

PHARMACOKINETIC MODEL CORRELATING EFFECTIVE EXPOSURE TIME AND CONCENTRATION OF AN INHALED SUBSTANCE

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Haber's product and other empirical relationships used to express experimental correlation between the duration of effective exposure and the concentration of a biologically active substance (S) in the inhaled air are, in general, presented without a theoretical justification. In this paper, these empirical relationships will be discussed in terms of a pharmacokinetic model in which we consider the uptake and the elimination rates of S. We also take into account that the uptake is limited by the partition coefficient of S between the atmosphere and the organism. We assume that the biological effect becomes observable only when the concentration of S in the body fluid reaches a certain critical value. It is shown how this critical value can only be reached if the concentration of S in the air is above a certain threshold. It is also shown how limiting case of our model correspond to Haber's product proposed to correlate experimental data. Treatments of experimental data able to test the applicability of the model are outlined.

Keywords: CT correlation; theoretical model; pharmacokinetics.

INTRODUCTION

When an animal is exposed to an atmosphere containing a biologically active substance, S, the time required to achieve observable effects depends on the form of variation of the concentration of S in the atmosphere.

From the mathematical and experimental viewpoints, the simplest case corresponds to a sudden change from pure air, at the instant $t = 0$, to a continuous exposure to air with a constant concentration, c_a , of the S to be tested. Under these conditions the exposure time, t_e , necessary to achieve a certain observable effect, is a function of the value of c_a . To express this functional dependence, at least five relationships have already been proposed. All these proposals were made in attempt to get better correlation for experimental data¹⁻⁵.

The first and the most simple of this kind of relationship is Haber's product, where K is a constant²:

$$t_e c_a = K \quad (1)$$

Fritz Haber, better known for his work on ammonia synthesis, found this very simple relationship in researches on toxic gases to be employed in the First World War (1914-1918). Exposing cats to air contaminated with poisonous gases or vapors, he found that the value of the constant $K = t_e c_a$ could be used as a reasonable measure of the toxicity of the gas under test: - a smaller K implies a more toxic gas. It may be useful to point out an analogy between Haber's product and the effect of the factors "light intensity" and "duration of exposure" on photographic film.

The validity of Haber's product is a key element of the "time-weighted average" (TWA), widely used in occupational health⁵.

The other four relationships have the following forms:

$$t_e(c_a - c_t) = K \quad (2)$$

$$(t_e - t_i)(c_a - c_t) = K \quad (3)$$

$$t_e(c_a - c_t)/c_a = k' \quad (4)$$

$$t_e(c_a)^n = k'' \text{ or } (t_e)^n c_a = k''' \quad (5)$$

In all these expressions, besides the measurable variables c_a and t_e , there are some of the following parameters to be adjusted by regression:

- c_t , which may be understood as a threshold concentration of S in the inhaled air. For $c_a < c_t$, the effect under consideration will not be observed, even if the exposure continues indefinitely.
- t_i , which may be understood as the minimal effective exposure time. For $t_e < t_i$, the effect will not be observed even for the largest values of the concentration of S in the air.
- n , an empirically adjustable exponent, which generally results in a non integer number without a reasonable physical meaning.
- k' , k'' , k''' , qualitatively analogous to the constant K in equations (1) to (3), but their physical dimensions are not the same.

A critical review of these relations, equations (1) to (5), points out that a theoretical justification for them has not yet been given⁵.

Roach⁶ attempted to explain the effects of exposure to a toxic substance, S, present in the air, in terms of how the substance is "incorporated" by the organism. In order to develop the concept of "body burden", in the case of exposure to air with a constant concentration of S, he started from the following assumptions:

- a) S is taken up by the body from the breathed air, where its constant concentration is c_a , at a rate $A c_a$, where A is a characteristic kinetical constant;
- b) at the same time, the body eliminates, at a rate $B x$, where B is another characteristic kinetical constant and x is the "amount" of S present in the body at time t, counted from the start of the exposure. This x is the so called "body burden". Its eventual value in the beginning of the exposure is x_0 .

These assumptions correspond to the following equation:

$$dx/dt = A c_a - B x \quad (6)$$

From this, by integration, he got

$$x = (A c_a / B) + (x_0 - A c_a / B) \exp(-Bt) \quad (7)$$

In his analysis, Roach⁶ shows that $x \sim Ac_a t_e$ is the limiting case for negligible elimination rate. This limiting case corresponds to Haber's product, provided that one accepts the assumption that the effect of S is proportional to the body burden.

Our goal is to discuss a more general pharmacokinetic model for exposure to air containing a constant concentration of a biologically active S. We consider diffusion and partition law limited absorption in parallel with zero and/or first order elimination processes. The "driving force" for absorption will be assumed to be proportional to the following thermodynamic "potential difference": - The concentration which S would reach inside the "body fluid", if the partition equilibrium with S containing air could be achieved, minus the actual concentration of S in the "body fluid". We also will assume that the biological effect of S only becomes observable, if the concentration of S in the body fluid or in a particular receptor in the organism reaches a certain critical value.

THE MODEL

Let us consider that a certain "normal young adult" animal, until now living in clean air, at the instant $t = 0$, begins a continuous exposure to an atmosphere with a constant concentration, c_a , of the substance S under study. This "outside" c_a will result in an uptake and elimination of S by the "body fluid". This changing concentration of S "inside" will be called c_i .

From what follows, it should become clear why our model, with a single body fluid, can be extended to living organisms with several kinds of fluids, such as blood plasma and the fluids inside different types of cells. A crucial point is the assumption that the partition equilibration of S through different body fluids, even across membranes, occurs "without any perceptible delay", in accordance with Nernst's distribution law for a solute across different phases in contact. This internal equilibration is assumed to be "very fast" in comparison with the "slow" uptake and elimination rates occurring at the same time.

In order to understand our assumptions regarding the uptake rate of S from the air into the body fluid via respiration, we begin considering $c_{i,p}$ the "saturation" concentration which S would reach in the body fluid by partition equilibration, due to contact with an atmosphere where the concentration of S is c_a in the absence of elimination processes. These two values, according to Nernst's law, are related to the pertinent partition coefficient P:

$$c_{i,p} = P c_a \quad (8)$$

Taking this thermodynamically limiting concentration, $c_{i,p}$, into account, the rate of uptake of S from the air is assumed to be $k_u(c_{i,p} - c_i)$, where the constant k_u is characteristic of the "diffusion" of S from the atmosphere to the body fluid through the respiratory system. This assumption for the uptake rate amounts to say that the driving force for the diffusion is the departure from saturation in the body fluid.

We will assume that the elimination rate is of the form $(k_0 + k_1 c_i)$. This implies the consideration that a "zero order" and a "first order" elimination occur in parallel. By this assumption we gain in generality without increasing the mathematical complexity of our problem. In the following developments, it will be very easy to obtain particular results by just setting $k_0 = 0$ or $k_1 = 0$.

Combining our hypothesis for the uptake and for the elimination rates results in the following differential equation:

$$dc_i / dt = k_u(c_{i,p} - c_i) - (k_0 + k_1 c_i) \quad (9)$$

Before discussing the consequences of this basic equation for our model, one should notice that c_i represents a time-dependent variable, while $c_{i,p}$, and later similar symbols with two

subscript indices such as $c_{i,s}$ and $c_{i,e}$, represent some particular values of this variable.

Since uptake and elimination are simultaneous, it is possible that the concentration of S in the body fluid reaches a steady state, which corresponds to assume that dc_i / dt can become equal to zero. In this case, equation (9) shows us that such a steady-state concentration of S in the body fluid, $c_{i,s}$, is simply a fraction, α , of the "partition equilibrium" concentration $c_{i,p}$:

$$c_{i,s} = \alpha c_{i,p}, \text{ where } \alpha = (k_u - k_0 / c_{i,p}) / (k_u + k_1) \quad (10)$$

Introducing this relation into equation (9) we get:

$$dc_i / dt = (c_{i,s} - c_i) / \tau, \text{ where } \tau = 1 / (k_u + k_1) \quad (11)$$

This equation shows us that the rate which the concentration of S in the body fluid changes is proportional to its departure from the steady-state value. Integrating equation (9), after being put in the form of equation (11), we obtain:

$$c_i = c_{i,s} \{1 - \exp(-t/\tau)\}, \text{ reminding that } c_{i,s} = \alpha c_{i,p} = \alpha P c_a \quad (12)$$

From equations (10) and (11) it can be concluded that τ represents the "time constant" for the achievement of the steady-state, counted from the start of the exposure.

Let us now assume that the effect of our S on the animal becomes observable only when its concentration in the body fluid reaches a critical value, $c_{i,e}$. This value will be reached at the instant $t = t_e$, measured since the beginning the continuous exposure to air containing a concentration c_a of S. Introducing this particular pair of values into equation (12), we can see that:

$$t_e = -\tau \ln(1 - c_{i,e} / c_{i,s}) \quad (13)$$

Since only $t_e > 0$ has a physical meaning, in accordance with equation (13) the effect can occur only if $c_{i,e} < c_{i,s}$. From equations (8) to (12) one sees that $c_{i,s}$ is proportional to c_a , hence, it follows that, for concentrations of S in the air (c_a), below a certain threshold value, c_{crit} , the effect of S can not be observed even after extremely long exposures. Therefore, we can write:

$$c_{crit} = c_{i,e} / (\alpha P) \quad (14)$$

and

$$(t_e / \tau) = -\ln\{1 - (c_{crit} / c_a)\}, \text{ only if } c_a > c_{crit} \quad (15)$$

Considering our definitions of $c_{i,e}$, c_{crit} and $c_{i,s}$, whose values depend on the nature of S and of the animal, equation (12) can be written in the following form:

$$(c_i / c_{i,e}) = (c_a / c_{crit}) \{1 - \exp(-t/\tau)\} \quad (16)$$

This last equation has the following merits:

- It shows what happens inside the animal as a function of the duration of the exposure and of the level of S in the air.
- All parenthesis, (), contain an adimensional ratio of what we have at a given moment, versus a critical value for that same kind of physical entity.

Three curves in accordance with equation (16) are drawn in Figure 1. The dotted horizontal line in Figure 1 indicates the level which the concentration of S in the body fluid has to reach in order to produce an observable effect. The lower curve for $c_a = c_{crit} / 2$ is typical for all cases in which the concentration of S in the air is below c_{crit} , hence the effect cannot be observed even after extremely long exposures. The upper curve in the same figure is an example of a value for c_a above c_{crit} , hence the effect will begin to be observable at the instant $t = t_e$, indicated by the dotted vertical line in that figure. Once the meaning of the three curves in Figure 1 is understood, it should be easy to visualize that, for instance, a curve for $c_a = 1.5 c_{crit}$,

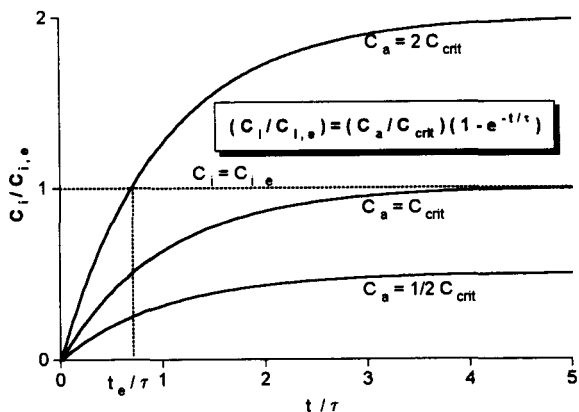


Figure 1. The time evolution of S in the body fluid, c_i , of animals exposed to 3 levels of S in the inhaled air (c_a), as indicated on each curve. The effect becomes observable, only if $c_i > c_{i,e}$. See equation (16).

should be located between the upper and the middle curve in this figure. Where this curve would cross the dotted horizontal line? The answer is a point in the abscissa which has a greater value of (t_e/τ) than the one indicated by the vertical dotted line. In other words: $-t_e$ increases as c_a decreases. One should remember that the time constant τ does not depend on c_a , but, depends only on rate constants as can be seen in equation (11).

The quantitative relationship between t_e and c_a can be clearly seen in equation (15), also written in terms of adimensional ratios and the curve corresponding to it is shown in Figure 2. In this figure one should notice:

- the vertical dotted line (asymptote) indicating that for $c_a < c_{crit}$, the effect cannot be observed in a finite time interval;
- the dashed line hyperbola corresponding to $(t_e/\tau)(c_a/c_{crit}) = 1$. In order to get a better feeling for implications of the dotted and dashed lines in Figure 2, let us just multiply both sides of equation (15) by (c_a/c_{crit}) :

$$[(t_e c_a)/(\tau c_{crit})] = - (c_a/c_{crit}) \ln\{1 - (c_{crit}/c_a)\} \quad (17)$$

The new curve corresponding to such a "transformation of variables" is shown in Figure 3. Notice how the dashed line hyperbola in Figure 2 changed into the lower asymptote (horizontal dotted line) in Figure 3. That hyperbola and this hori-

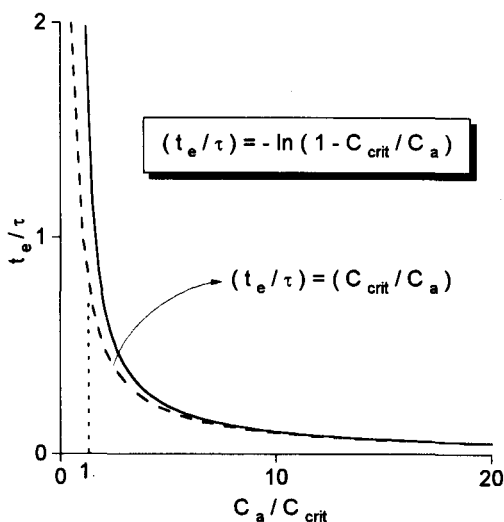


Figure 2. The exposure duration until the effect becomes observable as a function of the concentration of S in the air, according to equation (15).

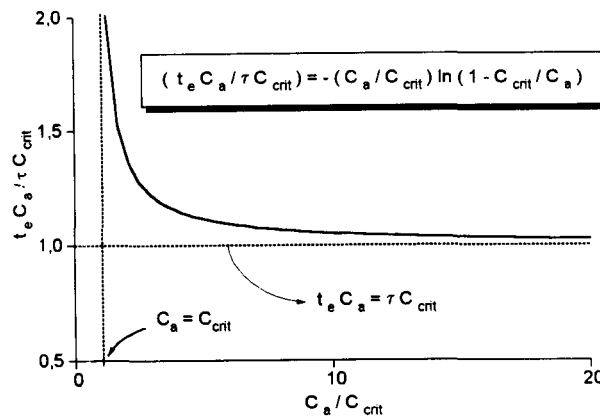


Figure 3. Dependence of the product $t_e c_a$ with the level of S in the inhaled air (c_a), according equation (17).

zontal asymptote look like graphical representations of Haber's classical product presented in equation (1).

LIMITING CASES

Researchers like to find what remains constant (such as Boyle's "pressure multiplied by volume") or at least, to show that the collected experimental data "fits nicely" to a straight line. Empirical "polynomial regression" and similar procedures with several "adjustable" parameters are "brute force" last resorts. Therefore let us see under what conditions, experimental data pertinent to our model, can be "linearized". One approach is applying the following form of series expansion for $\ln(1+x)$ to equation (15):

$$\ln(1+x) = x - x^2/2 + x^3/3 - \dots, \text{ convergent for } x^2 < 1 \quad (18)$$

Retaining only the first term, we get the following first order approximation:

$$t_e c_a \sim \tau c_{crit}, \text{ constant, only if } c_a \gg \gg c_{crit} \quad (19)$$

This shows us under which conditions Haber's product is consistent with our model. A better second order approximation we get by retaining the first two terms of the expansion:

$$t_e c_a \sim \tau c_{crit} + (\tau c_{crit}^2/2)(1/c_a), \text{ only if } c_a \gg c_{crit} \quad (20)$$

This last equation could be useful for data analysis. Notice that if we set $y = t_e c_a$ and $x = (1/c_a)$, then, equation (20) is of the form $y = a + bx$. If experimental data is plotted in this form, we can estimate the values of c_{crit} , ($= 2b/a$) and of τ , ($= a^2/[2b]$). It should be emphasized that even error free experimental points, in accordance with the model, will not sit exactly on the straight line corresponding to equation (20). This straight line is only the tangent to the curve y versus x at the point with $x = \text{zero}$.

In principle, this almost linear plot may be useful for data in the extreme $c_a \gg c_{crit}$. The other extreme, c_a near c_{crit} , corresponds to very long effective exposures, whose duration changes very much, even for relatively small changes in c_a . Considering the experimental difficulties inherent in very short or very long effective exposures, a more reasonable approach would be to use experimental points in the "intermediate range", not too near to those extremes. From such pairs of (c_a, t_e) one can get the time constant and the critical concentration by a non linear regression method in which one "imposes" a function in the form of our equation (15), or its equivalent exponential form. This "intermediate range" corresponds to the region of greatest curvature in the curves shown in Figures 2 and 3.

DISCUSSION

Our assumptions about the uptake rate are consistent with experimental evidence on transport across membranes. The drug elimination, in actual practice, often follows a complex mechanism; however, in a large number of cases, the overall rate of elimination can be realistically described by a first order or zero-order rate law⁷. For this reason our model assumes zero and/or first order elimination rates. We have shown that these alternatives lead to the same kind of relationships, except the values for the time constant τ , equation (11) and the fraction α , equation (10).

A more questionable assumption is that "the effect of our S on the animal becomes observable only if its concentration in the body fluid reaches a certain value", independently of the time interval necessary to achieve this level and without any regard to previous exposures to S. For many drugs, in fact, there is a minimum concentration that must be present in the blood stream or in the body tissues in order to be pharmacologically active. Calder, in a very instructive chemical kinetics discussion of the time evolution of ethanol in "homo sapiens", shows numerical examples (of what we call $c_{i,e}$), for some of the physiological and psychological effects for this S on that species⁷. This very particular example, however, also reminds us of problems such as increasing or decreasing "tolerances", addiction, cirrhosis of the liver, etc... For an experimental set-up for exposure of rats to air containing alcohols, aromatic

hydrocarbons and aldehydes, the sets of data obtained and their discussion in terms of models, see reference 8.

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