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Distribution of Cimetidine in Postmortem Tissues

REFERENCE: Berg, M. J., Lantz, R. K., Schentag, J. J., and Vern, B. A., **"Distribution of Cimetidine in Postmortem Tissues,"** *Journal of Forensic Sciences*, JFSCA, Vol. 29, No. 1, Jan. 1984, pp. 147-154.

ABSTRACT: The postabsorptive distribution of cimetidine is described. Assays by high pressure liquid chromatography (HPLC) of postmortem samples of cerebrospinal fluid, serum, and solid tissues were used to determine pharmacokinetic parameters as well as mean tissue:serum concentration (T:S) ratios in seven patients with renal and liver dysfunction. Correlations were calculated between the T:S ratio and the volume of distribution, and between the T:S concentration ratio and the time of sampling after death. The highest T:S ratios occurred in the eliminating organs, the liver and kidneys, and the lowest in fat. As the time of autopsy increased after death, the T:S ratios decreased.

KEYWORDS: pathology and biology, cimetidine, chromatographic analysis

Cimetidine (*N'*-cyano-*N*-methyl-*N'*-2-[(5-methylimidazol-4-yl)methylthio]ethyl guanidine) is a histamine H_2-receptor antagonist used in the treatment of duodenal ulcers and hypersecretory states [*1*]. The side effects of this drug are usually minor; however, three reports of agranulocytosis, including a fatal case have been reported [*2-4*], and mental changes have been seen, primarily in elderly patients, and in cases of either renal or liver failure [*1*]. Although mortality directly attributable to cimetidine toxicity appears to be rare, knowledge of the distribution of cimetidine is essential to the postmortem toxicological examination.

It was initially believed that cimetidine was not present in the central nervous system because studies in animals indicated that the drug did not cross the blood-brain barrier [*5*]. However, in a previous study involving patients with impaired renal or hepatic function or both, cimetidine was identified in spinal fluid and its presence correlated with the appearance of mental impairment [*6*].

Pharmacokinetics of Cimetidine

Cimetidine pharmacokinetics are described as a two-compartment open model with the following constant and parameters:

$t_{1/2\beta}$ = the amount of time it takes the drug concentration to decrease by one half after it has distributed throughout the body (hours);

Presented at the Meeting of the American Society for Clinical Pharmacology and Therapeutics, Kansas City, MO, 22 March 1979. Received for publication 29 March 1983; revised manuscript received 16 May 1983; accepted for publication 17 May 1983.

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V = volume in which the drug distributes, this term is normalized for weight (L/kg);
Cl = total body clearance is the volume of drug that is eliminated per time. This term is normalized for weight (mL/min/kg);
K_α = the constant for the time that it takes for the drug to distribute after it is given intravenously; expressed a reciprocal time (min^{-1}); and
F = fraction of dose D which is available to the systemic circulation (absolute bioavailability). When the drug is administered intravenously, F is always 1.0.

Cimetidine has a $t\,1/2_\beta$ ranging 1 to 2 h, a V of 1.0 to 2.0 L/kg, a Cl of 8.5 to 11.4 mL/min/kg, and a K_α of approximately 6.8 min^{-1}. Plasma protein binding is minimal, 15 to 20% [*2*]. Following intravenous administration, approximately 77% of the dose is found in the urine; following an oral dose during the first 24 h, only 48% of the cimetidine found in the urine is present as unchanged drug. Absolute bioavailability is 70% [*7*]. The major metabolite of cimetidine is the sulfoxide [*5*].

Although the above pharmacokinetic parameters have been reported for living patients and subjects, no studies have related the concentration of cimetidine in tissues to the pharmacokinetic parameters. Such studies in tissues are essential to a complete understanding of the pharmacokinetics of cimetidine, and to the interpretation of postmortem findings.

Methods

Seven patients (four women and three men) ages 22, 56, 57, 66, 68, 72, and 74 years who were receiving cimetidine therapy were placed in one of three possible clinical subgroups based on the indices of serum creatinine and total bilirubin. The groups were labeled "no disease," "renal only," "liver only," or "both renal and liver." Renal failure was diagnosed when serum creatinine was greater than 1.5 mg/dL and total bilirubin was normal. A diagnosis of liver disease was based upon the presence of a total bilirubin greater than 2.0 mg/dL [*8*]. Both renal and hepatic disease were diagnosed when both clinical indices were abnormal. Criteria for inclusion in this study were defined as follows: (a) be receiving multiple intravenous cimetidine dosages (300 to 1200 mg per day), (b) be in the postdistributive elimination phase for cimetidine at death, and (c) have both the time of the last antemortem dose and the time interval between death and autopsy recorded. Pharmacokinetic monitoring before death was not an inclusive criteria; however, five of the seven patients were monitored during their hospitalizations. The values Cl, V, and $t\,1/2_\beta$ for cimetidine were calculated for all except two (M. J. and D. R.) patients.

Analysis

Cimetidine has an ultraviolet absorption maximum of 233 nm, a pKa value of 7.2, and an octanol to water partition ratio of 2.5 at 37°C. The cimetidine concentration in postmortem serum and cerebrospinal fluid (CSF) were determined in duplicate by a high pressure liquid chromatographic (HPLC) determination which used a 4.6-mm by 25-cm Dupont Zorbax® Column with a mobile phase of acetonitrile, glass-distilled methanol, distilled deionized water, and concentrated ammonium hydroxide (1000:150:20:2) [*9,10*]. Concentrations of the drug were determined in approximately 1.0-g homogenates of bone marrow, duodenum, fat, heart, kidney, liver, lung, pancreas, skeletal muscle, spleen, and stomach. A double aqueous extraction was performed on each tissue before chromatographic assay. Recovery of cimetidine added to tissue was 95 to 97% after a two-week period. Tissue:Serum (T:S) concentration ratios were calculated.

Linear least squares regression analysis was used to test for possible correlations between T:S ratios and the pharmacokinetic parameter of V and between V and the time of autopsy after death.

TABLE 1—*Clinical data on the seven patients.*

Patient, Sex	Age, Year	Serum Creatinine, mgm/dL	Calculated Creatinine Clearance, mL/min	Total Bilirubin, mg/dL	Dosing Regimen, Amount per Hours	Time of Last Dose Before Death, h	Time after Death of Autopsy, h
A. G. (m)	66	2.2	35	4.9	300 mg at 6 h	3.25	9
R. D. (m)	74	4.3	16	15.0	300 mg at 6 h	72.0	6
R. H. (f)	68	2.7	24	11.0	300 mg at 8 h	7	6
M. J. (f)	72	5.3	12	3.5	150 mg at 12 h	10.5	4
M. C. (f)	56	1.5	50	7.5	150 mg at 12 h	10.0	15
D. R. (m)	57	1.0	86	2.7	300 mg at 8 h	6.5	6.5
C. D. (f)	22	10.5	0	0.4	300 mg at 8 h	6.5	6.5

TABLE 2—*Pharmacokinetic parameters.*

Patient	*Cl*, mL/min/kg	*V*, L/kg	$t_{1/2\beta}$, h
A. G.	2.94	0.89	3.5
R. D.	0.74	1.15	18.0
R. H.	5.90	1.54	3.0
M. J.	no data	no data	no data
M. C.	4.04	0.84	2.4
D. R.	no data	no data	no data
C. D.	1.62	1.81	7.2
Mean	3.05 ± 2.03	1.09 ± 0.28	6.82 ± 6.52

Results

Clinical data on the seven patients, the dosing of cimetidine, the time of the last intravenous dose of cimetidine, and the time of the postmortem examination are listed in Table 1. The doses of cimetidine for the seven patients ranged from 300 to 1200 mg per day. The time between the last dose and death varied from 3.25 to 72.0 h. Since the distributive time of cimetidine is less than 1.0 h, all patients were in the postdistributive elimination phase at the time of death. The time of postmortem tissue sampling varied from 4 to 15 h.

TABLE 3—*Tissue*

	Renal and Liver Disease Patients					Liver	
	A. G.	R. D.	R. H.	M. J.			
Tissue	*Vd*[a] 0.89 *PM*[b] 9.0	*Vd* 1.15 *PM* 6.0	*Vd* 1.54 *Pm* 4.0	*Vd* X *PM* 5.0	Mean	r^{2d} *Vd*	r^{2d} *PM*
Bone marrow	1.07	1.94	3.04	X	2.02 ± 0.99	0.99(3)	0.97(3)
Duodenum	X[c]	2.08	X	2.08	2.08 ± 0.00	X	X
Fat	X	0	0.71	1.25	0.65 ± 0.63	X	X
Heart	2.04	2.08	3.17	1.14	2.11 ± 0.83	0.86(3)	0.67(4)
Kidney	X	X	X	19.73	X	X	X
cortex	8.02	X	X	X	X	X	X
medulla	8.92	11.3	42.92	X	21.05 ± 18.98	0.88(3)	0.70(3)
Liver	1.88	3.51	9.08	3.92	4.60 ± 3.12	0.96(3)	0.83(4)
Lung	X	2.34	2.66	1.62	2.21 ± 0.53	X	0.09(3)
Pancreas	0.32	1.41	1.23	2.38	1.34 ± 0.84	0.50(3)	0.50(4)
Skeletal muscle	1.91	2.76	2.02	1.29	2.00 ± 0.60	<0.01(3)	<0.01(4)
Spleen	1.54	1.95	5.85	1.53	2.72 ± 2.10	0.90(3)	0.40(4)
Stomach	1.46	2.08	X	2.13	1.89 ± 0.37	X	0.97(3)
Serum, mg/L	10.0	1.10	1.95	1.75	3.7 ± 4.21	0.56(3)	0.79(4)
CSF, mg/L	4.3	0.25	0.95	0.42	1.48 ± 1.9	0.48(3)	0.73(4)
CSF/serum	0.43	0.23	0.49	0.24	0.35 ± 0.13	0.11(3)	0.01(4)

[a] *Vd* = apparent volume of distribution (L/kg).
[b] *PM* = time after death of autopsy (hours).
[c] *X* = no value obtained.
[d] r^2 = correlation from least squares regression.
[e] r^2 = correlation from least squares regression for the two types of patients: renal and liver, and liver.
[f] r^2 = correlation from least squares regression for all patients.
[g] Data not included since sample contained blood.

Pharmacokinetic Parameters

Total body clearance *Cl*, volume of distribution *V*, and beta half-life $t\,{}^{1}/_{2\beta}$ for the five patients in whom these determinations were made before death are presented in Table 2. The mean values found were $Cl = 3.05 \pm 2.03$ (standard deviation [S.D.]) mL/min/kg, $V = 1.09 \pm 0.28$ L/kg, and $t\,{}^{1}/_{2\beta} = 6.28 \pm 6.52$ h.

Tissue Assay Results

Table 3 lists the T:S ratios in the seven patients. All tissues, except for adipose, yielded T:S ratios greater than 1.0. The highest concentrations ratios were found in the liver and kidneys. Other tissues had ratios similar to each other, but lower than those for liver and kidneys. Figure 1 shows the T:S ratio among the three subgroups of patients.

Figure 2 shows the correlation between the T:S ratios and both the *V* and the time of autopsy after death. In general, the T:S ratio declined with time after death.

Cimetidine in the Central Nervous System

Cimetidine was found in the CSF, and this is indicated by the CSF:serum ratios in Table 4. All CSF samples were clear and colorless except for one (D. R.), which was xanthochromic. This sample was not included in the calculation of the mean CSF:serum ratio which was 0.37 ± 0.11 (S.D.). There was no correlation between the CSF:serum ratio and the volume of

Serum Ratios.

Disease Patients			Renal Failure				
M. C.	D. R.				C. D.		
Vd *PM* 0.84 15	*Vd* *PM* X 6.5	Mean	r^{2e} Vd	r^{2e} PM	*Vd* *PM* 1.01 15	r^{2f} *Vd*	r^{2f} *PM*
1.17	22.74	11.95 ± 15.25	0.99(4)	0.63(5)	X	X	X
1.42	1.93	1.67 ± 0.36	X	0.99(3)	X	X	X
0	0	0	0.81(5)	X	3.41	X	X
1.11	1.93	1.52 ± 0.58	0.83(4)	0.77(4)	4.21	X	<0.01(7)
5.26	X	X	X	X	X	X	X
X	31.0	X	X	X	X	X	X
X	28.36	X	X	0.65(4)	X	X	X
2.42	7.58	5.00 ± 3.65	0.93(4)	0.50(5)	30.66	0.01(5)	0.21(7)
1.28	3.80	2.54 ± 1.78	0.87(4)	0.51(5)	4.61	0.02(5)	<0.01(7)
1.49	1.40	1.44 ± 0.06	0.07(4)	0.04(5)	4.93	0.01(5)	0.23(6)
1.44	1.89	1.66 ± 0.32	X	0.11(5)	3.08	X	0.04(6)
2.27	2.47	2.37 ± 0.14	0.79(4)	0.09(5)	5.07	0.48(5)	0.01(6)
X	2.08	X	X	0.91(4)	X	X	X
4.4	0.40	3.26 ± 3.56	0.40(4)	0.21(6)	0.56	0.05(5)	0.18(7)
1.9	0.17[g]	X	0.35(4)	0.23(5)	X	X	X
0.43	0.85[g]	X	0.02(4)	0.001(5)	X	X	X

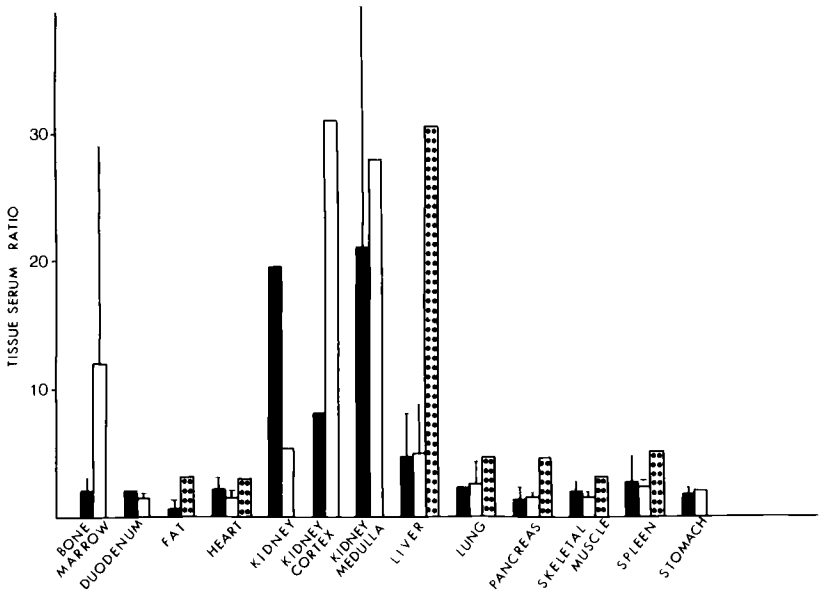

FIG. 1—*Tissue: serum ratio versus specific tissues. The three subgroups of disease states are as follows: solid column = renal and liver disease patients, open column = liver disease patients, and dotted column = renal disease patients.*

distribution. Table 4 shows the concentration of cimetidine in various regions of the brain of one patient. The highest concentrations of cimetidine appeared in or near the brainstem, basal ganglia, and in the motor and visual cortex. In this regard, a previous study of the distribution of radiolabeled cimetidine in guinea pigs demonstrated a specific binding of cimetidine to similar regions of the brain [*11*].

Discussion

Drug concentration and distribution in postmortem specimens may be markedly affected by drug catabolism and by changes in the tissues themselves. The permeability of intertissue barriers changes after death, as do the pH and ionic strength of intra- and extra-cellular fluids. Therefore, the extent of tissue and soluble protein binding of drugs may also be expected to change. Tissue damage occurring prior to death, especially in severly debilitated patients, also affects the chemical environment of the drug and, as a result, the distribution pattern of a given drug.

The T:S cimetidine concentration ratios increased with the volume of distribution for the majority of patients, and the largest T:S ratio was found for liver and kidney tissues. The T:S ratios also decreased with increasing time after death. Since all of the patients had either kidney or liver failure or both, no statement can be made about the T:S ratios in normal patients. Also there is no information about the distribution of this histamine receptor antagonist in postmortem samples of disease free patients. However, in two healthy dogs who received cimetidine intravenously, the serum concentration from the femoral artery (concentrations in both femoral artery and vein were equivalent) increased after the time of death (unpublished data). Further animal and human data are needed in the area to characterize the distributional patterns of this drug after death.

The mean CSF/serum concentration ratio (0.37) was higher for the deceased patients than for five living patients (0.24) [*6*] suggesting a postmortem distributional change. However, the time of autopsy did not correlate with CSF:serum concentration ratio for this study.

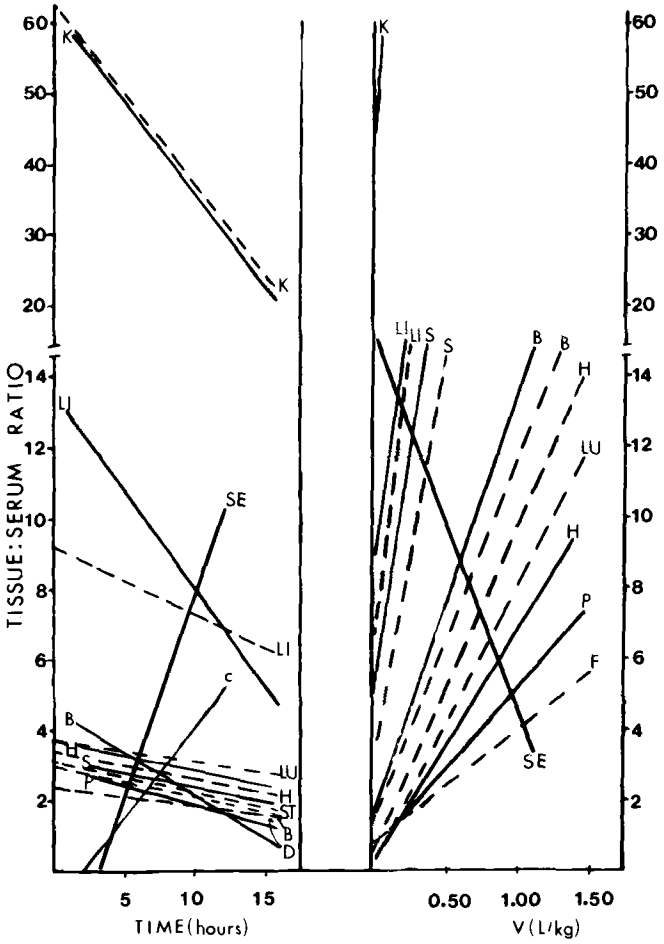

FIG. 2—*Tissue: serum ratio versus time of autopsy after death (hours): and tissue: serum ratio versus volume of distribution* V *(L/kg).* —— = *renal and liver disease patients and* ---- = *renal and liver disease patients combined with liver disease patients.* B = *bone marrow,* C = *cerebrospinal fluid,* D = *duodenum,* F = *fat,* H = *heart,* K = *kidney medulla,* LI = *liver,* LU = *lung,* P = *pancreas,* S = *spleen,* SE = *serum, and* ST = stomach.

TABLE 4—*Central nervous system.*

Brain Tissue	Cimetidine Concentration, μg/g Tissue
Basal ganglia	2.73
Cerebellum	0.86
Cortex (cerebral)	0.91
Cortex (motor)	2.21
Cortex (visual)	1.66
Hippocampus	0.71
Hypothalamus	2.78
Medulla	4.20
Pons	1.06
CSF	4.30 mg/L
Serum	10.0 mg/L
CSF: Serum ratio	0.43 : 1

Therefore, it appears that the time of the autopsy after death is important in determining the concentration of cimetidine in serum, cerebrospinal fluid, and other tissues.

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