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Report

Constant-Rate Intravenous Infusion Methods for Estimating Steady-State Volumes of Distribution and Mean Residence Times in the Body for Drugs Undergoing Reversible Metabolism

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Equations for the steady-state volumes of distribution (V_{ss}) and the mean residence times in the body (MRT) are derived for a drug and its metabolite subject to reversible metabolism and separately infused intravenously at a constant rate to steady state of both compounds. The V_{ss} and MRT parameters are functions of the integrals of plasma concentrations, plasma concentrations at steady state, and times to reach steady state of both drug and metabolite. In addition, the MRT values are functions of the infusion rates. These equations were validated by computer simulations and comparison with IV bolus dose parameters. These relationships extend the ability to assess the pharmacokinetics of linear reversible metabolic systems.

KEY WORDS: intravenous infusion; volume of distribution; mean residence time; reversible metabolism; pharmacokinetics.

INTRODUCTION

Reversible metabolism confounds the traditional meanings of clearance, volume of distribution, and mean residence time when these pharmacokinetic parameters are calculated by classical methods (1–4). Although methods for estimating the steady-state volume of distribution (V_{ss}) and mean residence time in the body (MRT) for drugs undergoing reversible metabolism have been developed (2–4), they have been limited to the consideration of drugs administered as an intravenous bolus dose. This report extends these principles to include methods for calculating V_{ss} and MRT for a drug which undergoes reversible metabolism and is infused intravenously at a constant rate to steady state of both the drug and its metabolite.

THEORETICAL

A drug undergoing linear reversible metabolism (Fig. 1) is intravenously infused at a constant rate, R_o^p, until a time (t_{ss}^p) when the steady-state concentrations of both drug ($C_{p,ss}^p$) and metabolite ($C_{m,ss}^p$) are reached. Similarly, the metabolite is infused separately to the same subject at a constant rate, R_o^m, until a time (t_{ss}^m) when steady-state concentrations of both drug ($C_{p,ss}^m$) and metabolite ($C_{m,ss}^m$) are achieved. The fundamental clearances for elimination of drug (CL_{10}) and metabolite (CL_{20}) and their interconversion (CL_{12}, CL_{21}) can be calculated as follows (1,2):

$$CL_{10} = \frac{R_o^p \cdot C_{m,ss}^m - R_o^m \cdot C_{m,ss}^p}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \quad (1)$$

$$CL_{12} = \frac{R_o^m \cdot C_{m,ss}^p}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \quad (2)$$

$$CL_{20} = \frac{R_o^m \cdot C_{p,ss}^p - R_o^p \cdot C_{p,ss}^m}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \quad (3)$$

$$CL_{21} = \frac{R_o^p \cdot C_{p,ss}^m}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \quad (4)$$

Note that the superscripts refer to the dosed compound and the subscripts denote the measured compound in plasma. From Eqs. (1)–(4) it follows that total clearances of drug (CL_{11}) and metabolite (CL_{22}) are

$$CL_{11} = \frac{R_o^p \cdot C_{m,ss}^m}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \quad (5)$$

$$CL_{22} = \frac{R_o^m \cdot C_{p,ss}^p}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \quad (6)$$

where $CL_{11} = CL_{10} + CL_{12}$, and $CL_{22} = CL_{20} + CL_{21}$. The rate of change of the amount of metabolite in the body [$A_m^p(t)$] with time (t) following constant intravenous infusion of parent drug can be described by the equation

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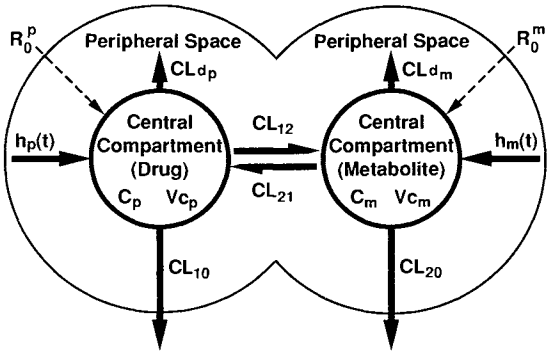

Fig. 1. Basic reversible metabolic system. C_p and C_m are plasma concentrations of parent drug and of metabolite at time t; Vc_p and Vc_m are central volumes of distribution of parent drug and of metabolite; CL_{12} is the conversion clearance of parent drug to metabolite; CL_{21} is the conversion clearance of metabolite to parent drug; CL_{dp} and CL_{dm} are the distribution clearances of parent drug and of metabolite; CL_{10} and CL_{20} are the total exit clearances of parent drug and of metabolite; and $h_p(t)$ and $h_m(t)$ are the distribution functions of parent drug and of metabolite.

$$dA_m^p(t)/dt = CL_{12} \cdot C_p^p - CL_{22} \cdot C_m^p \tag{7}$$

with an initial condition of $A_m^p(0) = 0$, and where C_p^p is the plasma concentration of the parent drug at time t, and C_m^p is the plasma concentration of the metabolite at time t. Multiplying both sides of Eq. (7) with dt and integrating the result from time 0 to time t_{ss}^p yields

$$A_{m,ss}^p = CL_{12} \cdot \int_0^{t_{ss}^p} C_p^p dt - CL_{22} \cdot \int_0^{t_{ss}^p} C_m^p dt \tag{8}$$

where $A_{m,ss}^p$ is the amount of the metabolite in the body at steady-state following constant-rate intravenous infusion of parent drug. Since at steady state,

$$CL_{12} \cdot C_{p,ss}^p = CL_{22} \cdot C_{m,ss}^p \tag{9}$$

it follows that

$$CL_{12} = CL_{22} \cdot C_{m,ss}^p/C_{p,ss}^p \tag{10}$$

Substituting Eq. (10) into Eq. (8) and simplifying the result yields

$$A_{m,ss}^p = CL_{22} \cdot \int_0^{t_{ss}^p} (C_{m,ss}^p \cdot C_p^p - C_{p,ss}^p \cdot C_m^p) dt/C_{p,ss}^p \tag{11}$$

By definition,

$$A_{m,ss}^p = V_{ss}^m \cdot C_{m,ss}^p \tag{12}$$

where V_{ss}^m is the steady-state volume of distribution of metabolite. Combining Eqs. (11) and (12) yields

$$V_{ss}^m = CL_{22} \cdot \int_0^{t_{ss}^p} \left(\frac{C_p^p}{C_{p,ss}^p} - \frac{C_m^p}{C_{m,ss}^p} \right) dt \tag{13}$$

Substituting Eq. (6) into Eq. (13) yields

$$V_{ss}^m = \frac{R_o^m \cdot C_{p,ss}^p \cdot \int_0^{t_{ss}^p} \left(\frac{C_p^p}{C_{p,ss}^p} - \frac{C_m^p}{C_{m,ss}^p} \right) dt}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \tag{14}$$

Similarly, the following equations for estimating the amount of drug in the body at steady state ($A_{p,ss}^m$) and steady-state volume of distribution of drug (V_{ss}^p) following constant-rate intravenous infusion of metabolite can be derived:

$$A_{p,ss}^m = CL_{11} \cdot \int_0^{t_{ss}^m} (C_{p,ss}^m \cdot C_m^m - C_{m,ss}^m \cdot C_p^m) dt/C_{m,ss}^m \tag{15}$$

$$CL_{21} = CL_{11} \cdot C_{p,ss}^m/C_{m,ss}^m \tag{16}$$

and

$$V_{ss}^p = CL_{11} \cdot \int_o^{t_{ss}^m} \left(\frac{C_m^m}{C_{m,ss}^m} - \frac{C_p^m}{C_{p,ss}^m} \right) dt = \frac{R_o^p \cdot C_{m,ss}^m \cdot \int_0^{t_{ss}^m} \left(\frac{C_m^m}{C_{m,ss}^m} - \frac{C_p^m}{C_{p,ss}^m} \right) dt}{C_{p,ss}^p C_{m,ss}^m - C_{m,ss}^p C_{p,ss}^m} \tag{17a,b}$$

By definition (5), the mean residence times (MRT) can be obtained from

$$MRT_p^p = A_{p,ss}^p/R_o^p = V_{ss}^p \cdot C_{p,ss}^p/R_o^p \tag{18a,b}$$

and

$$MRT_m^m = A_{m,ss}^m/R_o^m = V_{ss}^m \cdot C_{m,ss}^m/R_o^m \tag{19a,b}$$

Combining Eqs. (17) and (18) as well as Eqs. (14) and (19) separately yields

$$MRT_p^p = \frac{C_{p,ss}^p \cdot C_{m,ss}^m \cdot \int_0^{t_{ss}^m} \left(\frac{C_m^m}{C_{m,ss}^m} - \frac{C_p^m}{C_{p,ss}^m} \right) dt}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \tag{20}$$

and

$$MRT_m^m = \frac{C_{p,ss}^p \cdot C_{m,ss}^m \cdot \int_0^{t_{ss}^p} \left(\frac{C_p^p}{C_{p,ss}^p} - \frac{C_m^p}{C_{m,ss}^p} \right) dt}{C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m} \tag{21}$$

Similarly, the following equations can also be derived:

$$MRT_m^p = \frac{R_o^m \cdot C_{p,ss}^p \cdot C_{m,ss}^m \cdot \int_o^{t_{ss}^p} \left(\frac{C_p^p}{C_{p,ss}^p} - \frac{C_m^p}{C_{m,ss}^p} \right) dt}{R_o^p \cdot (C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m)} \tag{22}$$

$$MRT_p^m = \frac{R_o^p \cdot C_{p,ss}^m \cdot C_{m,ss}^m \cdot \int_0^{t_{ss}^m} \left(\frac{C_m^m}{C_{m,ss}^m} - \frac{C_p^m}{C_{p,ss}^m} \right) dt}{R_o^m \cdot (C_{p,ss}^p \cdot C_{m,ss}^m - C_{m,ss}^p \cdot C_{p,ss}^m)} \tag{23}$$

METHODS

Consider the separate intravenous infusions at a constant rate of drug and metabolite, each of which follows a two-compartment model and undergoes reversible metabolism (Fig. 2).

(i) When drug is administered,

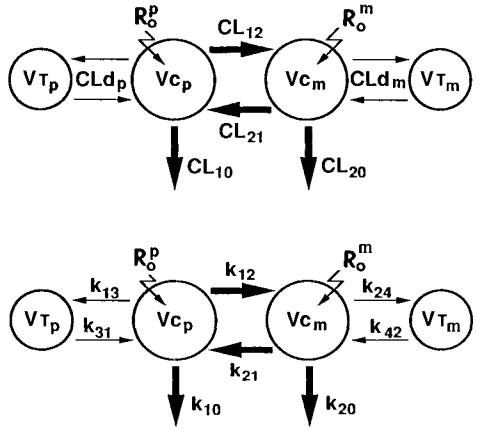

Fig. 2. Equivalent two-compartment models of reversible drug metabolism based on metabolic (heavy arrows) and distribution (thin arrows; CL_d) clearances (top) or rate constants (k_{ij}) for metabolism and distribution (bottom), where k_{ij} (i = 1, 2, 3, or 4; j = 0, 1, 2, 3, or 4) are the first-order rate constants. Vc_p, Vc_m, V_{Tp}, and V_{Tm} are the apparent volumes of distribution of the central (c) and tissue (T) compartments of the drug (p) and its metabolite (m). The models convert by means of the conventional rate constant = clearance/volume relationship (e.g., $k_{10} = CL_{10}/Vc_p$).

$$Vc_p \cdot dC_p^p/dt = R_o^p - k_1 \cdot Vc_p \cdot C_p^p + k_{21} \cdot Vc_m \cdot C_m^p + k_{31} \cdot V_{Tp} \cdot C_{Tp} \quad (24)$$

$$V_{Tp} \cdot dC_{Tp}^p/dt = -k_{31} \cdot V_{Tp} \cdot C_{Tp}^p + k_{13} \cdot Vc_p \cdot C_p^p \quad (25)$$

$$Vc_m \cdot dC_m^p/dt = -k_2 \cdot Vc_m \cdot C_m^p + k_{12} \cdot Vc_p \cdot C_p^p + k_{42} \cdot V_{Tm} \cdot C_{Tm}^p \quad (26)$$

$$V_{Tm} \cdot dC_{Tm}^p/dt = -k_{42} \cdot V_{Tm} \cdot C_{Tm}^p + k_{24} \cdot Vc_m \cdot C_m^p \quad (27)$$

(ii) When metabolite is administered,

$$Vc_p \cdot dC_p^m/dt = -k_1 \cdot Vc_p \cdot C_p^m + k_{21} \cdot Vc_m \cdot C_m^m + k_{31} \cdot V_{Tp} \cdot C_{Tp}^m \quad (28)$$

$$V_{Tp} \cdot dC_{Tp}^m/dt = -k_{31} \cdot V_{Tp} \cdot C_{Tp}^m + k_{13} \cdot Vc_p \cdot C_p^m \quad (29)$$

$$Vc_m \cdot dC_m^m/dt = R_o^m - k_2 \cdot Vc_m \cdot C_m^m + k_{12} \cdot Vc_p \cdot C_p^m + k_{42} \cdot V_{Tm} \cdot C_{Tm}^m \quad (30)$$

$$V_{Tm} \cdot dC_{Tm}^m/dt = -k_{42} \cdot V_{Tm} \cdot C_{Tm}^m + k_{24} \cdot Vc_m \cdot C_m^m \quad (31)$$

where the rate constants arise from the designated arrows in Fig. 2 with $k_1 = k_{10} + k_{12} + k_{13}$ and $k_2 = k_{20} + k_{21} + k_{24}$ and Vc and V_T are the apparent volumes of the central and peripheral compartments for drug (p) or metabolite (m). The corresponding clearances are $CL_{10} = Vc_p \cdot k_{10}$, $CL_{12} = Vc_p \cdot k_{12}$, $CL_{20} = Vc_m \cdot k_{20}$, $CL_{21} = Vc_m \cdot k_{21}$, $CL_{dp} = Vc_p \cdot k_{13} = V_{Tp} \cdot k_{31}$, and $CL_{dm} = Vc_m \cdot k_{24} = V_{Tm} \cdot k_{42}$. Plasma concentrations of both compounds were generated by numerical integration of the above equations using PCNONLIN (6). Simulations were performed with R_o^p (2.5 mg/hr) or R_o^m (2.5 mg/hr), Vc_p (73.4 liters), Vc_m (39.0 liters), V_{Tp} (40.0 liters), V_{Tm} (20.0 liters), k_{10} (0.817 hr^{-1}), k_{20} (0.246 hr^{-1}), k_{12} (0.188 hr^{-1}), k_{21} (0.385 hr^{-1}), k_{13} (0.123 hr^{-1}), k_{31} (0.300 hr^{-1}), k_{24} (0.103 hr^{-1}), and k_{42} (0.400 hr^{-1}). The values of $\int_0^{t_{ss}} Cdt$ were calculated using the LAGRAN program (7). Values for V_{ss} and MRT were calculated using Eqs. (14) and (17) as well as Eqs. (20)–(23). In addition, these MRT values were compared with those calculated previously (4) with simulated intravenous bolus data generated previously (4) using the above parameter values and $Dose^p$ (5 mg) or $Dose^m$ (5 mg). The values of V_{ss} calculated from Eqs. (14) and (17) were also compared with those calculated using IV bolus dose equations (Eqs. 29 and 30 in Ref. 2) as well as the corresponding values of $Vc + V_T$ used originally to generate the simulated data.

RESULTS

Simulated plasma concentration versus time profiles of drug and metabolite from time zero to steady state are shown in Fig. 3. Following R_o^p, the ratio $C_{p,ss}^p/C_{m,ss}^p$ = 38.23/21.45 = 1.78, while R_o^m produces a $C_{m,ss}^m/C_{p,ss}^m$ = 114.7/23.31 = 4.92. These values confirm the predicted ratios according to Eqs. (10) and (16).

Table I lists the values of V_{ss}^p and V_{ss}^m calculated from the simulated data using the designated equations as well as the theoretical values of these parameters used for computer simulations. As shown in this table, both the calculated and the assigned values of V_{ss}^p and V_{ss}^m are identical as 103.5 and 49.0 liters. Similarly, as shown in Table II, the values of MRT_p^p, MRT_m^p, MRT_p^m, and MRT_m^m calculated using the listed equations for steady-state or single dosing are 1.58, 0.42, 0.96, and 2.25 hr.

DISCUSSION

Equations for the V_{ss} parameters of drugs that undergo reversible metabolism and are infused intravenously, have been derived. According to Eqs. (14) and (17), V_{ss}^p and V_{ss}^m can be calculated from constant infusion rates, the integrals of plasma concentrations, plasma concentrations at steady state, and times to reach steady state of both drug and metabolite.

Equations for MRT parameters of drugs demonstrating reversible metabolism and infused intravenously at a constant rate have also been derived. As shown in Eqs. (20)–(23), these MRT parameters are functions of the integrals of

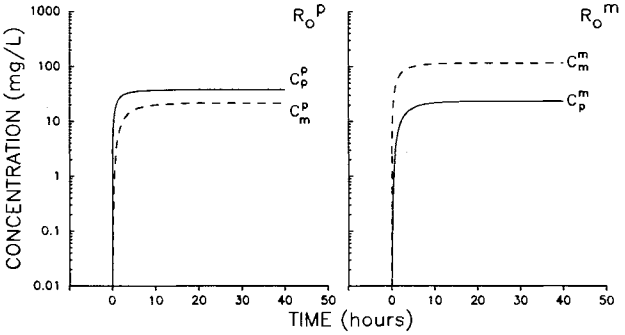

Fig. 3. Simulated concentration–time profiles for the two-compartment model of reversible drug metabolism during separate constant-rate intravenous infusion of parent drug and metabolite to steady states of both compounds. Parameter values are listed under Methods. Lines depict profiles of parent drug (——) and metabolite (----).

Table I. Comparison of the Steady-State Volume of Distribution Values for a Two-Compartment System

Parameter	Parameter value (liters)		
	Eqs. (14) & (17)	IV bolus[a]	Theoretical[b]
V_{ss}^{p}	103.5	103.5	103.5
V_{ss}^{m}	49.0	49.0	49.0

[a] Obtained using Eqs. 29 and 30 in Ref. 2.
[b] Calculated as $V_{ss}^{p} = Vc_p \cdot [1 + (k_{13}/k_{31})]$ and $V_{ss}^{m} = Vc_m \cdot [1 + (k_{24}/k_{42})]$.

plasma concentrations, plasma concentrations at steady state, and times to reach steady state of both drug and metabolite. In addition, MRT_m^p and MRT_p^m are also functions of the constant rates of intravenous infusion.

Equations for V_{ss} [Eqs. (14) and (17)] and MRT [Eqs. (20)–(23)] were also verified with computer simulations by comparing the V_{ss} and MRT values calculated from these equations with theoretical values (only for values of V_{ss}) and with those obtained previously for IV boluses (4). As shown in Table I, values of V_{ss} calculated using Eqs. (14) and (17) were identical to theoretical values and those obtained under bolus conditions. In addition, as shown in Table II, values of MRT calculated using Eqs. (20)–(23) were identical to those obtained previously (4). Thus, with mathematical derivations and computer simulations, we have shown that the proposed equations are meaningful for a drug subject to reversible metabolism and infused intravenously at a constant rate to steady state of both drug and its metabolite.

Methods for measuring V_{ss} of drugs not subject to reversible metabolism (mammillary models) have been described (8–10). In terms of the mode of drug administration, these methods can be divided into three approaches, namely, the intravenous bolus injection method, the short-term intravenous infusion method, and the steady-state intravenous infusion method. The advantages of the last method over the others have been addressed (9,10) and include the following: (a) the last method does not require extrapolating the area under the plasma concentration–time curve to infinity and, thus, shortens the time required for measuring V_{ss} for drugs with a prolonged half-life; and (b) the last method has no source error from plasma sampling since both arterial and venous plasma concentrations of a drug are theoretically identical at steady state. However, since there may be marked differences in arterial and venous plasma concentrations prior to reaching the steady state (11), the proposed method may still have source error from plasma sampling. Thus, only advantage (a) applies to the proposed method for estimating V_{ss}^{p} and V_{ss}^{m} using either Eq. (17) or Eq. (14).

Table II. Comparison of the Mean Residence Time Values for a Two-Compartment System

Compound		MRT_j^i (hr)	
Administered	Measured		
i	j	Eqs. (20)–(23)	IV bolus[a]
p	p	1.58	1.58
p	m	0.42	0.42
m	p	0.96	0.96
m	m	2.25	2.25

[a] Obtained in Ref. 4.

Constant-rate intravenous infusion technique has previously been used to study rates of production and of metabolism of steroid hormones (12,13) and to measure V_{ss} (9,10,14–16) and MRT (16) for drugs not subject to reversible metabolism. This report applies similar infusion techniques to extend the principles for measuring V_{ss} and MRT to drugs subject to reversible metabolism and demonstrates the validity of the proposed method by computer simulations.

ACKNOWLEDGMENT

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NOMENCLATURE

$A(t)$	Amount of compound in body at time t
A_{ss}	Steady-state amount of compound in body
CL_{12}	Conversion clearance of parent drug to metabolite
CL_{21}	Conversion clearance of metabolite to parent drug
CL_{10}	Sum of all irreversible elimination clearance processes operating on parent drug
CL_{20}	Sum of all irreversible elimination clearance processes operating on metabolite
CL_{11}	Sum of conversion (CL_{12}) and all irreversible elimination (CL_{10}) processes operating on parent drug
CL_{22}	Sum of conversion (CL_{21}) and all irreversible elimination (CL_{20}) processes operating on metabolite
CL_{dp}	Distribution clearance of parent drug
CL_{dm}	Distribution clearance of metabolite
C_p	Plasma concentration of parent drug at time t
C_m	Plasma concentration of metabolite at time t
C_{Tp}	Tissue concentration of parent drug at time t
C_{Tm}	Tissue concentration of metabolite at time t
$C_{p,ss}$	Steady-state plasma concentration of parent drug
$C_{m,ss}$	Steady-state plasma concentration of metabolite
k_{10}	First-order elimination rate constant of parent drug
k_{20}	First-order elimination rate constant of metabolite
k_{12}	First-order conversion rate constant of parent drug to metabolite
k_{21}	First-order conversion rate constant of metabolite to parent drug
k_{13}	First-order rate constant to describe drug distribution from central compartment to tissue compartment
k_{31}	First-order rate constant to describe drug distribution from tissue compartment to central compartment
k_{24}	First-order rate constant to describe metabolite

	distribution from central compartment to tissue compartment
k_{42}	First-order rate constant to describe metabolite distribution from tissue compartment to central compartment
MRT	Mean residence time of compound in body
^{p} or ^{m}	Administered parent drug (p) or metabolite (m)
$_{p}$ or $_{m}$	Measured parent drug or metabolite
R_o^p	Constant intravenous infusion rate of parent drug
R_o^m	Constant intravenous infusion rate of metabolite
t_{ss}	Time when steady-state concentrations of both drug and metabolite are reached
Vc_p	Central volume of parent drug
Vc_m	Central volume of metabolite
V_{Tp}	Apparent tissue volume of parent drug
V_{Tm}	Apparent tissue volume of metabolite
V_{ss}^p	Steady-state volume of distribution, parent drug
V_{ss}^m	Steady-state volume of distribution, metabolite

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