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Concentrations of Lidocaine and Monoethylglycylxylidide (MEGX) in Lidocaine Associated Deaths

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ABSTRACT: Concentrations of lidocaine and MEGX were determined in a variety of tissues and other samples collected at autopsy. In 13 of the cases examined in which lidocaine was associated with death, tissue concentrations were greater than 15 mg/kg. Tissue concentrations in other patients treated with lidocaine were significantly lower.

KEYWORDS: pathology and biology, toxicology, lidocaine

Lidocaine is often used as an antiarrhythmic agent in the treatment of ventricular arrhythmias. Although the mechanism of action is similar to that of quinidine and procainamide, it has the advantage that it can be safely administered intravenously (IV). The pharmacokinetics of lidocaine have been extensively studied over the past decade [*1-4*], and it has been shown to have a short plasma half-life, primarily as a result of metabolism and redistribution in the body. Thus, the pharmacological effects of lidocaine rapidly diminish after infusion is stopped. This decline in pharmacological activity also allows for close monitoring of ventricular ectopic activity [*5*].

Lidocaine is metabolized in the liver to monoethylgycylxylidide (MEGX) and glycylxylidide (GX). Both metabolites produce antiarrhythmic effects; however, only MEGX has been reported to contribute significantly to the toxic effects of the drug [*6*]. Therapeutic lidocaine plasma concentrations of between 2 and 5 mg/L are considered satisfactory for antiarrhythmic control; concentrations greater than 5 mg/L may cause toxicity. The major toxic actions of lidocaine are associated with the central nervous system and include dizziness, drowsiness, disorientation, respiratory depression, convulsions, and coma. Cardiac toxicity including heart block, induction of ventricular tacharrhythmias, and widening of the QRS complex is also observed [*7*].

Postmortem blood concentrations of 6 to 33 mg/L have been reported in five adults who died after the accidental injection of between 250 to 1000 mg of lidocaine [*8*]. Poklis et al [*9*] recently

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reported a blood concentration of 30 mg/L in a 64-year-old male who accidentally received 2000 mg.

This report describes tissue concentrations of lidocaine and MEGX in a series of deaths in which a nurse was convicted of injecting overdose amounts of lidocaine. The deaths occurred in the first few months of 1981 and autopsies were performed in May 1981. Some of the bodies had been embalmed and exhumed before autopsy. Not all of the deceased were thought to have died from lidocaine overdose. Samples collected at autopsy included blood, liver, kidney, brain, lung, heart, vitreous humor, and urine.

Methods

A complete toxicological examination was performed on each set of specimens. Analytical techniques used included radioimmunoassay (RIA), gas chromatography (GLC), high performance liquid chromatography (HPLC), and gas chromatography-mass spectrometry (GC-MS) as outlined by Crouch et al [*10*]. Blood and vitreous humor digoxin concentrations were determined by direct RIA and tissue glycoside concentrations by RIA following extraction dichloromethane. The presence of digoxin was confirmed by HPLC-RIA [*11*].

Concentrations of lidocaine and MEGX were determined by GC with nitrogen phosphorous detection (GC-NPD) according to a modification of the method of Hawkins et al [*12*]. Briefly, tissues were homogenized with an equal volume of water and 1 g of this homogenate, or a further dilution thereof, taken for analysis. Fluid specimens, such as blood, vitreous humor, and urine, were diluted with drug-free blood or water before analysis. Mepivicaine (3 μg) was added to each sample as internal standard and 2 mL of saturated sodium borate (pH 9.0) then added. After extraction with 8 mL of *n*-butyl chloride and centrifuging, the organic layer was evaporated to dryness after the addition of 50 μL of 1% methanolic hydrochloric acid solution. This extraction was found to be satisfactory for all tissues except lung, which required back extraction into 1*N* sulfuric acid. Standards of lidocaine and MEGX prepared in drug-free tissue specimens were used to prepare calibration curves. The column used was 1.2-m by 6.35-mm (4-ft × ¼-in.) inside diameter glass column packed with 0.5% potassium hydroxide, 2% Carbowax 20*M* on Gas Chrom Q (100–120 mesh). The injector port, column, and detector temperatures were 250, 210, and 300°C, respectively.

Results

Using the GC-NPD procedure as outlined, clean chromatograms were obtained. Figure 1 shows a typical chromatogram for a standard of 4.0 mg/L of lidocaine and 0.4 mg/L of MEGX in a drug-free liver homogenate, a chromatogram of a 1 : 1 case liver homogenate, and one of a tenfold dilution of this case homogenate. The concentrations of lidocaine and MEGX were determined, after correcting for the dilution, to be 58 and 0.7 mg/kg, respectively.

Tables 1, 2, and 3 show the results of analysis for cases in which death was associated with lidocaine (Group 1) and those in which the antiarrhythmic agent was not associated with death (Group 2). In Group 1 hepatic lidocaine concentrations ranged from 15 to 71 mg/kg and in Group 2 from 0 to 14 mg/kg. MEGX was detected at relatively low concentrations in all of the cases examined. Other drugs and metabolites were found in a number of the cases; digoxin and morphine were among the most frequently detected. The range of hepatic concentrations (mg/kg) were as follows:

Group 1: digoxin 0.001 to 0.033 ($n = 6$), morphine 0.10 to 0.28 ($n = 4$)
Group 2: digoxin 0.007 to 0.008 ($n = 2$), morphine 0.11 to 0.14 ($n = 2$)

In two cases from Group 1 liver was unavailable. Drugs detected in blood (Case 12) and lung (Case 13) are shown in Table 2. The concentrations of lidocaine and MEGX in the heart blood sample were 130 and 0.78 mg/L, respectively.

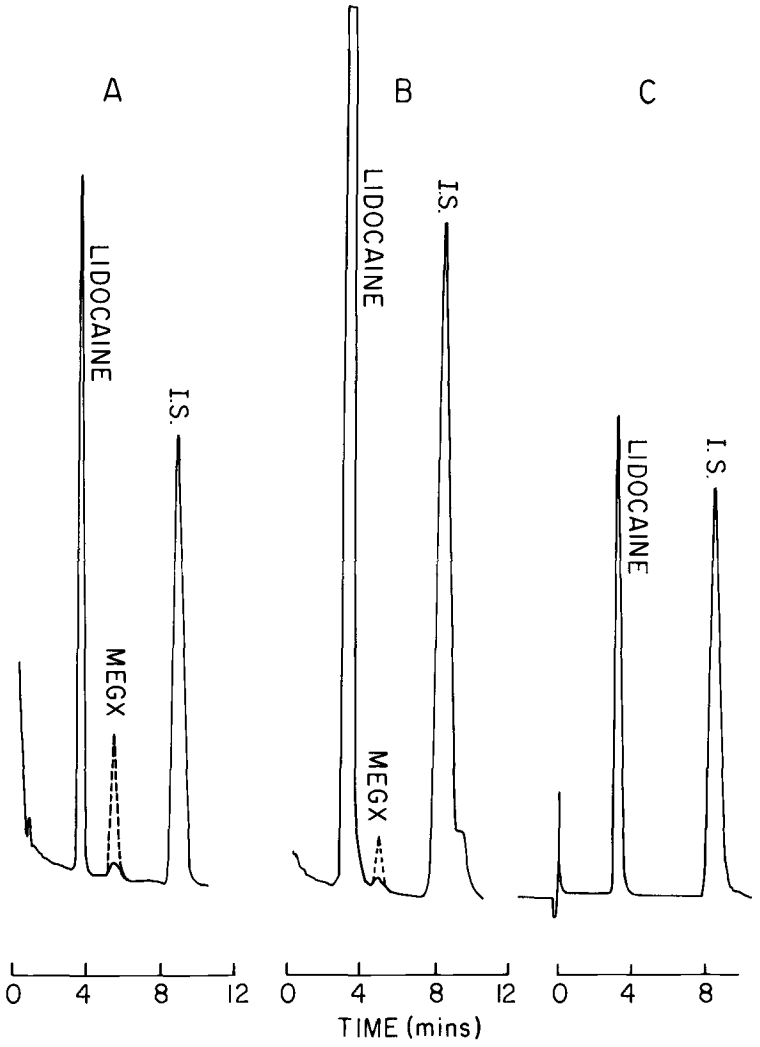

FIG. 1—*Chromatograms of extracts of* (a) *a drug-free liver homogenate containing 4.0 mg/L of lidocaine and 0.4 mg/L of MEGX;* (b) *an 1 : 1 liver homogenate from a case sample; and* (c) *a tenfold dilution of the 1 : 1 liver homogenate. After correcting for dilutions the liver specimen was found to contain 58.0 and 0.7 mg/kg of lidocaine and MEGX, respectively. For chromatographic conditions see text. The dotted line indicates a tenfold increase in sensitivity over the solid line for MEGX.*

Figures 2 and 3 illustrate histograms for tissue concentrations of lidocaine in Group 1 and Group 2. In all cases significantly higher ($p < 0.05$) tissue concentrations of lidocaine were detected in Group 1 when compared to Group 2. The range of lidocaine concentrations (mg/kg) detected in Group 1 were as follows: liver 15 to 48, lung 23 to 134, kidney 20 to 92, heart 17 to 75, and brain 23 to 60. Also shown are the concentrations of lidocaine in the vitreous humor specimens collected from nine cases in Group 1; this range was 7 to 45 mg/L. Table 4 shows the range of concentrations of MEGX detected in the tissues. No significant differences were found between Groups 1 and 2.

A number of the samples were reanalyzed for lidocaine approximately two years after the initial analyses. The same analytical procedure was used. The samples re-assayed included

TABLE 1—*Hepatic concentrations (mg/kg) of drugs and metabolites detected in cases in which death was associated with lidocaine (Group 1).*

	Case										
Drug	1[a]	2	3	4	5	6	7	8	9	10	11
Lidocaine	47	33	58	48	36	71	23	32	15	21	28
MEGX	0.3	<0.05	0.7	0.46	3.3	ND[b]	<0.05	1.8	0.42	ND	0.2
Digoxin		0.001					0.033	0.032	0.018	0.006	0.008
Morphine							0.10	0.28	0.27		0.11
Diazepam								<0.1	<0.1		
Nordiazepam								<0.1	<0.1		
Desalkylflurazepam									<0.1		
Diphenhydramine									5		
Propoxyphene									0.8		
Norpropoxyphene									12		
Amitriptyline									2.6		
Nortriptyline									1.4		

[a]This sample was only analyzed for lidocaine and MEGX.
[b]ND: none detected.

TABLE 2—*Blood and lung concentrations of drugs and metabolites detected in cases in which death was associated with lidocaine (Group 1).*

	Case	
	12	13
Drug	Blood, mg/L	Lung, mg/kg
Lidocaine	130	134
MEGX	0.78	>10.0
Diazepam	0.19	
Nordiazepam	<0.1	
Digoxin		0.0021

TABLE 3—*Hepatic concentrations (mg/kg) of drugs and metabolites detected in cases in which lidocaine was not associated with death (Group 2).*

	Case				
Drug	14[a]	15	16	17	18
Lidocaine	14 (12)	0.67	3.6	NDD[b]	3
MEGX	<0.05	<0.2	ND[c]		0.07
Morphine	(<0.05)	0.14	0.11		
Codeine		0.33			
Digoxin	(0.012)		0.008		0.007
Diazepam	(0.16)		<0.1		
Nordiazepam	(<0.05)		<0.1		
Quinidine					41
Procainamide	(11)				
N-acetylprocainamide	(2)				

N.B. Liver was not available in one case (19), the blood concentrations (mg/L) of drugs detected were as follows: lidocaine 2.8, MEGX 0.16, and digoxin 0.004.

[a]Blood was available, the concentrations (mg/L) of drugs detected are listed in parenthesis.

[b]NDD: no drugs detected.

[c]ND: none detected.

blood, lung, brain, liver, and kidney. There was a significant correlation between the two sets of data ($r = 0.948, y = 1.07x - 6.4$).

Case Histories

Group 1

Case 3—A 52-year-old male was admitted to the emergency room with a myocardial infarction; shortly after admission the deceased was transferred to the coronary care unit. At 2:30 a.m. he developed ventricular tachycardia and was administered a 100-mg bolus of lidocaine followed by a 2 mg per min drip at 2:40 a.m. Seizure activity was noted at 3:00 a.m. and the lidocaine infusion was stopped. At approximately 4:00 a.m. the deceased had a second seizure and respiratory arrest; he was treated with diazepam and phenytoin. At this time cardiopulmonary resuscitation (CPR) was started and at 4:05 a.m. he was given a 100-mg bolus of lidocaine. At 5:00 a.m. the patient had another seizure and a broad QRS complex was noted; he died at 5:07 a.m. Tissue concentrations (mg/kg) were as follows: brain 43, heart 72, lung 40, liver 58, and kidney 92. The vitreous humor concentration was 22 mg/L.

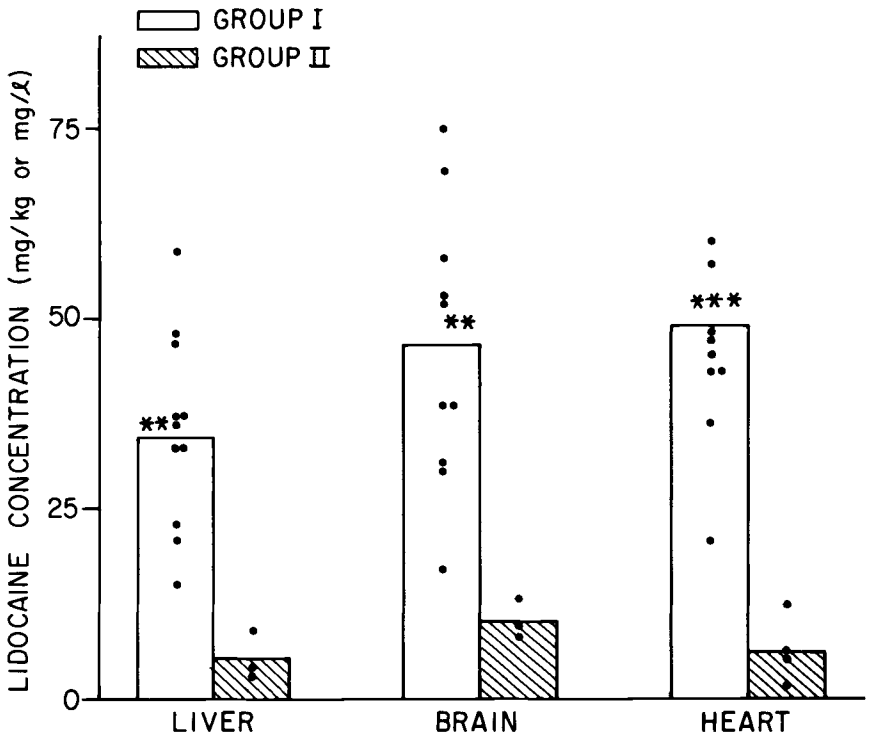

FIG. 2—*Liver, brain, and heart concentrations (mg/kg) of lidocaine. Individual concentrations are represented by* •.

$^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.005$ by student *t*-test.

Case 7—An 80-year-old female was admitted to the coronary care unit with respiratory failure, possible congestive heart failure, and possible pneumonia. Four days later at approximately 4:00 a.m. she received 75 mg of lidocaine for premature ventricular contractions. A code was called at 5:55 a.m. and the patient was pronounced dead at 6:15 a.m. Tissue concentrations (mg/kg) of lidocaine were: brain 23, heart 58, lung 57, liver 23, and kidney 20. The vitreous humor concentration was 13 mg/L.

Case 8—A 79-year-old female was admitted to the emergency room with severe chest pain; following admission she was transferred to the coronary care unit. At 1:52 a.m. she was treated with atropine and within 2 min went into tonic clonic seizure, and respiratory and cardiac arrest. A code was called at 2:00 a.m. and CPR commenced. During the code her rhythm reverted to ventricular tachycardia. She was given a 100-mg bolus of lidocaine followed by a 2 mg per min drip which ran for approximately 20 min. At 2:32 a.m. she was pronounced dead. Tissue concentrations (mg/kg) of lidocaine were as follows: brain 60, heart 52, lung 44, liver 32, and kidney 36. The vitreous humor concentration was 29 mg/L.

Group 2

Case 16—An 85-year-old male was admitted to the coronary care unit for congestive heart failure with a myocardial infarction. Twenty-five hours later he was given a 75-mg bolus of lidocaine. Three and a half hours later there was a second bolus, and a drip of 2 mg per min was started. Approximately 30 min later he was diagnosed as being in electromechanical dissocia-

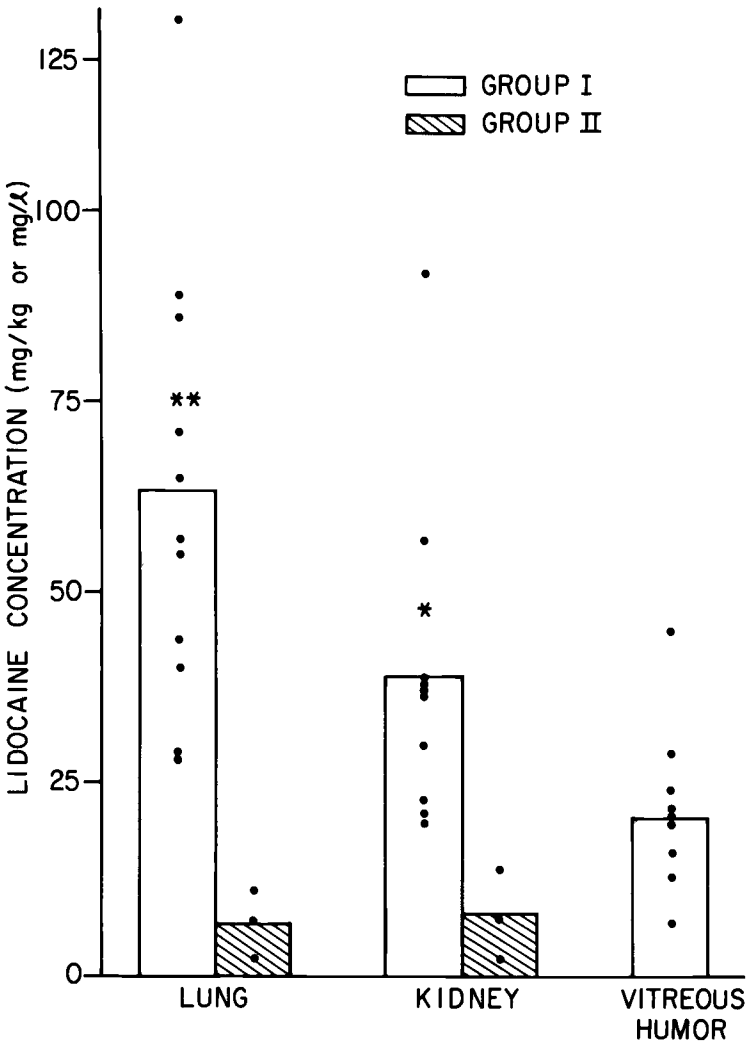

FIG. 3—*Lung, kidney, and vitreous humor concentrations of lidocaine. Individual concentrations are represented by* •.

$^{*}p < 0.05$, $^{**}p < 0.01$ by student t-test.

tion. He was pronounced dead approximately 3 h after the second bolus. Tissue concentrations (mg/kg) of lidocaine were: brain 5.1, heart 9.3, lung 11, liver 3.6, and kidney 7.4. Vitreous humor concentration of lidocaine was 1.5 mg/L.

Case 18—A 65-year-old male was admitted to the emergency room with an acute myocardial infarction at 9:59 a.m. CPR was performed by paramedics for approximately 30 min prior to admission. At 10:16 a.m. in the emergency room the patient was given a 100-mg bolus of lidocaine. At 10:27 a.m. he was given a second 100-mg bolus injection. At 10:32 a.m. he was pronounced dead. Tissue concentrations (mg/kg) of lidocaine were: brain 1.4, heart 7.3, lung 7, liver 3, and kidney 2.

All of the tissues in these cases (3, 7, 8, 16, and 18) were from embalmed and exhumed bodies.

TABLE 4—*Range of MEGX concentrations (mg/L or mg/kg) detected.*

	Group 1		Group 2	
Specimen	Range	*n*	Range	*n*
Blood	0.78 and 4.3	2	0.16	1
Liver	ND[a] to 1.8	11	ND to 0.07	3
Lung	ND to >10	10	ND to <0.3	3
Kidney	<0.05 to 1.2	10	ND to <0.05	3
Brain	<0.3 to 8	10	ND	2
Heart	ND to 1.8	8	ND to <0.05	3

[a]ND: none detected.

Discussion

It is obvious from the data presented in Tables 1 and 2 and in the case histories that there is a large difference between the lidocaine concentrations detected in Groups 1 and 2, even though the deceased were apparently treated with similar doses of lidocaine under similar conditions. All of the deceased in Group 1 were treated by the nurse under suspicion. He was charged with homicide in the fall of 1981 and found guilty in early 1983.

It has been suggested [*13,14*] that at steady state, plasma concentrations of MEGX may be one third of the lidocaine concentrations. The very low tissue concentrations of MEGX relative to lidocaine may indicate that the deceased were not in steady state and could support the hypothesis that the deceased had died rapidly following the administration of overdoses of lidocaine. However, other workers [*15,16*] have suggested that MEGX is chemically unstable and Nelson et al [*15*] have shown that the secondary amine forms adduct products with aldehydes. It is therefore possible that tissue concentrations of MEGX at the time of death in those who were embalmed were higher than those actually detected.

Although the interpretation of these data would appear to be straight forward, that is, the tissue concentrations detected in the cases from Group 1 being consistent with the administration of overdose amounts of lidocaine, defense experts at trial postulated that such tissue concentrations may have arisen from the administration of therapeutic doses of licocaine during CPR. Benowitz et al [*2*] proposed that within 4 min of injection the blood pool contains approximately 20% of the total dose, whereas the rapidly equilibrating tissue (RET) (liver, heart, brain, lung, kidney, and spleen) contains nearly 40%. By 32 min the amount in the muscle and adipose tissue exceed that in the RET, but at this time a significant percentage of the dose has been metabolized. It is obvious from this work that the amount of lidocaine found in any given tissue during the distribution phase is very much dependent on the blood flow to that tissue. Disease states or trauma resulting in tissue hypoperfusion, sympathetic nervous system stimulation, and redistribution of blood flow would be expected to alter tissue concentrations of lidocaine. Computer simulations [*17*] of lidocaine distribution during cardiac failure have predicted higher blood concentrations because of a reduction in blood flow to the tissues. Lidocaine concentrations in the brain and heart might be expected to be higher because of the preservation of blood flow to these organs during cardiac failure.

Recently Chow et al [*18*] studied the effects of CPR on lidocaine pharmacokinetics in dogs. Following a 2-mg/kg intravenous dose of lidocaine they collected multiple plasma samples over 60 min in animals subjected to continuous CPR and in control animals. At 60 min the dogs were killed and the RET and skeletal muscle were collected. Dramatic differences in the pharmacokinetics between the CPR group and the control animals were observed. In the CPR dogs blood concentrations of lidocaine were significantly higher than the control dogs for the entire 60 min and clearance was reduced at least eightfold. In addition, significantly higher tissue concentrations were observed in the CPR group; for example, there was approximately a

fivefold increase in the brain and liver concentrations of lidocaine. Using these data together with computer simulated models generated by Benowitz et al [2,17], defense experts postulated that the normal distribution of lidocaine would be dramatically altered in the patients included in Group 1; all of whom suffered from either cardiac or pulmonary disease and may have been administered lidocaine during CPR.

This hypothesis was disproved by comparing the differences seen between the cases in Group 1 and Group 2. CPR had been administered to patients in both groups. Figures 1 and 2 show that there were significant differences between the lidocaine concentrations, with those in Group 1 being higher than Group 2. Table 5 shows the amount of lidocaine found in the RET of the cases described above using tissue weights taken from Butler [19]. The amounts of lidocaine detected in the RET of Group 1 exceeded the dose calculated from the case histories in these three cases, whereas the amount detected in the RET of Group 2 was less than 10% of the estimated dose.

A second factor used to refute the hypothesis was the concentrations of other drugs detected. If the distribution of lidocaine was abnormal in the Group 1 cases then it might be expected that any drug which redistributes significantly between the RET and skeletal muscle or adipose tissue would show similar characteristics. Drugs such as atropine or morphine, with similar volumes of distribution to lidocaine, were also administered to a number of the patients during CPR. No significant differences were seen between the groups in the hepatic concentration of morphine or in the detection of atropine. In fact, atropine was not detected in any of the cases examined even though the sensitivity limit of the GC-MS assay used was 0.1 mg/kg of tissue.

Recently, Poklis et al [9] reported the tissue concentrations of lidocaine in a case involving the accidental injection of 2 g of lidocaine. The patient was in CPR for 25 to 30 min, and therefore it might be expected that skeletal muscle would be poorly perfused. However, 20 mg/kg of lidocaine was detected in the skeletal muscle. From the models proposed by Benowitz et al [2,17] and from the data of Chow et al [18], this was unexpected. Although, neither skeletal muscle or adipose tissue were collected in the cases described in this report, the data from Poklis et al [9] was useful in evaluating the arguments of the defense experts.

Acknowledgment

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TABLE 5—*Amounts of lidocaine in rapidly equilibrating tissue (RET).*

Case	Dose, mg[a]	Lidocaine, mg					
		Liver	Lung	Brain	Heart	Kidney	Total
			GROUP 1				
3	240	92.8	77.0	64.5	28.4	42.3	305.0
7	75	36.8	61.0	34.5	22.9	9.2	164.4
8	140	51.2	47.1	90.0	20.5	16.6	225.4
			GROUP 2				
18	200	4.8	7.5	2.1	2.9	0.92	18.2
16	210	5.8	11.8	7.7	3.7	3.4	32.4

N.B. Tissue weights used in the calculations were as follows: brain 1.5 kg, heart 0.395 kg, kidney 0.46 kg, liver 1.6 kg, and lung 1.07. Ref: Butler [19].

[a]Calculated from case history.

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