RESEARCH ARTICLE

Conceptual Underestimation of the Total Body Clearance by the Sum of Clearances of Individual Organs in Physiologically Based Pharmacokinetics

LEONID M. BEREZHKOVSKIY

Genentech Inc., South San Francisco, California 94080

Received 9 July 2012; revised 30 August 2012; accepted 5 September 2012

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23327

ABSTRACT: It is commonly assumed for linear pharmacokinetics that the total body clearance (CL) is equal to the sum of clearances of individual elimination organs. This is not quite valid because, in general, the concentration of drug in arterial blood entering the elimination organ is not the same as the measured venous blood concentration that is used to calculate CL. Consideration of physiologically based pharmacokinetic model that differentiates between venous and arterial blood shows that CL exceeds the sum of clearances provided by individual organs. Assuming liver as the only elimination organ, it was found that the underestimation of CL by the sum of clearances of individual elimination organs would not exceed 35% for mammals. The underestimation of CL would be more pronounced for high extraction ratio drugs. Thus, for the case when *in vivo* measured CL considerably exceeds the *in vitro* predictions (assuming that they provide the organ clearances correctly), a possible reason for discrepancy could be the initial nonlinear phase of drug distribution and excretion. Probably, at this stage a substantial amount of drug is eliminated before distribution into the organs and tissues. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: total body clearance; hepatic clearance; physiological model; lung metabolism; distribution; elimination; venous blood; arterial blood

INTRODUCTION

The total body clearance, CL, is the major pharmacokinetic parameter that characterizes the removal of drug from the body by all routes of elimination. It is commonly assumed that for a linear pharmacokinetic system with negligible lung metabolism CL is the sum of the clearances, CL_i, of each elimination organ or tissue, that is,

$$CL = \frac{D}{AUC} = \sum_i CL_i \qquad (1)$$

where D is the dose of drug entering the blood stream [D_{iv} for intravenous drug injection, or FD_{po} for oral administration], AUC is the area under plasma concentration–time curve, and F is the drug oral bioavailability. For routine screening studies, the total body CL should be compared with hepatic CL obtained from *in vitro* assays since liver metabolism is frequently the major route of elimination. The *in vitro* stability data from liver microsomes and hepatocytes are often used to predict the human clearance.[1] The discrepancy between *in vivo* CL and *in vitro* hepatic clearance (assuming that the measured value is obtained correctly) may indicate the existence of other routes of drug elimination.[2] Though it is rather frequently observed that *in vitro* hepatic clearance underestimates the total body clearance, but no other routes of drug elimination could be found to compensate for this underestimation.

Weiss considered the problem of overestimation of CL as a result of incorrectly obtained AUC for the drug arterial plasma concentration profile.[3] It was shown that the initial concentration peak of plasma concentration could be hardly observed because the routine plasma sampling starts not earlier than 1 or 2 min after bolus injection. Thus, AUC would be underestimated, which would lead to exaggerated values of CL = D/AUC. The accurate determination of the initial drug distribution is a very complicated problem.[3,4]

Corresponding to: Leonid M. Berezhkovskiy (Telephone: +650-225-1798; Fax: +650-467-4836; E-mail: berezhkovskiy.leo@gene.com)

Journal of Pharmaceutical Sciences

A short-term infusion rather than bolus administration should provide less bias because of the more accurate estimation of the initial AUC. The bias of inappropriate estimation of initial concentration is also dependent on the elimination rate. For fast clearing drug, the bias is most likely more pronounced than for slow clearing drugs. The simulations that were done for arterial plasma concentrations showed a possible 15% overestimation of CL.[3]

Actually, most often the peripheral venous sampling is applied to measure drug plasma concentrations, and consequently calculate AUC. The overestimation of CL, which occurs because of the difference between the drug concentration in arterial blood that enters the elimination organs and in the venous blood that is collected to determine plasma concentrations, is studied in this work. Consideration of the steady state of the system is a convenient approach to the problem, and provides accurate results on the difference between *in vivo* CL and the sum ΣCL_i.

The goal of the article is to obtain the equation that allows predicting the possible underestimation of CL for a linear pharmacokinetic system as the sum of clearances of all elimination organs (Eq. 1). Also, a possible inconsistency in the calculation of CL as D/AUC that could be because of the nonlinear effects pertinent to a bulk iv bolus dosing is discussed.[5]

RESULTS

A linear pharmacokinetic system is considered further. The clearance of each elimination organ is defined as a proportionality constant between the rate of drug elimination, R_i^{ss}, and drug–plasma concentration, C_{org}^{ss}, in blood entering the organ at steady state

$$R_i^{ss} = CL_i C_{org}^{ss} \tag{2}$$

For a steady-state condition R_i^{ss} equals to the difference between drug incoming and outgoing rates, so that

$$\begin{aligned} R_i^{ss} &= rQ_i C_{org}^{ss} - rQ_i C_{out,i}^{ss} \\ &= rQ_i C_{org}^{ss}\left(1 - \frac{C_{out,i}^{ss}}{C_{org}^{ss}}\right) = rQ_i C_{org}^{ss} E_i \end{aligned} \tag{3}$$

where r is the equilibrium blood–plasma concentration ratio, Q_i is the rate of blood flow to the organ, $C_{out,i}^{ss}$ is the drug concentration in plasma exiting the i-th organ, and E_i is the extraction ratio of i-th organ. An instantaneous equilibration of drug between blood cells and plasma is assumed in Eq. 3.

As linear pharmacokinetics is considered, this implies that each portion of drug ΔD entering the circulation at a given instant of time contributes independently to the total concentration of drug in any compartment, and the contribution is proportional to ΔD. This property, also known as molecular stochastic independence,[6] is conveniently expressed in the form of convolution integral, which provides the drug concentration in systemic plasma, $C_{p,inf}$, generated by drug infusion into plasma at arbitrary rate $I(t)$[6,7]

$$\begin{aligned} C_{p,inf}(t) &= \frac{1}{D}\int_0^t I(\tau) C_p(t-\tau)\mathrm{d}\tau \\ &= \frac{1}{D}\int_0^t I(t-\tau) C_p(\tau)\mathrm{d}\tau \end{aligned} \tag{4}$$

where $C_p(t)$ is the drug concentration profile in systemic plasma generated by iv bolus dose D. This equation reflects the fact that the quantity of drug $I(\tau)d\tau$, which entered the circulation in the time interval from τ to $\tau + d\tau$, contributes to the total concentration $C_{p,inf}(t)$ at instance of time t as $[I(\tau)\mathrm{d}\tau/D]C_p(t-\tau)$. For the condition of the constant rate iv drug infusion, $I(t) = I_o$, setting $t \to \infty$ to obtain the steady-state plasma concentration, C_p^{ss}, the convolution formula above yields[6,7]

$$\frac{D}{AUC} C_p^{ss} = CL \times C_p^{ss} = I_o \tag{5}$$

where AUC is the area under $C_p(t)$ curve from $t = 0$ to infinity.

The considered physiologically based pharmacokinetic (PBPK) model is shown in Figure 1. The drug is dosed into venous blood. Then, it is delivered by the blood stream to the elimination organ after passing the lungs. The lung blood flow, Q_a, and consequently the arterial blood flow to the organs, are equal to cardiac output. According to the mass balance at steady state, the rate of drug infusion I_o is equal to the rate of drug elimination by all organs

$$I_o = C_L^{ss} CL_L + \Sigma R_i^{ss} \tag{6}$$

where the first term in the right-hand side of Eq. 6 is the rate of possible lung elimination. Here, C_L^{ss} is steady-state drug–plasma concentration in blood entering the lung, CL_L is the lung CL

$$CL_L = rQ_a E_L \tag{7}$$

where E_L is the lung extraction ratio. According to the blood flow diagram in Figure 1, the steady-state plasma concentration of drug entering the elimination organ (except lung) is equal to

$$C_{org}^{ss} = C_L^{ss}(1 - E_L) \tag{8}$$

DOI 10.1002/jps