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Brain Concentrations of Cocaine and Benzoylecgonine in Fatal Cases

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ABSTRACT: Since cocaine in blood rapidly hydrolyzes to benzoylecgonine, cocaine concentrations determined in postmortem blood may not reflect the presence or concentration of cocaine in the body at the time of death. The interpretative value of the determination of cocaine and benzoylecgonine in brain tissue was investigated. Cocaine and benzoylecgonine were quantitated by coextraction and formation of the propyl derivative of benzoylecgonine followed by selected ion monitoring gas chromatography/mass spectrometry (GC/MS) using electron ion impact ionization. Cocaine and benzoylecgonine were found to be evenly distributed throughout the brain. Cocaine and benzoylecgonine concentrations were stable in frozen brain tissue (−4°C) on reanalysis after 1 to 3 months of storage, and in refrigerated tissue (10°C) after 30 days of storage. Blood, brain, and liver concentrations of cocaine and benzoylecgonine in 37 cocaine overdose cases and 46 cases in which cocaine was incidental to the cause of death were reviewed. The ratios of cocaine/benzoylecgonine in the toxic cases (brain mean 14.7 and blood mean 0.64) were clearly different from those found in the incidental cases (brain mean 0.87 and blood mean 0.27). The brain/blood ratios of cocaine and benzoylecgonine concentrations generally were characteristic of the time elapsed since cocaine dosing. In cocaine overdose cases, the mean ratio was 9.6 for cocaine and 0.36 for benzoylecgonine. These are within the range found in animal studies for brain/blood ratios of cocaine and benzoylecgonine 0.5 to 2 h after cocaine administration. In incidental cases, the brain/blood ratios were mean 2.5 for cocaine and 1.4 for benzoylecgonine. These ratios confirm the accumulation of benzoylecgonine in brain tissue and its persistence in the body after disappearance of the parent drug.

KEYWORDS: toxicology, cocaine, benzoylecgonine, brain

Cocaine abuse is increasing in Orange County as it is in many other areas of the United States [*1,2*]. This has resulted in increased numbers of cocaine-induced fatalities as well as increased findings of cocaine or its hydrolysis product, benzoylecgonine, incidental to the cause of death. Recent studies show that cocaine is unstable in blood or aqueous solutions [*3-6*]. For this reason, it may be difficult to draw conclusions from the concentrations found in postmortem blood about the presence or concentration of cocaine in the body at the time of death or about the involvement of the drug in the events leading to death. An alternative approach to answering the question of cocaine's contribution to a death is to determine the body distribution of the drug. In this paper, the concentrations of cocaine and benzoylecgonine found in blood, brain, and liver in 37 toxic cases and 46 incidental cases, from Orange County, California, were reviewed to determine the value of brain and liver tissue analysis as an indicator of the presence or absence of cocaine at the time of death and as an index of the concentrations present at the site of action in the brain at the cessation of circulation.

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Methods

Blood samples were obtained from the heart at autopsy and mixed with sodium fluoride and potassium oxalate. These samples were then refrigerated at 4°C until assayed. Tissue samples obtained at autopsy were frozen until assayed. Blood samples from all coroner's cases submitted for toxicological examination were screened by radioimmunoassay (Abuscreen® for benzoylecgonine, Hoffman LaRoche, Nutley, NJ) for cocaine, benzoylecgonine, and related compounds. Radioimmunoassay-positive blood samples, liver, and brain tissue, as well as nasal swabs and antemortem blood samples (if available from these cases) were then analyzed for cocaine and benzoylecgonine by extraction, derivation, and selected ion-monitoring gas chromatography/mass spectrometry (GC/MS) using electron impact ionization.

Cases reported here are from the years 1979 through 1984. Originally, a modification of the method of Chinn et al [7] was used. Continual modification of this method has occurred. The following procedure was used for blood and tissue quantitation of cocaine and benzoylecgonine.

A stock solution of 10 mg/L each of cocaine and benzoylecgonine was prepared in dimethyl formamide (DMF) and diluted with water just before each assay to obtain standards of 50, 200, and 1000 ng/mL. The internal standard was deuterated cocaine (cocaine-D_3) and deuterated benzoylecgonine (benzoylecgonine-D_3), prepared as a 10 mg/L each stock solution in dimethylformamide (DMF) and diluted 1 : 10 with water just before each assay to make a 1-mg/L working solution. In a screw-cap test tube, 1 mL of blood, 1 g of tissue (as 2 g of 1 : 1 homogenate in water), or 1 mL of standard were added to 1 mL of internal standard working solution with 1 mL of 1.0*M* (pH 7) phosphate buffer. These solutions were mixed and 1.5 g of sodium chloride was added with a premeasured scoop. The tube contents were again mixed. Then, 5 mL of 10 : 1 chloroform : isopropanol were added to the tube and the cap firmly tightened. The mixture was shaken until an emulsion formed (about 1 min). The emulsions were then centrifuged for 5 min at 3000 $\times g$. After centrifugation, the clear supernatant was poured off the blood and tissue samples. If the blood or tissue plug was not less than 15 mm (½ in.) thick, the emulsion was shaken and recentrifuged. This was repeated until the organic layer was well separated. The organic layer was then filtered through washed glass wool in Pasteur pipettes into a clean screw-cap tube. The organic phase was then evaporated to dryness. At this stage, the extract can be stored at room temperature up to a week.

To prepare the propyl ester of benzoylecgonine, approximately 100 μL of DMF and 100 μL of dimethyl formamide dipropyl acetal were added to each of the above extract residues in the screw-cap tubes. This amount was doubled for tissue homogenates. The mixture was refluxed very gently for 30 s over a gas burner and then allowed to stand for 5 min. Three millilitres each of butyl chloride and 0.5*N* sulfuric acid were then added to the tubes which were capped and shaken for 30 s. The tubes were centrifuged and the butyl chloride aspirated from the top of the aqueous layer. A further 3 mL of butyl chloride was added to the tubes, which were shaken, centrifuged, and aspirated. The aqueous layer was then saturated with sodium bicarbonate and a final 3 mL of butyl chloride added. The tubes were shaken 30 s and then centrifuged.

The organic phase was then transferred to a conical bottom disposable test tube and evaporated to dryness. The residue was taken up in 50 μL of chloroform and injected onto a 5-m OV-17 megabore column (0.53 mm in diameter) on a GC/MS (Hewlett-Packard Model 5987) at 270°C. Masses 303 AMU (cocaine), 306 AMU (deuterated cocaine), 331 AMU (propyl benzoylecgonine), and 334 AMU (propyl deuterated benzoylecgonine) were monitored. The ratio of cocaine to deuterated cocaine (internal standard) and the ratio of propyl benzoylecgonine to its deuterated internal standard were used for quantitation. Either peak height or peak areas were used to calculate the ratios.

Results

In 1981, 79 coroner's cases were positive for cocaine, benzoylecgonine, or related compounds by radioimmunoassay. Of these, 46, or 58%, were confirmed by GC/MS. In 1982 and

1983, 112 and 125 cases were positive by radioimmunoassay, and 46 and 63, or 41 and 50%, respectively, of the radioimmunoassay positives were confirmed by GC/MS. In 1984, one year after introduction of a new radioimmunoassay kit based on a double-antibody precipitation method and introduction of the extraction-GC/MS method described in the Methods section, 146 cases were positive by radioimmunoassay and 108 cases, or 75%, were confirmed by GC/MS. This increase in confirmed positives may be due to changes in cocaine use in this jurisdiction as well as to improvements in laboratory methodology and faster turnaround time for blood cocaine analysis.

In 1981, there were 6 cocaine overdose fatalities in Orange County; in 1982, there were 3; in 1983, 8 occurred; and in 1984, there were 23 overdose fatalities. The presence of cocaine or benzoylecgonine was considered incidental (or related) to the cause of death in 40 (1981), 43 (1982), 55 (1983), and 85 (1984) cases where death was caused by accident, traffic accident, homicide, or overdose as a result of other drugs. This increase of incidence in the cases cited here may be due to greater availability, lowered cost, and increased use of cocaine in Orange County, California. In 1984, the amount of cocaine seized by the Orange County Sheriff's Department was more than two-and-one-half times that seized in 1981. For city police agencies in Orange County, cocaine seizures have increased from 10 to 40 times in the same period. The price of cocaine has dropped from $125/g in 1981 to $80 to $100/g in 1984, or from $56 000/kg in 1981 to $37 000/kg in 1984. During this same time, the average purity of the seized drug has increased from approximately 42% in 1981 to 78% in 1984.

Blood, brain, and liver concentrations of cocaine and benzoylecgonine from body distribution studies performed on 37 cocaine overdose fatalities from 1979 to 1984 in this laboratory are shown in Table 1. The mean blood concentrations in these cases were 4.6 mg/L of cocaine (range 0.04 to 31 mg/L) and 7.8 mg/L of benzoylecgonine (range 0.74 to 31 mg/L). The mean brain concentrations were 13.3 mg/kg of cocaine (range 0.17 to 31 mg/kg) and 2.9 mg/kg of benzoylecgonine (range 0.1 to 22 mg/kg). The mean liver concentrations were 6.7 mg/kg of cocaine (range 0 to 393 mg/kg) and 21.3 mg/kg of benzoylecgonine (range 1.3 to 87 mg/kg). Brain cocaine levels exceeded blood levels in 30 of the 34 toxic cases and were most often approximately 4 times the blood concentrations. The mean brain/blood ratio was 9.60 (range 0.65 to 155, mode 3.8, median 3.8) for cocaine (Fig. 1) and 0.36 (range 0.04 to 1.0, mode 0.35, median 0.38) for benzoylecgonine.

Blood, brain, and liver cocaine and benzoylecgonine concentrations from body distribution studies performed in this laboratory during 1979 to 1984 on 46 cases where cocaine was incidental to the cause of death are shown in Table 2. The mean blood concentrations were 0.05 mg/L of cocaine (range 0 to 0.5 mg/L) and 0.88 mg/L of benzoylecgonine (range 0 to 7.4 mg/L). The mean brain concentrations were cocaine 0.12 mg/kg (range 0 to 0.7 mg/kg) and benzoylecgonine 1.4 mg/kg (range 0 to 5.1 mg/kg). The mean liver concentrations were 0.08 mg/kg of cocaine (range 0 to 1.6 mg/kg) and 1.3 mg/kg of benzoylecgonine (range 0 to 10 mg/kg). In 13 of the incidental cases, both blood and brain cocaine concentrations were 0; that is, only benzoylecgonine was detected. In the 25 other cases, the brain cocaine concentration was higher than the blood cocaine levels in 22 cases, including 11 cases in which no cocaine was found in the blood but cocaine was detected in the brain. In five incidental cases, the blood cocaine concentration was higher than that found in the brain.

In the 14 incidental cases in which cocaine was found in both the brain and blood, the mean brain/blood ratio was 2.5 (range 0.6 to 9.2). The mean brain/blood ratio for benzoylecgonine in the incidental cases was 1.4 (range 0.05 to 6.5).

The ratio of cocaine to its hydrolysis breakdown product benzoylecgonine was calculated for each tissue in each case and the values then summed and averaged. The mean ratios of cocaine/benzoylecgonine in the toxic cases were 0.64 for blood (range 0.006 to 1.83), 14.7 for brain (range 0.12 to 100), and 0.50 for liver (range 0.007 to 4.8). The mean ratios of cocaine/benzoylecgonine in the incidental cases were 0.27 for blood (range 0.016 to 1.5), 0.87 for brain (range 0.04 to 6), and 0.48 for liver (range 0.018 to 2).

TABLE 1—*Cocaine overdoses, mg/L or mg/kg.*

Case	Blood		Brain		Liver		Other Drugs	Comments COD
	Cocaine	B.E.	Cocaine	B.E.	Cocaine	B.E.		
1	31	17	30	6	393	82	no	Suicide
2	20	31	20	1.5	71	87	no	Injected cocaine
3	12.8	9.3	19	2.2	6.0	22	no	
4	9.1	20	19	6.0	3.8	45	no	Injected cocaine
5	7	9	18	1.7	49	71		
6	...	...	21	22	35	80	EtOH	Decomposed
7	7	22	27	4	7	53	no	87% pure cocaine
8	6.3	15	27	6.8	2.5	30	given anti-convulsants	Swallowed bindle
9	6.0	17	26	9.0	4.3	47	no	
10	5.8	5.8	22	1.6	3.9	18	EtOH	
11	5	13	15	1	3.3	23	EtOH	Anal suppository of cocaine
12	4.8	17	...	...	2.2	32	no	
13	4.7	3.5	3	0.5	2.7	9.5		
14	4.4	2.4	17	0.8	2.8	1.5	no	Homicide, injected cocaine
15	4.3	2.3	20	0.9	2.2	5.6	no	Rapid death, injected cocaine
16	4.2	4.9	8.1	3.1	0.8	9.8	no	Rapid death, injected cocaine
17	4	4.3	16	2.6	0.8	1.3	no	
18	4	4.3	14	1.1	2.6	14.2	EtOH	
19	3	7.5	...	...	...	...	no	
20	2.6	8.0	10	3	15	3.8	EtOH	Rapid death, 75% pure cocaine
21	2.5	4.3	13	1.1	0.5	12	no	Rapid death
22	2.2	4.0	...	...	...	...	no	
23	2.1	1.2	9.7	0.6	0.6	3.6	no	Convulsions and rapid death
24	2.0	9.9	5.2	1.4	1.4	6.8	no	Jumped from pier
25	1.8	2.2	5.4	0.38	0.4	4.1	no	
26	1.7	5.9	...	...	1.5	12	EtOH	
27	1.6	1.9	10.5	0.8	1.9	6.6	no	Injected cocaine
28	1.6	3.4	1.4	1.5	0.4	5.6	no	Free based cocaine
29	1.5	3.2	10.2	0.7	0.9	8.6	no	Rapid death
30	1.0	5.9	6.4	3.2	1.9	11.5	no	Rapid death
31	0.7	0.7	3.4	0.1	0.9	2.0	no	Injected 70% pure cocaine
32	0.7	4	0.9	1.5	0.32	4.3	morphine	Heroin OD
33	0.6	1.0	2	0.3	0.2	1.9	EtOH	Delusional
34	0.4	6.7	0.5	4.3	0	7.2	no	3 days in hospital
35	0.2	11.3	31.4	...	0.8	13.3	PCP	20 h in hospital
36	0.1	3.1	5.5	2.2	1.0	7.6	no	
37	0.04	1.4	0.17	1.4	0.02	1.9	no	
Ave	4.6	7.9	13.3	2.9	6.7	21.3		

The brain's regional distribution of cocaine and benzoylecgonine were determined for two cases. These results are shown in Table 3. The first case, an overdose, was Case 17 from Table 1. The deceased was a 38-year-old woman. She and a male friend each injected cocaine at his residence. She lost consciousness immediately and he called the paramedics who found her unrevivable. Residue from the syringe she had used contained 1.8 mg of cocaine; the white powder, residue from the glass, and other paraphernalia found at the scene were positive for cocaine.

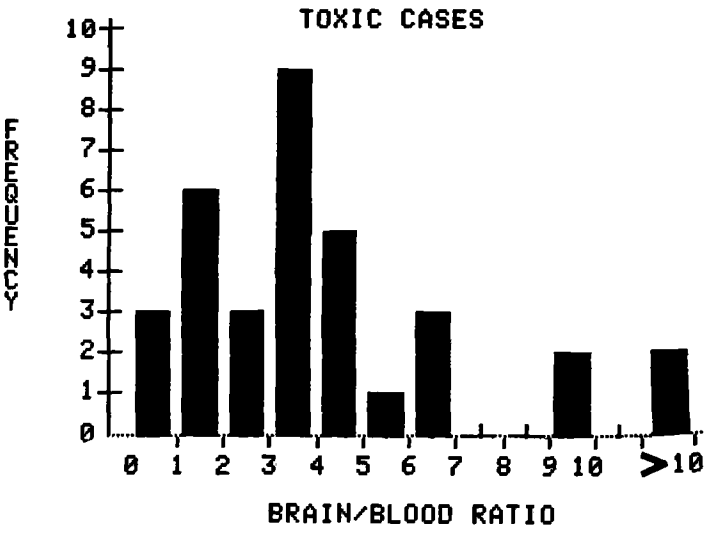

FIG. 1—*Distribution of the cocaine brain/blood ratio for toxic cases.*

The second is Case 44 from Table 2. The deceased was a 21-year-old female with a long history of heart disease with numerous heart surgeries, including valve replacement. In the last surgery two years before, she had received an internal pacemaker. She was prescribed digoxin and propranolol. Investigation indicated that she had used cocaine for four to five years. She and her husband snorted about ¼ g at 2300 h and went to bed at 2400 h. He awoke at 0215 h and found the decedent gasping. At that time, he called the paramedics. She was pronounced dead on arrival at the hospital at 0346 h. Both cocaine and benzoylecgonine were found to be distributed evenly throughout the brain with no regional concentration in the regions analyzed (Table 3).

Brain specimens stored frozen (−16°C) and refrigerated (8 to 10°C) were reanalyzed periodically to determine the stability of cocaine and benzoylecgonine in brain tissue. Both cocaine and benzoylecgonine were found to be stable in frozen brain tissue after one, two, and three months of storage. Cocaine and benzoylecgonine concentrations were not significantly decreased in refrigerated brain tissue on reanalysis 30 days after the initial analysis (Table 4).

Discussion

In the living body, cocaine is rapidly metabolized ($t_{1/2}$ = 0.7 to 1.5 h [*8,9*]) to ecgonine methyl ester, ecgonine, and other fragments by serum cholinesterase and liver esterases, and to benzoylecgonine by chemical hydrolysis [*3-6*]. These processes probably continue postmortem in the blood, liver, and in drawn blood in vitro. Enzymatic breakdown can be inhibited by any number of enzyme inhibitors, including fluoride, organophosphate pesticides, physostigmine, and heavy metals, or by refrigeration or freezing [*3*]. Hydrolysis can be slowed by refrigeration or freezing [*3*] and by decreasing the pH below neutral [*4,6*]. Because many processes cause the breakdown of cocaine, cocaine itself may not be found in postmortem blood obtained from the heart at autopsy from overdose cases even with timely screening and confirmation [*10*].

Furthermore, the cocaine concentrations that are found in postmortem blood may not be representative of the concentrations existing at the time of death. Reanalysis of cocaine-containing blood at a later time commonly reveals a diminished cocaine concentration and often an increased benzoylecgonine concentration. The kinetics of this hydrolysis have been

TABLE 2—*Cocaine incidental to cause of death, mg/L or mg/kg.*

	Blood		Brain		Liver			
Case	Cocaine	B.E.	Cocaine	B.E.	Cocaine	B.E.	Other Drugs	Comments COD
1	0	0	0	...	0	0.41		
2	0	0.02	0.18	0.13	0	0		
3	0	0.03	0.05	0	0	0.05	morphine	Heroin OD
4	0	0.03	0	0	0	0.04		
5	0	0.04	0	trace	0	0.03		SIDS mother used
6	0	0.04	...	...	0	0.04	morphine	Heroin OD
7	0	0.04	0	0.08	0	0.06		Suffocation of infant
8	0	0.04	0	0.10	0	0.14		Propoxyphine OD
9	0	0.05	0	0.19	0	0.49	morphine	Heroin OD
10	0	0.05	0	0	0	0.02		In custody
11	0	0.05	0.02	0.13	0.03	0.07		Homicide
12	0	0.07	0.3	0.5	0	1.4		GSW
13	0	0.10	0	...	0	10		Cerebral hemorrhage
14	0	0.13	0	0.15	...	...		Accident, fell from cliff
15	0	0.15	0	0.15	0	0.17		Homicide stabbing
16	0	0.18	0	0.08	0	0.19		Homicide
17	0	0.2	0.04	0.3	...	...	doxepine	
18	0	0.2	0.16	0.27	0	0.6		Epilepsy, 5 days in hospital
19	0	0.24	0.16	0.27	0	0.61	epileptic	12 h in hospital
20	0	0.33	0	0.17	0	0.57		Homicide, stabbing
21	0	0.38	0.14	0.18	0.11	0.68		GSW
22	0	0.45	0.04	0.09	0	0.41		
23	0	0.7	0.3	0.5	0	1.4		GSW homicide
24	0	2.3	0	2.0	0	2.2		In custody
25	0	6.4	0	3.4	0	6.2		Complications of diabetes
26	0	7.4	0.05	5	0	5.3		Jumped through window, delayed death in hospital
27	0.01	0.62	...	...	0.02	1.1	morphine	Heroin OD
28	0.02	0.11	0.03	0.03	0.03	0.12		Traffic accident
29	0.03	0.05	0	0	0	0.05	EtOH	Homicide, beating
30	0.05	0.16	0.04	...	0.04	0		Homicide GSW
31	0.05	0.17	...	...	0.04	0.02		Traffic accident pedestrian
32	0.05	0.18	0.12	0.02	0	0.15	morphine	Heroin OD
33	0.05	0.28	0.10	0.13	0	0.40	morphine	Heroin OD
34	0.05	1.2	0.11	0.6	0.44	1.3		
35	0.05	2.6	0.46	1.6	0.13	4.6		Homicide GSW
36	0.06	1.2	0.20	0.9	0.09	2.5		Homicide GSW
37	0.09	0.06	...	...	0.13	0.07		Homicide drowned
38	0.11	0.25	0.32	0	...	...		
39	0.13	2.7	0.23	0.14	0.12	2.8		Traffic accident
40	0.14	1.1	0.48	0.42	0.06	1.3		Subdural hemorrhage
41	0.15	0	0	0	0.05	0		Homicide trauma
42	0.15	0.9	0.17	0.55	0.2	1.3		Homicide GSW
43	0.17	5.9	0.14	3.1	0.35	6	codeine	OD, free based cocaine 24 h previously
44	0.2	1.0	0.7	0.3	0.04	1.4		Cardiovascular collapse
45	0.3	0.95	...	...	0	1.2		Suicide GSW
46	0.5	1.4	0.3	5.1	1.6	0.9		
Ave	0.05	0.88	0.12	1.4	0.08	1.3		

TABLE 3—*Regional distribution of cocaine and benzoylecgonine in brain tissue.*

38-yr-old	Cocaine	B.E.	21-yr-old F	Cocaine	B.E.
AM blood:	3.5 mg/L	4.8 mg/L	AM serum:	0 mg/L	0.4 mg/L
PM blood:	4.0 mg/L	4.3 mg/L	PM blood:	1.0 mg/L	1.0 mg/L
liver:	0.8 mg/L	1.3 mg/kg	liver:	0.04 mg/L	1.4 mg/kg

Brain Region	Cocaine (μg/g)	B.E. (μg/g)	Cocaine (μg/g)	B.E. (μg/g)
Frontal cortex	16	1.9	0.8	0.3
Occipital cortex	16	2.6	0.7	0.2
Cerebellum	16	2.6	0.7	0.3
Substania nigra	16	2.0	0.4	0.3
Medulla	16	2.1	0.4	0.3
Spinal cord	16	2.0	...	...

TABLE 4—*Stability of cocaine and benzoylecgonine in brain tissue, μg/g.*

	1st Analysis		2nd Analysis		3rd Analysis	
Case	Cocaine	B.E.	Cocaine	B.E.	Cocaine	B.E.
			FROZEN (−4°C)			
28	1.4	1.5	1.8	1.4[a]	1.9	1.3[b]
18	14	1.1	14	1.4[b]	14	1.3[c]
10	22	1.6	19	2.2[b]	21	2.0[c]
			REFRIGERATED (10°C)			
5	18	1.5	16.5	1.9[a]		
3	19	2.2	17	2.2[a]		

[a]One month after first analysis.
[b]Two months after first analysis.
[c]Three months after first analysis.

published [*3,6*]. The total concentration of cocaine and benzoylecgonine has been reported to remain stable in vitro [*11*]. On this basis, it has been recommended that the total concentration of cocaine products can be determined by adding the concentration of cocaine and benzoylecgonine [*6*]. This assumes that all of the benzoylecgonine present is due to hydrolysis of the most recent cocaine dose before death. However, since the inactive metabolites, benzoylecgonine and ecgonine methyl ester, have a much longer lifetime in the body ($t_{1/2}$ = 5 to 7 h and 4 to 5 h, respectively [*12–14*]), they can accumulate. The concentrations in postmortem blood might be present as a result of an earlier, more remote or chronic use of cocaine, as well as postmortem in vivo or in vitro decay of the parent drug.

From the above results, it appears that brain tissue may be a better sample for cocaine determination than postmortem blood or liver tissue. From animal studies, there appears to be no blood brain barrier for cocaine [*15–18*]. Cocaine enters and leaves the brain rapidly [*15–18*]. Some researchers feel that there is an active transport of cocaine into brain tissue [*18*]. At peak plasma cocaine concentrations, the brain cocaine concentration is just over four times the plasma or serum concentration [*15*]. This brain/blood ratio is the most frequent (median) ratio found for cocaine in cocaine overdose fatalities in our laboratory (Fig. 1). As blood cocaine concentrations fall slightly more rapidly than brain tissue concentrations [*15*], the brain/

blood ratio increases, reaching a peak of approximately 10 (range 8 to 12) between 1 and 2 h after cocaine administration [*15–17*]. This is close to the mean brain/blood ratio for cocaine found in cocaine overdose cases (Fig. 1). Wetli and Wright [*19*] reported that in 18 cases in which witnesses were able to supply a description of terminal events, death as a result of cocaine overdose occurred either from with a few minutes up to an hour later, or after 1 to 3 h of coma. Deaths occurring from a few minutes to 1 to 3 h after administration of cocaine would be expected, by extension of the animal studies, to be characterized by brain/blood cocaine ratios of 4 to 10. This is confirmed by a review of the cases presented in Table 1.

At 3 and 6 h after administration, the brain/blood ratio of cocaine falls to 0.8 and 0.4, and cocaine in brain tissue is not detectable in animal studies after 6 to 8 h [*17*].

Chronic use of cocaine can alter the disposition of cocaine and metabolites in the brain [*15*]. After 14 days of chronic treatment of rats with intravenously administered cocaine, the brain-blood cocaine ratio following an acute dose was 2.4. However, after the daily dose of cocaine was discontinued for 14 days, the brain/blood ratio after an acute dose of cocaine was again found to be just greater than 4.

In contrast to the lilophilic parent drug, the hydrolysis product of cocaine, benzoylecgonine, is restricted in its passage across the blood brain barrier [*15–18,20*]. In rat studies in which cocaine was given intravenously (i.v.), brain benzoylecgonine concentrations were 10% of the serum concentrations in acutely dosed animals, and were 20% of serum concentrations after 14-day chronic daily treatment with high doses of cocaine intraperitoneally (i.p.) [*15*]. Misra et al [*17*] found that after i.v. injection of radiolabeled benzoylecgonine, the brain/plasma ratio of benzoylecgonine steadily increased with time from a ratio of 0.05 at 0.25 h to 0.71 at 6 h [*17*]. The 0.36 mean brain/blood ratio of benzoylecgonine in toxic cases, like the 9.60 mean brain/blood ratio for cocaine, appears to be typical of the disposition ratio at 1 to 3 h after cocaine administration and is consistent with the time course described for fatal cocaine overdoses by Wetli and Wright [*19*]. On the other hand, the 1.4 average brain/blood ratio of benzoylecgonine in the incidental cases described in Table 2 suggests either accumulation from chronic cocaine abuse or use occurring more than 8 to 10 h before death.

Although no animal studies on the regional brain distribution of cocaine were found, the absence of a blood brain barrier and of sequestering of cocaine in brain tissue is consistent with the even distribution of cocaine and benzoylecgonine through all brain regions investigated (Table 3) in these two cases.

Conclusions

Brain tissue appears to be a better sample for cocaine determination that postmortem blood or liver tissue for the following reasons. Cocaine is stable during storage in frozen (−4°C) or refrigerated (10°C) brain tissue. Cocaine is evenly distributed throughout the brain so that the regional source of the tissue sample does not present a source of variation in concentration. Cocaine rapidly enters and leaves the brain so that concentrations found by postmortem analysis are representative of the drug at the site of action at the time of death. In addition, information on the recent or remote use of cocaine can be obtained from the relative concentrations of cocaine and benzoylecgonine in blood and brain tissue.

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