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Renal Transit Time: Its Measurement by the ^{131}I Hippuran Renogram

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Transit time is the mean time interval required for the molecules of an indicator to traverse a particular system (1). The system usually employed contains a fluid which is in motion, and transit time is calculated from the graph of indicator concentration in the effluent fluid plotted against time (1-3). This graph is called the indicator-dilution curve through the system under study.

During the performance of the ^{131}I hippuran renogram, hippuran traverses the kidney and is carried away in the urine (4). Therefore, the graph of the urine hippuran concentration plotted against time is, by definition, an indicator-dilution curve from which the renal transit time of hippuran can be calculated. In this study, it will be shown that renal transit time can also be measured by directly employing the renogram curve, thus obviating the necessity for determining urine hippuran concentration.

In the derivation of equations necessary for calculating renal hippuran transit time from the renogram, it is useful to define a number of terms. For convenience, these are listed below:

$\bar{t}_r$ = renal transit time of hippuran (min).

K = hippuran clearance of a single kidney (cc/min).

$C_{(t)}$ = graph of blood hippuran concentration plotted against time.

$U_{(t)}$ = graph of urine hippuran concentration plotted against time.

V = urine flow rate (cc/min).

SR = the amount of ^{131}I labeled hippuran within the kidney.

$SR_{(t)}$ = graph of renal hippuran radioactivity content plotted against time.

CALCULATION OF $\bar{t}_r$ FROM $U_{(t)}$

Let $M_{(t)}$ be the total amount of hippuran which leaves the kidney during the time t. Let $h_{(ti)}$ be defined as the fraction of $M_{(t)}$ leaving the kidney at a given time. If time zero is defined as the moment when hippuran becomes available to the kidney, ($C_{(t)} > 0$), $h_{(ti)}$ is the magnitude of that fraction requiring ti minutes to enter and traverse the kidney. Thus, the graph of $h_{(ti)}$ against time, $h_{(t)}$, is

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the frequency distribution function of a set of time intervals, each representing the sum of an entry time and a renal transit time. It can be shown that the mean renal transit time for hippuran ($\bar{t}_r$) is obtained by subtracting the mean entry time ($\bar{t}_e$) from the mean of $h_{(t)}$ (1-3).

Let the total dose of hippuran which enters a kidney be denoted by D. Let $g_{(ti)}$ be the fraction of D which enters the kidney at a particular time, ti, and let $g_{(t)}$ be the graph of $g_{(ti)}$ against time. Thus, $g_{(t)}$ is the frequency distribution of entry times, and its mean is $\bar{t}_e$. Employing standard equations for the means of $h_{(t)}$ and $g_{(t)}$ (1, 2, 3):

$$1.\quad \bar{t}_r = \int_0^\infty t h_{(t)}\,dt - \int_0^\infty t g_{(t)}\,dt$$

In terms of actually observed concentrations:

$$2.\quad \bar{t}_r = \frac{\int_0^\infty tU_{(t)}\,dt}{\int_0^\infty U_{(t)}\,dt} - \frac{\int_0^\infty tC_{(t)}\,dt}{\int_0^\infty C_{(t)}\,dt}; \quad h_{(t)} = U_{(t)} \Big/ \int_0^\infty U_{(t)}\,dt \quad g_{(t)} = C_{(t)} \Big/ \int_0^\infty C_{(t)}\,dt$$

CALCULATION OF $\bar{t}_r$ FROM THE RENOGRAM CURVE

Until now, we have defined $\bar{t}_r$ as the mean time interval required for hippuran to traverse the kidney. It is now possible to define $\bar{t}_r$, with greater operational specificity, as the mean time interval during which a molecule of ^{131}I hippuran constitutes a portion of intrarenal radioactivity, SR. Since the value of SR at a given time is the difference between the amount of hippuran which has entered and the amount which has left the kidneys:

$$3.\quad SR_{(ti)} = K\int_0^{ti} C_{(t)}\,dt - V\int_0^{ti} U_{(t)}\,dt; \text{ or, } \dot{SR}_{(ti)} = KC_{(ti)} - VU_{(ti)}$$

By substituting equation 3 into equation 2, $\bar{t}_r$ may be directly calculated in terms of $SR_{(t)}$ and $C_{(t)}$, without the necessity of estimating $U_{(t)}$:

$$4.\quad \bar{t}_r = \frac{K\int_0^t tC_{(t)}\,dt - \int_0^t t\dot{SR}_{(t)}\,dt}{K\int_0^t C_{(t)}\,dt - SR_{(t)}} - \frac{\int_0^t tC_{(t)}\,dt}{\int_0^t C_{(t)}\,dt}$$

It is obvious that this expression specifies the mean transit time of only those hippuran molecules which leave the kidney during the time interval 0 to t. The equation for calculating the transit time of all the hippuran molecules which traverse the kidney is obtained by assuming that the renogram study is prolonged until $SR_{(t)}$ becomes quantitatively insignificant. Calling this time $t = \infty$ and letting $\lim_{t \to \infty} SR_{(t)} = 0$:

$$5.\quad \bar{t}_r = -\int_0^\infty t\dot{SR}_{(t)}\,dt \Big/ K\int_0^\infty C_{(t)}\,dt$$

Integrating by parts, this can be further simplified:

$$6.\quad \int_0^\infty t\dot{SR}_{(t)}\,dt = tSR_{(t)}\Big/_0^\infty - \int_0^\infty SR_{(t)}\,dt$$

It is apparent that $\lim_{t \to 0} tSR_{(t)} = 0$.

It is known that indicator-dilution curves such as $U_{(t)}$ become exponential as they decay (1, 3). From equation 4, the decline of $SR_{(t)}$ depends upon $U_{(t)}$. Therefore, $\lim_{t \to \infty} t\ SR_{(t)} = \lim_{t \to \infty} te^{-\lambda t} = 0$ (where λ is an arbitrary time constant).

Employing this result and equation 6, one then obtains the equation for the mean transit time of all the hippuran molecules which traverse the kidney:

$$7.\quad \bar{t}_r = \frac{\int_0^\infty SR_{(t)}\,dt}{K\int_0^\infty C_{(t)}\,dt} = \frac{\text{area}}{\text{dose}}$$

DISCUSSION

The preceding derivation indicates that a serious limitation is inherent in the measurement of renal transit time. Since equation 4 is based upon the single assumption that all the hippuran in the effluent urine has traversed some portion of the kidney, it is possible, by employing this equation, to calculate values of mean transit time with an accuracy that is limited solely by errors in the measurement of K, $SR_{(t)}$ and $C_{(t)}$. However, values of transit time calculated in this manner reflect the traversal rates of only those hippuran molecules that leave the kidney during the time of the renogram study. As a result, such values represent an underestimate of $\bar{t}_r$ which is, by definition, the mean transit time of all the hippuran molecules that traverse the kidney.

This systematic error in the measurement of $\bar{t}_r$ may be lessened by merely increasing the time of the renogram study. Whether sufficient accuracy may be achieved in this manner without unduly prolonging the renogram can only be ascertained by experiment and by clinical experience.

Another approach to this problem derives from the previously noted fact that $SR_{(t)}$ becomes exponential in the latter phases of its decline. Therefore, a semilogarithmic plot of $SR_{(t)}$ will ultimately become linear, whereupon the graph can be extrapolated to a value $SR_{(t)} = 0$, and $\bar{t}_r$ can be calculated from equation 7. Of necessity, this approximation excludes those hippuran molecules with transit times greater than the time at which $SR_{(t)}$ is extrapolated to zero. Therefore, the accuracy with which $\bar{t}_r$ is estimated can only be determined experimentally.

In addition to the problems inherent in the measurement of $\bar{t}_r$, the preceding mathematical analysis provides insight into the mechanism by which certain alterations of renogram contour are produced.

The reasoning process employed in the derivation of equation 4 relies upon

the fact that the fraction $h_{(ti)} = \frac{U_{(ti)}}{\int_0^\infty U_{(t)}\,dt}$ specifies, in effect, the frequency with which the particular time interval ti is required for hippuran to enter and traverse the kidney. A consequence of this fact is that $U_{(t)}$ has the contour of a frequency distribution function. This may be shown by expanding and rearranging the definition of $h_{(t)}$:

8. $U_{(t)} = \frac{Mh_{(t)}}{V}$; where $\frac{M}{V}$ is the total amount of hippuran which leaves the kidney divided by urine flow rate.

Thus, $U_{(t)}$ derives its contour from the frequency distribution function $h_{(t)}$ and its magnitude from a constant M/V.

Because of this, $U_{(t)}$ shares a well known property of distribution functions: as $\bar{t}_r$ increases, such a curve rises more slowly and attains a peak which becomes progressively decreased in amplitude and delayed in onset (1—3).

The effect of these alterations in $U_{(t)}$ upon the renogram curve derives from equation 4. $SR_{(t)}$ attains its peak at a time when:

9. $\dot{S}R_{(t)} = 0$; $\therefore KC_{(t)} = VU_{(t)}$

By definition, this time is called Tmax (4, 5). The renogram declines at a rate given by:

10. $-\dot{S}R_{(t)} = VU_{(t)} - KC_{(t)}$

Therefore, a more gradual rise of $U_{(t)}$ will prolong Tmax, a decreased amplitude of $U_{(t)}$ will proportionally decrease the descent rate of the renogram curve, and a delayed peak of $U_{(t)}$ will correspondingly delay the attainment of the maximal renogram descent rate. As a result, the renogram curve associated with prolonged transit time will be characterized by a prolonged Tmax, a slow decline, and, consequently, an increased area as predicted by equation 7.

This is a well known pattern which has been described both in obstructive renal disease (5) and in the presence of decreased urine flow rate (6). The occurrence of this single pattern in these two dissimilar states has not been explained by previous studies. However, an immediate explanation arises from the properties of $\bar{t}_r$.

It can be shown that if V is the volume and Q the flow rate of a fluid-filled system, the transit time, $\bar{t}$, of an indicator dissolved in the fluid is given by:

11. $\bar{t} = \frac{V}{Q}$. (1-4).

If flow varies as a continuous function of volume, one may write the transit time contribution, $d\bar{t}$, of a small volume element, dV, with a flow, $Q_{(v)}$ as:

12. $d\bar{t} = \frac{dV}{Q_{(v)}}$

Then, integrating and employing the mean value theorem of the integral calculus:

13. $\bar{t}_r = \int_0^V \frac{dV}{Q_{(t)}} = \frac{V}{\bar{Q}}$, where $\bar{Q}^{-1}$ is the mean value of the integral; *i.e.*, the average flow rate through the volume V.

Undoubtedly, many factors affect renal transit time. However, the fact that all hippuran leaving the kidney must traverse some volume of urine assures that $\bar{t}_r$ depends to some extent upon the volume to average flow ratio of urine within the kidney and renal pelvis.

Therefore, obstructive disease with increase in urine volume or states characterized by a decreased urine flow rate would both tend to produce the renogram pattern of prolonged transit time. The same pattern would also be produced by mechanical interference to urine drainage caused by irregular ureteral peristalsis (6), as well as by polycystic renal disease and hemodynamically significant renal artery stenosis (5). Moreover, since a significant portion of renal transit time appears experimentally to be secondary to actual traversal of parenchymal structures (7), infiltrative or inflammatory diseases of the kidney may also prolong $\bar{t}_r$.

The preceding relationship between renal transit time and the dynamics of urine flow applies only to mean transit time. Mean transit time has, on occasion, been confused with other parameters, such as median transit time or the first appearance time of the indicator in the effluent fluid (3). Such confusion is particularly likely to arise in discussion of renal transit time, because the first appearance time of hippuran in the urine has been employed in a previous study (8). The relative importance of mean transit time and first appearance time can only be established by experiment. However, unlike first appearance time, mean transit time has well established theoretical significance and is universally employed in indicator-dilution calculations (3).

SUMMARY

The mean renal transit time of hippuran can be calculated from the ^{131}I hippuran renogram, and is the common denominator which explains the occurrence of a single renogram contour in a variety of disease states. Furthermore, several well known properties of mean transit time indicate that this parameter may be useful in characterizing the effects of disease upon both the permeability of renal parenchyma and the dynamics of urine flow. Finally, mean transit time must be distinguished from the first appearance time of hippuran in the urine.

APPENDIX

The renogram transit time equations may be derived using integral equations. While no increase of rigor results, this form of derivation simplifies comparison between the renogram and indicator-dilution curves.

The outflow rate of hippuran, $VU_{(t)}$, can be written as the convolution of $h_{(t)}$ on $KC_{(t)}$(ref. 3):

1) $VU_{(ti)} = K\int_0^{ti} h_{(t)}C_{(ti-t)}dt$

thus:

$$2)\quad SR_{(t_i)} = K\int_0^{t_i} C_{(t)}dt - K\int_0^{t_i}\int_0^{t_i} h_{(t)}C_{(t_i-t)}dt$$

By definition, $\int_0^{t_i} C_{(t)}dt = \int_0^{t_i} C_{(t_i-t)}dt$. Therefore, rewriting the double integral and letting $\int_0^{t_i} h_{(t)}dt = H_{(t_i)}$:

$$3)\quad SR_{(t_i)} = K\ (1\text{-}H_{(t_i)})\int_0^{t_i} C_{(t)}dt$$

Integrating, and letting $SR_\infty = 0$:

$$4)\quad \int_0^\infty SR_{(t)}dt = K\int_0^\infty C_{(t)}dt \bullet \int_0^\infty (1\text{-}H_{(t)})dt = Dose\int_0^\infty (1\text{-}H_{(t)})dt$$

Integrating by parts:

$$5)\quad \int_0^\infty (1\text{-}H_{(t)})dt = (1\text{-}H_{(t)})t\ \Big|_0^\infty + \int_0^\infty th_{(t)}dt = \int_0^\infty th_{(t)}dt = \bar{t}.$$

Using this result and equation 4, the fundamental renogram transit time equation (equation 7) is obtained:

$$6)\quad \bar{t} = \frac{\int_0^\infty SR_{(t)}dt}{K\int_0^\infty C_{(t)}dt} = \frac{Area}{Dose}$$

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