A simple equation to estimate the fraction of drug remaining in the body after an intravenous injection

Riegelman, Loo & Rowland (1968) and Gibaldi, Nagashima & Levy (1969) have derived equations to calculate the amount of drug remaining in the body after intravenous injection on the basis of a two compartmental open model with elimination of the drug taking place only in the central compartment. Gibaldi & others estimated the amount of drug left in the body from the summation of the amount of the drug present in the central and tissue compartments, while Riegelman & his colleagues calculated directly the fraction of the drug lost from the body from the loss in the central compartment. This is the simpler in both equation derivation and practical application and can also be applied to more complex multicompartmental open models provided that the elimination of drug takes place exclusively (or predominantly) in the central compartment.

After intravenous injection, the decay of the blood or plasma concentrations of drugs, C_p, can usually be described by a series of exponential terms, $\sum_{i=1}^{n} A_i e^{-x_i t}$. The number of the exponential terms is dependent upon the distribution characteristics of each drug (Rescigno & Segre, 1966; Riegelman & others, 1968). If one assumes that the elimination (metabolism and excretion of the intact drug) of the drug occurs only in a central compartment with a volume of distribution, V_p, then the elimination rate of the drug from the body can be represented by

$$\frac{dA_{el}}{dt} = K_{el}V_pC_p$$

$$= K_{el}V_p \sum_{i=1}^{n} A_i e^{-x_i t} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where A_{el} is the amount of the drug eliminated, and K_{el} is the first order elimination rate constant, and C_p is the concentration in the central compartment which is assumed to be equal to the drug concentration in the blood or plasma. Integration of Equation 1 from time zero to time t and also to infinite time yield

$$A_{el}^{t} = K_{el}V_p\left(\sum_{i=1}^{n} \frac{A_i}{x_i} - \sum_{i=1}^{n} \frac{A_i}{x_i} e^{-x_i t}\right) \quad .. \quad .. \quad .. \quad (2)$$

$$A_{el}^{\infty} = \text{dose} = K_{el}\, V_p \sum_{i=1}^{n} \frac{A_i}{x_i} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (3)$$

where A_{el}^{t} is equal to the cumulative amount of the drug eliminated up to time t and A_{el}^{∞} is the total amount of the drug eliminated in the infinite time which is also equal to the dose administered. The fraction of the drug remains in the body at time t will then be equal to

$$\frac{A_{el}^{\infty} - A_{el}^{t}}{A_{el}^{\infty}} = \frac{\sum_{i=1}^{n} \frac{Ai}{x_i} e^{-x_i t}}{\sum_{i=1}^{n} \frac{A_i}{x_i}} \quad .. \quad .. \quad .. \quad (4)$$

The assumption that most of drugs are eliminated from the central compartment is reasonable because the major sites for drug elimination such as liver, kidney, lung, blood and gastrointestinal tissues can be included in that compartment. This was advocated by Riegelman & others (1968) in the two compartmental open model systems. It is believed to be also applicable to more complex model systems. However, the above derived equation cannot be directly applied to situations in which a significant amount of drug is eliminated during its first pass to the general circulation system such as metabolism in the liver after oral administration or direct administration through portal vein (Harris & Riegelman, 1969).

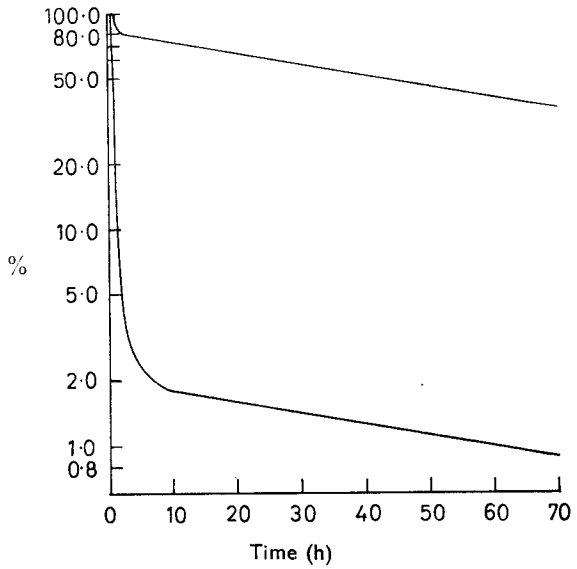

FIG. 1. Initial plasma concentration in the central compartment (%) (lower curve) and amount (%) of the administered drug remaining in the body (upper curve) after intravenous injection of 0·5 mg of digoxin to a subject (data from Ewy & others, 1969).

Digoxin which is predominantly excreted by the kidney will be used to illustrate the application of the above derived equation to a three compartmental open model system. Its plasma level decay after an intravenous administration of 0·5 mg to an adult can be fitted into a tri-exponential equation,

$$C_p^{\cdot}(\mu g/\text{litre}) = 0{\cdot}029e^{-0.173t} + 0{\cdot}0071e^{-0.0193t} + 0{\cdot}00068e^{-0.000204t}$$

(t in terms of minutes, data from Ewy, Kapadia & others, 1969). The semilogarithmic plot of the percent of the initial plasma concentration and that of the dose remaining in the body as a function of time calculated according to Equation 4 is shown in Fig. 1. It is interesting to note that at 5 h after administration, the plasma concentration of the drug drops to about 2% of the initial concentration, while there is still approximately 77% of the drug remaining in the body.

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A rapid photographic method for the determination of vein-islet number and stomatal index of leaves

The use of the camera lucida to assess stomatal index and palisade ratio is convenient and rapid but for the determination of vein-islet number, the usual low power (10X) objective gives too small a field ($\sim$ 1 mm^2). To obtain a wider field for a more accurate count of the vein-islets it is necessary to use objectives of much lower magnification, e.g. 2·5X or even 1X, at which the islets appear very small and numerous. Tracing from a camera lucida then becomes tedious.

A simple photographic technique which obviates camera lucida tracing is now described. A wide area of leaf is photographed and in addition a permanent record of the specimen is obtained. After it has been cleared in chloral hydrate, the leaf sample is photographed through a microscope using 2·5X or 1X objectives. Concurrently, photographs of a stage micrometer (0·1 mm) are made at the same magnification. The negative film after processing is viewed in a microfilm reader when an enlarged image of the vein-islets can be seen. An exact enlarged area of 1 mm^2 is obtained from the photographed micrometer scale. As the film is negative the veinlets appear white on a black background. This facilitates viewing and reduces eye-strain and the veinlets can thus be traced with ease and rapidity and from a large area of leaf.

Leaf samples were photographed on a Leitz Ortholux microscope fitted with the Orthomat automatic camera using both 1X and 2·5X objectives. Kodak Panatomic X or Plus X negative films were used. When projected through a Kodagraph Film Reader, Model MPE, the final magnifications of the images were approximately 80X and 210X respectively and the areas of leaf included within a standard 24 $\times$ 36 mm film frame were slightly over 24 mm^2 for the 1X objective and 6 mm^2 for the 2·5X objective.

The method was also suitable for the determination of stomatal index, using the 10X objective.

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