J Clin Pharmacol. 1983; **23**:134-138.

Relationship Between Urine Flow Rate and Renal Clearance of Caffeine in Man

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Abstract: The renal clearance of caffeine was calculated following both oral and intravenous doses of 5 mg/kg caffeine in eight young and eight elderly, healthy human volunteers. There was a highly statistically significant positive correlation ($P < 0.001$) between the renal clearance of both unbound (CL_Ru) and total (CL_R) caffeine and the mean urine flow rate over the 24-hour period after dosing. Attempted correlations of CL_Ru and CL_R with hydrogen ion concentration or creatinine clearance and of creatinine clearance with urine flow rate all proved to be statistically nonsignificant. It is suggested that the control of salt and fluid intake and other factors affecting urine flow rate may be a worthwhile endeavor in pharmacokinetic studies of drugs with properties similar to caffeine.

To date, there have been very few studies in which possible relationships between urine flow rate and renal clearance have been investigated.[1,2] In a recent study[3] comparing the pharmacokinetics of caffeine in young and elderly men, it was observed that the renal clearance of caffeine varied in relation to the total volume of urine excreted over the 24-hour collection period immediately after dosing. A description of these findings follows.

Methods

Eight healthy, young males aged 18 to 24 years (mean 20.5 years) and eight healthy, elderly males aged 66 to 78 years (mean 70.5 years) each received both oral and intravenous doses (5 mg/kg) of caffeine about one week apart, in a randomized crossover design. The subjects were instructed to abstain from caffeine-containing foods and beverages, alcohol, and smoking for the three days before and during the study. They were fasted from at least 10 hours before until 2 hours after the oral dosing. Blood samples were obtained at frequent intervals over the 24 hours after dosing. A "blank" urine sample was voided at time zero, and total urine was collected into tightly sealed 3-liter glass containers over the 24-hour period after dosing. The volumes and pH values of the blank and 24-hour urines were recorded within 1 hour after collection, and two 20-ml aliquots were retained. One aliquot of urine was used immediately for the creatinine clearance determination; the other aliquot was stored at −20°C for subsequent caffeine assay in bulk.

Caffeine analyses in urine were performed as described previously.[4] Creatinine concentrations in urine were determined on a Beckman analyzer employing the Jaffé reaction,[5] while plasma creatinine was determined with a Sigma kit (Sigma Chemical Co., St. Louis, Mo. 63178) which also utilized a modified Jaffé reaction.

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TABLE I

Summary of Mean Urine Data for Caffeine in Young and Elderly Males*

Subject group	Route of administration	Renal clearance of unbound caffeine (ml/hr/1.73 m^2)	Amount of caffeine excreted		Volume of urine (ml/24 hr)	Urinary acidity	
			mg	% of dose		$[H^+] \times 10^7$ *M*	pH**
Elderly (*N* = 8)	oral	182.5 (176.4)*	6.21 (6.95)	1.89 (2.29)	1583 (776)	14.63 (17.24)	5.83
	iv	113.7 (58.0)	3.65 (1.06)	1.07 (0.36)	1289 (554)	14.93 (22.18)	5.83
Young (*N* = 8)	oral	108.7 (41.8)	4.17 (1.63)	1.13 (0.41)	1481 (622)	6.59 (8.39)	6.18
	iv	93.9 (25.9)	4.21 (2.35)	1.12 (0.46)	1309 (385)	1.80 (1.84)	6.75

* Values in parentheses represent one standard deviation.
** Average urine pH calculated from the average urine hydrogen ion concentration.

The renal clearance of total caffeine (CL_R) was calculated using a one-point determination as follows:

$$CL_R = \frac{A_e(0\text{-}24)}{AUC(0\text{-}24)} \quad (1)$$

where $A_e(0\text{-}24)$ is the amount of caffeine excreted in the 24 hours after dosing and AUC(0-24) is the area under the plasma concentration-versus-time curve from zero to 24 hours. The renal clearance of the unbound caffeine (CL_Ru) was calculated by dividing the renal clearance of total caffeine in each subject by the unbound fraction of caffeine measured in that subject, as determined in a separate experiment.[6]

Results

The mean urine data for the 16 subjects are summarized in Table I. The average amount of caffeine excreted unmetabolized, i.e., 1 to 2 per cent of the administered dose, is in good agreement with values reported by others.[7,8] In addition, the renal clearance values for caffeine are similar in magnitude to those reported elsewhere for elderly subjects.[9]

The renal clearance of unbound caffeine (CL_Ru) was highly correlated with the average urine flow rate over the 24-hour collection period, as shown in Fig. 1. The CL_Ru was used in this comparison because the renal clearance can be affected by plasma protein binding since only the unbound drug can be filtered at the glomerulus. Since the extraction ratio of caffeine across the kidney is very low, renal clearance would be expected to be sensitive to changes in plasma binding. In fact, a good linear correlation between CL_R (ml/hr/1.73 m^2) and urine flow rate (ml/hr/1.73 m^2) was also observed ($r = 0.7483$, $P < 0.001$). This finding was not surprising in view of the fact that the unbound fraction of caffeine was relatively constant both between subjects as well as within each subject over the range of caffeine concentrations encountered.[6] In other words, plots of CL_R or CL_Ru versus urine flow rate (f_u) will both exhibit about the same *r* values if f_u is relatively constant since $CL_Ru = CL_R/f_u$.

A number of correlations of the renal clearance of caffeine with some of the other experimental variables were attempted and found to be statistically nonsignificant in all cases tested. For example, CL_Ru and

CL_R (ml/hr/1.73m^2) did not correlate with either the hydrogen ion concentration of urine ($P = 0.2763$ and 0.2822, respectively) or with the creatinine clearance (ml/min/1.73 m^2), $P = 0.3702$ and 0.3377, respectively. Similarly, an attempt to correlate creatinine clearance (ml/min/1.73 m^2) with the urine flow rate (ml/min/1.73 m^2) produced a P value of 0.2007.

Discussion

Caffeine possesses diuretic properties[10] which would cause an increase in urine flow rate after its administration. However, this effect was probably very transient, and it is likely that the different urine volumes excreted by each subject represent variations in their fluid and salt intake and/or kidney function. Regardless of the cause, Fig. 1 illustrates clearly that the renal clearance of unbound caffeine is linearly related to urine flow rate.

An increase in renal clearance with increasing urine flow rate may occur via a number of mechanisms.[1,2,11] Caffeine is an un-ionized, nonpolar molecule which read-

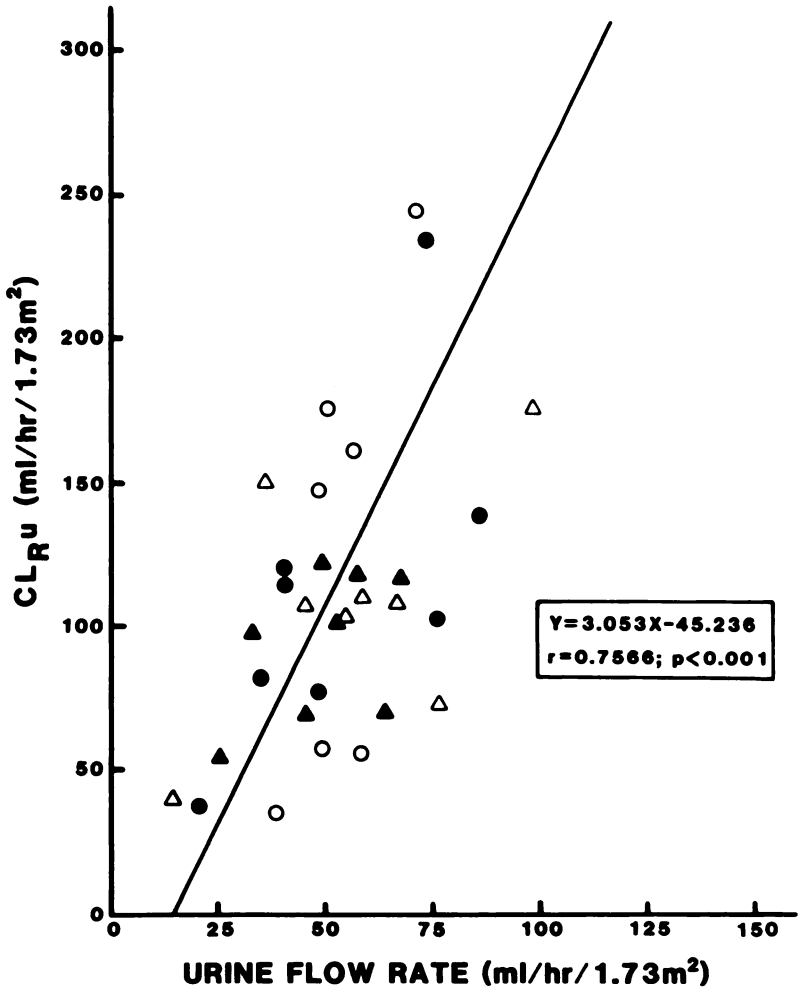

Fig. 1. Relationship between renal clearance of unbound caffeine and mean urine flow rate over 24 hours: (o) elderly, oral dose; (•) elderly, iv dose; (Δ) young, oral dose; (▲) young, iv dose.

ily penetrates biologic membranes. It is believed that about 99 per cent of the caffeine filtered at the glomerulus is reabsorbed, thereby producing a virtual equilibration of caffeine across the renal tubule after filtration.[12] The driving force for passive tubular reabsorption is largely produced by the reabsorption of water, which causes the drug present in tubular fluid to be concentrated about 100-fold or more relative to its unbound concentration in the plasma.[11] An increase in the urine flow rate, therefore, decreases the concentration gradient for caffeine between the fluid in the lumen of the renal tubule and the plasma. Curry[2] has postulated that reabsorption of a drug such as caffeine, which can freely transfer across the renal tubular epithelium and other membranes of the urinary system including the bladder, occurs distally from the most distal sites of water transfer. Thus, an increased urine flow rate will reduce the tubular reabsorption of the drug resulting in an increase in its renal clearance. A similar mechanism is also believed to be responsible for the previously observed relationships between urine flow rate and renal clearance of other drugs such as ethanol, phenytoin, sulfafurazole, glutethimide, and theophylline.[1,2,13] In contrast, the renal clearance of polar substances such as mannitol, gentamicin, penicillin, creatinine, and para-aminohippuric acid will not be influenced by urine flow since they are not reabsorbed.[1,11] These observations help to explain why no significant correlation between the urine flow rate and creatinine clearance was observed in this study. It appears that the related xanthine, dyphylline, is too polar to be substantially reabsorbed since its renal clearance is also uncorrelated with the urine flow rate.[14]

The urine pH is also known to be a significant factor in altering the renal clearance of a variety of compounds.[1,15] However, caffeine is such a weakly acidic substance,[16] pK_a = 13.85, that it is essentially totally nonionized at all pH values normally encountered in the urine (i.e., 4.5 to 7.5); and thus it should not be affected by variations in urine pH. The actual range of urine pH values observed here was 5.30 to 8.91. Thus, our inability to observe a significant correlation between the renal clearance of caffeine and the hydrogen ion concentration of the urine is consistent with these facts.

Because renal clearance would be expected to yield progressively smaller values as the urine flow rate approaches zero, the data in Figure 1 could also be fitted to a line which is constrained to pass through the origin (i.e., $y = mx$). When subjected to this treatment, the regression coefficient (m) was 2.366. Rowland and Tozer[1] showed that when reabsorption equilibrium of a drug between the tubular fluid and blood is established

$Cl_R = fu \cdot$ Urine Flow Rate, and it follows that

$Cl_R u =$ Urine Flow Rate.

This latter relationship implies that a plot such as Figure 1 should have a slope equal to unity. The deviation of our slope from unity is probably a reflection of the fact that the diuretic effect of caffeine caused the average renal clearance based on the one-point determination to be greater than the average that would be calculated using individual urine collections since the transient diuretic effect would have its greatest impact on clearance immediately after dosing, when most of the drug is being eliminated.

The renal clearance of unmetabolized caffeine is clearly a relatively minor component of its overall elimination in man. Thus, changes in urine flow rate are not likely to exert a major influence on its elimination kinetics. Nevertheless, it is apparent that urine flow rate variations should be considered in studies involving the calculation of pharmacokinetic parameters (e.g., absorption rate constants, urinary metabolite profiles) when urinary excretion data are used.[2] It is further suggested that salt and fluid intake be monitored carefully

in studies involving drugs with properties similar to those whose renal clearance has previously been shown to be related to urine flow rate. Such well-controlled studies will help further establish both the incidence and importance of this behavior.

Acknowledgments

Thanks are extended to Dr. Laurie F. Prescott and the technical staff of The Royal Infirmary, Edinburgh, who helped make portions of this study possible. The receipt of Fellowship No. 1 FO6 TW00491-01 by James Blanchard from the John E. Fogarty International Center and the National Institute on Aging is gratefully acknowledged.

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