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Creatinine distribution dynamics in the dog

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Abstract

The dynamics of the distribution of creatinine infused into 5 anesthetized, heparinized dogs in moderate diuresis were analyzed in terms of the simplest serial compartmental model (4 chambers with passive exchanges) which would describe the data accurately. During 3-hr experiments, the intravenous infusion rate was continuously varied over a wide range, resulting in large variations in arterial plasma concentration (measured continuously by AutoAnalyzer), thus providing an exacting test of the model. Input into first chamber of the model was the experimental rate of creatinine infusion. Output, also from this chamber, was determined by matching the integral of the product of clearance times the concentration of the first chamber (delayed 2 min) to the observed creatinine output measured over 10-min periods. The concentration in this chamber, after passing through a dispersive delay line analogous to the AutoAnalyzer, was matched to the observed AutoAnalyzer record by varying the volumes of the chambers and the passive exchange rates. This simple model provides an accurate description of the observed creatinine concentration and output and therefore can be used either as a building block in more extensive descriptive systems or as a basis for summarizing and comparing data obtained under varied physiological or pathological conditions.

Keywords

compartmental analysis; renal clearance; blood-tissue exchange; simulation; mathematical model; indicator dilution; transient analysis

Dominquez et al. (4,5) and Sapirstein et al. (11) analyzed the dynamics of creatinine distribution in the dog in terms of a model consisting of two mixing chambers. One chamber was considered to be the analog to the plasma volume into which intravenous infusions entered and from which urinary excretion occurred. The second chamber was considered as the analog to an extravascular region exchanging with the first by a single rate constant. Their analyses were limited to curves of disappearance of creatinine from the plasma following a bolus injection but the model failed to fit the initial portion of the disappearance curves. Robertson's four-compartment catenary model (10) was a great improvement. It correctly described the blood creatinine concentration during and immediately following a 30-min infusion. Unfortunately the details, the chamber volumes and rate constants, were not given.

These models were designed to describe, at least roughly, the available experimental data. Similarly, the goal of the present analysis is to provide the simplest model for creatinine distribution that describes the data. For this analysis, experimental data with high-frequency content were chosen from experiments previously described (8) in which continuous intravenous infusions were made at known but widely and rapidly varied rates. Arterial

plasma concentration was measured continuously with an AutoAnalyzer system having a rapid dynamic response. Comparisons between such experimental data and solutions from a model permit exacting tests of any model. Any model providing solutions fitting such data can be said to describe the real system quite well. Precise and concise descriptions obtained via the model will then be useful either as components of larger systems or possibly as a basis for comparing normal and pathological responses to the infusion of creatinine and presumably of other substances which are distributed passively in body spaces.

Methods

The methods used for acquiring the data for the present analysis have been described previously in detail (8). In brief, the experimental set up was a closed-loop system consisting of 1) a variable-rate pump for the infusion of a solution (creatinine 5 g/liter, mannitol 117 g/liter) into one femoral vein of an anesthetized dog, 2) the dog, 3) a detector system consisting of a low-volume high-flow AutoAnalyzer system for measuring plasma creatinine concentration in blood samples from a femoral arteriovenous fistula (to reduce circulatory delays), and 4) a pump rate controller which was essentially a proportional controller in a narrow region around a set point usually near 15 mg/liter arterial plasma creatinine concentration. Although the system was devised in order to achieve near-constant plasma creatinine levels in spite of continuous clearance of creatinine from the blood into urine and body tissues, the early experiments showed highly oscillatory plasma levels and are therefore ideal for the present analysis. The analysis concerns the relationship between the input (femoral vein infusion site) and outputs (arterial plasma level and urinary excretion). Characterization of this relationship for these experiments in terms of a model composed of a family of differential equations then provides a dynamic description of the physiological system in which creatinine is distributed in the dog.

The experimental data were digitized and stored on IBM cards for the simulation analysis. Data points representing average values over each 20-sec period were stored for 1) the observed plasma creatinine concentration from the calibrated AutoAnalyzer record, $C(t)$, milligrams per liter; and 2) the pump infusion rate, dq_{in}/dt , milligrams per minute. For each 10-min period the average urinary creatinine excretion rate, dq_{out}/dt , milligrams per minute, was recorded. The total amount of creatinine infused, $q_{in}(t)$, milligrams, in the experiments was determined independently of the infusion rate at longer intervals and used as a check on dq_{in}/dt by comparing the integral of the pump infusion rate with the observed total amount of solution used.

Model

Several compartmental models were tested and some were found to provide appropriate descriptions of one experiment. The simplest one, which was used for the analysis of all of the experiments, is diagrammed in Fig. 1. A compartment is defined as a volume whose contents are continuously instantaneously mixed so that its concentration is uniform throughout. The infusion, at a rate dq_{in}/dt , enters the first compartment; creatinine leaves this compartment by clearance into the urine at a rate K_u , milliliters per min, times the concentration $C_1(t)$, milligrams per liter, and by passive exchange into a second compartment. These clearances or exchange rates, K , are independent of concentration (the system is linear) and the compartment volumes are assumed not to change during the experiment (the system is stationary). The system of equations is:

$$V_1 \frac{dC_1}{dt} = \frac{dq_{in}}{dt} + K_1(C_2 - C_1) - K_u C_1 \quad (1)$$

$$V_2 \frac{dC_2}{dt} = K_1(C_1 - C_2) + K_2(C_3 - C_2) \quad (2)$$

$$V_3 \frac{dC_3}{dt} = K_2(C_2 - C_3) + K_3(C_4 - C_3) \quad (3)$$

$$V_4 \frac{dC_4}{dt} = K_3(C_3 - C_4) \quad (4)$$

where V_i is the volume, milliliters, and C_i or $C_i(t)$ is the concentration of the i th instantaneously mixed chamber, the K_i are the exchange rates, milliliters per minute, between the i th and the $(i + 1)$ th compartments. The rate of loss from the system is $K_u C_1$ milligrams per minute or dq_{out}/dt . The quantities in each compartment, q_i , are merely the products, $C_i V_i$; their sum, $q_1 + q_2 + q_3 + q_4$ is the difference between the total input, $q_{in}(t)$, and the total amount excreted, $q_{out}(t)$, and is the total amount $q_T(t)$ accumulated in the animal. Since q_{in} and q_{out} were measured in the experiment, they were used for additional checks on the adequacy of the solutions.

Simulation method

A combination of analog and digital computer techniques were used to fit the model to the data and to minimize the time required to accomplish this task. The digitized values of $C(t)$ and dq_{in}/dt were transferred from the digital computer (model 3200, Control Data Corporation, Minneapolis, Minn.) via a D/A converter and stored, with an accompanying triggering signal on separate channels of an analog FM magnetic tape (model FR1200, Ampex Corp., Redwood City, Calif.) using a time compression of 1,200 to 1.

The four first-order equations, 1–4, were set up on a 100-v analog computer using integrators with positive or negative inputs and three-decade coefficient input potentiometers (SK5-U, G. A. Philbrick Researches Inc., Dedham, Mass.) as diagrammed in Fig. 1, lower panel. The initial conditions on all four integrators, $C_i(0)$, were set to the endogenous plasma creatinine concentration observed prior to starting the infusion. The analog computer system error was determined to be less than 1 %.

Although none of the C_i had been directly measured in the experiments, it seemed reasonable to assume that the blood was sampled from the most accessible compartment, V_1 . Therefore, the concentration recorded via the Auto-Analyzer was simply the convolution of $C_1(t)$ with the impulse response of the whole AutoAnalyzer system, $h_A(t)$; i.e., the simulated AutoAnalyzer output, $C_{sim}(t)$, to be compared with the observed recording, $C(t)$, is:

$$C_{sim}(t) = C_1(t) * h_A(t) = \int_0^t C_1(\tau) h_A(t - \tau) d\tau \quad (5)$$

The analog system used to describe the AutoAnalyzer system is shown in Fig. 2. It consists of a Paynter filter (7) set up in the analog computer, and a delay, $\exp(-T_p)$, set up as a digital delay line (lower panel, Fig. 2). (The times are shown as 1/1,200 of the experimental times, which was done to speed up the solutions.) Sampling system delay was digitally simulated by sampling the output analog signal at constant time intervals through an analog-

to-digital converter, storing each incoming value as the first point of an N -point array after shifting the stored points one position through the array and putting out via a digital-to-analog converter the value in the N th point of the stored array. (The initial values stored were all $C_1(0)$.) The delay was therefore N times the interval between conversions, and the output was $C_{\text{sim}}(t)$ as in Fig. 2. The adequacy of the AutoAnalyzer analog is shown in Fig. 3. The AutoAnalyzer analog was unchanged during the iterative runs made to fit the model to the data of the animal experiments.

The adjustments of the parameters of the model were made manually on the three-decade potentiometers governing the coefficients of equations 1–4. Repeated solutions were made using the timing signal on the magnetic tape loop to trigger the analog computer from initial condition to integrate mode. The dq_{in}/dt signal from the tape was the input function to the model, and the visual comparison was made between $C_{\text{sim}}(t)$ and the playback of $C(t)$ from the tape loop. Up to eight signals could be displayed simultaneously on the oscilloscope against an electronic grid (Philbrick Researches model 5934) so that there were no errors due to parallax. The parameters of the first two compartments, K_1 , V_1 , and V_2 and to a lesser extent, K_2 , were determined primarily by the initial minutes of the experimental data, so that the quickest approach was to use rather approximate values for K_3 , V_3 , and V_4 , then to adjust K_1 , K_2 , V_1 , and V_2 to fit the early data approximately. K_u could be set fairly accurately by estimating the renal clearance from the experimental data. Then K_3 , V_3 , V_4 , and K_2 were adjusted so that $C_{\text{sim}}(t)$ matched $C(t)$ during the later part of the experiment. When an approximate fit was obtained for the whole of the curve then $q_{\text{out}}(t)$ or $\int_0^t K_u C_1(\tau) d\tau$ was compared with the measured total accumulated urinary creatinine excretion and K_u adjusted if necessary. The procedure was then repeated until good fits were obtained between $C_{\text{sim}}(t)$ and $C(t)$ and between $q_{\text{out}}(t)$ and the experimental excretory output. Since, at 1,200 times real time, the solutions took 5–10 sec each, it was possible, after some practice, to produce a good fit in less than 1 hr of computation.

Results

Results in three of the five experiments are shown in Fig. 4, A–C. In all experiments the “simulated” $C_{\text{sim}}(t)$ fitted the “observed” $C(t)$ very closely, as can be seen in the upper panels. The exchange rates and compartment volumes are given in the Table. In the experiment shown in Fig. 4A, relatively good control had been achieved with the servo controller so that the ability of the model to fit rapid transients was tested only by the first 30 min of data. In the other four experiments, for example as seen in Fig. 4B and C, the oscillations persisted, so that the data from the later parts of the experiment were being used to find K_3 , V_3 , and V_4 but also to continue to test the accuracy of K_1 , K_2 , V_1 , and V_2 throughout the experiment. Any oscillations in $C_1(t)$ were always quite obvious in $C_2(t)$ but much less so in $C_3(t)$ and scarcely at all in $C_4(t)$. This is to be expected since the time constants of exchange of $C_4(t)$ with $C_3(t)$, given by V_4/K_3 , averaged 28.8 min, the longest of any in the system (Table 1). The oscillations in $C_1(t)$ appeared virtually undiminished in $C_{\text{sim}}(t)$ illustrating that the frequencies contained in $C_1(t)$ were low enough that they were not significantly attenuated by the sampling system analog, but the signal was delayed.

Discussion

The close approximation of the observed data by the results computed by the model attests to the stability of the animal over the period of experimentation and to the applicability of the model to these experiments. If the animals were physiologically unstable, then the apparent exchange rates or volumes would have been changing during the experiment and likewise some K s and V s would have to be changed during the simulation in order to achieve

a close fit both at the beginning and toward the end of the experiment. Figure 4,B and C, are therefore particularly helpful because of the high-frequency content of $C(t)$ throughout the period of analysis. If blood loss due to sampling at 2 ml/min were to have caused a reduction in plasma volume, then V_1 (and probably V_2) would have to be decreased continuously; if there were increasing vasoconstriction and decreasing peripheral blood flow, then also K_1 and K_2 and possibly K_3 would have to be decreased with time. Since these events did not occur during the first 60–90 min in spite of the anesthetic, the heparinization, and the blood loss, it appears that the volume replacement provided by the creatinine-mannitol infusion (averaging about 1.5–3 ml/min) prevented significant fluid shifts in spite of the large urinary volume loss. Actually the average net fluid deficit at the end of the experiment was 5 ml/kg, which was neglected in the analysis.

The validity of the approximation that all the initial compartmental concentrations, $C_i(0)$, were equal to the endogenous plasma creatinine concentration, $[Cr]_p$, has not been critically tested by this analysis. The presence of significant barriers to exchange is indicated by finding that extravascular concentrations in organs where creatinine is produced are higher than plasma concentrations, and that concentrations might be less in tissues into which creatinine can only permeate slowly. Baker and Miller (1) observed rat muscle creatinine to be about three times $[Cr]_p$ while in parenchymal organs it was only 1/10 to 1/2 $[Cr]_p$. The level in human amniotic fluid was three times $[Cr]_p$ (9), again indicating the presence of significant barriers to exchange. In rabbit brain and cerebrospinal fluid Bradbury and Davson (2) found the level to be 1/3 $[Cr]_p$. Therefore, since a third or more of the body is muscle, it seemed reasonable to use an average $C_i(0)$ equal to $[Cr]_p$. If there were a substantial error in this average or if the four $C_i(0)$ differed greatly, it would not be shown by a poor fit in the simulation but would give different values for the V_i , particularly V_3 and V_4 , and a different total volume of distribution, V_T . Since the observed average V_T of 430 ml/kg body wt is somewhat more than the expected extracellular fluid space but less than total body water, it seems likely that our assumption was reasonable.

The use of a single concentration-independent exchange rate, K_i , for both directions between adjacent compartments implies that the exchange process is purely passive. This is equivalent to saying that the process is simple diffusion, an assumption which is supported by the observations in erythrocytes (6,12), and cerebrospinal fluid (2) and on the isolated chorionic-amniotic membrane (9). (The high Q_{10} s obtained by Gary-Bobo and Lindenberg (6) may, if verified imply the existence of a mechanism for facilitated diffusion.)

The circulatory transport delays have been in part accounted for by the $C_1:C_2$ exchange, but it is obvious that the compartments V_1 and V_2 provide a poor analog to the circulation, even though the sum of the volumes V_1 and V_2 is approximately the blood volume. The model suffices to describe even the rapid transients in $C(t)$ presumably because the choice of femoral artery sampling site permitted significant dispersion between infusion site and sampling site, and the rate of change of infusion rate was usually not very rapid. The important point is that even this analog is quite good enough to describe events that are of higher frequency content than are usually encountered in clinical and experimental situations, and therefore should be descriptive of a wide variety of situations in which substrates or drugs are infused intravenously.

In fitting models to data one must consider both the “uniqueness” of the set of parameters used to fit a given model to the data, and the “uniqueness” of the model itself. In our analysis it became clear that only small variability in the individual parameters could be allowed while achieving a visually tested “good fit,” so that the parameter set for this model can be considered unique. To fit the data required a minimum of four components. However, the model used is certainly not unique, and quite a variety of four-compartmental or higher

order models might provide fits that are just as good. Therefore this choice of model has simplicity as its greatest virtue. A companion virtue is the “uniqueness” of the parameter set for this model: higher order models, even though they may be more realistic, lose this virtue. With very complex models, a wide variety of internally contradictory parameter sets will provide equally good fits, unless more data on individual components of the real system are also obtained in order to limit the choices of parameters. Even in our simple model the choice of parameters has been limited: V_3 was chosen to always be less than V_4 , the value for K_u has been fixed by the experimental observations of the renal excretion, and the sampling system was described separately, so that only the three exchange rates and the four volumes were adjustable. Because the experimental data on one hand contained high-frequency information in $C(t)$ and on the other did approach steady state, which limits the range of possible values for V_T since dq_{in}/dt and dq_{out}/dt were known, therefore the number of degrees of freedom in fitting model to data was actually quite small.

Interpretation of parameters

Because the model is primarily intended to be the simplest descriptive one, specification of the physiological meanings of the volumes or of the exchange rates is difficult. Nevertheless some broad analogies may be sufficiently meaningful that they should be suggested.

The observation that the sum $V_1 + V_2$ is approximately equal to the blood volume appears to be more a coincidence than anything else: exchange between erythrocytes and plasma is so slow (we calculate a half-time of 2–3 hr from the data of Van Slyke et al. (12)) that the erythrocytes must be a part of the more slowly exchanging “compartments” V_3 or V_4 . Therefore, it appears that the closest analogy that can be considered is that V_1 is roughly equivalent to the most rapidly mixed fraction of the plasma volume (central circulation plus peripheral beds through which recirculation is very rapid, such as coronary, renal, cerebral) and that V_2 is a combination of the plasma in regions where recirculation is slower and of the more accessible parts of extravascular space.

A more reasonable analogy is between K_2 or K_3 and an average capillary permeability-surface area product, PS , for the whole body. Assuming that there is no restricted diffusion for hydrophilic solutes across the capillary membrane (3,13), then a calculation of this average PS can be made from data obtained on a variety of organs with tracers other than creatinine by considering the permeability to be inversely proportional to the square root of the molecular weight. Thus for the heart, PS for sucrose was about $0.3 \text{ ml g}^{-1} \text{ min}^{-1}$ (13) and therefore for creatinine might be $\sqrt{360/113}$ times this, or about $0.5 \text{ ml g}^{-1} \text{ min}^{-1}$. But brain capillaries are almost impermeable to hydrophilic solutes like creatinine, and other capillary beds such as muscle have a much smaller capillary surface area, S , square centimeters per gram, so that an average PS is likely to be as low as 1/20 to 1/10 of that for the heart or $25\text{--}50 \text{ ml kg}^{-1} \text{ min}^{-1}$. This is not much larger than K_2 , $20 \text{ ml kg}^{-1} \text{ min}^{-1}$.

Another way of looking at it may be to consider the rate constants K_2/V_3 or K_3/V_4 or perhaps the approximate average $(K_2 + K_3)/(V_3 + V_4)$, which is not mathematically exactly appropriate but is not too unreasonable in view of the variation in circulation times in different organs. Using PS of $40 \text{ ml kg}^{-1} \text{ min}^{-1}$ divided by an extravascular volume of distribution of creatinine of $320 \text{ ml kg}^{-1} \text{ min}^{-1}$ we obtain a rate constant for the whole body of $40/320$ or 0.12 min^{-1} which is not too different from the 0.08 min^{-1} for $(K_2 + K_3)/(V_3 + V_4)$ provided by our analysis. While such numbers as these may become useful through empirical association and repeated usage, they cannot be considered as providing accurate data on the permeability-surface area products for capillary beds throughout the body.

The simplicity of this descriptive model is its fundamental virtue; this permits it to be used to provide good descriptions of tracer movements or of drugs in the body provided the exchange rates and volumes of distribution for the substance can be obtained. This model is probably wholly appropriate for any substance that is passively distributed and excreted via only the kidney. It may also be appropriate if the excretion occurs through lung or liver but is not appropriate if the substance is only metabolized, for then K_u should be from V_4 or V_3 . Of course this type of model can be very easily modified to account for metabolism of the substance in the tissue or for degradation in the plasma, if these happen to be first order processes whose rate constant is independent of concentration.

Perhaps the most important conclusion from this study is that four compartments are the minimum for a reasonably accurate description, and that the use of only two or three in analyzing disappearance curves after intravenous injection is significantly less accurate and invites misinterpretation of the data.

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FIG. 1.

Four-compartment catenary model for the distribution of creatinine in the dog. *Upper panel:* passive exchanges occur between compartments; input to and output from system occur only in first compartment. *Lower panel:* analog computer configuration for model.

FIG. 2.

Computer simulation of AutoAnalyzer sampling system. Time scale is 1,200 times real time. *Top panel:* a voltage representing the plasma creatinine concentration is first dispersed by a Paynter filter and then delayed by a digital delay line, in order to yield a voltage which corresponds to the plasma creatinine concentration recorded by the AutoAnalyzer. *Bottom panel:* analog computer set up for the Paynter filter and block diagram of linkages to the digital delay line.

FIG. 3.

Response of real and simulated Auto Analyzer systems to a step input. Output of Paynter filter, labeled 4th order analog, was delayed digitally, resulting in $C_{\text{sim}}(t)$, simulated output of Auto-Analyzer recorder for comparison with an actual record, labeled "real," obtained in response to a step change in creatinine concentration at arterial sampling site.

FIG. 4.

A–C: computer simulation of creatinine distribution in 3 experiments. *Top panels:* close agreement between observed $C(t)$ and output of model, “simulated” $C_{\text{sim}}(t)$ was obtained in all analyses, using infusion rate dq_{in}/dt as input to the first compartment. *Middle panels:* creatinine concentration in each of the four compartments is shown. *Lower panels:* computed amounts of creatinine infused, excreted, and accumulated in model are shown. Simulated amount of creatinine “excreted” was matched to the observed excretion (not shown). In B note that result of small error in digitizing infusion rate (showing positive values instead of zero from the 34th to 36th min) is a very obvious deviation of $C_{\text{sim}}(t)$

(above) from $C(t)$ (below) from 35th to 40th min. This illustrates the sensitivity of computed concentrations to input experimental data.

TABLE 1

Values for parameters of analog model

Exp No.	Body Wt, kg	Volumes, ml kg ⁻¹ body wt					Exchange Rates, ml min ⁻¹ kg ⁻¹ body wt			
		V ₁	V ₂	V ₃	V ₄	V _T	K ₀	K ₁	K ₂	K ₃
3064	21.0	19	71	143	184	417	3.35	57.1	14.3	5.7
1674	19.1	21	78	125	193	417	2.60	15.6	9.4	9.4
1384	25.0	24	96	96	228	444	3.11	36.0	19.2	7.2
1484	24.0	13	50	101	216	380	3.15	126.	25.2	7.6
2084	19.7	25	61	122	285	493	2.53	122.	30.5	9.1
Mean ± SD	21.8 ± 2.3	20.4 ± 4.5	71.4 ± 16.	117 ± 17	221 ± 35	430 ± 37	2.95 ± 0.36	71.3 ± 50.3	19.7 ± 8.4	7.8 ± 1.5