissue to plasma concentration ratio (Kp) is an important parameter for the development of a PBPK model (Jansson et al., 2008; Rowland et al., 2011). Kp describes the ratio of a drug concentration between plasma and the tissue at steady state. The most accurate method to determine Kp of an organ is through *in-vivo* experiment but such a method is expensive and time consuming. Therefore, over the years, many investigators have developed *in-vitro* and *in-silico* methods to predict Kp for different tissues (Arundel, 1997; Berezhkovskiy, 2004; Jansson et al., 2008; Poulin and Theil, 2009; Rodgers et al., 2005; Rodgers and Rowland, 2006). These empirical methods may not be always accurate but are useful.

The concept of PBPK can also be applied to macromolecules such as monoclonal antibodies (mAbs) and their fragments. In 2013, Shah et al. (Shah and Betts, 2013) described a simple method to predict tissue concentrations of monoclonal antibodies. They developed "antibody bio-distribution coefficients" (ABC) based on plasma concentrations and suggested that the product of plasma concentrations and ABC values will predict the tissue concentrations. This interesting and simple method was proposed based on the authors' previous experience in developing a "platform PBPK" model in various species (Shah and Betts, 2012).

The objective of this study was twofold: 1) to propose new empirical methods for predicting Kp values for mAbs; and 2) to predict tissue concentrations of mAbs in mice using *in-vivo* plasma concentration-time profiles and the Kp values. The predictive performance of our new method was evaluated with experimentally determined Kp values and tissue concentrations. We also compared the predictive performance of our method with ABC.

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https://doi.org/10.1016/j.yrtph.2018.06.004
Received 24 January 2018; Received in revised form 4 June 2018; Accepted 5 June 2018

2. Methods

Plasma-concentrations and tissue-concentrations time data of mice for 20 mAbs were obtained from the literature (Supplementary references). In this study, the Kp values and tissue concentrations were predicted for gut, heart, kidneys, liver, lung, muscle, skin, and spleen. The following two allometric methods were used to predict Kp values of mAbs in the aforementioned tissues of the mice.

2.1. Allometric methods using exponent 1

In this approach, Vss in a given tissue was predicted (equation (1)) using a fixed exponent of 1.0 and in-vivo estimation of mice Vss (whole body). This was done because it is widely believed that the volumes of distribution (central, at steady state, and terminal) can be predicted across species using exponent 1.0.

$$\text{Predicted Vss in a tissue} = \text{In-vivo Vss in mice x (wt of the tissue/20)}^{1.0} \quad (1)$$

Where, in-vivo Vss was estimated from pharmacokinetic analysis in the mice following intravenous administration of a mAbs and 20 g is a standard body weight of mice. Vss is in absolute number (for a 20-g mice and not in kg basis). The physiological parameters for tissue weight and volume (Table 1) were compiled from published studies (Brown et al., 1997; Davies and Morris, 1993).

2.2. Allometric method using exponent 0.9

Most of the time, exponent 1.0 provided reasonably accurate prediction of volume of distribution (30–50% prediction error) across species. However, experience from interspecies allometric scaling of volumes of distribution indicates that exponents of volume of distribution do not necessarily always revolve around 1. After the analysis of eight mAbs, it was noted that exponent 1.0 systematically underpredicted (lower than observed values) for all the tissues except muscle. Therefore, in order to improve the predictive performance of method 1, allometric method II was developed. This method uses exponent 0.9 as shown below.

$$\text{Predicted Vss in a tissue} = \text{In-vivo Vss in mice x (wt of the tissue/20)}^{0.9} \quad (2)$$

The Kp values was then predicted using equation (3) as shown below.

$$\text{Predicted Kp} = \text{Predicted Vss in a given tissue/tissue volume} \quad (3)$$

The observed Kp values were calculated based on the previously published method (Gallo et al., 1987) using equation (4).

$$\text{Observed Kp} = \text{AUC of the tissue/AUC of plasma} \quad (4)$$

Where, AUC is area under the curve and was calculated by trapezoidal rule.

After Kp values were estimated from equation (3), the tissue concentration-time profiles were determined from equation (5).

$$\text{Tissue concentration} = \text{Plasma concentration x Kp of the tissue} \quad (5)$$

Where, plasma concentrations were determined in-vivo following intravenous administration to mice.

Table 1
Weights and the volumes of the tissues of mice used in the study.

Tissues	Weight (grams)	Volume (mL)
Brain	0.33	0.33
Gut	1	1.5
Heart	0.1	0.1
Kidneys	0.32	0.3
Liver	1.1	0.95
Lungs	0.12	0.1
Muscle	10	10
Skin	3.3	2.9
Spleen	0.1	0.1

2.3. Antibody bio-distribution coefficients (ABC) method

The tissue concentration-time profiles were predicted using ABC values obtained from published study (Shah and Betts, 2013).

3. Statistical analysis

Prediction fold error between predicted and observed AUC, and individual tissue-concentration (TC) values as a function of time were calculated from the following equation:

$$\text{Prediction-fold error} = \text{AUC or TC predicted/ AUC or TC observed} \quad (6)$$

In this study, an acceptable prediction error was set as between 0.5 and 2 fold (a widely accepted range). The comparison among three methods was based on:

- Percent of total number of tissues for which AUC ratios (predicted/observed) were within < 0.5, 0.5–1.5, or 0.5–2 fold error
- Percent of concentration ratios (predicted/observed) were within < 0.5, 0.5–1.5, or 0.5–2 fold error
- Percent of individual tissue for which AUC ratios were within < 0.5, 0.5–1.5, or 0.5–2 fold error

Average fold error (AFE), which is the log transformed ratio of the predicted and observed clearance values, was also reported for each method. For AFE, a value of 1.0 indicates no prediction error and AFE was calculated as follows:

$$AFE = 10^{1/N \sum \log(\text{AUCpred/AUCobs})} \quad (7)$$

Where; N is the total number of observations, and AUC_{pred} and AUC_{obs} are predicted and observed AUC values for tissue, respectively.

4. Results

In this study, tissue concentration-time profiles were predicted for 20 mAbs. In total, there were 121 tissues for which Kp values were predicted. There were 665 observed and predicted concentration-time values for 20 mAbs. The organ weights and organ volumes of mice used in this study are shown in Table 1. A representative tissue concentration versus time profile for a single monoclonal antibody (M75) is displayed in Fig. 1. The ratio of tissue AUC predicted to observed values for each monoclonal antibody is shown in Fig. S1.

4.1. Allometric method with exponent 1.0

The Kp values were reasonably predicted with allometric method using exponent 1 for all 20 mAbs. Out of 121 tissues from 20 mAbs, 63% Kp values were within 0.5–2.0-fold prediction error. The AUC ratios (predicted/observed) were within 0.5–1.5 and 0.5–2.0 fold error for 58% and 64% of the tissues (Table 2), respectively. For 31% of the tissues analyzed, the AUC ratios were below < 0.5-fold prediction error. Only 6% of the tissues were over 2-fold prediction error. The predicted and observed AUC values for all mAbs are shown in Fig. 2 and supplementary materials (Table S1, S2& Fig.S1). As shown in Table S3, average fold error for the prediction of AUC were within 0.5–1.5 range for all tissues except muscle (see suggestion for adjusting muscle prediction).

Among the 8 tissues studied (gut, heart, kidneys, liver, lung, muscle,