

Steady-state concentration of drugs in plasma: a pharmacokinetic model for clinicians

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ABSTRACT

Several pharmacokinetic equations have been derived to calculate the steady-state concentration of a drug in plasma. In this short report, a straightforward equation for repeated-dosage is presented, that allows determination of the effective plasma steady-state concentration of a drug from its peak and trough concentration, independent of clearance parameters. This may prove to be particularly useful in therapeutic regimens with a preset concentration range or in drugs with a narrow therapeutic window.

Keywords: Steady-state concentration, first-order kinetics, pharmacokinetics, equation

INTRODUCTION

Over the years, many equations have been developed in the field of pharmacokinetics to determine or evaluate the steady-state concentration of drugs in plasma. Many of these equations describe steady-state concentrations during constant intravenous drug infusion in terms of – hepatic and/or renal – drug clearance, a parameter which can sometimes be difficult to quantify for an individual patient (Rang, 2009; Stehouwer, 2010). In this report, we present a straightforward and – to our knowledge – novel derivation of a pharmacokinetic equation that describes the steady-state plasma concentration of a drug in terms of its peak and trough concentration during repeated dosing, bypassing the need for determination of a clearance parameter or the volume of distribution. This can be particularly useful for the majority of opioid dosage regimens, where the therapeutic goal is to maintain plasma opioid concentration within a preset concentration range, or for evaluating the effect of drugs with a narrow therapeutic range, among which phenytoin, digoxin, aminoglycosides and lithium carbonate (Raebel, 2006). A stepwise mathematical derivation is presented below.

MATHEMATICAL DERIVATION

Assuming a single-compartment model (i.e., assuming rapid distribution of an administered drug throughout the body), the rate of elimination of a drug X from the body according to first-order kinetics is dependent on its plasma concentration (C_x). This can be described by the following simple differential equation:

$$-\frac{dC_x}{dt} = k_e C_x$$

In which k_e represents the elimination constant. The solution to this equation is as follows:

$$C_x(t) = C_{x,0} e^{-k_e t}$$

$C_{x,0}$ represents the plasma concentration of the drug at time $t = 0$. Assume that the drug reaches a peak plasma concentration $C_{x,max}$ after its administration at time $t = 0$ and is then eliminated from the body until it reaches $C_{x,min}$ at $t = \tau$. This means:

$$C_{x,min} = C_{x,max} e^{-k_e \tau}$$

Therefore:

$$k_e \tau = -\ln(C_{x,min}/C_{x,max}) = \ln(C_{x,max}/C_{x,min})$$

The plasma concentration of a drug that is administered in repeated doses will fluctuate between a peak and a trough concentration - $C_{x,max}$ and $C_{x,min}$, respectively - depending on the administered dose, volume of distribution, clearance from the body and dosing interval τ (Stehouwer,2010). Assuming that the average plasma concentration of the drug (\bar{C}_x) correlates with its effective steady-state concentration (and therefore its clinical effects, which holds true for many - albeit not all - drugs), and that C_{max} is reached almost instantaneously after drug administration, the effective steady-state concentration during each dosing interval can be described as follows (see Figure 1) (DiPiro, 2010).

$$\bar{C}_x = \frac{1}{\tau} \int_0^{\tau} C_x(t) dt = \frac{C_{x,max}}{\tau} \int_0^{\tau} e^{-k_e t} dt$$

This can be solved as follows:

$$\bar{C}_x = -\frac{C_{x,max}}{k_e \tau} [e^{-k_e t}]_0^{\tau} = -\frac{C_{x,max}}{k_e \tau} (e^{-k_e \tau} - 1) = \frac{C_{x,max}}{k_e \tau} (1 - e^{-k_e \tau})$$

Substitution of the expression for $k_e \tau$ in the equation above produces:

$$\bar{C}_x = \frac{C_{x,max}}{k_e \tau} (1 - e^{-k_e \tau}) = \frac{C_{x,max}}{\ln(C_{x,max}/C_{x,min})} (1 - e^{-\ln(C_{x,max}/C_{x,min})})$$

This results in:

$$\bar{C}_x = \frac{C_{x,max}}{\ln(C_{x,max}/C_{x,min})} (1 - e^{\ln(C_{x,min}/C_{x,max})}) = \frac{C_{x,max}}{\ln(C_{x,max}/C_{x,min})} (1 - C_{x,min}/C_{x,max})$$

A final rearrangement of the equation above produces an expression of the effective steady-state concentration of a drug in terms of its peak and trough plasma concentration:

$$\bar{C}_x = \frac{C_{x,max} - C_{x,min}}{\ln(C_{x,max}/C_{x,min})}$$

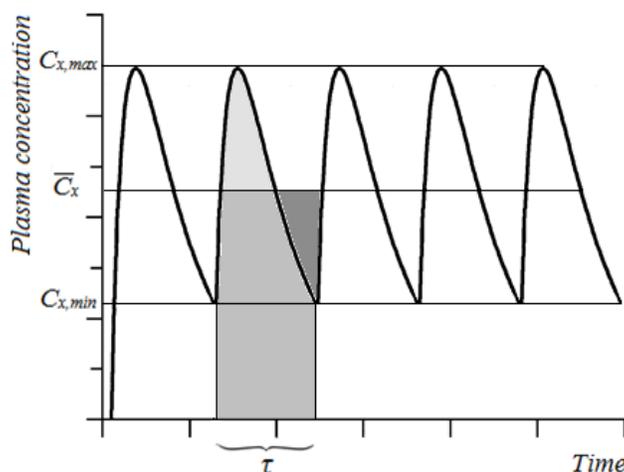


Figure.1. Schematic representation of first-order elimination of a drug from plasma in a repeated-dose regimen. The area under the curve shaded in light gray equals the area shaded in dark gray.

DISCUSSION

From this model, it follows that the steady-state concentration of a drug in plasma within a preset concentration range is independent of its rate of elimination. As mentioned before, the derived equation is especially well-suited for pharmacokinetic evaluation of drugs with a narrow therapeutic window and bypasses the need for determination of a clearance parameter, which is particularly convenient if clearance cannot be measured reliably (e.g., in patients where the MDRD equation either overestimates or underestimates the glomerular filtration rate) (Stehouwer, 2010; Raebel, 2006). It should be noted that this model for repeated-dose pharmacokinetics ignores accumulation effects and is therefore most applicable when a drug is administered using a loading dose, after which the follow-up doses are administered at a fixed interval (τ). This is common clinical practice, especially if a drug has a relatively long half-life and if a rapid clinical effect is required (Rang, 2009; Stehouwer, 2010). Although the assumption of a single-compartment model of the human body should be considered a simplified representation of reality, it is a very useful means for evaluating pharmacokinetics in everyday clinical practice and can easily be justified for modeling purposes, especially in the case of rapidly distributing drugs (Rang, 2009). Furthermore, it stands to reason that the premise of a strong correlation between the average plasma concentration of a drug and its effectiveness does not apply to drugs that display peak concentration-dependent activity, such as several antibiotics (Vinks, 2004).

CONCLUSION

In summary, the straightforward steady-state equation that has been proposed in this report may aid clinicians and pharmacologists in evaluating repeated-dose drug administration without the need for determining clearance parameters or the volume of distribution, provided that the described preconditions have been met.

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