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Kinetic equations and related residence time distributions

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Abstract: - The mean residence time is recommended as a useful summarising characteristic for complex pharmacokinetic systems. In this context, particularly Exponential and WEIBULL lifetime distributions are discussed. The classic compartment models of pharmacokinetics are connected with deterministic kinetic equations. On the other hand, they provide a natural interpretation in a probability theoretical context in terms of a residence time random variable.

We are analysing the correspondence of solutions of kinetic equations describing compartment models and life time distributions. Examples are given that in the nonlinear case such correspondence does not exists generally. This indicates one must clear in every application case whether the observable concentration-time course actually characterizes the residence time of a pharmacon molecule.

Key-Words: - pharmacokinetics, compartment systems, life time distributions, mean residence time

1 Introduction

Compartment models are used e.g. in pharmacokinetics [1] and in urea kinetics [2] to describe the time course of the concentrations of the substance being in observation. The method is taken from chemical reaction kinetics. We can confine ourselves to the simplest models in the following.

The so-called One-Compartment-iv-Model describes the time course of a substance administered rapidly at time zero, $t = 0$, to a body, which is regarded to be a single homogenous compartment. The related differential equation is the diffusion equation

$$\frac{d}{dt}c(t) = -k_{el}\ c(t) \tag{1}$$

with time $t \geq 0$, elimination constant $k_{el} > 0$ and initial value $c(0) = c^0$. The unique solution of this homogenous linear differential equation with constant coefficient is

$$c(t) = c^0 \exp(-k_{el}t)\ . \tag{2}$$

The inhomogenous linear initial value problem, the so-called One-Compartment-ev-Model,

$$\frac{d}{dt}c(t) + k_{el}\ c(t) = k_i c_i^0 \exp(-k_i t)\ , \tag{3}$$

$k_{el} > 0$, $k_i > 0$, $c_i^0 > 0$ and initial value $c(0) = 0$, has the unique solution

$$c(t) = c_i^0 kt \exp(-kt)\ , \tag{4}$$

abbreviated $c(t) = At \exp(-at)$, for $k_i = k_{el} =: k$ and

$$c(t) = \frac{c_i^0 k_i}{k_{el} - k_i}[\exp(-k_i t) - \exp(-k_{el}t)]\ , \tag{5}$$

abbreviated $c(t) = A[\exp(-at) - \exp(-bt)]$, for $k_i \neq k_{el}$.

The so-called system parameters a, b, A are functions of the model parameters $k_{el} > 0$, $k_i > 0$, $c_i^0 > 0$.

The Two-compartment model of pharmacokinetics is given by the differential equation system

$$\frac{d}{dt}C(t) = K\ C(t) + I(t) \tag{6}$$

with the transposed compartments concentration functions vector

$$C(t) = \left[c_1(t), c_2(t)\right]^T\ , \tag{7}$$

the transposed compartments input functions vector

$$I(t) = \left[I_1(t), I_2(t)\right]^T \tag{8}$$

and the model parameter matrix

$$K = \begin{pmatrix} -(k_{10} + k_{12}) & k_{21} \\ k_{12} & -(k_{20} + {}_{21}) \end{pmatrix}. \tag{9}$$

Here the model parameters k_{ij} are the transfer parameters from compartiment i to compartiment j and k_{i0} the compartiments elimination parameters. For

simplicity, we consider $I(t) = 0$ and initial condition $\left[c^0, 0\right]^T$. The solutions of this differential equation system arise with the known standard methods.

There are 16 different Two-compartment models depending on whether the model parameters are different from zero. Additionally, the solutions of the differential equation system require case distinctions. The relations between the model parameters and the system parameters, calculable from the data, get complicated with that. Therefore the mean residence time was recommended as a useful summarising characteristic for complex pharmacokinetic systems. This is a probability theoretic concept with the residence time of a pharmacon molecule as random variable.

Relations between concentration-time functions and residence time distributions are examined in the following.

2 Compartment models and residence time distributions

Every non-negative continuous real function whose integral over ú equals 1 defines a probability distribution.

Definition 1: Let $c(t) = c(t, a, b, A, B)$ be a function that corresponds with one of the observed compartment models, dependent on system parameters *a, b, A, B,* and integratable on $ú^+$. Then

$$f_c(t) = \frac{c(t)}{AUC} \quad \text{with} \quad AUC = \int_0^\infty c(t)dt < \infty \tag{10}$$

denotes the so-called standardized concentration-time function of $c(t)$. Ñ

Proposition 1
Not every function $c(t)$ associated with a compartment model can be assigned a standardized function $f_c(t)$.
Proof: The function $c(t) = A\exp(at) + B$ is among the solutions of a two-compartment model and only locally integratable. Ñ

A random variable has to be defined in a suitable way in order to be able to theoretically interpret the standardized concentration-time-functions of compartment models.

Definition 2: The duration of presence, synonymously: residence time, of a pharmacon molecule in an organism is regarded to be a random variable $\underline{X}$.

With respect to a compartment model, $m_e(t)$ denotes the drug quantity of applied dose *DOS* eliminated from the organism up to time *t*. The probability distribution of $\underline{X}$ is defined as

$$F_X(t) = Prob(\underline{X} < t) = \frac{m_e(t)}{DOS}\ , \tag{11}$$

the density is denoted by $f_X(t)$. Ñ

Agreement: Probability distribution and density are defined on all ú. Without being expressed, the courses of concentration over tome *c*(*t*) which are brought into relation are therefore thought to be extended from $ú^+$ to the whole ú with the value zero. The same technical simplifications concern the derived probability distributions, the density derived from *c*(*t*) as well other functions.

Proposition 2
For a One-Compartment-iv-Model, the residence time of a pharmacon molecule is exponentially distributed. $f_X(t) = f_c(t)$ is true. Ñ

Proposition 3
The following is true under the assumption $k_i \neq k_{el}$ for the One-Compartment-ev-Model:

1. The random variable $\underline{X}$ has the distribution function

$$F_X(t) = 1 + \frac{k_{el}k_i}{k_{el} - k_i}\left(\frac{\exp(-k_{el}t)}{k_{el}} - \frac{\exp(-k_i t)}{k_i}\right). \tag{12}$$

2. $f_X(t) = f_c(t)$ is true for the density function.
3. $f_X(t)$ is the linear combination of the densities of two exponential distributions. Ñ

Proposition 4
The following is true under the assumption $k_i = k_{el} =: k$ for the One-Compartment-ev-Model:
1. The random variable $\underline{X}$ is Gamma distributed and has the distribution function

$$F_X(t) = 1 - (kt + 1)\exp(-kt). \tag{13}$$

2. The following is true for the density function:

$$f_X(t) = f_c(t) = k^2 t\exp(-kt). \quad Ñ \tag{14}$$

The proofs of these propositions are straightforward.

Due to Proposition 1, not every one of the two-compartment models corresponds with a residence time distribution. The stochastic model is meaningfully in relation to the one-compartment models. It should be stressed that the distribution functions are independent from the applied drug quantity *DOS*

and that the densities correspond with the observable time courses of concentration.

This is fundamentally based on the qualities of the pharmacokinetic model:

Consider a so-called elimination process of 0-th order

$$c(t) = -k_{el},\ c(0) = c^0. \tag{15}$$

The solution only applies to the interval $[0,\ c^0 / k_{el}]$ where it is not negative. One goes over of the concentration-time-course to the mass-time-function by introducing the constant distribution volume *V*. So

$$m_c(t) = Vc(t) = DOS - k_{el}Vt, \tag{16}$$

$$m_e(t) = k_{el}Vt, \tag{17}$$

$$F_X(t) = Vk_{el}t / DOS \quad \text{and} \tag{18}$$

$f_X(t) = Vk_{el} / DOS$ yield from $c(t) = c^0 - k_{el}t$.

The distribution is dependent from *DOS*. In addition,

$$f_X(t) \neq f_c(t) \tag{19}$$

because

$$f_c(t) = 2(1 - k_{el}t / c^0)k_{el} / c^0. \tag{20}$$

A sufficient condition for the coincidence of residence time density and standardized concentration-time function gives

Proposition 5

The residence time $\underline{X}$ of a molecule in an organism is a continuous distributed random variable with density $f_X(t)$. Elimination of the pharmacon is only carried out in the observation compartment. Quantity and concentration are connected by the equation $m(t) = Vc(t)$ and *V* is a distribution volume. The elimination can be described by $m'_e(t) = k_{el}\ m(t)$. Here k_{el} is an elimination constant.

Then the following is true: For every density $f_X(t)$, a time course of concentration $f_c(t)$ exists such that

$$f_X(t) = f_c(t). \tag{21}$$

Proof: With regard to the Definition 2,

$f_X(t) = m'_e(t) / DOS$ is true.

The relation $c(t) = DOS\ f_X(t) / Vk_{el}$ then follow from the assumption $m'_e(t) = k_{el}m(t)$. Ñ

3 Nonlinear differential equations

Two variants of the one-compartment model are looked at. In the two cases time course of drug concentration and residence time distribution cannot be brought about to connection.

First, the nonlinear attempt

$$\frac{d}{dt}c(t) = -k_{el}\ c^2(t),\quad c(0) = c^0, \tag{22}$$

leads to

$$c(t) = \frac{c^0}{(c^0 k_{el}t + 1)}, \tag{23}$$

$$F_X(t) = 1 - \frac{1}{(DOS\ k_{el}\ t)} \quad \text{and}$$

$$f_X(t) = \frac{DOS\ k_{el}}{(DOS\ k_{el}\ t + 1)^2}.$$

$f_c(t)$ does not exist because $c(t)$, equation (23), is only a locally integratable function.

Second, consider the delay differential equation

$\frac{d}{dt}c(t) = -k_{el}\ c(t-\tau)$ for real $t > 0$, $\tau > 0$ and $k_{el} > 0$.

The clear attainability of a unique solution for this differential equation puts the handicap of a starting condition in the form of a steady function $g(t)$ on $[-\tau, 0]$. Let $g(t) = G$ a constant. The solution is than

$$c(t) = G\left[1 + \sum_{j=1}^{m} \frac{(-k_{el})^j}{j}(t - \{j-1\}\ \tau^j\right]. \tag{24}$$

It is an oscillating function, [3, p.67]. Negative values of concentrations do not make sense.

4 Conclusions

Associated residence time distributions were derived for concentration-time courses of simple pharmacokinetic models. Not every of these models corresponds with such a distribution. Such a stochastic description of a pharmacokinetical process proves to be interpretable. As executed, time courses of concentration do not necessarily define residence time distributions. A sufficient condition for the coincidence of residence time density and standardized concentration-time function is given. Pharmacokinetical literature about this topic is found to be vague, e.g. [4,5,6,7].

Oppositely, a family of probability distributions is the starting point of the mathematical modeling of pharmacokinetical processes. For example, [8] studies Gamma distributed residence times and [9] deals with WEIBULL-distributed residence times. Adequate conditions should be formulated in order to bring such ideas into connection with observable courses of time of concentration.

Regardless of these considerations, mean residence times are widely used in pharmacokinetics as you can find in the PubMed database.

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