The Relationship Between Urine and Plasma Concentrations of Carbamazepine: Implications for Therapeutic Drug Monitoring

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Received February 13,1990; accepted July 17, 1990

KEY WORDS: carbamazepine; therapeutic drug monitoring; plasma levels; urine levels.

INTRODUCTION

Therapeutic drug monitoring is a common practice for antiepileptic drugs. The interest in noninvasive methods to monitor anticonvulsant drug therapy (1,2) has centered on the use of saliva as a readily available biological fluid for the determination of drug concentration (3,4). However, for certain types of compounds, urine may prove a suitable alternative to saliva for noninvasive drug monitoring. This communication conveys the relationship between plasma (C_p) and urine (C_u) concentrations of carbamazepine, a drug for which therapeutic drug monitoring using urine concentrations may be useful.

The physicochemical characteristics of a drug that would make it a candidate for urine monitoring relate to the ability of the drug molecule to be reabsorbed across the renal tubular membrane. If the effective tubular membrane permeability of a compound is high enough to allow a rapid approach toward an equilibrium condition between the urine concentration and the free drug concentration in peritubular plasma, then the urine concentration should approximate the unbound concentration in plasma at any physiological urine flow rate. The diffusible species should be nonionized so that candidate compounds would not be significantly ionized at physiological pH. Carbamazepine is a highly lipophilic, neutral compound that fits these physicochemical criteria. For such compounds, renal clearance is essentially proportional to urine flow, and the C_u/C_p ratio is largely independent of urine flow.

MATERIALS AND METHODS

The subjects in this study were six healthy male volunteers who were participating in a study to determine the urine flow dependence of the renal clearance of carbamazepine and two of its metabolites. Each subject received 400 mg carbamazepine (2 × 200 mg Tegretol) as a single oral dose and blood and urine were sampled extensively for 216 hr postdose. Plasma and urine were frozen at −20°C until analysis. Unbound plasma concentrations were measured following ultrafiltration (Centrifree, Amicon, Danvers MA). Plasma, urine, and ultrafiltrate carbamazepine concentrations were determined by a microbore liquid chromatographic method that has previously been reported for plasma carbamazepine determination (5). The plasma carbamazepine concentrations used to determine the urine/plasma concentration ratios were calculated by interpolating the plasma concentration–time profile at the midpoint of the corresponding urine collection interval. Subject water intake was controlled during the first 2 days of the 9-day study period to achieve a wide range of urine flow rates.

Preliminary data from nine epileptic patients receiving carbamazepine alone or in combination with other antiepileptic agents are also reported. These patients are part of an ongoing study in which epileptic patients who are visiting the clinic for routine plasma carbamazepine therapeutic drug monitoring are asked to supply a spot urine collection for comparison. The analytical methods for determination of patient plasma, urine, and unbound plasma carbamazepine concentrations are the same as reported above.

RESULTS AND DISCUSSION

The mean plasma, urine, and unbound plasma carbamazepine concentration–time profiles for the six healthy volunteers are shown in Fig. 1. The mean urine concentration–time profile is proportional to the mean plasma curve throughout the 9-day study period. The mean free plasma curve closely approximates the urine data, which would indicate that carbamazepine in the urine rapidly approaches an equilibrium with the unbound drug in plasma. The urine flow rate was quite variable over the study period, ranging from approximately 0.5 to 15 ml/min, but this variability did not

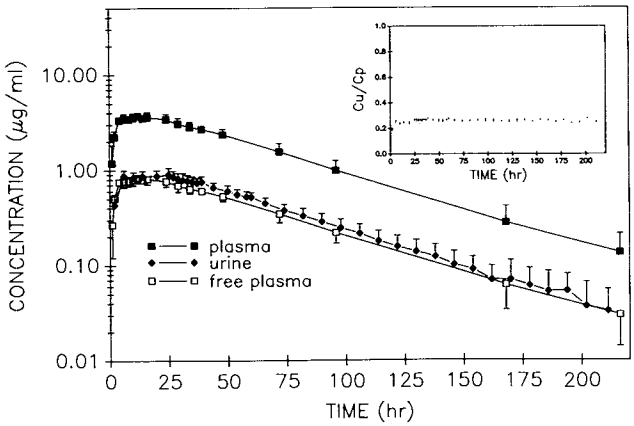

Fig. 1. Mean (±SD) carbamazepine concentration-vs-time profile for plasma (■——■), urine (◆——◆), and unbound plasma (□——□) for the six normal volunteers. Inset: mean (±SD) urine/plasma concentration ratio vs time for the six normal volunteers.

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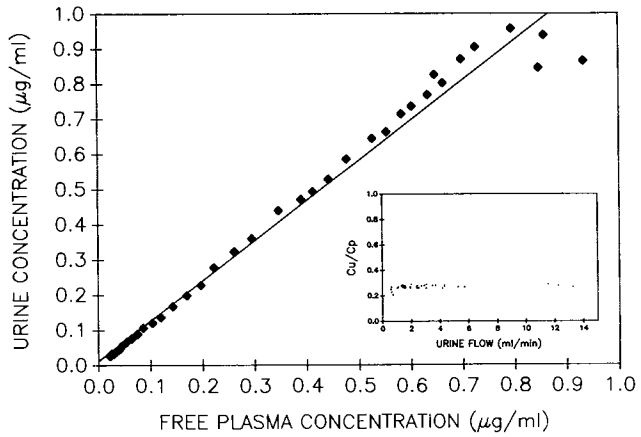

Fig. 2. Urine carbamazepine concentration vs midpoint interpolated carbamazepine free plasma concentration for subject 1. Solid line is orthogonal regression fit: $C_u = 1.14\ [C_{p\ (free)}] + 0.012$, $r = 0.988$. Inset: Urine/plasma concentration ratio vs urine flow rate for subject 1.

affect the urine concentration of carbamazepine. This result is important since the urine flow rate is a key physiological determinant for the urine concentration of drugs with low tubular membrane permeability. Therefore, in the case of carbamazepine, typical variations in urine flow rate would not preclude the use of the urine concentration as a marker for the unbound concentration in plasma.

In addition to being independent of urine flow rate, the mean urine/plasma carbamazepine concentration ratios (C_u/C_p) in the healthy volunteers were constant with time. These data, shown as the inset in Fig. 1, indicate that the proportionality between the urine and the plasma concentrations does not vary with time or plasma concentration, since the plasma concentration is decreasing with time. The mean (±S.D.) of the C_u/C_p ratios in these subjects was 0.26 ± 0.027. Comparison of the urine/plasma concentration ratio with the free fraction in plasma for each subject shows that this ratio approximates the free fraction. This relationship is remarkably evident in Fig. 2, where the urine concentration data for subject 1 are plotted versus the interpolated free plasma concentration. The lack of dependence of C_u/C_p on urine flow for this subject is shown in the inset in Fig. 2, which typifies the relationship observed in all subjects.

The renal clearance of carbamazepine was linearly related to urine flow. The mean slope of this relationship in the six healthy volunteers was 0.268 ± 0.0202. If this drug were reabsorbed to equilibrium across the tubular epithelium after filtration, this slope would equal the free fraction in plasma. The extent to which the slope approximates the free fraction is a measure of the approach to equilibrium achieved during transit through renal tubules.

The preliminary urine/plasma carbamazepine data from nine patients are listed in Table I. The mean (±SD) urine/plasma concentration ratio and the mean (±SD) free fraction were 0.27 (±0.06) and 0.25 (±0.02), respectively, and there was no significant difference between them by paired t test ($P > 0.2$). These values are similar to those observed in the healthy volunteers. The mean (±SD) urine-to-free plasma carbamazepine concentration ratio in the patients was 1.08 (±0.2), which is close to the anticipated ratio of unity in the equilibrium condition. Given that the standard deviation of this ratio is 0.2, the range of the observed values (0.81–1.42) is consistent with the expected value, assuming a normal distribution.

These results show that therapeutic drug monitoring of carbamazepine may be feasible with urine as the biological fluid sampled rather than plasma. Urine concentration monitoring may also be a viable alternative for several other drugs that approach an equilibrium across the renal tubular membrane with the free concentration in the peritubular plasma. Urine concentration monitoring of such compounds offers the advantage of direct measurement of a concentration that is reflective of the pharmacologically and toxicologically active free plasma concentration without laborious and costly separation techniques. The use of urine concentration monitoring may be particularly applicable to anticonvulsant and psychoactive drugs, where the urine concentration may approximate the concentration in the cerebrospinal fluid. It has been shown for some anticonvulsant drugs that the cerebrospinal fluid concentration is similar to the free concentration in plasma (1).

Table I. Urine/Plasma Carbamazepine Concentration Data from Epileptic Patients

Patient	Carbamazepine dosage (mg)	Concurrent medications	C_p (μg/ml)	$C_{p(free)}$ (μg/ml)	C_u (μg/ml)	Free fraction	C_u/C_p	$C_u/C_{p(free)}$
1	400–400	Valproic acid	6.80	1.84	2.62	0.27	0.39	1.42
2	100–200–200–300	Phenytoin	3.90	1.03	0.84	0.26	0.21	0.81
3	300–300–300	Monotherapy	4.56	1.08	1.05	0.24	0.23	0.97
4A	400–300–400–300	Phenytoin	6.84	1.71	2.28	0.25	0.33	1.33
4B	400–300–400–300	Phenytoin	7.60	1.87	1.80	0.25	0.24	0.96
5	600–600–600	Phenytoin	9.12	2.41	2.36	0.26	0.26	0.98
6	400–200–400	Phenytoin	4.64	0.95	0.91	0.21	0.20	0.95
7	200–200–200	Phenytoin	6.52	1.76	1.67	0.27	0.26	0.95
8	400–400–400–400	Phenytoin	5.48	1.35	1.57	0.25	0.29	1.16
9	300–200–300	Monotherapy	6.04	1.60	2.02	0.26	0.33	1.26
Mean						0.25	0.27	1.08
SD						0.02	0.06	0.20
RSD %						7.0	22.4	18.5

The ease of sample collection and increased patient acceptance would be distinct advantages for urine therapeutic drug monitoring with suitable compounds. The technique is less invasive than plasma monitoring and therefore would not suffer from the adverse effects that are associated with venipuncture. Urine monitoring may be particularly appropriate in those patients where venipuncture is difficult, such as in the geriatric and pediatric populations.

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