APPLICATIONS OF HIPPURATE KINETIC MODELS

The authors (*1*) of "Clinical applications of a kinetic model of hippurate distribution and renal clearance" state that the urine OIH concentration is derived from the equation OIH $Conc_{I.}$/OIH $Conc_{R}$ $= \tau_{I.}/\tau_{R}$. This relationship can only hold true when $ERPF_{I.}=ERPF_{R}$ for ERPF=UV/P and $\tau \propto 1/V$ $\tau_{I.}(ERPF_{I.})/\tau_{R}(ERPF_{R}) = [(1/V_{I.})(U_{I.}V_{I.}/P)]/[(1/V_{R})(U_{R}V_{R}/P)]\tau_{I.}(ERPF_{I.})\tau_{R}(ERPF_{R}) = U_{I.}/U_{R}$ = OIH $Conc_{I.}$/OIH $Conc_{R}$.

In addition, as a result of this relationship between OIH concentration, ERPF, and τ it is obvious that if they were able to show good correlation between urine concentration ratios obtained by RP/ED and constant infusion split-function tests as demonstrated in their Fig. 4, this was because in the seven normal patients the ratio of $ERPF_{I.}/ERPF_{R} = 1$ and in the case of the two main renal artery stenosis patients because a fortuitous coincidence resulted in an incorrect $\tau_{I.}/\tau_{R}$ applied to a wrong formula giving a correct OIH $Conc_{I.}$/OIH $Conc_{R}$.

In main renal artery stenosis (*2*) in the affected kidney, the ERPF is reduced by at least 40% and the minute volume is less than half and the PAH concentration more than twice that of the other kidney, e.g., $(ERPF_{I.}/ERPF_{R})(\tau_{I.}/\tau_{R})$ = OIH $Conc_{I.}$/OIH $Conc_{R}$, $(0.6/1)(\tau_{I.}/\tau_{R}) = 2$, $\tau_{I.}/\tau_{R} = 3.33$, and $3.33 \neq 2$.

The ratio of "total renogram" (*3*) transit times does not give good ratios of minute volumes. By flagging an area of interest, "cortical transit time" ratios will give good approximations to ratios of minute volumes. The authors TTT includes time spent in calyces and renal pelvis which diminishes the $\tau_{I.}/\tau_{R}$. If a correlation of RP/ED and constant infusion split functions were carried out on patients with unilateral disease, the apparent correlation would disappear.

The OIH volume of distribution is 28% of body weight and it takes from 20–40 min to reach this distribution depending on the cardiovascular status. The late λ of the blood disappearance curve is approx 0.04/min. Good OIH clearances can be approximated closely by using this late slope times a volume of distribution estimated at 28% of ideal body weight, or better still by analysis of the double exponential curve. Various workers, in the interest of economy of time, have used the early slope times an empirical volume of distribution equal to the plasma volume. This gives a good approximation in those with both normal renal function and normal cardiovascular status. The present authors have done likewise. In patients with poor cardiovascular status and poor renal function these calculated ERPFs can be out as much as 50%. This accounts for the impossible relationship in their patient shown in Fig. 6, who presumably had an ERPF of 500 ml/min and a creatinine clearance of only 26 ml/min. A creatinine clearance of 26 ml/min goes with an ERPF of about 130 ml/min and conversely an ERPF of 500 ml/min with a creatinine clearance of about 100 ml/min.

Until these errors in the RP/ED protocol are corrected, the values of the parameters produced are not valid.

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THE AUTHORS' REPLY

We will treat the objections to our paper in order. First let us consider the comments relative to the estimation of transport time. Dr. Reese's statements are L/R OIH Conc Ratio $= \tau_{I.}/\tau_{R}$ only if $ERPF_{R}'$ and $\tau \sim 1/V'$.

We believe the first statement to be incorrect and the second to be incomplete. In our work, estimates of urine flow rates are related to the mass of functioning tubular cells as well as to the transport time of hippuran in renal tubules. For this it is assumed that $V_{I.} = k\beta_{I.}/\tau_{I.}$ and $V_{R} = k\beta_{R}/\tau_{R}$ as given on p. 105 of our paper (*1*). Direct substitution into the steady-state clearance equation, ERPF = UV/P, gives $ERPF_{I.} = U_{I.}k\beta_{I.}/P\tau_{I.}$ and $ERPF_{R} = U_{R}k\beta_{R}/$

$P_{\tau R}$. Division of these two relations yields

$$ERPF_L/ERPF_R = (U_L/U_R)(\beta_L/\beta_R)(\tau_R/\tau_L)$$

This equation may be compared with the assumptions suggested by Dr. Reese when it is noted that $ERPF_T/ERPF_T = 1$, that

$$ERPF_L/ERPF_R = (U_L/U_R)(\beta_L\, ERPF_T/\beta_R\, ERPF_T)(\tau_R/\tau_L)$$

Since

$$\beta_L\, ERPF_T = ERPF_L$$

and

$$\beta_R\, ERPF_T = ERPF_R$$

$$1 = (U_L/U_R)(\tau_R/\tau_L)$$

or

$$U_L/U_R = \tau_L/\tau_R$$

as we stated. This result also precludes the necessity of concluding that $3.33 \neq 2$.

We regret that Dr. Reese was misled by our figures. There was, in fact, no data from normal subjects in Figs. 3, 4, or 5. Over half of the patients with both split-function test and the RP/ED had unilateral disease. In the majority of our data we do not have $ERPF_L/ERPF_R = 1$. As shown in Fig. 3, only a minority of the flow fractions were in the range of 0.4–0.6. This could happen only when most of the flow ratios were less than 0.67 or greater than 1.5. In addition, Fig. 4 shows that the relation $U_L/U_R = \tau_L/\tau_R$ holds even for flow fractions on the order of 0.2 or 0.8, or ERPF ratios of about 0.25 and 0.12, our lowest value.

The tubular transport times reported are *not* comparable to the conventional "transit" times of compartmental analysis [as a glance at Eqs. 6 or 7 on p. 112 of (*1*) will show], since they estimate transit within tubular lumina only. "Cortical transit times" referred to by Dr. Reese are believed to be a composite measurement of OIH flow through the proximal tubular cells and the transport of the OIH in the lumen of the nephrons (*3,4*). The intracellular flow and content of OIH has been considered in detail in the excellent work of Wedeen (*2*).

Dr. Reese has stated three possible ways to estimate the distribution volume (and hence ERPF) in his letter. Strictly speaking, we do not use any of these methods since our initial conditions begin with the assumptions that OIH has already entered all of the body compartments. Analysis is based upon the conditions assumed to exist after mixing is completed. The solutions of Eqs. 1, 5, and 11 along with the adjoined initial conditions, accounts for the initial distribution. Detailed analysis of the solution shows that the initial distribution of isotope must be included in the analysis.

Finally, Dr. Reese asserts that "A creatinine clearance of 26 ml/min 'goes' with an ERPF of about 130 ml/min." This relationship does not necessarily pertain in the sick kidney (*5*). One must be prepared to separate the effects of disease on a glomerulus with relatively little reserve capacity from that on tubular cells which have an extremely efficient mechanism for OIH transport (*6*) and a sizable (1000-fold) reserve capacity. It does not surprise us that a patient with arteriolarnephrosclerosis, glomerular nephritis, or acute transplant rejection will have a significant dissociation between ERPF and GFR. Indeed this is a partial justification for this work and PAH studies. Dr. Reese is quite right to observe this separation; indeed review of our paper will show dissociation is also present in other cases (Figs. 7–9). The creatinine clearance fraction was particularly useful in our initial evaluation of MC (Fig. 7) who suffered renal vein thrombosis.

We would like to thank Dr. Reese for his interest in our work.

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INTRAPERITONEAL ^{99m}Tc-SULFUR COLLOID DISTRIBUTION

The March issue of the *Journal of Nuclear Medicine* contains a concise communication by Drs. Tully, Goldberg, and Loken (*J. Nucl. Med.* 15: 190–191, 1974). We have used ^{99m}Tc-sulfur colloid prior to intraperitoneal installation of therapeutic radiocolloids for a number of years. A preliminary report of