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Plasma terminal half-life

P. L. TOUTAIN &
A. BOUSQUET-MÉLOU

UMR 181 Physiopathologie et Toxicologie Expérimentales INRA/ENVT, Ecole Nationale Vétérinaire de Toulouse, Toulouse cedex 03, France

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Terminal plasma half-life is the time required to divide the plasma concentration by two after reaching pseudo-equilibrium, and not the time required to eliminate half the administered dose. When the process of absorption is not a limiting factor, half-life is a hybrid parameter controlled by plasma clearance and extent of distribution. In contrast, when the process of absorption is a limiting factor, the terminal half-life reflects rate and extent of absorption and not the elimination process (flip-flop pharmacokinetics). The terminal half-life is especially relevant to multiple dosing regimens, because it controls the degree of drug accumulation, concentration fluctuations and the time taken to reach equilibrium.

P. L. Toutain, UMR 181 Physiopathologie et Toxicologie Expérimentales INRA/ENVT, Ecole Nationale Vétérinaire de Toulouse, 23, chemin des Capelles, 31076 Toulouse cedex 03, France. E-mail: pl.toutain@envt.fr

INTRODUCTION

The plasma half life (half life of elimination or half life of the terminal phase) is the most frequently reported of all pharmacokinetic parameters. It has the apparent advantage of being a familiar term, immediately comprehensible because it is expressed in units of time. This is not the case for body clearance (the most important pharmacokinetic parameter), which is more difficult to conceive because it has the units of flow.

The half life is (apparently) easy to compute and it is often the only reported pharmacokinetic parameter in some *in vitro* or *in vivo* assays. In some circumstances, it is generally the only parameter which can be computed, e.g. for a drug metabolite or any analyte disposition when the dose is unknown.

Actually, plasma half life is very often wholly misunderstood and many non kineticists continue to mistakenly believe that it represents the time required to eliminate half the administered dose of a drug.

In this review, we will re state the definition of terminal half life and qualify its pharmacokinetic meaning, which can be very different after intravenous (i.v.) and extra vascular administra tion. The clinical relevance of terminal half life will also be discussed together with its value in the rational selection of dosage interval. Finally, some technical issues concerning its estimation (sampling time and level of quantification of the analytical technique) will be addressed.

In this review, the term 'terminal half life' is preferred to 'elimination half life', because it does not prejudge the mechan ism controlling plasma concentration decay.

DEFINITION OF TERMINAL HALF LIFE

Following i.v. administration, the terminal half life is the time required for plasma/blood concentration to decrease by 50% after pseudo equilibrium of distribution has been reached; then, terminal half life is computed when the decrease in drug plasma concentration is due only to drug elimination, and the term 'elimination half life' is applicable. Therefore, it is not the time necessary for the amount of the *administered drug* to fall by one half.

The decay of a drug following first order pharmacokinetics being exponential, the terminal half life is obtained from Eqn 1:

$$t_{1/2} = \frac{0.693}{\lambda_z} \quad (1)$$

where 0.693 is the natural logarithm of 2 and λ_z, the slope of the terminal phase.

Figure 1 shows two drugs having the same terminal half life but with very different clearances. In order to express the overall persistence of a drug in the body using a time parameter, then the mean residence time (*MRT*), and not the terminal plasma half life, should be selected.

The confusion in the definition of half life is historical. In the early stages of pharmacokinetics, analytical performances were poor and many drug dispositions were described by a single mono exponential phase. In this situation, and only in this situation, the half life is also the time it takes to eliminate half the administered dose of the drug. It is also relevant to note that when the pseudo equilibrium has been reached, the disposition curve becomes mono exponential and here also, the terminal half time becomes the time taken to eliminate half the *remaining fraction* (not half the administered dose).

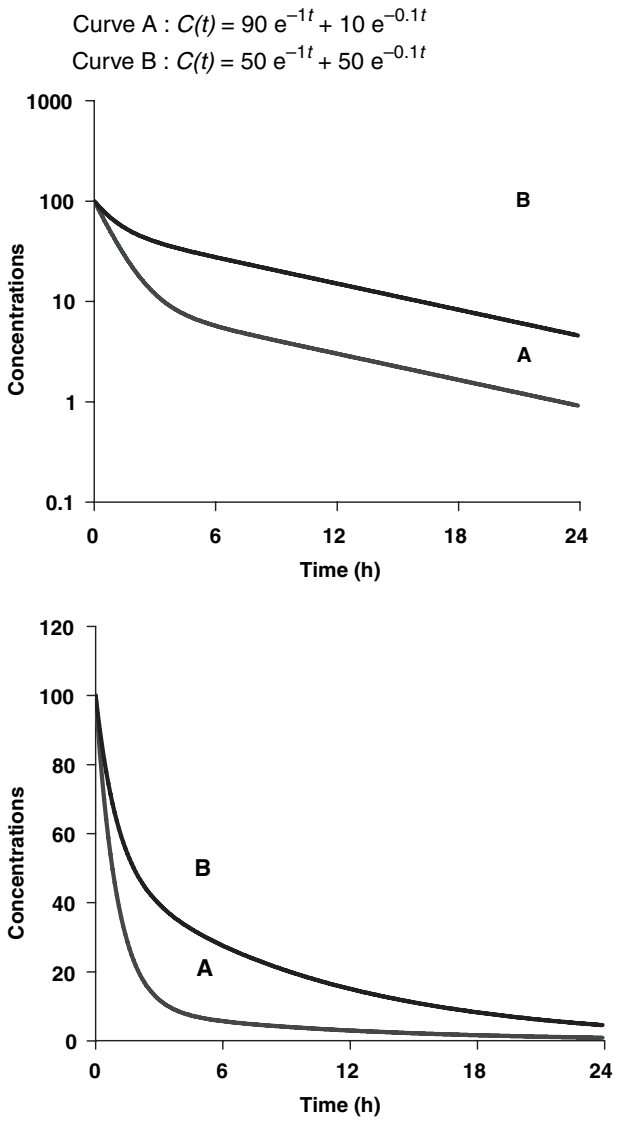


Fig. 1. Terminal half life is the time required for the plasma concentration to fall by 50% during the terminal phase, and not the time required to eliminate half the administered dose. The figure shows two drugs (A and B) having exactly the same terminal half life (6.93 h) (see top figure semi logarithmic plot), but for which the time required to eliminate half the administered dose is very different (6 h for drug B and 2 h for drug A) (see bottom figure arithmetic plot). This difference is due to the fact that drug B has a lower clearance than drug A (0.182 mL/kg/h vs. 0.526 mL/kg/h), and a lower V_{area} (1.82 mL/kg vs. 5.26 mL/kg). It is only when the pseudo equilibrium state has been reached (e.g. 12 h after drug administration), that the time required to eliminate half the *remaining* amount of drug in the body becomes equal to the terminal half life.

PHARMACOKINETIC MEANING OF HALF LIFE

It is sometimes difficult for a non pharmacokineticist to understand the difference between information conveyed by plasma clearance and terminal half life. Table 1 gives an example of antibiotics having the same clearance in dog but very different terminal half lives. The plasma clearance expresses only the ability of the body to eliminate the drug (see Toutain & Bousquet Mélou, 2004a). In contrast, terminal half life expresses the overall rate of the actual drug elimination process during the terminal phase; this overall rate of elimination depends not only on drug clearance but also on the extent of drug distribution.

Figure 2 provides a pictorial representation of the influence of clearance and distribution on terminal half life. More formally, Eqn 2 expresses the dependency of the terminal half life on the volume of distribution and clearance:

$$t_{1/2} = \frac{0.632 \times \text{Volume of distribution}}{\text{Plasma clearance}} \qquad (2)$$

Equation 2 indicates that a long terminal half life can be associated to a large volume of distribution (V_d) or/and attributable to a small plasma clearance. During the terminal phase, the drug will be eliminated only if it is presented to the clearing organs, regardless of the capacity level of these clearing organs to eliminate the drug. In mammals, the two most important clearing organs are the liver and kidney. In the framework of compartmental models, both are located in the central compartment and if the drug is present mainly in a peripheral compartment, the efficiency of the overall clearance process of drug elimination will be low and terminal half life will be long.

HOW TO USE TERMINAL SLOPE TO EXPRESS THE EFFICIENCY OF DRUG ELIMINATION

A simple way to express the efficiency of drug elimination is to consider the numerical value of the slope (λ_z) of the terminal phase. For instance, the terminal half life of phenylbutazone in cattle following i.v. administration is about 48 h, which corresponds to a terminal slope of 0.0144/h (Toutain *et al.*, 1980), a figure not easy to conceptualize. However, if this rate constant is multiplied by 100, it will mean that during the terminal phase of elimination, about 1.44% of the residual

Table 1. Terminal half life vs. plasma clearance for different antibiotics in the dog

Parameters	Benzyl penicillin	Gentamicin	Oxytetracycline	Tylosin
Plasma clearance (mL/kg/min)	3.5	3.1	4.0	22
Terminal half life (min)	30	75	360	54

Note that for three antibiotics (penicillin, gentamicin and oxytetracycline) the plasma clearances are very similar but the terminal half lives are very different, indicating that terminal half life and plasma clearance do not convey the same information. The terminal half life is also influenced by the extent of drug distribution, so that, for almost the same plasma clearance, oxytetracycline having the largest volume of distribution also has the longest half life.

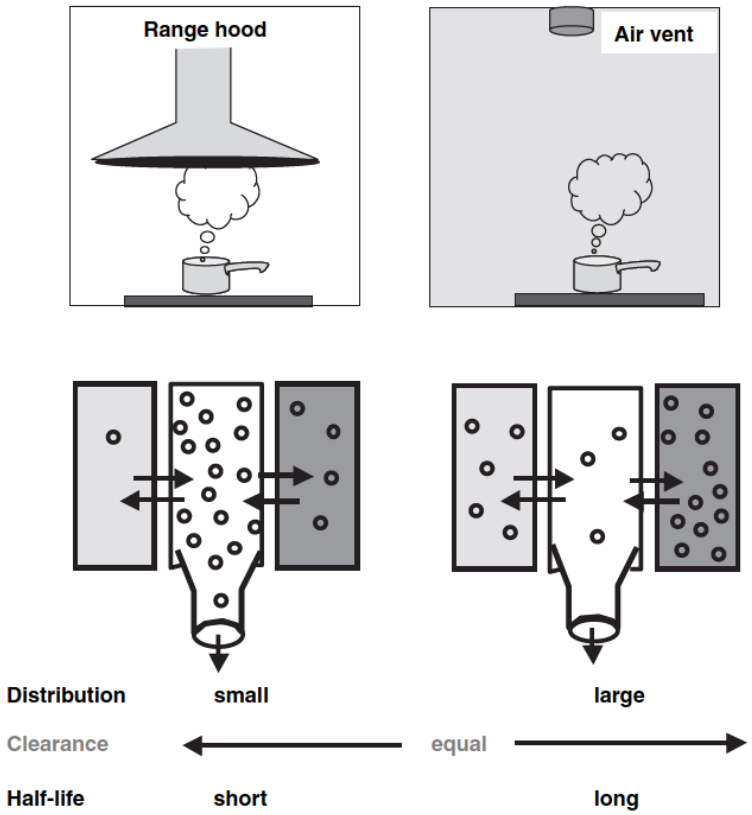


Fig. 2. Top: A pictorial explanation of the hybrid characteristic of a half life. Imagine that we have to boil water (drug) in a kitchen (the body). In a modern kitchen (left), the boiling kettle is placed just under an efficient range hood (high clearance) and the steam produced (the dose) is quickly eliminated from the kitchen (with a short half life) because the volume in which the steam is scattered (volume of distribution of the steam) is small. In a less ideal situation, there is no kitchen range hood but an air vent having exactly the same intrinsic capacity as the range hood (the same clearance). In this situation, the time required to eliminate the same amount of steam (the same dose) will be longer (longer half life), because the steam disperses all over the kitchen (has a larger volume of distribu tion). Bottom: a compartmental view of the preceding system.

amount of phenylbutazone is eliminated per hour. This approximation is relatively accurate if λ_z is expressed with an appropriate time unit in order to obtain a low numerical value of λ_z (e.g. lower than 0.02).

PLASMA HALF LIFE AND OTHER TIME PARAMETERS USED IN PHARMACOKINETICS ARE HYBRID PARAMETERS

Plasma half life is a dependent parameter in contrast to plasma clearance and volume of distribution, which are said to be independent parameters, because they have a primary physiological basis and they are not determined by a combination of other basic pharmacokinetic parameters (at least at the macroscopic level). In pharmacokinetics, all time parameters (derived from rate constants) are hybrid (compos ite) parameters (Fig. 3), and terminal half life is the most hybrid of all pharmacokinetic parameters, i.e. it is influenced by many other kinetic parameters (Fig. 4). Figure 5 explains the dependence of terminal half life on the different micro constants for a bi compartmental model.

The dependency of time parameters (rate constants) on clearance and volume of distribution should be recognized to avoid misinterpretation. A classical equation in compartmental analysis used to compute clearance is (Eqn 3):

$$Cl = K_{10}\mathrm{V_c} \tag{3}$$

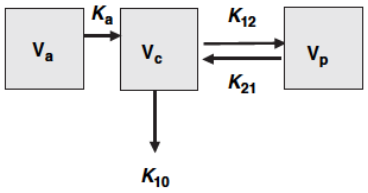
where K_{10} is the rate constant of drug elimination from the central compartment of volume V_c (see Fig. 3).

This equation should not be used to interpret plasma clearance (e.g. to say that plasma clearance is low because K_{10} is small); rather the following relationship holds (Eqn 4):

$$K_{10} = \frac{Cl}{\mathrm{V_c}} \tag{4}$$

so that K_{10} can be explained in terms of Cl and $\mathrm{V_c}$, which in turn can be explained in terms of blood flow, binding to plasma pro teins and so on.

The consequence of the hybrid character of terminal half life is that half life is a poor parameter to evaluate the influence of physiological factors (age, sex, etc.) or of pathology (renal failure, etc.) in drug disposition. For instance, the pharmacokinetics of gentamicin was investigated in horse before and after occurrence of nephrotoxicity. It was shown that body clearance was reduced by 40%, indicating impairment of the body capacity to eliminate gentamicin but with the terminal half life remaining unchanged (192 min vs. 204 min). This was because of the fact that the



K_{12} = distribution clearance / V_c
K_{10} = plasma clearance / V_c
K_{21} = distribution clearance / V_p
MRT = steady-state volume of distribution / plasma clearance
MTT_C = V_c / (plasma clearance and distribution clearance)
K_a = absorption clearance / V_a
$t_{1/2}$ = 0.693 V_{area} / plasma clearance

Fig. 3. Physiological primary determinants of the main time parameters in pharmacokinetics. The time parameters such as half life ($t_{1/2}$), mean residence time (*MRT*), mean transit time (*MTT*) in the central compart ment, and rate constants (K_a, K_{12}, K_{21}, K_{10},…) are called hybrid parameters because they are actually a combination of parameters having a direct physiological meaning. All the rate constants can be interpreted in terms of ratio of a solute conductance term (clearance of absorption, clearance of distribution, clearance for elimination, etc.) and as capacitance terms (a volume of distribution) such as V_a: volume of the site of administration, V_c: volume of the central compartment, V_p: volume of the peripheral compartment, V_{ss}: steady state volume of distribution, V_{area}: volume of distribution by area method. For rate constants like the rate constant of absorption (K_a), it is seldom possible to evaluate separately the two physiological determinants (clearance of absorption and volume of the site of administration), unless it is possible to sample the administration site (e.g. udder after an intra mammary administration) (see Chiou, 1995 for the application of the clearance concept to absorption). *MRT*: mean residence time of the system, MTT_C: mean transit time in the central compartment, i.e. the average interval of time spent by a drug molecule from its entry into the central compartment to its next exit; $t_{1/2}$: terminal half life.

volume of distribution was reduced in the same proportion as clearance (Riviere *et al.*, 1983).

WHY CALCULATE A TERMINAL HALF LIFE

Terminal half life is an index of drug persistence in the body during the terminal phase. The main clinical application of terminal half life is to select an appropriate length for the dosing interval in circumstances of multiple dose administration. Indeed, terminal half life allows prediction of drug accumulation and the time to reach steady state equilibrium. This explains why the consequence of the value of terminal half life is not the same for drugs having a short terminal half life vs. a long terminal half life. The impact of the value of half life also differs for drugs requiring only a single dose administration vs. those requiring a multiple dose regimen.

For drugs having a short terminal half life, it is important to maintain the plasma therapeutic concentration, and this will require dosage forms with a low input rate in order to obtain a flip flop condition (*vide infra*). In contrast, if terminal half life is long and the drug is to be administered repeatedly, questions of

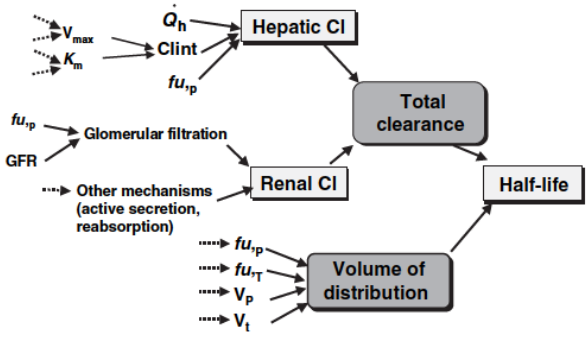
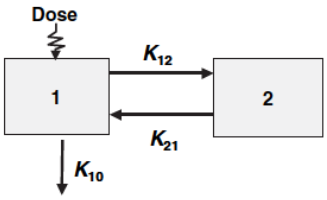


Fig. 4. Physiological factors influencing the terminal half life ($t_{1/2}$) and giving it the status of a hybrid parameter. The value of $t_{1/2}$ is linked to that of clearance and volume of distribution. In turn, plasma clearance is the sum of different organs clearances (e.g. hepatic and renal clearances) themselves depending on many factors, including (for hepatic clearance) hepatic blood flow ($\dot{Q}h$), intrinsic hepatic clearance (Clint), free fraction in plasma ($fu_{,P}$). Intrinsic hepatic clearance reflects maximum metabolism capacity (V_{max}), and the Michaelis Menten constant which is linked to drug affinity for the metabolic enzymatic system (K_M). Many factors also influence renal clearance. In addition, $t_{1/2}$ is influenced by the extent of drug distribution, which in turn depends on the drug affinity for circulating proteins ($fu_{,P}$), for tissues ($fu_{,T}$), on the volume of plasma (V_P) and tissues (V_T) etc.



$$t_{1/2} = \frac{0.693}{1/2\left[(K_{12}+K_{21}+K_{10}) - \sqrt{(K_{12}+K_{21}+K_{10})^2 - 4K_{21}K_{10}}\right]}$$

$$t_{1/2} = \frac{0.693}{\lambda_2}$$

Fig. 5. The terminal half life for a bi compartmental model. The terminal half life reflects both capacity of elimination (K_{10}), and processes of distribution (K_{12}) and redistribution (K_{21}). The numerical value of $t_{1/2}$ is a combination of K_{10}, K_{12} and K_{21}.

drug accumulation and delay in the time to reach steady state conditions arise.

TERMINAL HALF LIFE AND REPEATED ADMINISTRATION

Terminal plasma half life is an important determinant of drug concentration time profiles following repeated drug adminis

tration, which are characterized by an initial accumulation phase, followed by a steady state with fluctuations of concen tration during the inter dosing interval. Plasma half life can be used to predict these different factors (*vide infra*). For simplification, the calculations presented in the following sections were performed assuming a mono compartmental disposition of the drug.

Drug accumulation for drugs having a monophasic disposition

The terminal half life can be used to predict drug accumulation. This is straightforward for a drug which obeys monophasic decay (mono compartmental model), where it can easily be demonstrated that the accumulation ratio (R) is equal to (Eqn 5):

$$R = \frac{1}{\left[1 \quad e^{-\left(\frac{0.693}{\text{Terminal half life}} \times \text{Dosing interval}\right)}\right]} = \frac{1}{\left[1 \quad (0.5)^{\tau/t_{1/2}}\right]} \tag{5}$$

where R is the index which corresponds to the ratio of AUC at steady state (i.e. AUC over the dosage interval) on the AUC following the first dosing interval, τ is the dosing interval and $t_{1/2}$, the terminal half life (Fig. 6). Inspection of Eqn 5 indi cates that there are two determinants of drug accumulation during multiple dosing: the first one is the terminal half life, which is a drug property and the second one is the dosing interval, which is a clinician's decision. Thus, the accumula tion ratio can be controlled by clinicians when selecting the dosing interval. If the dosing interval (i.e. τ) is equal to $t_{1/2}$, the accumulation ratio will be of 2. Table 2 presents the values of R for different values of the ratio $\tau/t_{1/2}$ assuming administration of a fixed dose.

Many veterinary drugs have terminal half lives shorter than 12 h. When these drugs are given once daily ($\tau = 24$ h), their accumulation ratios are less than 1.3. In consequence, the concentrations at equilibrium will not be more than 30% greater than plasma concentrations obtained following the first admin istration. From a practical clinical point of view, problems associated with accumulation are likely to be minimal for drugs exhibiting plasma half lives shorter than 12 h.

The time to reach steady-state conditions

In contrast to the accumulation ratio, the time to reach the steady state is not influenced by the dosing interval but is only a function of terminal half life. Figure 7 presents plasma concentration time profiles of the same drug obtained with three different dosage regimens but with the same daily dosage (repeated administration of the dose 100 once daily, $\tau = 24$ h; repeated administration of the dose 50 BID, $\tau = 12$ h; i.v. infusion at the rate of 100/24 h). For the three dosage regimens, the same average concentration (C_{ss}) is obtained at steady state (because C_{ss} depends only on drug entry, Dose/τ, and drug clearance), and the time required to reach this concentration is the same. Practically speaking,

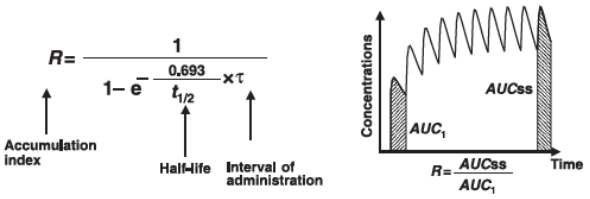


Fig. 6. Terminal half life and drug accumulation during a multiple dosing regimen. After the first drug administration, the entire adminis tered drug is not eliminated at the time of the second administration, and plasma concentration will be higher during the second dosing interval than after the first administration (superposition principle). With the repetition of dosing (at the same dose rate), plasma concentrations increase progressively until reaching a plateau, i.e. steady state condi tions. Under steady state conditions, the amount of administered drug exactly compensates for the amount of eliminated drug over the dosing interval (noted τ). An accumulation index can be defined as the ratio of the average amount of drug in the body under steady state conditions to the average amount of drug in the body after the first administration, thus,

$$R \quad \frac{\text{Amount (average) in steady state condition}}{\text{Amount (average) after the first dose}}$$

R is estimated by the ratio of the two corresponding areas under the curve (AUC) (hatched area) with $R \quad AUC_{ss}/AUC_1$. For a mono compartmental model or if drug is administered in the post absorption phase for a multi compartmental model, R is given by a simple mathematical expression having two parameters: terminal half life and τ. Therefore, drug accumulation is not an intrinsic drug property but rather a variable which relies on both the drug property ($t_{1/2}$) and a clinical decision (the dosing interval).

Table 2. Accumulation index (R) and peak/trough concentration ratio (P/T ratio) at steady state for different values of the ratio of the dosage interval (τ) and the terminal half life ($t_{1/2}$)

$\tau/t_{1/2}$	0.125	0.25	0.5	1	2	4
R	12	6	3	2	1.3	1.07
P/T ratio	1.09	1.2	1.4	2	4	16

R and P/T ratios are defined by Eqns 5 and 6, respectively, in the text. The calculation assumes administration of a fixed dose.

steady state is obtained after a delay of 3 5 times the half life. Thus, for any drug having a terminal half life of 12 h or less, the steady state will be reached after the second or third daily administration. For drugs exhibiting longer half lives (more than 24 h), the delay before reaching therapeutic concentra tions can be so long that initial administration of a loading dose is required.

Fluctuations of plasma concentrations at steady-state

Plasma concentration time profiles at steady state are charac terized by a succession of peak and trough concentrations. These fluctuations within a dosing interval are controlled by both τ and $t_{1/2}$, as indicated by the Peak Trough concentration ratio (P/T ratio) presented in the following equation:

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