ON THE DISTRIBUTION OF A PERMEABLE SOLUTE DURING POISEUILLE FLOW IN CAPILLARY TUBES

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ABSTRACT Equations are derived describing the dispersion of a permeable solute during Poiseuille flow in a capillary model. It is shown that for the normal range of physiological parameters such as capillary radius, capillary length, blood flow, permeability coefficients, and diffusion constants, the center of mass of a bolus of solute moves at a speed very close to the mean speed of flow and that the solute leaves the capillary with an exponential time course depending on the permeability but not on the diffusion constant. There is no appreciable difference in the dispersion of the solute or in its rate of permeation from the capillary whether one considers piston flow or Poiseuille flow. A bolus of arbitrary radial shape tends to become radially uniform very close to the arterial end of the capillary.

INTRODUCTION

When one turns from the consideration of the flow of nonpermeating indicators in models of arteries and veins to a consideration of events occurring in capillaries, the permeability of the capillary wall becomes of great physiological significance. In the analytical treatments of Taylor (1953, 1954) and Aris (1956) it was assumed that the walls of the tube were impermeable. It becomes important, therefore, to evaluate the effect of laminar flow on the rate of permeation of a solute from a capillary into the surrounding tissue. The analytical treatment developed here would be directly applicable to the dispersion of solutes from lymph vessels or from capillaries perfused with plasma. In the circulation of blood, however, the red blood cells, being almost as wide as the capillary, alter the pattern of flow so that it is not laminar, but may approximate compartmentalized plug flow. Studies with model capillaries suggest that there may be some stirring by eddy currents within each "compartment" (Prothero and Burton, 1961). Since the analytical treatment to be presented will also predict the rate of dispersion of a solute during piston flow (and in principle for any reasonably smooth velocity profile) in a tube with permeable walls, we will be able to place limits on the possible effects of the flow profile on diffusion of a solute from a capillary into the extravascular space.

THEORY

In this paper we treat a model for flow in a capillary, which allows us to calculate the rate at which solute initially injected at the arterial end of the vessel is dispersed into the surrounding tissue. We assume that this is Poiseuille flow, that the vessel is straight, and that edge effects at the arterial end may be neglected. The blood flow pattern may be represented by

$$\vec{v} = \hat{k}\left(1 - \frac{r^2}{a^2}\right)v_0, \tag{1}$$

where $\hat{k}$ is a unit vector in the z direction assumed along the capillary length, v_0 is the flow velocity along the axis of the capillary, and a is the capillary radius.

The diffusion equation including convective effects with the velocity profile given by equation (1) is:

$$\frac{\partial c}{\partial t} - D\nabla^2 c + v_0\left(1 - \frac{r^2}{a^2}\right)\frac{dc}{dz} = 0, \tag{2}$$

where c is the solute concentration and D, the diffusion coefficient. It should also be recalled that $\nabla^2 c$ in cylindrical coordinates is equal to $\partial^2 c/\partial r^2 + 1/r \times dc/dr + d^2c/dz^2$ if the concentration is independent of the angular coordinate θ.

Appended to equation (2) must be appropriate boundary conditions and initial conditions. These are:

Boundary conditions:

$$c = 0 \quad \text{at} \quad z = \pm\infty$$

$$Hc = -D\,\partial c/\partial r \quad \text{at} \quad r = a$$

Initial condition:

$$c(t = 0) = f(r)\,\delta(z) \tag{3}$$

where H is the permeability of the wall and $\delta(z)$ is the Dirac δ function. From this we may write

$$Q_0 = 2\pi \int_0^1 f(r)r\,dr \tag{4}$$

where Q_0 is the total amount of solute injected into the capillary.

A dominant influence on the distribution of the solute is the average convective flow. Even without the parabolic velocity profile or diffusion the solute would flow down the capillary in a particularly simple way. To include this effect in our calculation we introduce a coordinate transformation employed by Aris (1956). Let

$$\rho = r/a; \qquad \xi = (z - \bar{v}t)/a; \qquad \tau = Dt/a^2, \tag{5}$$

where $\bar{v}$ is the average flow velocity defined by

$$\bar{v} = \frac{1}{\pi a^2} \int_0^{2\pi} \int_0^1 vr\, dr\, d\phi = v_0/2. \tag{6}$$

Then equation (2) can be written

$$\frac{\partial c}{\partial \tau} - \nabla_{\xi\rho}{}^2 c = \mu(1 - 2\rho^2)\frac{\partial c}{\partial \xi}, \tag{7}$$

where $\mu = \bar{v}a/D$. Aris encounters equation (7) and proceeds by deriving a hierarchy of equations for the moments of the distribution of c. We will instead write the equivalent integral equation for c. By this means we can display a formal series solution, which allows one to see the factors determining each of the moments of the distribution. To obtain the integral equation solution we introduce the Green function for this equation satisfying appropriate boundary conditions. The Green function satisfies

$$\frac{\partial G(\tau - \tau'; \xi - \xi'; \rho; \rho')}{\partial \tau} - \nabla_{\xi\rho}{}^2 G = \delta(\tau - \tau')\, \delta(\xi - \xi')\, \frac{\delta(\rho - \rho')}{\rho}, \tag{8}$$

where

$$\begin{aligned} G &= 0 \quad \text{for} \quad \tau' > \tau \\ G &= 0 \quad \text{for} \quad \xi, \xi' = \pm\infty \\ \partial G/\partial \rho &= -\frac{aH}{D} G \quad \text{at} \quad \rho = 1 \end{aligned} \tag{9}$$

Using G one can rewrite equation (7) as an integral equation:

$$c(\tau, \xi, \rho) = c_0(\tau, \xi, \rho) - \mu \int G(1 - 2\rho'^2)\frac{\partial c}{\partial \xi'}\, \rho'\, d\rho'\, d\xi'\, d\tau' \tag{10}$$

where c_0 obeys the equation

$$\frac{\partial c_0}{\partial \tau} - \nabla_{\xi\rho}{}^2 c_0 = 0 \tag{11}$$

and the same initial and boundary conditions as c.

Using equation (8) one can easily see that c given by equation (10) obeys the proper equation. Furthermore, the boundary conditions on G and c_0 insure the satisfaction of the proper conditions for c. Assuming the existence of an iterative solution to equation (10) we may write

$$\begin{aligned} c = c_0 &- \mu \int G(\tau - \tau'; \xi - \xi'; \rho; \rho')(1 - 2\rho'^2)\frac{\partial c_0(\tau'\xi'\rho')}{\partial \xi'}\, \rho'\, d\rho'\, d\xi'\, d\tau' \\ &+ \mu^2 \int G(\tau - \tau'; \xi - \xi'; \rho; \rho')(1 - 2\rho'^2)\frac{\partial G(\tau' - \tau''; \xi' - \xi''; \rho'; \rho'')}{\partial \xi'} \\ &\cdot \frac{\partial c_0(\tau'', \xi'', \rho'')}{\partial \xi''}\, \rho'\rho''\, d\rho'\, d\rho''\, d\xi'\, d\xi''\, d\tau'\, d\tau'' \cdots \text{etc.} \end{aligned} \tag{12}$$

The moments of the solute distribution are defined by

$$C^{(k)}(\tau) = 2\pi \int_{-\infty}^{\infty} \int_{0}^{1} c\xi^{k} \rho \, d\rho \, d\xi. \tag{13}$$

The zeroth moment [$k = 0$ in equation (13)] is the total amount of solute remaining at any time. Only the first term in the expansion, equation (12), contributes to $C^{(0)}(\tau)$ since by successive partial integrations with respect to the ξ variables and use of the fact that G is a function of $\xi - \xi'$, $\xi' - \xi''$, etc., one can show that all the successive terms vanish. Thus the total amount of solute present after a time, τ, may be evaluated merely by solving the much simpler equation (11).

The first moment of the distribution [$k = 1$ in equation (13)] is related to the mean position of the solute relative to a plane moving with the average velocity. Here one can prove that $C^{(1)}(\tau)$ is determined only by the first two terms of the expansion equation (12). Similarly, the second moment of the distribution is determined by only the first three terms of the expansion, etc. Thus all the moments of the distribution are displayed in the expansion, equation (12). To compute the moments, however, an explicit expression for the Green function is necessary.

Methods for determining the Green function are well known (e.g., Morse and Feshbach, 1953) and will not be reviewed here. Instead we merely introduce Green's function and verify that it satisfies equations (8) and (9). We use

$$\begin{aligned} &G(\xi - \xi'; \tau - \tau'; \rho; \rho') \\ &\quad = \frac{h(\tau - \tau')}{2\pi} \int_{-\infty}^{\infty} \sum_{n=0}^{\infty} e^{-(\beta_n^2 + \alpha^2)(\tau - \tau')} J_0(\beta_n \rho) J_0(\beta_n \rho') e^{i\alpha(\xi - \xi')} \, d\alpha \end{aligned} \tag{14}$$

where $h(\tau - \tau')$ is the step function defined by

$$\begin{aligned} h(x) &= 0, \qquad x < 0 \\ &= 1, \qquad x > 0 \end{aligned} \tag{15}$$

and $J_0(x)$ is the zeroth order Bessel function.
Using

$$dh/dx = \delta(x)$$

$$\frac{1}{\rho} \frac{d}{d\rho} \rho \frac{d}{d\rho} J_0(\beta_n \rho) = -\beta_n^2 J_0(\beta_n \rho)$$

$$\frac{1}{2\pi} \int_{-\infty}^{\infty} e^{i\alpha(\xi - \xi')} \, d\alpha = \delta(\xi - \xi')$$

$$\sum_{n=0}^{\infty} J_0(\beta_n \rho) J_0(\beta_n \rho') = \delta(\rho - \rho')/\rho \tag{16}$$

and inserting G as given by equation (14) into equation (8), it can be seen that equation (8) is satisfied.

The boundary condition at $\rho = 1$ is automatically satisfied by requiring that

$$\beta_n J_1(\beta_n) = \eta J_0(\beta_n) \quad \text{where} \quad \eta = aH/D. \tag{17}$$

The integral over α can be performed explicitly, giving

$$\int_{-\infty}^{+\infty} e^{-\alpha^2(\tau-\tau')} e^{i\alpha(\xi-\xi')}\, d\alpha = \sqrt{\frac{\pi}{\tau-\tau'}}\, e^{-(\xi-\xi')^2/4(\tau-\tau')} \tag{18}$$

which vanishes for $\xi \to \infty$ and $-\infty$. Thus G satisfies both the differential equation (8) and the boundary conditions, equation (14).

To get the total mass of the solute, we need c_0 from equation (11), which can be written as

$$c_0 = \frac{h(\tau)}{2\pi} \sum_{n=0}^{\infty} \int_{-\infty}^{\infty} A_n e^{-(\beta_n^2+\alpha^2)\tau} e^{i\alpha\xi} J_0(\beta_n \rho)\, d\alpha \tag{19}$$

where the values of A_n are to be determined by the initial conditions, equation (3)

$$A_n = \frac{\int_0^1 f(\rho)\, J_0(\beta_n\rho)\rho\, d\rho}{\int_0^1 J_0(\beta_n\rho)\, J_0(\beta_n\rho)\rho\, d\rho} = \frac{\int_0^1 f(\rho)\, J_0(\beta_n\rho)\rho\, d\rho}{d_n} \tag{20}$$

Having found c_0 we obtain the total solute mass remaining in the vessel, $C^{(0)}(\tau)$, by performing the integration specified in equation (13), making use of the definition of the δ function given in equation (16).

$$C^{(0)}(\tau) = 2\pi h(\tau) \sum_{n=0}^{\infty} A_n e^{-\beta_n^2\tau} \int_0^1 J_0(\beta_n\rho)\rho\, d\rho. \tag{21}$$

For the impermeable wall, the β_n are chosen so that the integral in equation (21) vanishes unless β_n vanishes. Thus, for the impermeable wall the total solute mass is independent of time.

$$C^{(0)}(\tau) = 2\pi h(\tau) A_0 = Q_0. \tag{22}$$

When the wall is permeable, however, the amount of solute remaining in the capillary decreases with time according to equation (21).

To determine the average solute position, we rewrite equation (13) with $k = 1$ as follows:

$$\bar{\xi} = \frac{C^{(1)}(\tau)}{2\pi} = \int_0^1 \int_{-\infty}^{\infty} c\xi\rho\, d\rho\, d\xi. \tag{23}$$

As shown above, only the first two terms of c in equation (12) contribute to the first moment. In fact, the contribution of the first term of equation (12) to the integral, equation (23), vanishes. The second term of equation (12) contributes to $\bar{\xi}$ as follows:

$$\bar{\xi} = -\mu \int \xi G(\xi - \xi'; \tau - \tau'; \rho; \rho')(1 - 2\rho'^2) \frac{\partial c_0(\xi', \tau', \rho')}{\partial \xi'} \rho\rho'\, d\rho\, d\rho'\, d\xi\, d\xi'\, d\tau' \tag{24}$$

Integrating by parts and using $\partial G/\partial\xi = -(\partial G/\partial\xi')$ and inserting the expressions for G and c_0 we get

$$\bar{\xi}(\tau) = \frac{\mu}{4\pi^2} \int \sum_{n=0}^{\infty} \sum_{m=0}^{\infty} e^{-(\beta_n^2+\alpha^2)(\tau-\tau')} J_0(\beta_n\rho)\, J_0(\beta_n\rho') e^{\alpha(\xi-\xi')}(1 - 2\rho'^2)$$

$$\times\, h(\tau - \tau')h(\tau')\, A_m e^{-(\beta_m^2+\gamma^2)\tau'} e^{i\gamma\xi'}\, J_0(\beta_m\rho')\rho\rho'\; d\rho\; d\rho'\; d\xi\; d\xi'\; d\tau'\; d\alpha\; d\gamma. \tag{25}$$

The ξ' integration gives $2\pi\delta(\alpha - \gamma)$, and the ξ integration gives $2\pi\delta(\alpha)$. The remaining expressions in the integrand relevant to the τ' integration can then be written and evaluated:

$$\int_0^\infty h(\tau')h(\tau - \tau')e^{-(\beta_m^2-\beta_n^2)\tau'}\, d\tau' = \int_0^\tau e^{-(\beta_m^2-\beta_n^2)\tau'}\, d\tau' \tag{26}$$

$$= \tau\delta_{nm} + \frac{1}{\beta_m^{\;2} - \beta_n^{\;2}}\,\{1 - e^{-(\beta_m^2-\beta_n^2)\tau}\} \tag{26'}$$

where

$$\delta_{nm} = 0 \quad \text{if} \quad n \neq m \quad \text{and} \quad \delta_{nm} = 1 \quad \text{if} \quad n = m.$$

Thus

$$\bar{\xi} = \mu \sum_{n=0}^{\infty} A_n e^{-\beta_n^2\tau}\tau a_n b_{nn} + \mu \sum_{n\neq m} \frac{1}{\beta_m^{\;2} - \beta_n^{\;2}}\, A_m(e^{-\beta_n^2\tau} - e^{-\beta_m^2\tau})a_n b_{nm} \tag{27}$$

where

$$a_n = \int_0^1 J_0(\beta_n\rho)\rho\; d\rho$$

$$b_{nm} = \int_0^1 (1 - 2\rho^2)\, J_0(\beta_n\rho)\, J_0(\beta_m\rho)\rho\; d\rho \tag{28}$$

The average position is obtained by dividing $\bar{\xi}$ by the total amount of solute remaining at time τ.

$$\bar{\xi}\text{ (position average of remaining distribution)} = \bar{\xi}(\tau)/C^{(0)}(\tau). \tag{29}$$

The second moment of the distribution is of limited physiological interest and will not be evaluated here, although this may be done in a manner completely analogous to the treatment for $\bar{\xi}$.

RESULTS

Because of the values of the parameters which characterize typical capillaries and solutes of physiological interest, good approximations to the results may be achieved without prolonged computational work. We shall confine ourselves to the case where the initial distribution is radially uniform; i.e., $f(\rho)$ in equation (20) is a constant.

The total amount of solute remaining in the capillary after time τ, given in equation (21), can be written

$$C^{(0)}(\tau) = 2\pi \sum_{n=0}^{\infty} \frac{a_n^2}{d_n} e^{-\beta_n^2(\tau)}. \tag{30}$$

Using standard results in the theory of Bessel functions we get

$$a_n = J_1(\beta_n)/\beta_n$$

and

$$d_n = [J_0^2(\beta_n) + J_1^2(\beta_n)]/2. \tag{31}$$

Using the boundary condition, equation (17), and these expressions for a_n and d_n, we get for $C^{(0)}(\tau)$

$$C^{(0)}(\tau) = 4\pi \sum_{n=0}^{\infty} \frac{e^{-\beta_n^2\tau}}{\beta_n^2\left(1 + \frac{\beta_n^2}{\eta^2}\right)} \tag{32}$$

It is convenient (but not necessary) to introduce an approximation at this point. For physiological ranges of a, D, and H, as will be discussed more fully below, $\eta \ll 1$, and we can analyze equation (17) for small η. It is easy to show that the roots β_n differ from the corresponding roots in the impenetrable wall problem by numbers of the order of η. This applies for all n except $n = 0$, for which $\beta_0^{(0)}$ vanishes. In that case:

$$\beta_0^2 = \frac{4\eta}{\eta + 2} \sim 2\eta - \eta^2. \tag{33}$$

Inserting these results into equation (32) gives

$$C^{(0)}(\tau) = 4\pi \sum_{n=1}^{\infty} \frac{e^{-(\beta_n^{(0)} + [\eta/\beta_n^{(0)}])^2\tau}}{\left(\beta_n^{(0)} + \frac{\eta}{\beta_n^{(0)}}\right)^2\left[1 + \frac{1}{\eta^2}\left(\beta_n^0 + \frac{\eta}{\beta_n^0}\right)^2\right]} + \frac{4\pi e^{-2\eta\tau}}{2\eta\left(1 - \frac{2}{\eta}\right)}. \tag{34}$$

The range of values for η can be estimated from the following considerations. An average value for the capillary radius is 5×10^{-4} cm (Krogh, 1919). For permeable solutes, the diffusion coefficient is likely to vary between 10^{-5} and 10^{-6} cm^2/sec. The data of Pappenheimer et al. (1951) suggest that H will range from 3×10^{-4} cm/sec for NaCl to 0.5×10^{-4} cm/sec for saccharose. Generally, large molecules with small diffusion coefficients will permeate slowly, so that the ratio aH/D will probably not vary beyond the limits 0.005 to 0.05 for permeable solutes. For relatively impermeable solutes, η will become even smaller. Since $\beta_1^{(0)}$, the smallest of the roots greater than β_0, is approximately 3.83, neglecting $\eta/\beta_n^{(0)}$ as compared with $\beta_n^{(0)}$ in the summation in equation (34) introduces an error of less than 0.04τ in the exponent, and this, in turn, introduces less than a 1% error in the numerator of the first term ($n = 1$) of the summation. The error introduced into the numerator of terms for $n \geq 2$ will be even smaller. Similarly, neglecting all terms in the denominator except $(\beta_1^{(0)})^4/\eta^2$ introduces errors of less than 1%. Thus we can write

$$C^{(0)}(\tau) \approx 4\pi\left[\sum_{n=1}^{\infty} \frac{\exp\,(-\beta_n^{(0)^2}\tau)\eta^2}{\beta_n^{(0)^4}} + \frac{e^{-2\eta\tau}}{4}\right] \tag{35}$$

where we have neglected $\eta/2$ compared with 1 (an error of 1% at most) in the last term. The neglect of entire summation in equation (35) can be shown to make a very small fractional error in $C^{(0)}(\tau)$ ($\sim 10^{-6}$). Thus for all practical purposes equation (35) reduces to:

$$C^{(0)}(\tau) \approx \pi e^{-2\eta\tau}. \tag{36}$$

It should be emphasized that this result depends critically on the assumption that the initial distribution is radially uniform. If $f(r)$ is not a constant, we may develop it in a Fourier-Bessel expansion as given in equation (19). The assumption that $f(r)$ is a constant is then essentially equivalent to saying that only the first term in equation (20) is significant. Suppose, however, that the $f(r)$ is such that it requires the first two terms in equation (20) to adequately describe it; i.e., $f(r) = A_0 J_0(\beta_0 \rho) + A_1 J_0 \beta_1(\rho)$. Since $f(r)$ must be positive, the approximate maximum value of A_1, given by $0 \approx A_0 + A_1 J_0(3.83\rho)$, occurs when $\rho = 1$, so that $A_0 - 0.4A_1 = 0$. Thus if $f(r)$ is not uniform but is distributed in such a way that, say, the amplitude of the A_1 term (to which we will refer as the first mode) in the Fourier-Bessel series representation of $f(r)$ is 40% of the A_0 term, we would get some solute which would vanish rapidly, with a lifetime of the order $(1/\beta_n^{(0)})^2$, as well as solute which would vanish more slowly, with a lifetime of the order $1/2\eta$. For initial distributions of solute of this type (e.g., the solute more concentrated near the periphery than near $\rho = 0$) one would obtain compound exponential dependence, with one rapid and one slow component.

In order to get a picture of where the solute is being deposited in the tissue, we calculate the position of the center of mass of the solute remaining in the capillary at time, τ, from equations (27) and (29). From our previous calculations we have a_n and A_n, and now need to compute b_{nn} and b_{nm}. Again, because of the large values of β_n for $n > 0$ the expression for ξ simplifies. After a very short time only the terms with β_o in the exponent are important.

Neglecting terms of order η^2 compared with unity and deriving our results only for time intervals of experimental significance we get:

$$\hat{\xi} = \frac{\bar{\xi}(\tau)}{C^{(0)}(\tau)} = \frac{\mu\tau\eta}{8\pi} = \frac{H\bar{v}t}{4\pi D}. \tag{37}$$

If we choose $L = 0.06$ cm, $H = 10^{-4}$ cm/sec, $D = 5 \times 10^{-6}$ cm²/sec, $a = 5 \times 10^{-4}$ cm, and $\bar{v} = 0.06$ cm/sec as typical values for capillary beds, then $\mu = \bar{v}a/D = 6.0$, $\eta = aH/D = 0.01$, and $\tau = Dt/a^2 = 20t$. The departure of the center of mass from the position of a plane moving with the average speed of flow, obtained from equation (37), would be about $2.5 \times 10^{-3}\tau$. Thus the center of mass would, for all practical purposes, move with the average speed of flow.

It was mentioned above that if $f(r)$ were of such form that a significant fraction of the solute were initially in the first mode (i.e. A_1 not negligible compared to A_0) then the solute in the first mode would be discharged into the surrounding tissue according to the factor $e^{-\beta_0^2\tau}$. For the amount of solute in the $n = 1$ mode to be reduced to 1% of its original value, i.e. $e^{-\beta_0^2\tau} = 0.01$, $\beta_0^2\tau$ would have to be 4.6 and τ would have to be $4.6/(3.83)^2 \approx 0.31$. Blood flowing at a speed of 0.06 cm/sec would take 1 sec to reach the end of a capillary 0.06 cm long, so τ would equal 20 at the venous end of the capillary. Thus almost all the solute injected in the $n = 1$ mode would be discharged at the arterial end of the capillary. Since solute injected into modes with $n \geq 2$ would disappear even faster, we arrive at the important conclusion that the injection can be considered radially uniform (at least for the model we are using with zero concentration outside the capillary).

Renkin (1959) in his discussion of the rate of permeation of K^{42} from capillaries, for which the extracapillary space acts as an infinite sink, derived the formula

$$A(v) = A(a)e^{-PS/Q} \tag{38}$$

where $A(a)$ and $A(v)$ are the concentrations of K^{42} at the arterial and venous ends of the capillary, respectively, P is the permeability coefficient (H in our terminology), S is the surface area of the capillary, and Q is the flow rate. In our notation, $Q = \pi a^2\bar{v}$, $S = 2\pi aL$, and $t = L/\bar{v}$, so that equation (38) becomes equivalent to our equation (36). Since Renkin assumed piston flow and since our equation, derived for Poiseuille flow, is equivalent to his, we come to the conclusion that for any velocity profile likely to be encountered in a capillary the effect of diffusion is negligible compared with the resistance to mass transfer of the capillary membrane. This justifies the assumption made by Roughton and Forster (1957) and by Blum (1960), among others, that the solute behaves as if there were radial mixing within the capillary.

This work was supported in part by the Office of Naval Research under Contract Nonr-266(84) and in part by grant NGR 34-001-005 from the National Aeronautics and Space Administration. Dr. Blum also acknowledges the support of a Research Career Development Award, K3-GM-2341 from the National Institute of General Medical Science.

This paper is Hudson Laboratories of Columbia University Contribution No. 216.

Received for publication 19 April 1965.

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