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The Forensic Science Implications of Site and Temporal Influences on Postmortem Blood-Drug Concentrations

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ABSTRACT: The dependence of postmortem blood-drug concentrations on the collection site and on the postmortem interval before specimen collection has been studied. These studies consisted of both sequential sampling from the same collection site at defined time intervals and a comparison of the drug concentrations of postmortem blood simultaneously collected from various sites. A site and time dependence was observed for postmortem blood-drug concentrations. The heart blood-drug concentrations were, in general, significantly higher than those of peripheral specimens. As a result of this phenomenon, the analysis of peripheral blood specimens and solid tissues is often necessary before a definitive interpretation of postmortem toxicological analyses is possible.

KEYWORDS: toxicology, blood-drug concentrations, tissue-drug concentrations, postmortem interval, blood collection sites

One of the most fundamental questions of postmortem forensic toxicology is: "How much drug did the decedent take?" Historically, to answer this question, toxicologists have relied upon published case reports of fatal intoxications, in which the amount of ingested drug was known or reasonably approximated, and upon reports in the clinical literature that contain information concerning drug concentrations after single or chronic dosing. In recent years, pharmacokinetic equations have been increasingly used in an effort to estimate more precisely the total amount of a drug in the body and, subsequently, estimate the dose of the drug required to produce a measured blood concentration.

Fundamental principles and limitations of pharmacokinetic equations indicate that a calculation of dose from a single postmortem blood-drug concentration is perhaps an unwise exercise. These limitations include, but are not limited to, variations in several parameters: the volume of distribution of the drug; the percentage of the dose that is absorbed; the distribution model of the drug, one-compartment or multi-compartment; the elimination kinetics of the drug, linear or nonlinear; deviations from normal elimination kinetics as a result of enzyme saturation; the phase of elimination, alpha or beta; and the pattern of drug use, acute, chronic, or a combination of the two. Nevertheless,

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these estimations are frequently made and, in certain situations and with proper caution, may be quite useful. However, the authors have been involved in the investigation of numerous drug-related deaths in which attempts to estimate by pharmacokinetic calculations the amount of drug that was ingested yielded unreasonable and obviously overestimated predictions. These overestimations were usually based upon postmortem heart blood concentrations.

Regardless of all other factors, attempts at pharmacokinetic estimations of dose are dependent upon whether drug concentrations measured in autopsy blood specimens accurately reflect the concentration of the drug at the time of death. Since the authors' original presentation of this subject [1], a considerable amount of evidence has been presented which indicates that for some drugs this condition is not always met [2-12]. The authors have summarized much of this information in a recent review [13].

Perhaps the most widely recognized example of this phenomenon is digoxin, as reported by Vorphal and Coe [11]. These authors reported upon a detailed study of 24 cases in which the postmortem concentration of digoxin was greater in the heart blood than in a simultaneously collected femoral blood. They also observed that the concentration of digoxin in postmortem blood specimens from any origin exceeded the expected concentration at the time of death. These authors further postulated that digoxin was released from cardiac tissue and diffused into the heart blood, thus elevating the heart blood concentration of the drug.

In 1980, Bandt [12] suggested that a similar phenomenon may exist with the postmortem blood concentrations of tricyclic antidepressant drugs. His study included nine cases involving several tricyclics. Serial postmortem blood samples were taken from various sites. Bandt concluded that the concentration of the tricyclic antidepressant drugs changed with time and that the concentration varied from site to site. Unfortunately, neither Bandt nor other investigators conducted further research in this area for several years.

The work of Bandt, Vorphal, Coe, and others, and the inability of published pharmacokinetic data to explain satisfactorily the measured drug concentration in postmortem blood specimens, even in cases in which the amount of drug ingested was accurately known, combined to pique our interest in the area of postmortem distribution or redistribution of drugs or both.

Materials and Methods

Phase Studies

Initially, most of our cases that seemed to have an inexplicable relationship between the measured postmortem blood-drug concentration and the known dose of a drug involved tricyclic antidepressants. As a result of this fact and Bandt's suggestion that the concentration of these drugs may change during the postmortem interval, our initial investigations were concerned with the tricyclics and other antidepressants. There were two objectives of the Phase studies. The first was to collect simultaneously postmortem blood specimens from several sites and ascertain whether there were significant differences in the concentrations of drugs in these specimens. The second objective was to determine if the concentration of a drug from a given site changed with time. The first set of specimens that was collected was designated as Phase I specimens and included a portion or all of the following: blood from the left and right subclavian vein, blood from the left and right heart chambers, and blood from the left and right femoral vein. The chest plate was removed before the collection of the Phase I specimens. After at least 2 h, another set of specimens, designated as Phase II specimens, was collected in an analogous manner to the Phase I specimens. In a few instances, a third set of specimens, Phase III specimens, was collected after at least 2 h had elapsed since the collection of

the Phase II specimens. The last set of blood specimens was collected along with tissues and other biological fluids at autopsy. These additional specimens included all or a portion of the following: liver, kidney, brain, gastric contents, and vitreous humor. Both drug deaths and nondrug deaths were investigated; the only criterion for inclusion of the case in the Phase studies was the presence of an antidepressant.

Field Blood Studies

Oklahoma has a centralized State Medical Examiner System; consequently, the situation occasionally arises in which a local medical examiner will collect a heart blood specimen by cardiac puncture and forward that specimen along with the body to a regional morgue center for an autopsy. These specimens will be referred to as "field blood specimens." When a drug was detected in an autopsy blood specimen, all available blood specimens were assayed and the results compared. The field bloods were always collected several hours before the autopsy specimens, thereby affording the opportunity to study the change of drug concentrations in heart blood with time.

Comparison of Heart and Femoral Blood-Drug Concentrations

Initial studies indicated that drugs other than antidepressants may have differences in heart and femoral blood concentrations. As a result, a comprehensive study was undertaken in which both heart and femoral bloods were collected in as many cases as possible. When resources and specimen volume permitted, the concentrations of all drugs, detected in a general screen, were determined in heart blood, femoral blood, other biological fluids, and tissue specimens and the results compared.

Analytical Methods

Originally, the antidepressants were assayed by the method of Hebb et al. [14] with little or no modification. Subsequently, the assays for the antidepressants were performed by an in-house high-pressure liquid chromatographic (HPLC) method with an Econosphere[®] cyano (CN) column and a mobile phase consisting of 0.012M monobasic phosphate (pH 6.7), methanol, and acetonitrile. The solvent ratios of the mobile phase were adjusted for optimal resolution of each analyte and an appropriate internal standard. Most of the other drugs were assayed by gas chromatography. The basic drugs were extracted, after the addition of an appropriate internal standard, by the method of Foerster et al. [15] and the acid/neutral drugs were assayed by the method of Anderson and Fuller [16]. All specimens were assayed in duplicate, with the exception of a few vitreous humor specimens that were of insufficient volume for duplicate analysis. All duplicate results were within 10% or the assay was repeated. The coefficient of variation for these assays was typically less than 10%.

Results and Discussion

The data from the Phase studies are presented in Table 1. The most striking aspect of these data is the variation in drug concentration in bloods collected from different sites, irrespective of the time of collection. No one site consistently produced the highest concentration of drug, but, in general, the femoral bloods were lower in concentration than that of the heart and subclavian specimens. While this is generally true, it is not always the situation (see Case A-1977). There is a general tendency for the blood-drug concentration to increase with an increase in the postmortem interval, especially for heart blood concentrations. However, in some specimens the concentration did not change

TABLE 1—Drug concentrations (mg/L or mg/kg) versus site and time.*

Case A-2224 (OD)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	4.6	7.3	3.5	4.9
RSC	4.6	6.7	3.5	4.7
LH	...	6.6	...	7.8
RH	4.9	4.6	5.3	4.5
LF	...	3.4	...	2.6
RF	3.1	...	2.6	...
Liver	...	82.4	...	193.9
Found dead to Phase I = 28.5 h. Phase I to Phase II = 19 h.				

Case A-1541 (OD)				
Specimen	Doxepin		Nordoxepin	
	Phase I	Phase II	Phase I	Phase II
LSC	5.3	6.4	1.7	2.4
RSC	6.7	4.9	2.3	1.4
LH	5.7	5.9	3.2	3.0
RH	4.2	5.0	1.8	1.8
LF	2.8	...	0.71	...
RF	2.1	...	0.85	...
Liver	...	110.0	...	44.8
Brain	...	178.1	...	60.0
Kidney	...	27.5	...	7.9
Found dead to Phase I = 9.5 h. Phase I to Phase II = 4 h.				

Case A-1087 (OD)			
Specimen	Amoxapine		
	Phase I	Phase II	Phase III
LSC	2.0	1.7	2.0
RSC	3.1	3.0	2.2
LH	3.9	4.6	7.0
RH	1.8	3.9	4.9
LF	2.6	3.0	4.7
RF	2.4	4.2	4.7
Liver	132.0
Kidney	23.8
Found dead to Phase I = 17 h. Phase I to II = 4 h. Phase II to III = 2 h.			

Case A-2045 (OD)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	6.8	6.0	1.6	0.80
RSC	9.2	7.2	1.0	1.1
LH	...	5.2	...	0.80
RH	7.9	...	2.1	...
LF	...	4.1	...	1.1
RF	4.3	...	1.1	...
Liver	...	124.5	...	43.0
Found dead to Phase I = 7 h. Phase I to Phase II = 11 h.				

TABLE 1—Continued.

Case A-2044 (OD)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	0.92	1.6	0.30	0.51
RSC	1.0	2.7	0.35	0.62
LH	...	1.4	...	0.41
RH	1.7	1.8	0.40	0.41
LF	...	1.6	...	0.43
RF	0.42	...	0.22	...
Liver	...	55.6	...	9.3
Trazodone				
LSC	7.0	9.6	0.46	1.1
RSC	7.4	11.7	0.52	0.83
LH	...	7.3	...	0.76
RH	8.2	11.4	0.88	0.84
LF	...	6.8	...	0.71
RF	4.8	...	0.19	...
Liver	...	82.0	...	34.8
Trimipramine				
LSC	7.0	9.6	0.46	1.1
RSC	7.4	11.7	0.52	0.83
LH	...	7.3	...	0.76
RH	8.2	11.4	0.88	0.84
LF	...	6.8	...	0.71
RF	4.8	...	0.19	...
Liver	...	82.0	...	34.8
Found dead to Phase I = 7 h. Phase I to Phase II = 20 h.				
Case B-0507 (PP)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	0.94	0.68	0.45	0.44
RSC	0.77	1.7	0.35	0.60
LH	2.0	2.3	1.3	2.5
RH	1.3	2.4	0.36	0.82
LF	...	0.37	...	0.28
RF	0.18	...	0.18	...
Liver	...	37.7	...	9.9
Brain	...	3.6	...	4.3
Kidney	...	3.6	...	2.0
Propoxyphene				
LSC	1.8	1.8	3.8	3.1
RSC	1.6	2.4	2.9	3.8
LH	5.6	6.2	8.5	10.4
RH	1.6	3.4	...	5.4
LF	...	1.3	...	2.0
RF	0.76	...	1.7	...
Liver	...	17.6	...	24.3
Brain	...	19.7	...	12.7
Kidney	...	6.0	...	12.7
Found dead to Phase I = 6 h. Phase I to Phase II = 19 h.				
Case A-2408 (PP)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	3.0	0.76	0.37	0.20
RSC	1.9	0.36	0.30	0.18
LH	1.3	0.70	...	0.27
RH	2.2	1.5	0.08	...
LF	...	0.22
RF	0.14
Liver	...	40.1	...	2.3
Brain	...	1.1	...	1.3
Kidney	...	3.7	...	1.5

TABLE 1—Continued.

Case A-2408 (PP) <i>Continued</i>				
Specimen	Propoxyphene		Norpropoxyphene	
	Phase I	Phase II	Phase I	Phase II
LSC	4.6	2.8	4.5	1.5
RSC	3.3	1.6	3.2	2.9
LH	3.3	...	3.2	...
RH	4.2	3.3	2.1	1.1
LF	...	0.91	...	0.54
RF	0.46
Liver	...	60.0	...	19.9
Brain	...	6.4	...	1.1
Kidney	...	8.1	...	4.9
Found dead to Phase I = 18 h.		Phase I to Phase II = 6 h.		
Case A-2327 (NOD)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	0.06	0.12	0.07	0.14
RSC	0.09	0.12	0.10	0.07
LH	0.02	0.16	0.07	0.07
RH	0.09	0.07	0.11	0.15
LF	...	0.14	...	0.09
RF	0.10	...	0.09	...
Liver	...	1.3	...	3.9
Brain	...	0.33	...	0.62
Kidney	...	0.36	...	0.63
Found dead to Phase I = 15.5 h.		Phase I to Phase II = 24 h.		
Case A-1977 (NOD)				
Specimen	Amitriptyline		Nortriptyline	
	Phase I	Phase II	Phase I	Phase II
LSC	0.12	0.12	0.44	0.49
RSC	0.12	0.12	0.43	0.47
LH
RH	0.09	0.12	0.39	0.49
LF	...	0.14	...	0.40
RF	0.15	...	0.43	...
Liver	...	0.61	...	7.1
Found dead to Phase I = 24 h.		Phase I to Phase II = 3.5 h.		

*OD = death as a result of drug overdose,

LSC = left subclavian vein blood,

RSC = right subclavian vein blood,

LH = left heart blood,

RH = right heart blood,

LF = left femoral vein blood,

RF = right femoral vein blood,

PP = death as a result of multiple drug overdose, and

NOD = not a drug-related death.

appreciably with time (see Case A-1977). In other instances, the drug concentration of a specimen decreased appreciably with time (see Case A-1541, right subclavian). Cases A-1541 and B-0507 are examples of cases in which some specimens increased in concentration from one phase to the next, while other specimens in the same case decreased in concentration. There appears to be no way to predict which specimen will exhibit the largest change in drug concentration with time. The concentration of a parent drug and its metabolite tended to change in the same direction, but no absolute relationship between the concentration of a drug and its metabolite could be identified.

The data from the field blood experiments, presented in Table 2, further substantiate that postmortem changes can and do occur in blood-drug concentrations. Twelve cases involving seventeen drugs were studied in this manner; in every case in which both specimens were collected, the drug concentration of the field blood was lower than that of the autopsy heart blood. The femoral blood-drug concentrations were generally greater than or the same as that of the field blood concentrations, but the magnitude of the increase in concentration was much less than that of the heart blood collected at autopsy.

Table 3 presents the comparison of heart and femoral blood-drug concentrations for a large variety of drugs. Tissue concentrations as well as other biological fluids are included

TABLE 2—*Field blood versus autopsy heart and femoral blood-drug concentrations (mg/L) and ratios.**

Case	Drug(s)	FLB	HB	FB	HB/FB	HB/FLB	FB/FLB
B-0325	amitriptyline	0.48	2.1	0.91	2.3	4.4	1.9
	nortriptyline	0.49	4.4	1.0	4.4	9.0	2.0
	thioridazine	2.0	3.5	1.8	1.9	1.8	0.90
	mesoridazine	3.5	3.5	3.0	1.2	1.0	0.85
C-0970	amitriptyline	0.36	1.5	0.51	2.9	4.2	1.4
	nortriptyline	0.02	0.35	0.05	7.0	17.5	2.5
	diphenhydramine	0.02	0.18	0.03	6.0	9.0	1.5
E-0467	amitriptyline	0.93	7.7	1.1	7.0	8.3	1.2
	nortriptyline	...	1.1	0.32	3.4
E-0850	chlorpromazine	10.8	10.9	4.4	2.5	1.0	0.41
	chlorpromazine-sulfoxide	1.1	1.2	1.5	0.80	1.1	1.4
A-0639	doxepin	5.6	14.9	2.7	...
	nordoxepin	1.5	2.0	1.3	...
C-2256	doxepin	1.9	16.8	2.2	7.6	8.8	1.2
A-2508	ethchlorvynol	6.2	9.5	1.5	...
	methadone	0.24	0.57	2.4	...
B-0521	meperidine	0.07	0.16	0.06	2.7	2.3	0.86
	phencyclidine	0.11	0.50	0.15	3.3	4.5	1.4
C-0582	meperidine	0.76	1.4	1.2	1.2	1.8	1.6
	normeperidine	0.21	0.40	0.50	0.80	1.9	2.4
B-1649	methamphetamine	0.66	1.6	2.4	...
	amphetamine	0.07	0.21	3.0	...
E-1027	phencyclidine	0.15	0.23	0.23	1.0	1.5	1.5
D-1681	phentermine	0.16	...	0.22	1.4

*FLB = heart blood collected in the field by cardiac puncture.

HB = heart blood collected at autopsy, and

FB = femoral vein blood collected at autopsy.

TABLE 3—*Postmortem drug concentrations (mg/L or mg/kg) in blood, vitreous, and tissues.^a*

Drugs	Case	HB	FB	HB/FB	SB	VH	L	B	K	Cause of Death	Comments
8-Hydroxyamoxapine Alprazolam	D-0537	5.4	2.7	2.0			178.0			OD	amoxapine
	E-1479	0.25	0.04	6.3						PP/ETOH (0.17)	doxepin, propoxyphene
	F-0277	0.70	0.45	1.6		0.12				OD	
Amantadine Amitriptyline	F-1741	1.8	1.1	1.6		0.65	5.6	3.3		PP	cocaine, doxepin
	A-1342	3.4	1.6	2.1			21.0		5.9	PP/ETOH (0.07)	doxepin, diphenhydramine
	A-1841	0.47	0.18	2.6	0.25		6.3	4.1	2.0	CVD	
	B-0325	0.98	0.91	1.1	0.84		32.5	10.0	0.93	PP	thioridazine
	B-0394	0.36	0.33	1.1			5.8			TR	
	B-0968	2.5	0.20	12.5			42.0	31.9	28.7	OD	
	B-1069	1.2	1.9	0.63			42.0	4.7	15.0	OD/ETOH (0.09)	
	B-1077	7.2	8.7	0.83		0.99	81.8	71.6	29.1	OD	
	B-1423	10.2	1.7	6.0			103.2	46.3	29.6	OD	
	B-2168	0.69	0.24	2.9			8.1			CVD	
	C-0962	43.2	8.7	5.0		1.6	223.6	167.8	92.7	OD	diphenhydramine
	C-0970	1.5	0.51	2.9			38.5		7.3	PP	
	C-1592	13.2	2.7	4.9			125.0			CU	
	C-1962	2.6	1.4	1.9		0.40	67.0			PP	butalbital
	C-2322	7.3	6.0	1.2		0.74	358.0	70.8	67.9	OD	
	C-2368	1.6	1.5	1.1		0.13	19.5		8.4	OD	
	D-0294	7.6	2.6	2.9						OD/ETOH (0.26)	
	D-0482	3.1	2.7	1.2		0.91	134.0	30.0	38.0	OD/ETOH (0.20)	
	D-1102	2.0	1.5	1.3			55.1			OD/ETOH (0.07)	
D-1890	0.70	0.36	1.9			8.9			U		
D-2313	5.6	0.90	6.2			130.0			OD/ETOH (0.14)		
E-0015	2.7	2.3	1.2			56.2			PP	chlor diazepoxide	
E-0467	7.7	1.1	7.1			300.5			PP	phenytoin, HB = 19.0	
E-1503	7.6	1.7	4.5			204.9			PP/ETOH (0.11)	imipramine	
E-2094	3.4	0.80	4.3			174.0			PP/ETOH (0.08)		
F-0164	15.6	6.4	2.4			257.0			OD		
F-0407	1.2	0.30	4.0			35.7			PP	butalbital	
F-0428	0.90	1.8	0.50			112.0			OD/ETOH (0.21)		
F-0928	6.8	3.4	2.0			165.0			OD		
F-1616	3.5	4.9	0.71			70.5	55.4		OD		
F-1657	0.24	0.18	1.3			31.5	7.6		PP	hydroxyzine, HB = 0.27; verapamil, HB = 3.3	
F-1664	1.9	0.85	2.2			3.9	0.88		PP	butalbital, codeine, thioridazine	
F-1981	0.23	0.30	0.77						PP	butalbital, FB = 0.34; theophylline, HB = 3.2; tirazepam, HB = 0.06	
G-0091	2.1	1.6	1.3			54.8			OD/ETOH (0.11)		
G-0429	3.7	0.92	4.0			292.5	5.2		OD		

Amobarbital	E-0248	11.6	7.2	1.6	13.0	5.5	4.9	PP	secobarbital
	F-0436	3.1	2.6	1.2	12.2			TR	
Amexapine	A-0802	13.0	5.3	2.5	0.81	300.0		OD/ETOH (0.15)	
	A-0860	0.28	0.20	1.4	0.22	6.5	2.6	CVD	
	B-0509	3.4	1.4	2.4	0.21	74.7		OD	
	C-2561	11.7	6.4	1.8	1.7	410.0		OD	
	D-0537	9.2	5.3	1.7	345.0			OD	
	D-1241	15.1	14.1	1.1	932.0			OD	72-h survival
	F-0596	0.55	0.65	0.85	16.5			OD	
Amphetamine	D-0631	0.64	0.31	2.1				TR	
	F-0031	1.5	0.05	30.4	0.60	3.6		OD	drug-induced cardiac arrhythmia
	F-0465	0.47	0.33	1.4	3.1			TR	
	F-2224	0.13	0.09	1.4	0.10	0.90		TR	
Antipyrine	E-0936	4.2	3.1	1.4				PP	thionidazine
Benzylcgonine	E-0594	7.7	7.7	1.0				PP	phenacyclidine
	F-0394	2.6	1.7	1.5	3.3	0.5		TR	
	F-0453	1.2	0.82	1.5	0.38	3.5	0.42	U	
	F-0526	3.7	3.4	1.1	3.8	8.3	1.1	OD	
	F-1041	8.9	3.4	2.6	32.0			PP	dextromethorphan
	F-1061	2.1	1.9	1.1	4.5	1.1		OD	
	F-1250	1.7	1.5	1.1	3.3			TR	
	F-1352	0.32	0.27	1.2				TR	
	F-1360	1.1	0.55	2.0				TR	
	F-1655	0.71	0.55	1.3	1.1			TR	
	F-1741	5.3	1.5	3.5	14.0	-0.50		PP	amantadine, doxepin
	F-1946	0.09	0.10	0.90				TR	
	F-2054	0.03	0.05	0.60	0.04			TR	
Benztrypine	F-0085	0.60	0.64	0.94	12.8			PP	trifluoperazine
Brompheniramine	F-1498	0.56	0.20	2.8	11.0	2.9		U	
Bupropion	E-2125	0.19	0.22	0.86	1.4			PP	imipramine, diphenhydramine, HB = 6.9
Buralbital	C-1962	2.6	3.7	0.70	1.9	7.1		PP	amitriptyline
	E-0476	45.6	22.9	2.0	73.6			PP	caffeine, codeine, diazepam, meperidine
	E-2333	5.8	5.7	1.0	17.4			PP	codeine, promethazine
	F-0001	6.5	5.8	1.1	15.7			PP	carisoprodol, HB = 0.60; phenobarbital, meprobamate, HB = 6.7
	F-0201	5.2	4.7	1.1	10.8			CVD	
	F-0407	5.9	5.5	1.1	12.8			PP	amitriptyline
	F-1472	15.5	17.9	0.87	53.2	25.8		PP	propoxyphene, diphenhydramine
	F-1664	3.4	2.9	1.2	6.2	3.8		PP	amitriptyline, codeine, thioridazine
	F-2380	11.6	9.6	1.2	24.9	14.0		PP	codeine

TABLE 3—Continued.

Drugs	Case	HB	FB	HB/FB	SB	VH	L	B	K	Cause of Death	Comments
Caffeine	E-0476	75.3	35.8	2.1			63.2			PP	butalbital, codeine, diazepam, meperidine
Carbamazepine	E-2252	2.3	2.6	0.89			6.2			PP	carisoprodol
	F-0995	4.3	3.1	1.4			14.0			TR	
	F-1145	12.6	11.0	1.2			26.0	21.0		TR	
	F-1607	2.3	1.8	1.3		0.70				CVD	ETOH 0.29%
Carisoprodol	D-0078	18.0	17.0	1.06						PP	propoxyphene
	D-2196	19.2	16.4	1.2			51.4			PP	propoxyphene
	D-2512	54.8	49.2	1.1			116.8			PP	propoxyphene
	E-0544	5.0	5.8	0.86						PP	diphenhydramine
	E-1965	16.9	9.9	1.7			52.5			PP	codeine, diphenhydramine
E-2252	33.0	31.0	1.1			133.0			PP	carbamazepine	
Chlordiazepoxide	B-2168	3.1	1.3	2.4			5.1			CVD	
	E-0015	1.4	1.1	1.3						PP	amitriptyline
	E-1837	0.40	0.40	1.0						PP/ETOH (0.07)	doxepin
Chlorpheniramine	E-0777	2.2	0.93	2.3		0.45	13.4			PP	dextromethorphan, doxylamine, salicylate, HB = 230.1
	B-0927	1.5	0.79	1.9			23.0			U	
Chlorpromazine	D-2211	1.4	1.4	1.0			63.5			OD/ETOH (0.17)	
	D-2320	5.5	4.2	1.3			191.8			OD	
	F-0580	0.95	0.60	1.6			13.5			TR	
	F-0430	12.2	9.1	1.3			25.2			TR	
Cocaine	E-0594	0.84	0.74	1.1						PP	phenylethidine
	F-0394	0.40	0.40	1.0			0.40	1.7		TR	
	F-0453	0.21	0.11	2.0		0.40	0.32	1.7		U	
	F-0526	4.1	4.1	1.0		<0.10	3.8	23.3		OD	
	F-1041	9.6	4.4	2.2			10.6			PP	dextromethorphan
	F-1061	0.30	0.62	0.48			0.30	0.86		OD	
	F-1250	0.30	0.23	1.3						TR	
	F-1352	0.05	0.03	1.7						TR	
	F-1360	0.36	0.17	2.1			0.23			TR	
	F-1655	0.03	0.02	1.5						TR	
	F-1728	1.6	1.8	0.89			1.0	20.6		OD	
	F-1741	1.0	1.2	0.83			1.6	11.0		PP	amniadine, doxepin
Codeine	E-0476	0.70	0.60	1.2			2.0			PP	butalbital, caffeine, diazepam, meperidine
	E-0804	3.0	1.6	1.9			32.0			PP	doxepin, trazodone
	E-2333	0.95	0.91	1.0			2.6			PP	butalbital, promethazine
	F-0803	1.1	0.95	1.2			2.0			U	

Desipramine	F-0201	0.23	1.1	1.3					CVD	
	F-1664	1.4	2.0	2.4					PP	amitriptyline, butalbital, thioridazine
	F-2380	0.54	1.4	1.1	1.0				PP	butalbital
	C-1260	11.9	5.7	0.90	437.4	40.3	153.8		OD	
	E-1503	0.40	4.0	20.3	9.7				PP/ETOH (0.11)	amitriptyline
E-2125	<0.50	<0.50	3.4	324.0				PP	bupropion, imipramine	
F-1487	9.2	5.8	1.6					PP/ETOH (0.20)	butalbital, HB = 0.31; chlordiazepoxide, HB = 2.2; nordiazepam, HB = 0.34	
Dextromethorphan	F-1944	3.4	2.6	1.3	67.0	22.0			PP	butalbital, theophylline, triazolam
	G-0008	12.5	3.2	3.9	151.0	60.9			OD	
	G-0214	4.3	5.6	0.77	174.6	149.3			OD	
	F-0777	2.2	0.99	2.2	1.1	17.5			PP	chlorpheniramine, doxylamine, salicylate, HB = 230.0
	F-1041	0.50	0.22	2.3	9.5				PP	cocaine
Diazepam	B-0096	0.80	0.57	1.4					PP	maprotiline
	B-1222	0.36	0.54	0.67	1.6				PP	propoxyphene
	C-1299	0.04	0.05	0.92	0.11				CVD	
	E-0476	2.1	1.4	1.5	11.8				PP	butalbital, caffeine, codeine, meperidine
	F-0129	2.9	2.1	1.4	8.2				PP	maprotiline
Diphenhydramine	F-0980	3.6	3.5	1.0	14.0				PP	propoxyphene, diphenhydramine
	F-1457	0.52	0.39	0.82					ASP	
	F-1498	0.38	0.40	0.95	1.4	0.68			U	
	F-1578	1.7	0.48	3.5	3.0				TR	
	G-0251	0.49	0.59	0.83	2.4	1.6			TR	
Doxepin	A-1342	1.5	0.77	2.0	3.8				2.6	amitriptyline, doxepin
	C-0653	13.5	6.5	2.1	188.0				OD	
	C-0970	0.18	0.03	6.0	1.7				PP	amitriptyline
	C-2142	28.0	13.8	2.0	291.0				OD/EToH (0.13)	
	D-0031	1.7	3.8	0.45	30.0				PP	doxepin
	D-1567	19.4	10.1	1.9	103.4				OD	
	E-0544	0.80	0.80	1.0	5.5				PP	carisoprodol
	E-0791	1.1	0.55	1.9	56.3				PP	metoprolol
	E-1965	2.6	1.2	2.2	63.1				PP	codeine, carisoprodol
	F-0372	1.7	1.5	1.1	40.2				PP/EToH (0.38)	doxylamine
	F-0980	4.7	3.1	1.5	120.6				PP	diazepam, propoxyphene
	F-1472	1.4	1.5	0.93	9.2				PP	butalbital, propoxyphene
	F-1944	0.90	0.74	1.2	7.5	2.9			PP	doxylamine, propanolol, HB = 1.9; imipramine
	F-2361	0.31	0.24	1.3	3.7	0.59			PP	metaclopramide, trazodone
	A-1342	0.98	0.48	2.0	4.7				1.9	amitriptyline, diphenhydramine
B-0128	3.1	0.60	5.2	0.19	4.7			U		
B-1276	31.4	5.7	5.5	2.3	23.1	29.8		32.3	OD	
B-2417	1.6	1.5	1.1	0.20	65.4	15.5		15.0	OD	

TABLE 3—Continued.

Drugs	Case	HB	FB	HB/FB	SB	VH	L	B	K	Cause of Death	Comments
	C-2256	16.8	2.2	7.6			84.2			OD/ETOH (0.17)	
	C-2544	5.2	1.8	2.9		1.6				OD/ETOH (0.24)	
	D-0031	3.3	3.9	0.85			211.0			PP	diphenhydramine
	D-2168	7.0	2.2	3.2			92.6			OD	
	D-0527	4.0	1.5	3.1			49.4			PP	methadone
	E-0804	14.8	4.1	3.6			243.0			PP	codiene, trazodone
	E-1837	3.7	2.1	1.8			49.1			PP/ETOH (0.07)	chloridazepoxide
	F-0008	5.4	7.0	0.77			154.8			OD	
	F-0633	6.2	4.8	1.3			125.0			PP	nordiazepam
	F-1741	1.2	0.60	2.0			11.0	2.8		PP	amantadine, cocaine
	F-1770	0.28	0.15	1.9			2.8			CVD	
	F-2194	0.29	<0.25				8.9	1.6		CVD	
	G-0344	2.4	2.2	1.1			59.5	21.4		OD	
Doxylamine	F-0372	2.6	2.1	1.2			16.1			PP/ETOH (0.38)	diphenhydramine
	F-0777	9.4	9.3	1.0		3.7	43.1			PP	chlorpheniramine, dextromethorphan, salicylate, HB = 230.0
	F-1944	1.9	1.6	1.2			6.4	3.0		PP	diphenhydramine, propranolol, HB = 1.9; imipramine
Fluoxetine	F-1259	0.80	0.23	3.5			12.8	3.6		OD/ETOH (0.22)	
Imipramine	A-1841	1.4	0.63	2.2	0.85		18.9	15.3	6.0	CVD	
	E-1503	4.4	1.5	2.9			134.8			PP/ETOH (0.11)	amitriptyline
	E-2094	1.8	0.60	3.0			67.0			PP/ETOH (0.08)	amitriptyline
	E-2125	2.5	2.0	1.3			73.7			PP	bupirone, diphenhydramine, HB = 6.9
	F-0385	2.9	2.1	1.4			173.0			OD	
	F-1944	15.1	6.8	2.2			350.0	108.0		PP	diphenhydramine, doxylamine, propranolol, HB = 1.9
Maprotiline	B-0096	2.6	1.9	1.4			413.0			PP	diazepam
	B-0869	35.0	16.0	2.2			698.0			OD	
	B-1081	10.6	1.0	10.6			17.3	20.2		OD	
	F-0129	2.4	2.7	0.89			79.0			PP	diazepam
Meperidine	B-0521	0.16	0.06	2.7			0.08	1.7		PP	phenylethidine
	C-0546	5.7	1.8	3.2			2.6	12.1		OD	
	C-0582	1.4	1.2	1.2			10.0			OD/ETOH (0.18)	
	C-0863	1.8	1.3	1.4			6.6			PP	promethazine
	D-1647	3.2	1.7	1.9			13.0			OD/ETOH (0.11)	
	E-0476	0.38	0.16	2.4			1.1			PP	butalbital, caffeine, codiene, diazepam
	F-0003	0.85	0.39	2.2			2.9			U	
	F-1457	0.87	<0.13							ASP	
	F-1816	0.07	0.07	1.0						CVD	
	F-2398	0.13	0.14	0.93						PP	propoxyphene, promethazine

Mephencyoin	F-0745	0.97	1.06	0.92	2.52	U	
Meprobramate	D-0078	25.0	17.0	1.47		PP	propoxyphene
	D-0156	7.1	7.7	0.92		TR/E/TOH (0.27)	
	D-2196	41.1	40.4	1.0	62.0	PP	propoxyphene
	D-2512	46.9	43.2	1.1	58.4	PP	propoxyphene
	E-0544	22.2	20.8	1.1	46.2	PP	diphenhydramine
	E-1965	23.7	20.1	1.2	42.3	PP	codeine, diphenhydramine
	E-2252	62.0	63.0	0.98	161.0	PP	carbamazepine
	F-0000	2.1	2.2	0.95	4.3	U	
Mesoridazine	B-0325	4.0	3.0	1.3	21.9	PP	amitriptyline
	E-0936	2.1	1.2	1.8	7.4	PP	antipyrine
	F-0341	0.33	0.84	0.39	5.8	OD	thioridazine
	F-0560	0.27	0.24	1.1	2.6	CVD	
	F-0995	0.70	0.70	1.0	1.1	TR	
	F-1729	0.43	2.0	0.22	6.0	U	thioridazine
	F-2235	0.95	0.50	1.9	5.3	U	
Methadone	D-2479	1.3	0.90	1.4	5.7	OD	
	E-0527	0.77	0.88	0.88	6.8	PP	doxepin
	F-0421	0.84	0.72	1.2	5.6	OD	
	F-1507	0.13	0.16	0.81	1.0	PP	triazolam, FB = 0.04
	F-1746	1.3	1.1	1.2	6.4	PP	nordiazepam
Methamphetamine	D-0846	0.33	0.22	1.5	1.7	OD	drug-induced cardiac arrhythmia
	F-0465	0.10	0.10	1.0	0.38	TR	
	F-1312	2.3	0.60	3.8	2.9	OD	
	F-1905	1.8	1.1	1.6	2.7	TR	
	F-2224	2.1	1.2	1.8	1.4	TR	
Metoclopramide	F-0615	0.58	0.42	1.4	2.0	CVD	diphenhydramine, trazodone
	F-1167	2.0	1.8	1.1	1.4	CVD	diphenhydramine
	F-2361	1.1	1.4	0.79	4.4	PP	diacepam, FB = 0.27; nordiazepam, FB = 0.37
Metoprolol	E-0791	68.9	18.0	3.8	167.0	PP	diphenhydramine
Morphine	F-2063	0.08	0.07	1.2	0.22	PP	diacepam, FB = 0.27; nordiazepam, FB = 0.37
Nordiazepam	B-0096	1.5	0.75	2.0	6.3	PP	maprotiline
	B-1222	1.3	0.97	1.3	5.3	PP	propoxyphene
	C-1299	0.08	0.08	1.0	0.46	CVD	
	D-2404	0.27	0.27	1.0		CVD	
	E-0015	0.44	0.20	2.0	4.2	PP	amitriptyline
	E-0476	0.30	0.30	1.0	2.1	PP	butalbital, caffeine, codeine, meperidine
	E-1837	3.1	3.5	0.89	13.6	PP/E/TOH (0.07)	chloridazepoxide, doxepin
	F-0129	0.81	0.61	1.3	3.9	PP	maprotiline
	F-0580	1.3	0.74	1.8	4.9	TR	
	F-0633	6.7	5.8	1.2	15.8	PP	doxepin

TABLE 3—Continued.

Drugs	Case	HB	FB	HB/FB	SB	VH	L	B	K	Cause of Death	Comments
Norfloxacin	F-0980	3.5	3.9	0.90			16.0			PP	propoxyphene, diphenhydramine
	F-1457	0.33	0.34	0.97			3.9	1.5		ASP	
	F-1498	0.40	0.36	1.1			2.2			U	
	F-1578	0.35	0.25	1.4			5.0			TR	methadone
	F-1746	1.2	0.58	2.1			3.2	2.8		PP	diazepam
	G-0251	0.39	0.43	0.91			2.1			TR	
	A-1342	1.2	0.41	3.0			100.5	8.3	1.0	PP/ETOH (0.07)	amitriptyline, diphenhydramine
	B-0128	0.47	0.08	5.9			0.99		9.7	U	
	B-1276	14.4	2.9	5.0			36.8	6.5	7.0	OD	
	B-2417	0.44	0.38	1.2			29.0			PP	diphenhydramine
	D-0031	0.70	0.83	0.84			37.7			PP	methadone
	E-0527	1.1	0.30	3.7			20.1			PP	codeine, trazodone
	E-0804	2.6	0.90	2.9			99.0			PP/ETOH (0.07)	chlorthalazepoxide
	E-1837	1.1	0.50	2.2			21.0			OD	nordiazepam
	F-0008	6.4	6.2	1.0			58.1	24.4		PP	
F-0633	1.0	0.95	1.1			8.8	3.2		OD/ETOH (0.22)		
G-0344	1.5	1.5	1.0			8.4			OD		
F-1259	0.65	0.25	2.6			7.0			OD/ETOH (0.18)		
C-0546	1.6	0.34	4.7		1.0	10.2			OD/ETOH (0.11)		
C-0582	0.40	0.50	0.80			2.4			PP	butalbital, caffeine, codeine, diazepam, diphenhydramine	
D-1647	1.7	0.83	2.1			0.40			U		
E-0476	0.30	<0.10							ASP		
F-0003	0.06	<0.06							CVD		
F-1457	0.27	<0.08							OD		
F-1816	0.72	0.46	1.6						OD		
A-1843	1.1	0.40	2.8			9.1			OD		
A-1890	22.6	1.9	11.9		2.2	240.0			OD		
B-1222	2.0	1.3	1.5			30.8			PP	diazepam	
B-2441	0.27	0.18	1.5			3.0			OD/ETOH (0.18)		
C-2514	8.2	4.6	1.8			46.3			OD		
D-0078	4.7	1.4	3.4			42.0			PP	carisoprodol	
D-0298	0.40	0.16	2.5			5.5			OD/ETOH (0.16)		
D-2174	2.8	1.7	1.7			15.7			OD/ETOH (0.11)		
D-2196	7.9	7.6	1.0			13.5			PP	carisoprodol	
D-2334	4.0	5.0	0.80			99.1			OD		
D-2512	3.7	3.3	1.1			91.5			PP	carisoprodol	
E-0123	4.7	0.57	8.1		0.40	58			OD		

TABLE 3—Continued.

Drugs	Case	HB	FB	HB/FB	SB	VH	L	B	K	Cause of Death	Comments
Oxazepam	F-0490	0.27	0.21	1.3			0.87			PP	phenobarbital, phenytoin, temazepam
	D-1133	6.4	5.2	1.2			148.0			OD/ETOH (0.22) CVD	
Pentazocine	D-2404	0.08	0.06	1.3							
	F-0768	20.4	11.7	1.7			84.9			OD CVD	
Phencyclidine	F-1816	0.99	1.0	0.99							
	B-0521	0.50	0.15	3.3		0.17	1.3			PP	meperidine
Phenobarbital	C-1251	0.14	0.08	1.8			0.19			TR	drug-induced cardiac arrhythmia propoxyphene cocaine
	C-1299	0.12	0.12	1.0			0.54			CVD	
	D-1717	0.37	0.40	0.93		0.23	2.4			OD	
	E-0224	0.01	0.01	1.2			0.04			PP	
	E-0594	0.07	0.07	1.0			0.16			PP	
	F-0379	0.06	0.07	0.86			0.34			TR	
	F-0393	0.19	0.22	0.86			1.6			CVD	
	F-0543	0.05	0.03	1.7				1.7		TR	
	F-1017	0.08	0.12	0.67		0.10	0.33			TR	
	F-1498	0.01	0.02	0.50			0.08			U	
Phenobarbital	D-1848	59.0	54.0	1.1			31.0			OD	butalbital, carisoprodol, HB = 0.60; meprobamate, HB = 6:7
	F-0001	21.6	24.5	0.88						PP	
Phentermine	F-0087	1.8	1.4	1.3			4.6			TR	phenytoin, temazepam
	F-0436	17.9	14.9	1.2			35.2			TR	
	F-0465	6.8	6.8	1.0			17.6			TR	
	F-0470	21.2	18.3	1.2		11.5	44.0			TR	
	F-0490	51.3	49.7	1.0			114.0			PP	
	F-0745	30.3	31.8	0.95		21.0	63.8			U	
	F-0988	1.6	1.4	1.1		1.1	2.7			TR	
	F-1060	17.8	17.6	1.0			8.8			CVD	
	F-1454	1.1	1.0	1.1			2.1			ASP	
	F-1564	10.8	10.4	1.1						TR	
Phenylethylmalonamide	D-2224	0.17	0.09	1.9						CVD	
	F-1288	1.1	0.84	1.3		1.3	4.4			TR	
Phenytoin	F-0470	12.5	12.2	1.0		10.4	17.6			TR	
	F-1040	3.2	3.3	0.97		2.9				CVD	
Phenytoin	F-0465	4.0	5.4	0.74			20.8			TR	phenobarbital, temazepam
	F-0470	4.9	4.7	1.0			18.0			TR	
	F-0490	3.1	3.2	0.97			13.2			PP	

Primadone	F-0995	15.6	15.9	0.98	56.6	TR	
	F-1060	1.9	2.1	0.90		CVD	
	F-1607	7.0	11.4	0.64		CVD/ETOH (0.29)	
	F-2075	0.40	0.34	1.2	1.2	CVD	
	F-0470	18.4	18.1	1.0	9.9	TR	
	F-1060	1.8	1.8	1.0	1.7	CVD	
Promethazine	C-0863	0.18	0.10	1.8	3.1	PP	meperidine
	D-2358	2.3	1.4	1.6	11.4	OD	
	E-2333	1.1	0.65	1.6	21.8	PP	butalbital, codeine
	F-1500	1.8	0.89	2.0	39.7	PP	propoxyphene
	F-2398	0.68	0.68	1.0	6.5	PP	meperidine, propoxyphene
Propoxyphene	A-1843	4.4	0.40	11.0	69.1	OD	
	A-1890	5.0	1.0	5.0	0.57	OD	
	B-1222	2.2	1.3	1.7	33.2	PP	diazepam
	B-2441	4.4	2.6	1.7	39.2	OD/ETOH (0.18)	
	C-2514	3.8	2.9	1.3	17.5	OD	
	D-0078	3.7	0.61	6.1	29.0	PP	carisoprodol
	D-0298	3.0	0.79	3.8	10.4	OD/ETOH (0.16)	
	D-2174	2.8	1.4	2.0	18.3	OD/ETOH (0.11)	
	D-2196	2.6	1.8	1.4	43.8	PP	carisoprodol
	D-2334	1.9	1.6	1.2	13.7	OD	
	D-2512	1.4	1.5	0.93	20.1	PP	carisoprodol
	E-0123	8.8	0.66	13.3	208.0	OD	
	E-0224	4.3	1.9	2.3	164.7	PP	phenacyclidine
	E-1479	9.8	2.3	4.3	38.8	PP	alprazolam, doxepin
	F-0374	1.5	1.3	1.2	5.7	OD	
	F-0980	4.6	3.3	1.4	1.7	PP	diphenhydramine, diazepam
	F-1472	0.47	0.68	0.69	3.2	PP	butalbital, diphenhydramine
	F-1500	4.6	1.5	3.1	72.8	PP	promethazine
	F-1674	0.31	0.12	2.6	0.78	OD	24-h survival
	F-2398	0.78	0.76	1.0	1.7	PP	meperidine, promethazine
Quinine	F-1167	4.9	3.5	1.4	1.8	CVD	
	F-2180	2.2	3.4	0.65		TR	
Saficylate	F-0261	1010.0	1048.0	0.96		OD	
Secobarbital	E-0248	9.4	5.3	1.8	12.0	PP	amobarbital
	F-0436	1.8	1.5	1.2	8.2	TR	
Temazepam	F-0490	0.90	0.48	1.9	3.1	PP	phenobarbital, phenytoin
	F-2351	0.60	0.57	1.1		U	
Thioridazine	B-0325	3.5	1.8	1.9	3.3	PP	amitriptyline
	E-0936	2.1	0.80	2.6	32.7	PP	antipyrine

TABLE 3—Continued.

Drugs	Case	HB	FB	HB/FB	SB	VH	L	B	K	Cause of Death	Comments
	F-0341	1.5	3.8	0.40			43.0			OD	
	F-0560	0.75	0.27	2.8			13.5	2.8		CVD	
	F-0745	0.38	0.40	0.95			2.5			U	
	F-0995	2.7	2.7	1.0			36.0			TR	
	F-1664	0.27	0.32	0.84			0.75	0.58		PP	amitriptyline, butalbital, cocaine
	F-1729	1.9	2.2	0.86			16.0			U	
	F-2235	1.5	1.7	0.88			27.0	3.4		U	
Trazodone	E-0804	8.9	6.9	1.3			53.0			PP	codeine, doxepin
	F-2361	0.38	0.48	0.79			2.0			PP	diphenhydramine, metoclopramide
Trichloroethanol	E-0757	80.2	23.7	3.4						PP	temazepam, HB = 0.48
Trifluoperazine	F-0085	0.16	0.23	0.70			1.8			PP	benztropine
Trimipramine	C-2133	9.5	3.0	3.2			180.6			OD/ETOH (0.15)	
Verapamil	B-0773	9.3	5.4	1.7			89.0			OD	
	F-1453	0.55	0.56	0.98			4.6			CVD	

^aHB = heart blood,
 FB = femoral blood,
 SB = subclavian vein blood,
 VH = vitreous humor,
 L = liver,
 B = brain,
 K = kidney,
 OD = death as a result of drug overdose,
 PP = death as a result of multiple drug overdose,
 ETOH = ethyl alcohol (blood concentration in g/dL),
 CVD = death as a result of cardiovascular disease,
 TR = death as a result of trauma,
 ASP = death as a result of aspiration of food, and
 U = cause of death undetermined.

for comparison. In the vast majority of cases, the heart blood-drug concentrations exceeded that of femoral blood. There are exceptions, however, and they can be significant (see amitriptyline, Case B-1069 and diphenhydramine, Case D-0031 in Table 3). These data clearly indicate a site dependence for drug concentrations in postmortem blood specimens. The difficulty of attempting a volume of distribution calculation to determine the amount of drug ingested is obvious.

There were two groups of cases in which the drug concentration in the heart and femoral blood did not appear to differ significantly. One was that in which advanced decomposition had occurred; the second was that in which extensive resuscitation attempts were made before death. Data from these two types of cases are presented in Tables 4 and 5, respectively.

The author's previous experience with postmortem specimens indicated that in vitro change was not likely the reason for the observed differences in the heart and femoral blood-drug concentrations. In vitro stability of several drugs has been documented by other authors [17-19]. Repeat analyses were conducted for several analytes to estimate the degree of in vitro change for a period of time that would greatly exceed that between specimen collection and assay. These data, presented in Table 6, indicate that in vitro change was not a significant factor. Cocaine and drugs with similar stability problems were not included in this study.

It is recognized that during the absorption phase of ethyl alcohol the blood-alcohol concentration in arterial blood is often greater than that in venous blood [20,21]. Williams [22] has reported that this phenomenon occurs during the absorption of tricyclic anti-depressants in mongrel dogs. It is to be expected that a similar situation occurs in humans during the absorption of a large oral dose of a drug.

In many instances, distribution as a result of absorption may be contributory to site dependence, but, for several reasons, it cannot account for all of the observed differences in concentrations of heart and femoral blood. Although site dependence tended to be more pronounced in overdose cases, it was often observed in therapeutic cases and in those in which the blood concentrations were not significantly elevated. In addition, metabolite concentrations, as well as parent drugs, exhibited a site dependence. Furthermore, there did not appear to be any relationship between the amount of drug remaining in the gastric and the observed heart:femoral blood-drug ratio as illustrated in Table 7. Cases involving parenteral drug administration also exhibited site dependence; these data are presented in Table 8. In a recent report, Jones [23] presented data from several cases in which site dependence was observed and absorption was deemed not to be a factor.

TABLE 4—Heart blood and femoral blood concentrations (mg/L) and ratios in decomposed cases.^a

Case	Drug	HB	FB	HB/FB
B-1069	amitriptyline	1.2	1.9	0.63
	nortriptyline	1.0	1.1	0.91
D-1102	amitriptyline	2.0	1.5	1.3
D-0031	diphenhydramine	1.7	3.8	0.45
	doxepin	3.3	3.9	0.85
	nordoxepin	0.70	0.83	0.84
D-0482	amitriptyline	3.1	2.7	1.2
	nortriptyline	1.7	2.4	0.71
D-0015	amitriptyline	2.7	2.3	1.2
	nortriptyline	1.3	1.3	1.0
	chlordiazepoxide	1.4	1.1	1.3

^aHB = heart blood and FB = femoral vein blood.

TABLE 5—Heart blood and femoral blood drug concentrations (mg/L) and ratios in cases involving extensive resuscitation.

Case	Drug	HB	FB	HB/FB Ratio
B-1077	amitriptyline	7.2	8.7	0.83
	nortriptyline	1.1	2.2	0.50
	diazepam	0.12	0.16	0.75
D-0482	amitriptyline	3.1	2.8	1.1
	nortriptyline	1.7	2.4	0.71
B-0509	amoxapine	3.4	1.4	2.4
D-0846	methamphetamine	0.25	0.22	1.1
D-2479	methadone	1.3	0.90	1.4
D-1133	pentazocine	6.4	5.2	1.2
C-1299	phencyclidine	0.12	0.12	1.0
	diazepam	0.04	0.05	0.92
	nordiazepam	0.08	0.08	1.0
D-1717	phencyclidine	0.37	0.40	1.0
D-1704	propoxyphene	2.3	1.2	1.9
D-2174	propoxyphene	2.8	1.4	2.0
	norpropoxyphene	2.8	1.7	1.7
D-2196	propoxyphene	2.6	1.8	1.4
	norpropoxyphene	7.9	7.6	1.0
	carisoprodol	19.2	16.4	1.2
D-2334	meprobamate	41.1	40.4	1.0
	propoxyphene	1.9	1.6	1.2
	norpropoxyphene	4.0	5.0	0.80

*HB = heart blood and FB = femoral vein blood.

TABLE 6—*In vitro* changes of drug concentration.

Analyte	Original Assay, $\mu\text{g/mL}$	Repeat Assay, $\mu\text{g/mL}$	Interval, Days
Amitriptyline	3.9	2.8	6
Nortriptyline	6.3	6.2	6
Doxepin	1.1	0.86	6
Nordoxepin	1.1	1.2	6
Diphenhydramine	1.5	1.4	6
Amitriptyline	1.8	1.4	6
Nortriptyline	2.4	2.1	6
Doxepin	0.51	0.45	6
Nordoxepin	0.27	0.25	6
Diphenhydramine	0.80	0.74	6
Doxepin	14.9	14.0	60
Nordoxepin	2.0	1.8	60
Doxepin	5.6	5.6	60
Nordoxepin	1.5	1.5	60
Amoxapine	4.7	4.5	120
Amoxapine	7.5	6.0	120
Amoxapine	3.1	3.4	230
Amoxapine	2.0	1.8	230
Amoxapine	1.8	1.4	230
Amoxapine	3.9	2.7	230

TABLE 7—Comparison of heart and femoral blood-drug concentrations (mg/L) and the amount of drug remaining in the gastric contents (mg total).

Drug	Case	HB	FB	Gastric	HB/FB
Amitriptyline	C-2368	1.6	1.5	0	1.1
	B-1077	7.2	8.7	5	0.80
	E-1631	4.5	1.2	6	3.8
	F-0428	0.90	1.8	6	0.50
	B-0968	2.5	0.20	6	12.5
	B-1069	1.2	1.9	17	0.60
	F-0928	6.8	3.4	25	2.0
	F-0407	1.2	0.30	31	4.0
	C-1962	2.6	1.4	31	1.9
	E-0015	2.7	2.3	33	1.2
	C-0970	1.5	0.51	34	2.9
	B-1423	10.2	1.7	49	6.0
	E-0138	0.71	1.3	89	0.54
	C-2322	7.3	6.0	91	1.2
	C-1592	13.2	2.7	94	4.9
	F-1664	1.9	0.85	131	2.2
	E-0467	7.7	1.1	296	7.1
	E-1787	5.2	2.6	421	2.0
	F-1616	3.5	4.9	435	0.71
	F-0164	15.6	6.4	454	2.4
E-1503	7.6	1.7	522	4.5	
D-2313	5.6	0.90	714	6.2	
C-0962	43.2	8.7	892	5.0	
E-2094	3.4	0.8	1379	4.3	
Amobarbital	E-0248	11.6	7.2	2	1.6
	B-0509	3.4	1.4	20	2.4
	A-0802	13.0	5.3	49	2.5
	D-0537	9.2	5.3	180	1.7
	D-1241	15.1	14.1	6400	1.1
Amphetamine	E-1926	1.0	0.50	0	2.0
Benztropine	F-0085	0.60	0.64	0	0.94
Brompheniramine	F-1498	0.56	0.20	0	2.8
Butalbital	E-0476	45.6	22.9	1	2.0
	C-1962	2.6	3.7	2	0.70
	F-1472	15.5	17.9	3	0.87
Caffeine	E-0476	75.3	35.8	1	2.1
Carbamazepine	F-1145	12.6	11.0	67	1.2
Carisoprodol	D-2196	19.2	16.4	143	1.2
	D-2512	54.8	49.2	8200	1.1
Chlordiazepoxide	E-1837	0.40	0.40	78	1.0
Chlorpheniramine	F-0777	2.2	0.93	20	2.3
Chlorpromazine	D-2211	1.4	1.4	0	1.0
	F-0580	0.95	0.60	3	1.6
	B-0927	1.5	0.79	4	1.9
	E-0872	0.94	0.35	28	2.7
	E-0850	10.9	4.4	286	2.5
	D-2320	5.5	4.2	1900	1.3
Chlorzoxazone	F-0430	12.2	9.1	106	1.3
Codeine	E-0804	3.0	1.6	1	1.9
	D-0677	8.1	2.3	6	3.5
	E-0476	0.70	0.60	40	1.2
	D-0354	46.0	20.0	296	2.3
Desipramine	C-1260	11.9	2.1	139	5.7
	G-0008	12.5	3.2	409	3.9
	F-1487	9.2	5.8	498	1.6
Dextromethorphan	F-1041	0.50	0.22	1	2.3
	F-0777	2.2	0.99	22	2.2
	F-0980	3.6	3.5	0	1.0
	E-0476	2.1	1.4	444	1.5

TABLE 7—Continued.

Drug	Case	HB	FB	Gastric	HB/FB	
Diphenhydramine	C-0653	13.5	6.5	0	2.1	
	F-0980	4.7	3.1	0	1.5	
	E-1965	2.6	1.2	1	2.2	
	E-1177	3.0	2.8	56	1.1	
	E-0791	1.1	0.55	72	1.9	
	F-0372	1.7	1.5	76	1.1	
	C-2142	28.0	13.8	230	2.0	
	E-1058	20.4	11.9	360	1.7	
	D-1567	19.4	10.1	993	1.9	
	Doxepin	E-0804	14.8	4.1	1	3.6
E-0918		6.8	3.9	26	1.7	
E-1081		2.5	0.80	31	3.1	
E-1837		3.7	2.1	50	1.8	
B-1276		31.4	5.7	54	5.5	
F-0008		5.4	7.0	94	0.77	
E-1071		7.2	5.6	160	1.3	
C-2256		16.8	2.2	439	7.6	
D-2168		7.0	2.2	483	3.2	
E-0478		6.0	2.0	585	3.0	
F-0633		6.2	4.8	2310	1.3	
Doxylamine		F-0372	2.6	2.1	31	1.2
		F-0777	9.4	9.3	63	1.0
Fluoxetine	F-1259	0.80	0.23	414	3.5	
Imipramine	F-1944	15.1	6.8	70	2.2	
	F-0385	2.9	2.1	98	1.4	
	E-1503	4.4	1.5	115	2.9	
	E-2094	1.8	0.60	454	3.0	
Maprotiline	B-1081	10.6	1.0	61	10.6	
	B-0096	2.6	1.9	98	1.4	
	F-0129	2.4	2.7	140	0.89	
	B-0869	35.0	16.0	1590	2.2	
Meperidine	B-0521	0.16	0.06	0	2.7	
	C-0582	1.4	1.2	0	1.2	
	C-0546	5.7	1.8	1	3.2	
	E-0476	0.38	0.16	55	2.4	
Mesoridazine	E-0936	2.1	1.2	139	1.8	
Metoclopramide	F-1167	2.0	1.8	1	1.1	
Methadone	F-1507	0.13	0.16	1	0.81	
	F-1746	1.3	1.1	3	1.2	
	F-0421	0.84	0.72	22	1.2	
Methamphetamine	E-1926	2.3	1.0	0	2.3	
Nordiazepam	F-0633	6.7	5.8	409	1.2	
Nortriptyline	E-0787	1.5	1.9	34	0.79	
Pentazocine	D-1133	6.4	5.2	7	1.2	
Pentobarbital	F-0768	20.4	11.7	156	1.7	
Phencyclidine	C-1251	0.14	0.08	0	1.9	
	B-0521	0.50	0.15	0	3.3	
Phenobarbital	D-1848	59.0	54.0	0	1.1	
	F-0490	51.3	49.7	1	1.0	
	F-0470	21.2	18.3	2	1.2	
Phentermine	F-1288	1.1	0.84	1	1.3	
Phenytol	F-0470	4.9	4.7	46	1.0	
	F-0490	3.1	3.2	82	0.97	
Primidone	F-0470	18.4	18.1	44	1.0	
Propoxyphene	D-1704	2.3	1.2	<1	1.9	
	F-0980	4.6	3.3	0	1.4	
	E-1479	9.8	2.3	2	4.3	
	A-1890	5.0	1.0	4	5.0	
	D-2196	2.6	1.8	5	1.4	
	F-1472	0.47	0.68	15	0.69	

TABLE 7—Continued.

Drug	Case	HB	FB	Gastric	HB/FB
	F-1500	4.6	1.5	21	3.1
	D-2174	2.8	1.4	36	2.0
	E-0123	8.8	0.66	83	13.3
	A-2408	4.2	0.46	99	9.1
	D-0298	3.0	0.79	111	3.8
	B-2441	4.4	2.6	375	1.7
	D-2334	1.9	1.6	638	1.2
	A-1843	4.4	0.40	648	11.0
	D-2512	1.4	1.5	1500	0.90
Quinine	F-1167	4.9	3.5	4	1.4
Secobarbital	E-0248	9.4	5.3	2	1.8
Temazepam	F-0490	0.90	0.48	1	1.9
Thioridazine	F-0560	0.75	0.27	0	2.8
	F-2235	1.5	1.7	2	0.88
	E-0936	2.1	0.80	39	2.6
Trazodone	E-0804	8.9	6.9	1	1.3
Trifluoperazine	F-0085	0.16	0.23	43	0.70
Trimipramine	C-2133	9.5	3.0	86	3.2
Verapamil	B-0773	9.3	5.4	4	1.7

Several factors have been proposed as to the reason for the observed site dependence of drug concentration. Included among these are tissue autolysis [1,12,13], changes in pH [13,24] or ionic strength [24], and depletion of energy-dependent binding processes [13]. However, a very recent report [25] does not lend credence to the hypothesis that changes in pH are the cause of drug release. Whatever the reason, the release of drug from drug-rich tissues, such as heart, lung, or liver, would cause an elevation of drug concentration in the blood adjacent to the tissue. Subsequent movement of the drug-rich blood into other parts of the vasculature would change the concentration of drug from that at the time of death. The amount of change would be a function of how much drug was released from a given tissue and the degree and direction of movement of the blood adjacent to the releasing tissue.

Fallini [26] has demonstrated that there is significant postmortem movement of blood through the vasculature. He has characterized an elaborate series of phases or stages of movement, during which he states that there is much less movement of blood with time in the vessels that are the most distal to the heart and lung area. This movement is above and beyond any fluid movement caused by gravity as a result of the original position of the body or that associated with repositioning of the body after death.

In an elegant experimental design, Jones and Pounder [6] have demonstrated that for two highly tissue-bound drugs the concentration of drug was indeed less for femoral and other peripheral sites than the concentration in heart blood or blood taken from vessels near the heart.

The postmortem movement of blood according to Fallini [26] was in large part caused by the pressure that results from the gases that accompany the early stages of decomposition. If increased movement is associated with increasing decomposition, it would follow that in cases of advanced decomposition there would be significant drug release from the tissues and also sufficient time for mixing of the blood from various sites. The data in Table 4 are consistent with such an hypothesis. The authors originally thought that the data in Table 5 was most likely the result of a similar mechanism, that is, prolonged resuscitation attempts promoted a mixing of the blood from many sites. However, a more detailed examination of these data indicated that these cases may be a reflection of the postmortem interval. The interval between death and autopsy was short in most of these

TABLE 8—Drug concentrations (mg/L) and ratios in cases involving parental administration.^a

Case	Drug	HB	FB	HB/FB
C-0546	meperidine	5.7	1.8	3.2
	normeperidine	1.6	0.34	4.7
C-0863	meperidine	1.8	1.3	1.4
	promethazine	0.18	0.10	1.8
D-1647	meperidine	3.2	1.7	1.9
	normeperidine	1.7	0.80	2.1
D-2358	promethazine	2.3	1.4	1.6
E-0038	methamphetamine	0.37	0.27	1.4
E-0594	cocaine	0.74	0.84	0.88
	benzoylecgonine	7.7	7.7	1.0
	phencyclidine	0.07	0.07	1.0
E-1100	meperidine	0.32	0.20	1.6
E-1188	meperidine	2.1	1.7	1.2
	normeperidine	0.42	0.41	1.0
E-1287	cocaine	2.7	4.7	0.57
	benzoylecgonine	5.0	4.9	1.0
E-1520	cocaine	7.7	5.0	1.5
	benzoylecgonine	5.5	1.8	3.1
E-1781	cocaine	9.2	5.7	1.6
	benzoylecgonine	27.0	10.5	2.6
E-1872	cocaine	0.02	0.01	2.0
	benzoylecgonine	5.5	4.4	1.3
	methamphetamine	0.04	0.03	1.3
	amphetamine	0.16	0.13	1.2
E-1926	methamphetamine	2.3	1.0	2.3
	amphetamine	1.0	0.49	2.0
F-0526	cocaine	4.1	4.1	1.0
	benzoylecgonine	3.7	3.4	1.1
F-1312	methamphetamine	2.3	0.60	3.8
F-1728	cocaine	1.6	1.8	0.89
	benzoylecgonine	5.2	2.9	1.8
F-1741	cocaine	1.0	1.2	0.83
	benzoylecgonine	5.3	1.5	3.5
F-2063	morphine	0.08	0.07	1.1
F-2341	promethazine	0.07	0.04	1.8
F-2398	promethazine	0.68	0.68	1.0
	meperidine	0.13	0.14	0.93

^aHB = heart blood and
FB = femoral vein blood.

cases; however, there is a general trend that the longer the postmortem interval, the greater the difference in the heart:femoral drug concentration ratio. We are continuing to study these types of cases to determine if they exhibit a quantifiable relationship between changes in concentration and time.

It is apparent from an inspection of the authors' data and that of many other investigators that a site dependence for postmortem drug concentrations is a very real phenomenon that must be acknowledged and dealt with accordingly. The existence of site dependence will not dramatically affect the interpretation of many overt drug overdoses, for the concentrations in blood specimens from all sites is usually sufficiently high to

TABLE 9—Drug concentration (mg/L) in heart, femoral, and subclavian bloods and ratios.^a

Case	Drugs	HB	FB	SB	SB/HB	SB/FB
A-0860	amoxapine	0.28	0.20	0.22	0.79	1.1
A-1087	amoxapine	3.9	2.5	2.0	0.51	0.80
A-1541	doxepin	4.2	2.1	5.3	1.3	2.5
	nordoxepin	1.8	0.85	1.7	0.94	2.0
A-1841	amitriptyline	0.47	0.18	0.25	0.53	1.4
	imipramine	1.4	0.63	0.85	0.61	1.4
A-1977	amitriptyline	0.09	0.15	0.12	1.3	0.80
	nortriptyline	0.49	0.40	0.44	0.90	1.1
A-2044	amitriptyline	1.7	0.42	0.92	0.54	2.2
	nortriptyline	0.40	0.22	0.30	0.75	1.4
	trazodone	8.2	4.8	7.0	0.85	1.5
	trimipramine	0.88	0.19	0.46	0.52	2.4
A-2045	amitriptyline	7.9	4.3	6.8	0.86	1.6
	nortriptyline	2.1	1.1	1.6	0.76	1.5
A-2224	amitriptyline	4.9	3.1	4.6	0.94	1.5
	nortriptyline	5.3	2.6	3.5	0.66	1.4
A-2327	amitriptyline	0.09	0.10	0.06	0.64	0.78
	nortriptyline	0.11	0.09	0.07	0.64	0.60
A-2408	amitriptyline	2.1	0.14	3.0	1.4	21.4
	nortriptyline	0.08	...	0.37	4.6	...
	propoxyphene	4.2	0.46	4.6	1.1	10.0
	norpropoxyphene	2.1	...	4.5	2.1	...
B-0128	doxepin	3.1	0.60	4.7	1.5	7.8
B-0325	amitriptyline	0.98	0.91	0.84	0.86	0.92
	nortriptyline	1.4	1.0	0.93	0.66	0.93
	mesoridazine	4.0	3.0	3.5	0.88	1.2
	thioridazine	3.5	1.8	3.3	0.94	1.8
B-0507	amitriptyline	1.3	0.18	0.94	0.72	5.2
	nortriptyline	0.36	0.18	0.45	1.3	2.5
	propoxyphene	1.6	0.76	1.8	1.1	2.4
	norpropoxyphene	3.2	1.7	3.8	1.2	2.2
B-1944	amitriptyline	...	0.97	3.1	...	3.2
	nortriptyline	...	0.15	0.44	...	2.9
	amoxapine	...	0.68	1.3	...	1.9
F-1230	amitriptyline	...	0.29	0.98	...	3.4
	diazepam	...	0.57	1.0	...	1.8
	nordiazepam	...	0.47	0.68	...	1.5
F-1487	butalbital	0.31	...	0.37	1.2	...
F-1585	doxepin	...	0.60	0.90	...	1.5
	nordoxepin	...	1.0	1.0	...	1.0
	trimethobenzamide	...	0.83	1.7	...	2.1

^aHB = heart blood.

FB = femoral vein blood, and

SB = subclavian vein blood.

render an unmistakable interpretation. However, there are situations in which postmortem redistribution of drugs could significantly impact the interpretation of analytical findings. Cases involving drivers who were killed as a result of a motor vehicle crash require special consideration. For example, the authors were asked to assess the significance of a drug concentration (intoxication, suicidal intent, and so forth) of a driver in such a case in which the amitriptyline and nortriptyline heart blood concentrations were 1.7 and 2.1 $\mu\text{g}/\text{mL}$, respectively. No femoral blood was available. It would have been difficult or impossible to interpret correctly this case without measuring the concentration of the drugs in the liver which revealed the following concentrations, amitriptyline, 2.0 $\mu\text{g}/\text{g}$, and nortriptyline, 4.7 $\mu\text{g}/\text{g}$. Subsequent investigation revealed a history consistent with the interpretation of therapeutic dosing as indicated by the liver data. The data in Table 3 indicate that similar problems are likely to occur with a variety of drugs of abuse.

Numerous cases have presented themselves over the last several years that clearly illustrate the difficulty or impossibility of rendering an informed opinion as to the role of drugs in the death of an individual when only a heart blood concentration is available to the toxicologist. Cases have appeared in which the heart blood concentration of a tricyclic antidepressant was determined to have been in the range of 0.8 to 1.5 $\mu\text{g}/\text{mL}$; yet, an in-depth investigation of the case presented no evidence of acute or chronic overdosage with the drug. Without supporting femoral blood or tissue concentrations or both to place the heart blood concentration in perspective, an incorrect interpretation of the findings would have been likely. The utility of peripheral blood specimens and tissue concentrations in interpretative forensic toxicology cannot be overemphasized.

It is not the authors' intent to imply that heart blood concentrations are of no probative value in postmortem investigations, for they are of significant value. However, one must be cognizant of the fact that estimates of dose that are based solely upon heart blood measurements are subject to error and should not be attempted. If one attempts to estimate the dose of a drug by using a concentration measured in postmortem blood, a better estimate can usually be made by collecting the blood from a femoral vein or some other vessel that is located as far from the central cavity as possible. Subclavian blood is considered by many to be a peripheral specimen, but our studies disclosed that drug concentrations in subclavian specimens are generally greater than those of femoral blood and tend to follow more closely those of the heart blood. A comparison of drug concentrations in subclavian, femoral, and heart bloods is presented in Table 9.

Caution should be taken when collecting peripheral specimens. If at all possible, the vessel should be ligated and the specimens withdrawn distal to the ligation. The authors have analyzed serial samples obtained from nonligated femoral veins and observed that the concentration rose with subsequent sampling until it reached the concentration of the vena cava. For this reason, very large specimens of femoral blood should be viewed with caution, for they most likely represent mixed specimens of femoral and vena cava blood. These precautions and observations have also been advocated by another investigator [23].

Conclusions

The concentrations of drugs in postmortem blood specimens often exhibit a site dependence; heart blood concentrations are usually greater than that in blood from peripheral sites such as the femoral veins. The concentration of drugs in postmortem blood specimens frequently increases with increasing postmortem interval; the change in peripheral specimens appears to be of less magnitude and a slower rate than that of heart blood. For these reasons, one should not attempt to calculate the amount of drug required to produce a measured concentration when the only available blood specimen is post-

mortem heart blood. In many more instances than was previously thought, it is desirable or necessary to analyze peripheral blood and tissue specimens to provide a proper foundation to render an opinion as to the role of a drug in the death of an individual.

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