Proceedings of the Iowa Academy of Science

Volume 67 | Annual Issue Article 64

1960

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Effects of Capillary Permeability On Tracers in the Blood[1]

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Abstract. Numerous advantages arise from a concise mathematical formulation of the influence of capillary permeability on tracers in the blood. The paper deals with a theoretical description of the depletion of a blood-borne tracer under the combined influences of the reversible process of transcapillary diffusion and irreversible processes such as renal excretion and first-order enzymatic degradations. Numerical calculations are illustrated graphically to show application of the theory to typical tracer dilution problems.

Numerous physiological experiments have shown that following intravenous injection of a transcapillary-diffusible substance such as fluorescein, its excretion or deactivation is accompanied by a reversible escape of the tracer into the interstitial fluid space. Several advantages arise from a concise mathematical formulation of the influence of capillary permeability on tracers in the blood.

The first mathematical analyses of the distribution of exogenous substances in a multi-compartment biological system appear to be the works of Teorell (1937) and Beccari (1938). However, those mathematical treatments seem not to have been conveniently reduced to the case to be reported here. The purpose of this paper is to develop a simplified theoretical description of the depletion of a blood-borne tracer under the combined influences of the reversible process of transcapillary diffusion and first-order irreversible processes of hepatic and renal elimination.

THEORETICAL ANALYSIS

A diffusible tracer dye injected intravenously is depleted by a combination of kidney excretion and diffusion into the interstitial fluid. The liver depletes the tissue concentration of the tracer.

When the depleting actions of the kidney and liver are first-order processes, the differential equations for the system are

$$V_b \frac{dC_b}{dt} = -m_k C_b - m_c(C_b - C_i)$$

$$V_i \frac{dC_i}{dt} = -m_g C_i - m_c(C_i - C_b)$$

[1]From the Department of Physiology and Pharmacology. Published as Paper No. 502, Veterinary Medical Research Institute, College of Veterinary Medicine, Iowa State University, Ames, Iowa.

where t represents time, V_b and V_i the volumes of the blood and interstitial fluid compartments, C_b and C_i the tracer concentrations in the blood and interstitial fluid compartments. The numbers m_c, m_k, and m_g are the "permeability constants" for the capillary membranes, and the kidney and liver elimination processes.

The above equations may be solved for the practical case in which the first contact of the tracer substance with the body is via a sudden intravenous injection. The solutions are

$$C_b = \frac{\gamma - \alpha}{\beta - \alpha} C_b^{\circ} e^{-\alpha t} + \frac{\beta - \gamma}{\beta - \alpha} C_b^{\circ} e^{-\beta t}$$

$$C_i = \frac{m_c C_b^{\circ}}{V_i(\beta - \alpha)} \left[e^{-\alpha t} - e^{-\beta t} \right]$$

where C_b° is the initial concentration of the tracer in the blood, while α, β, γ are defined by the equations

$$\alpha + \beta = \frac{m_g + m_c}{V_i} + \frac{m_k + m_c}{V_b}$$

$$\alpha \beta = \frac{(m_k + m_c)(m_g + m_c) - (m_c)^2}{V_b V_i}$$

$$\gamma = \frac{m_g + m_c}{V_i}$$

If the physiological constants m_k, m_c, m_g, V_b, V_i, and C_b° are given, the time courses of C_b and C_i may be obtained from the simple numerical evaluations of the secondary constants α, β, and γ. However, the determination of the physiological constants m_k, m_c, and m_g from experimental curves defining α, β, and γ involves the solution of a non-linear set of three simultaneous equations.

Experimental Application

A set of experimental data to which the foregoing equations may be applied is found in a paper by Crisman and Fuhrman (1947). They reported that following intravenous injection of fluorescein (75 mg/kg) in rabbits, the concentration of the dye in the blood diminished with time in a manner which after 20 minutes was definitely of simple exponential character, decaying from an "apparent" initial value of 31.5 mg/100 ml, with a "time-constant" of 33.3 minutes. As observed by a photocell and ultraviolet illumination arrangement, the relative concentration of fluorescein in the interstitial fluid was reported to rise to a peak in about 16 minutes and then fall in a manner which eventually became exponential; however, absolute concentrations were not measured. The theory discussed above has the advantage of providing a method of obtaining the absolute concentration of the dye in the interstitial fluid.

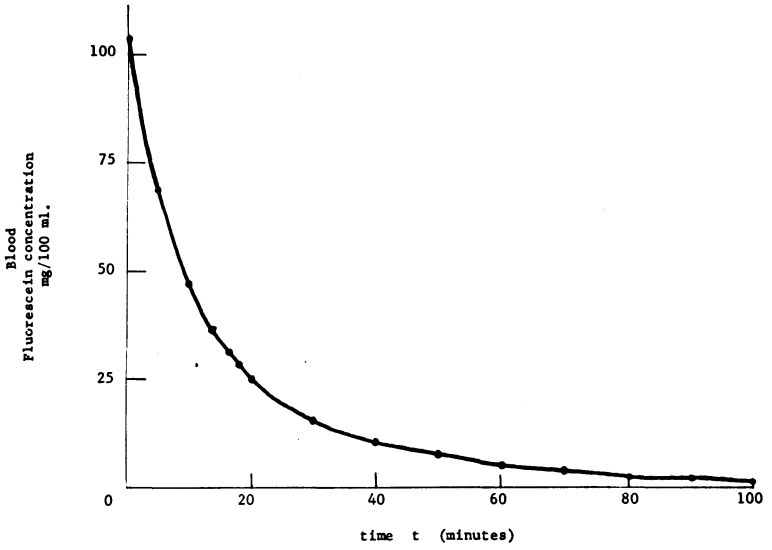

Figure 1. Calculated values of fluorescein concentration in the blood.

Applying the foregoing theory to the above-mentioned experimental data, and assuming the blood and interstitial fluid volumes are $V_b = 71$ ml/kg (Courtice, 1943) and $V_i = 200$ ml/kg (Spector, 1956),

$$\alpha = 0.030 \text{ minutes}^{-1}$$

$$\beta = 0.113 \text{ minutes}^{-1}$$

$$\gamma = 0.055 \text{ minutes}^{-1}$$

and the theoretical equations reduce to

$$C_b = 31.5e^{-0.030t} + 73.5e^{-0.113t}$$

$$C_i = 25.3e^{-0.030t} + 25.3e^{-0.113t}$$

where the dimensions of C_b and C_i are mg/100 ml, and time t is measured in minutes. The latter two equations are illustrated graphically in Figures 1 and 2.

If a $\pm$ 20 per cent error is allowed in the determination of β, due to a broad peak in the experimental curve for relative concentration of fluorescein in the interstitial fluid, the non-linear simultaneous equations for m_k, m_c, and m_g are

$$m_g + m_c = 11.0 \pm 1.4$$

$$71\, m_g + 271\, m_c + 200\, m_k = 2030 \pm 327$$

$$m_k\, m_g + m_k\, m_c + m_c\, m_g = 48.2 \pm 9.8$$

in which the units are ml/kg/min. Successive trial solutions indicate that compatible values for m_k, m_c, and m_g are

$m_k = 2$ ml/kg/min

$m_c = 4$ ml/kg/min

$m_g = 7$ ml/kg/min

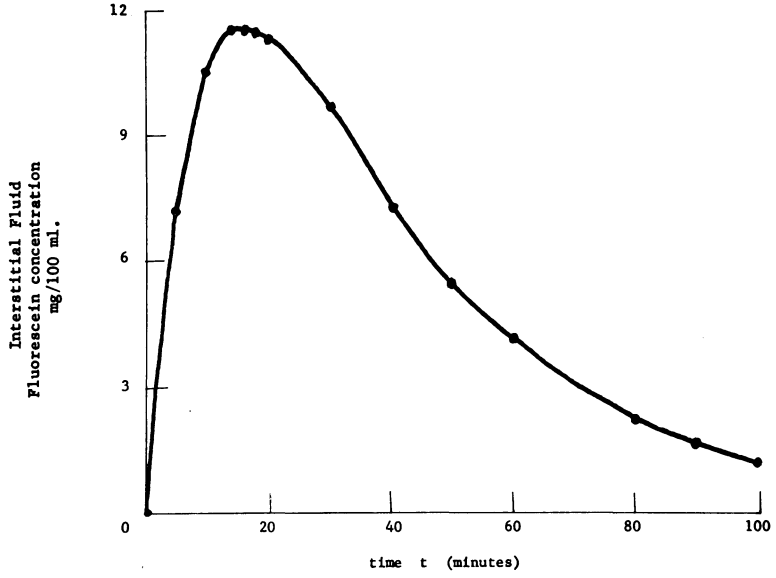

Figure 2. Calculated values of fluorescein concentration in the interstitial fluid.

Conclusion

The foregoing theory appears to be the simplest which will account for known experimental phenomena. An immediate result is a theoretical derivation of the absolute concentration of the tracer in the interstitial fluid. Further investigations into the significance of the numerical values and units for the constants m_k, m_c, and m_g should produce interesting results.

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