Application of Moment Analysis to the Sigmoid Effect Model for Drug Administered Intravenously

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INTRODUCTION

The basic concepts of moment analysis have been used for estimation of pharmacokinetic parameters such as *AUC*, *AUMC*, mean residence time (*MRT*), and steady-state volume of distribution (V_{ss}). The area the under the effect curve (AUC_E) and area under the moment curve of effect ($AUMC_E$) parameters can be obtained analogously to *AUC* and *AUMC* by numerical integration, but it is uncertain what these parameters mean in relation to the kinetics and dynamics of the drug. The concept of mean residence time for pharmacokinetic systems with nonlinear drug elimination is more complex than for linear systems (1,2). Since the sigmoid E_{max} model is also nonlinear, the ideas introduced in earlier work can be considered in pharmacodynamics. Contrary to previous pharmacokinetic results which are exact solutions, the pharmacodynamic parameters $AUMC_E$ and mean effect time *MET* cannot be evaluated exactly.

The purpose of this communication is to derive approximate equations for $AUMC_E$ and *MET* for a drug injected intravenously into a one-compartment model, eliminated by a first-order process, and producing a direct response according to the sigmoid E_{max} equation. The relationships between dose, elimination rate constant (k_{el}) and the mean effect parameter are discussed and new method of estimation of EC_{50} is presented.

THEORY

The condition is assumed of intravenous injection of a dose of drug D into a one-compartment system of apparent volume of distribution, V. The time course of drug concentration (C) can be described by the equation:

$$C = \frac{D}{V} e^{-k_{el}t} \tag{1}$$

where k_{el} is the drug elimination constant and D/V is the initial drug concentration (C_0). The drug effect (E) is expected according to the sigmoid E_{max} model (3):

$$E = \frac{E_{max}C}{EC_{50} + C} \tag{2}$$

where E_{max} is the maximum intensity of the pharmacologic response and EC_{50} is the drug concentration eliciting 50% of the maximum effect. The total net effect is defined as the area under the effect curve over the time interval $0 \le t \le \infty$:

$$AUC_E = \int_0^\infty E(t)\,dt \tag{3}$$

The AUC_E value for these conditions was derived previously by Wagner (4) and explored by Derendorf (5):

$$AUC_E = \frac{E_{max}}{k_{el}} \ln\left(1 + \frac{D/V}{EC_{50}}\right) \tag{4}$$

The total area under the moment curve for effect is given by:

$$AUMC_E = \int_0^\infty tE(t)\,dt \tag{5}$$

The mean effect time of drug (*MET*) can be defined as the ratio:

$$MET = \frac{AUMC_E}{AUC_E} \tag{6}$$

Eq. 5 cannot be integrated explicitly. Our objective is to derive approximate relationships between AUC_E and *MET* and dose D. A proposed approximate formula is:

$$AUMC_{Eaprx} = \frac{E_{max}}{k_{el}^2}\left(\frac{1}{2} ln^2\left(1 + \frac{D/V}{EC_{50}}\right) + \kappa - (3\kappa - 4)\frac{ln\left(1 + \frac{D/V}{EC_{50}}\right)}{\frac{D/V}{EC_{50}} + 2(2 - \kappa)} - \frac{2\kappa(2 - \kappa)}{\frac{D/V}{EC_{50}} + 2(2 - \kappa)}\right) \tag{7}$$

where κ is a dimensionless constant:

$$\kappa = \int_1^\infty \frac{ln\, x\, dx}{x(1 + x)} - \int_0^1 \frac{ln\, x\, dx}{1 + x} = 1.643913 \tag{8}$$

According to Eq. 4 and 6 the approximate formula for *MET* is

$$MET_{aprx} = \frac{1}{k_{el}}\left(\frac{1}{2} ln\left(1 + \frac{D/V}{EC_{50}}\right) + \frac{\kappa}{ln\left(1 + \frac{D/V}{EC_{50}}\right)} - \frac{3\kappa - 4}{\frac{D/V}{EC_{50}} + 2(2 - \kappa)} - \frac{2\kappa(2 - \kappa)}{\left(\frac{D/V}{EC_{50}} + 2(2 - \kappa)\right) ln\left(1 + \frac{D/V}{EC_{50}}\right)}\right) \tag{9}$$

Eq. 7 was derived using asymptotic expansion theory (6). It was assumed that the only varying parameter is dose D whereas the others remain fixed. Two limits have been considered: for

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large doses ($D \to \infty$) and for small doses ($D \to 0$). It can be shown that:

$$AUMC_E = \frac{E_{max}}{2k_{el}^2} ln^2\left(1 + \frac{D/V}{EC_{50}}\right) + \frac{E_{max}\kappa}{k_{el}^2} + O\left(\frac{ln\left(\frac{D/V}{EC_{50}}\right)}{\frac{D/V}{EC_{50}}}\right) \quad \text{as} \quad \frac{D/V}{EC_{50}} \to \infty \quad (10)$$

and:

$$AUMC_E = \frac{E_{max}}{k_{el}^2}\frac{D/V}{EC_{50}} - \frac{E_{max}}{4k_{el}^2}\left(\frac{D/V}{EC_{50}}\right)^2 + O\left(\left(\frac{D/V}{EC_{50}}\right)^3\right) \quad \text{as} \quad \frac{D/V}{EC_{50}} \to 0 \quad (11)$$

The symbol $O(\cdot)$ means that the relative error between the exact and the approximate values is proportional to the expression between the parentheses (for a more detailed definition see (6)). Eq. 7 is a combination of Eq. 10 and 11 resulting from the assumption that $AUMC_E$ is of the form:

$$AUMC_E = \frac{E_{max}}{2k_{el}^2} ln^2\left(1 + \frac{D/V}{EC_{50}}\right) + \frac{E_{max}\kappa}{k_{el}^2} + \phi\left(\frac{D/V}{EC_{50}}\right) \quad (12)$$

and the function ϕ is picked such that Eq. 10 and 11 hold. Eq. 9 is obtained by dividing Eq. 7 by Eq. 4. Hence *MET* for large doses becomes:

$$MET = \frac{1}{2k_{el}} ln\left(1 + \frac{D/V}{EC_{50}}\right) + \frac{1}{k_{el}}\frac{\kappa}{ln\left(1 + \frac{D/V}{EC_{50}}\right)} + O\left(\left(\frac{D/V}{EC_{50}}\right)^{-1}\right) \quad \text{as} \quad \frac{D/V}{EC_{50}} \to \infty \quad (13)$$

and for small doses:

$$MET = \frac{1}{k_{el}} + \frac{1}{4k_{el}}\frac{D/V}{EC_{50}} - \frac{7}{12k_{el}}\left(\frac{D/V}{EC_{50}}\right)^2 + O\left(\left(\frac{D/V}{EC_{50}}\right)^3\right) \quad \text{as} \quad \frac{D/V}{EC_{50}} \to 0 \quad (14)$$

Eq. 10–14 can be considered as simplifications of Eq. 7 and 9.

METHODS

The values of AUC_E for different doses (units = mg) were obtained from Eq. 4 for conditions of V = 90 l, EC_{50} = 100 ng/ml and E_{max} = 1.0. The simulations were done at k_{el} values of 0.5, 0.7, and 1.0 1/hr.

The parameter $AUMC_E$ was calculated numerically according to Eq. 5 by means of the Mathematica program (version 2.2 for SPARC, Wolfram Research Inc.) at different doses. The integration was performed over time intervals 50, 30, and 20 hr for the corresponding k_{el} values. The *MET* values were computed from Eq. 6.

The approximate values $AUMC_{Eaprx}$ and MET_{aprx} were found after evaluation of Eq. 7 and 9. Dose was employed as an independent variable in all calculations.

RESULTS AND DISCUSSION

The values of $AUMC_{Eaprx}$ and MET_{aprx} were compared with numerically obtained values of $AUMC_E$ and *MET* over a wide range of doses. The data in Figure 1 show the marked nonlinearity in these parameters with dose. Both calculations match very closely over the entire range of doses suggesting high accuracy of the approximations. The maximum relative error of both the $AUMC_E$ and *MET* approximations is of order 0.1% and it occurs for low doses of about 10 mg.

Approximate formulas obtained by asymptotic analysis are shown for large doses in Eq. 10 and 13 and for small doses in Eq. 11 and 14. The relative error of $AUMC_{Eaprx}$ is of order ln D/D for large doses and of order D^3 for small doses. The relative error of MET_{approx} is of order $1/D$ for large doses and of order D^3 if they are small.

The parameter $AUMC_E$ (or *MET*) depends on two combinations of parameters: E_{max}/k_{el}^2 and $D/V/EC_{50}$ (or $1/k_{el}$ and $D/V/EC_{50}$). The relative errors do not depend on the value of k_{el}. Therefore the approximations remain good for any values of this rate constant.

The limit of *MET* as D approaches 0 is $1/k_{el}$ as seen in Eq. 14. This is the intercept of the *MET* curves in Figure 1.

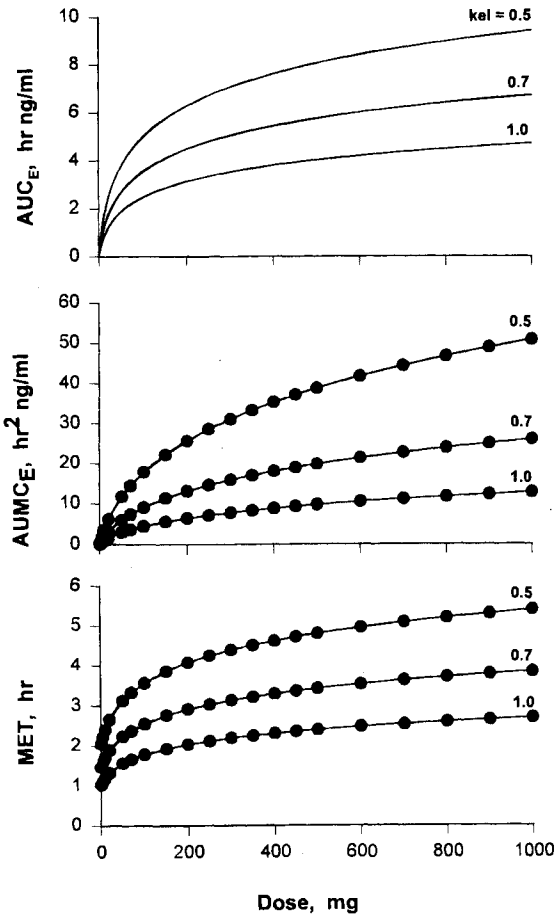

Fig. 1. Values of AUC_E (upper), $AUMC_E$ (middle), and *MET* (lower) vs dose. The solid circles are $AUMC_E$ and *MET* values obtained by numerical integration for k_{el} = 0.5, 0.7, and 1.0 1/hr. The AUC_E curves were obtained using Eq. 4, and the values of $AUMC_{Eaprx}$ and MET_{aprx} were calculated from Eq. 7 and 9.

Since this is the minimum value of *MET*, the mean time of effect must be greater than $1/k_{el}$. This is logical as the normalized (Effect/E_0) response profile must at least superimpose on the pharmacokinetic function when E_{max} is not attained.

The AUC_E, $AUMC_E$, and *MET* data presented in Figure 1 differ from each other only by the factors E_{max}/k_{el}, E_{max}/k_{el}^2, and $1/k_{el}$, respectively. Thus other curves can be obtained from that corresponding to $E_{max} = 1.0$ and $k_{el} = 1.0$ by multiplying by these factors.

A change of variable $\tau = k_{el}t$ in the integral in Eq. 5 leads to:

$$AUMC_E = \frac{E_{max}}{k_{el}^2} \int_0^\infty \frac{\tau e^{-\tau}\, d\tau}{\frac{EC_{50}}{D/V} + e^{-\tau}} \tag{15}$$

and consequently:

$$MET = \frac{1}{k_{el}} \int_0^\infty \frac{\tau e^{-\tau}\, d\tau}{\frac{EC_{50}}{D/V} + e^{-\tau}} \ln^{-1}\left(1 + \frac{D/V}{EC_{50}}\right) \tag{16}$$

Eq. 15 and 16 explain the fact that $AUMC_E$ depends only on E_{max}/k_{el}^2 and $D/V/EC_{50}$, and *MET* depends only on $1/k_{el}$ and $D/V/EC_{50}$. Since $AUMC_{Eaprx}$ and MET_{aprx} show the same type of dependence, their relative errors also depend only on $D/V/EC_{50}$.

Since the errors occurring for AUC_E, $AUMC_E$ and *MET* obtained from experimental data are typically much greater than 1%, then the approximate formulas $AUMC_{Eaprx}$ (Eq. 7) and MET_{aprx} (Eq. 9) are practically exact.

If the accuracy of these approximations is not an issue, then Eq. 10 and 11 imply that:

$$AUMC_E \sim \frac{E_{max}}{k_{el}^2} \ln^2\left(\frac{D/V}{EC_{50}}\right) \quad \text{for large values of} \quad \frac{D/V}{EC_{50}} \tag{17}$$

and:

$$AUMC_E \sim \frac{E_{max}}{k_{el}^2} \frac{D/V}{EC_{50}} \quad \text{for small values of} \quad \frac{D/V}{EC_{50}} \tag{18}$$

Hence for large doses $AUMC_E$ is proportional to $\ln^2 D$ and for small doses $AUMC_E$ is proportional to D. Similarly, Eq. 13 and 14 yield:

$$MET \sim \frac{1}{2k_{el}} \ln\left(\frac{D/V}{EC_{50}}\right) \quad \text{for large values of} \quad \frac{D/V}{EC_{50}} \tag{19}$$

and

$$MET \sim \frac{1}{k_{el}} + \frac{1}{4k_{el}} \frac{D/V}{EC_{50}} \quad \text{for small values of} \quad \frac{D/V}{EC_{50}} \tag{20}$$

Thus, for large doses *MET* is proportional to ln D and for small doses *MET* is close to $1/k_{el}$ which is the mean residence time (*MRT*) of drug with an iv type of concentration time profile (Fig. 2 and Eq. 1). If the drug effect is described by Eq. 2, then the mean effect time is always greater than $1/k_{el}$. Since for large doses $AUC_E \sim E_{max}/k_{el}$ ln $(D/V/EC_{50})$, then:

$$MET \sim \frac{1}{2E_{max}} AUC_E + \frac{\kappa}{E_{max}} \frac{AUMC}{AUC_E} \tag{21}$$

where κ is defined in Eq. 8. Of practical value, Eq. 19 and 20 show that the difference of *MET* and *MRT* is determined by

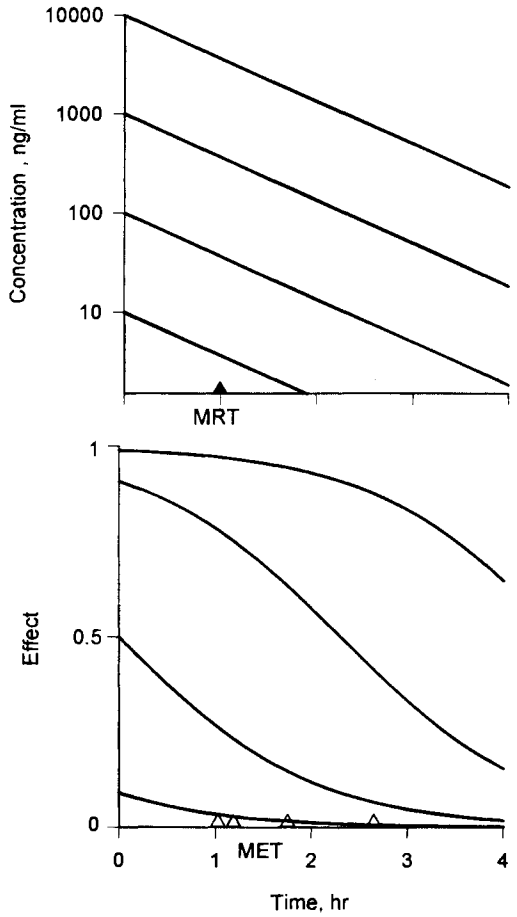

Fig. 2. Plasma concentration versus time and Effect versus time profiles for four doses of drug where $C_0 = EC_{50}$ for the low dose and $C_0 = 0.1$, 1.0, 10, and 100 × EC_{50}. Triangles mark the *MRT* for the kinetics and *MET* for the dynamics.

D/V and EC_{50} and can be used for estimation of the value of *MET*, viz:

$$MET \sim MRT + \frac{1}{4} \frac{D/V}{EC_{50}} MRT \text{ for small values of } \frac{D/V}{EC_{50}} \tag{22}$$

or for EC_{50}:

$$EC_{50} \sim \frac{D/V}{4\left(\frac{MET}{MRT} - 1\right)} \text{ (for small doses)} \tag{23}$$

The relative error of these estimations is about 4% for the ratio D/V close to the value of EC_{50} and becomes less for smaller doses. It is independent of the k_{el} value. Computer simulations show that Eq. 22 and 23 remain approximate if drug disposition (iv dose) is polyexponential but only if C_0 is less than EC_{50}.

If the effect is related to Eq. 2 modified with the Hill coefficient γ:

$$E = \frac{E_{max} C^\gamma}{EC_{50}^\gamma + C^\gamma} \tag{24}$$

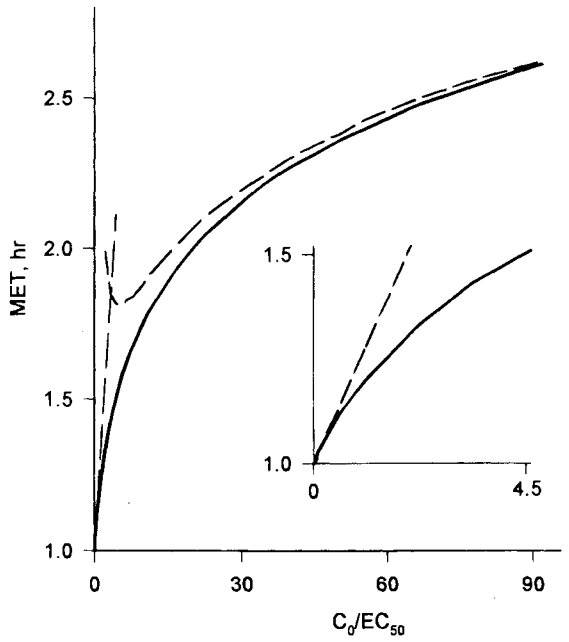

Fig. 3. Comparison of *MET* values obtained by numerical integration (Eq. 4–6, solid line), calculation (Eq. 9, also solid line), and approximation (Eq. 21 and 22, dashed lines) in relation to C_0/EC_{50} ratios. The insert shows results for small values of C_0/EC_{50}.

then all results remain valid after substitutions of $k_{el} \rightarrow \gamma k_{el}$ and $D/V/EC_{50} \rightarrow (D/V/EC_{50})\gamma$ in all equations. Eq. 23 becomes

$$EC_{50} \sim \frac{D/V}{4^{1/\gamma}\left(\frac{MET}{MRT} - 1\right)^{1/\gamma}} \quad \text{(for small doses)} \quad (25)$$

The use of numerical integration to calculate AUC_E and $AUMC_E$ may require extrapolation of the terminal effect (E^*) phase to infinity. Since the terminal phase is described by $E^*e^{-k_{el}t}$, the same equations for AUC (E^*/k_{el}) and $AUMC$ ($E^*T/k_{el} + E^*/k_{el}^2$) may be used.

Moment analysis and generation of *MET* has been of descriptive value in summarizing pharmacodynamic data (7). The present formulas for AUC_E, $AUMC_E$, and *MET* allow us to understand better the relationships between these parameters and other pharmacokinetic and pharmacodynamic factors. Eq. 4, 7, and 9 are useful in assessing the values of AUC_E, $AUMC_E$, and *MET* based on experimental data. They are also helpful in analysis of these parameters evaluated by computer. Eq. 22 provides an estimate of EC_{50} in low dose situations. Usually obtaining EC_{50} is dependent on having an accurate value of E_{max} with use of large doses of drug. The present equations pertain for direct drug effects and only if monoexponential or polyexponential (multicompartmental) drug disposition occurs; computer simulations show that they become inaccurate if the pharmacokinetic function is biphasic (absorption or biophase).

CONCLUSIONS

Approximate equations for $AUMC_E$ and *MET* are derived for a system where drug is injected intravenously into a one-compartment model and eliminated by a first-order process. The drug effect must be produced directly according to the sigmoid E_{max} model or Hill function. The equations are validated by comparison of results obtained by direct calculation versus numerical estimation. The *MET* is determined by a complex relationship involving Dose, V, k_{el}, and EC_{50}. The minimum value of *MET* is $1/k_{el}$ or *MRT* and the ratio of *MET*/*MRT* may provide a means of estimation of EC_{50} at low drug doses where such values are usually unobtainable.

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