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Fatal Consequences of Local Anesthesia: Report of Five Cases and a Review of the Literature

Recent publications [*1–8*] have emphasized that the use of local anesthetic substances is not entirely without risk to the patient and have stressed the difficulty in establishing what is the maximum safe dosage in any particular clinical situation. A search of the literature indicates that few reports are available on blood and tissue concentrations in fatalities after therapeutic misadventure with lidocaine or other local anesthetic agents.

The hazards of these drugs, when used in moderate or large doses, are not always fully appreciated. Furthermore, the toxic side effects of the local anesthetic may be unsuspected and the death attributed to an idiosyncrasy to the local anesthetic or to some unrelated cause. This view has been expressed elsewhere [*9,10*].

Materials

Thirteen cases of deaths associated with the administration of local anesthetics from the files of the Armed Forces Institute of Pathology are reported here. Cases in which the role of the local anesthetic agent seemed marginal or doubtful are excluded. Two cases from the Office of the Chief Medical Examiner, State of Maryland (Cases 4 and 5), are also included.

The less well-documented cases are only mentioned. Four involved the topical use of tetracaine; these were old cases, and conclusions regarding the ease of overdosage and the rapidity of absorption of topically applied local anesthetic are similar to those of Adriani and Campbell [*9*], whose cautionary remarks deserve attention. One case involved lidocaine in routine dental care. Two further cases involved tetracaine in spinal and epidural anesthesia, and three cases involved varying dosages of procaine.

The remaining three cases are presented in more detail. These involved the use of lidocaine or lidocaine with cocaine. Table 1 shows the anesthetics involved in the 15 cases. The toxicologic data uncovered in this study were surprisingly scanty (Table 2). Nevertheless, the information is presented because of the paucity of such data available at present in the literature.

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Case Reports

Case 1

A 7-year-old boy, 47 in. (1.2 m) in height and described as normally developed, underwent tonsillectomy. Bleeding occurred subsequently from the operative site. Meperidine (Demerol®), 35 mg, was given intramuscularly, and the throat was sprayed with 4% lidocaine (lignocaine, Xylocaine®), the precise amount being unstated. In addition, the right fossa was infiltrated and sprayed with 4 to 5 ml of 10% cocaine (400 to 500 mg).

About 2 to 3 min later, the patient began to suffer convulsions, which lasted 3 or 4 min. Subsequently, he had a few short episodes of seizures. Shortly afterwards he became cyanotic, and cardiac arrest occurred.

Prolonged attempts at resuscitation, including intubation and external cardiac massage, were unsuccessful, and the patient was pronounced dead 4½ h later. At autopsy, the brain weighed 1500 g and was edematous. Levels of cocaine, expressed as mg/100 g of tissue, were as follows: brain, 1.38 and liver, 0.21. The level of meperidine in the brain was 0.08 and in the liver, 0.03. Lidocaine and atropine were also present but were unquantifiable. The young patient had received an unusually large dose of cocaine, which is very rapidly absorbed from a raw surface [*9,11*], and an unknown amount of lidocaine. Both cocaine and lidocaine were detected by thin layer chromatography. Subsequently, cocaine was quantified by gas chromatography.

Case 2

A 19-year-old pregnant Caucasian woman at term underwent pudendal block and perineal infiltration with approximately 60 ml of 1% lidocaine (600 mg) without epinephrine. The procedure took about 4 min. She had already received premedication consisting of 100 mg of meperidine 2½ h previously, and 200 mg of secobarbital 3 h before that.

Several minutes after the administration of the lidocaine, the patient was noted to be cyanotic, and blood pressure was unobtainable. Respiration was spontaneous, but rapid

TABLE 1—*Local anesthetics involved in 15 deaths.*

Anesthetic	Cases, no.
Lidocaine	5
Lidocaine and cocaine	1
Procaine	3
Tetracaine	6
Total	15

TABLE 2—*Lidocaine concentrations (mg/100 ml or g) found by toxicologic analysis in five fatal cases.*

	Case 1 [a]	Case 2	Case 3	Case 4	Case 5
Brain	trace	1.0	...	...	...
Liver	trace	1.2	0.56	...	...
Blood	...	...	0.4	2.8	0.58
Kidney	...	1.9	...	...	...
Lung	...	3.3	...	...	...

[a] Cocaine also detected and quantified (see text).

and shallow. The patient was delivered of the infant promptly and successfully; resuscitative measures included an infusion of norepinephrine and injections of phenylephrine. These drugs, with intermittent positive pressure repiration (IPPR) to improve ventilation, restored the systolic blood pressure to 100 mg Hg, with clearing of the patient's sensorium. Subsequently, however, her blood pressure again became unobtainable, and the patient was pronounced dead about 2½ h after administration of the local anesthetic. No convulsions were described at any time. At autopsy, the body weight was 100 lb (50 kg), and the brain weighed 1100 g. There was no soft tissue hemorrhage to suggest intravascular injection of the drug. No evidence was found of amniotic fluid embolism. Tissue concentrations of lidocaine were as follows: brain, 1.0 mg/100 g; liver, 1.2 mg/100 g; kidney, 1.9 mg/100 g; and lung, 3.3 mg/100 g. The information available with the case suggests that assay of lidocaine was by paper chromatographic separation followed by elution and spectrophotometric assay. The obstetrician and the hospital pathologist considered the cause of death to be a reaction to lidocaine. Meperidine and secobarbital were not quantified.

Case 3

A 27-year-old Caucasian woman at term was given 100 mg meperidine by intramuscular injection, and 1 h later underwent right pudendal block with 10 ml of 2% lidocaine (200 mg). The solution did not contain epinephrine. She was said then to draw only three breaths of Trilene® (trichloroethylene) before suffering the onset of convulsions. She became cyanotic but forcefully expelled a viable child. The patient then took three or four spontaneous breaths but was effectively dead 15 min after administration of the local anesthetic. Resuscitative attempts were continued for 15 min more.

At autopsy, body weight was 135 lb (61 kg); the brain weighed 1300 g and appeared unremarkable. There was no hemorrhage in the area of injection, and there was no histologic evidence of amniotic fluid embolism. The blood concentrations showed lidocaine, 0.4 mg/100 ml; trichloroethylene, approximately 1.0 mg/100 ml; and meperidine, 0.1 mg/100 ml. The liver concentrations showed lidocaine, 0.56 mg/100 mg and meperidine, 0.46 mg/100 mg.

The assay of lidocaine in both blood and liver was by ultraviolet spectrophotometry and gas chromatography. Extraction was with ether, then acid prior to scanning; further extraction for gas chromatography was with chloroform.

Case 4 [2]

A 58-year-old Caucasian woman, a blind diabetic, was admitted for amputation of gangrenous second, third, and fourth toes of the right foot. Her history included a previous left below-knee amputation and a septal infarction 2 years before. Her current therapy included digoxin and chlorothiazide. Her blood urea nitrogen was 52 mg/100 ml.

Two blood pressure cuffs were placed around the right calf, the lower cuff at a pressure above 200 mm Hg, the upper cuff below 200 mm Hg. Forty millilitres of 1% lidocaine (400 mg) was given intravenously into the right saphenous vein at the medial malleolus, over a 4-min period. During that time, the patient also received 25 mg meperidine intravenously and 25 mg intramuscularly.

Approximately 3 min later, the patient suffered a convulsion lasting 20 s. Immediately thereafter, she received diazepam, 5 mg intravenously. She maintained a full pulse and spontaneous respiration. One minute later she suffered another convulsion

[2] Courtesy Chief Medical Examiner, State of Maryland.

and received another 5 mg diazepam intravenously. For 2 min pulse and spontaneous respiration were maintained, but the patient then became pulseless and apnoeic. The electrocardiogram (EKG) was then flat but showed episodes of ventricular tachycardia. Prolonged resuscitative attempts were unsuccessful.

At autopsy, the body weighed 141 lb (64 kg) and was 64 in. (1.6 m) in length. The brain showed atrophy of the optic nerves and tracts but was not edematous. The liver weighed 2950 g and showed accentuation of the lobular pattern. The kidneys showed diabetic glomerulosclerosis. The blood level of lidocaine was 2.8 mg/100 ml. The cause of death was considered to be the passage of the lidocaine into the systemic circulation.

Assay of lidocaine was by extraction into chloroform followed by thin-layer chromatography (TLC). The material was then taken from TLC and read in the ultraviolet spectrophotometer at 262 nm.

Case 5 [3]

A 34-year-old Negro man had a 6-year history of paroxysmal atrial fibrillation. Management had included digitalis, quinidine, propanolol, and electroshock to restore sinus rhythm.

During the current admission he received 1.2 mg of digoxin over a period of about 6 h. He then had seven paroxysmal ventricular contractions (PVC) per minute, with coupling and tripling of the PVCs. It was decided to give a bolus of 50 mg lidocaine intravenously; by mistake 50 ml of 2% lidocaine (1000 mg) was given. After 30 to 60 s the patient convulsed three times in rapid succession and went into cardiorespiratory standstill. Prolonged resuscitative attempts were unsuccessful.

At autopsy, the body weighed 213 lb (96 kg). The brain weighed 1440 g and was unremarkable. The liver weighed 2520 g and showed mild fatty metamorphosis. The blood concentration of lidocaine was 0.58 mg/100 ml. The cause of death was considered to be the overdose of lidocaine.

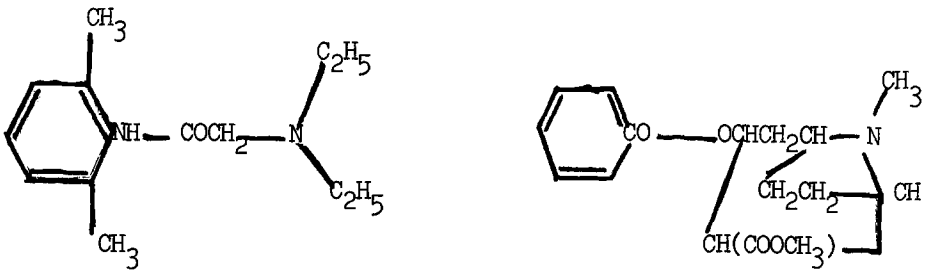
Lidocaine was assayed by extraction into ether, then hydrochloric acid, and read in the ultraviolet spectrophotometer at 262 nm.

Discussion

The biochemical structure of cocaine and allied synthetic derivatives is described in the standard texts. The molecule in each case consists of a hydrophilic amino group linked by an alcoholic intermediate group to a lipophilic aromatic residue. The linkage between the aromatic residue and the intermediate group is usually of ester type, but in the case of lidocaine is of amide type. (Figure 1 shows the biochemical structure of lidocaine and cocaine.) Changes in any part of the molecule affect the potency and toxicity of the compound, for example, increasing the length of the intermediate group or altering the terminal groups of the tertiary amino radical [*10,12–14*].

The metabolism and pharmacodynamics of these drugs in the adult and newborn have also received consideration [*1,3,6,10,15–19*]. Their toxicity is related to the balance obtained between absorption and metabolic destruction. For instance, while procaine is rapidly destroyed in the plasma, lidocaine and cocaine are predominantly destroyed in the liver. The toxicity of cocaine following infiltration is modified by its vasoconstrictor action [*11*], which reduces the rate of absorption. Lidocaine possesses little or no such vasoconstrictor action, but it may be administered with epinephrine. The vasoconstrictor action of cocaine does not reduce the rate of its absorption when it is applied topically; in such cases, as with tetracaine and lidocaine, absorption of a large

[3] Courtesy Chief Medical Examiner, State of Maryland.



LIDOCAINE COCAINE

FIG. 1—*Biochemical structure of lidocaine and cocaine.*

dose may be dangerously rapid [*9,11,12*]. Cocaine is roughly four times more potent and more toxic than lidocaine [*12,14*].

A suggested maximum dosage for cocaine applied topically is 200 mg [*14*], but clearly the body size of the patient must also be considered. The manufacturer's recommended dosage of lidocaine when used in infiltration anesthesia without epinephrine is up to 300 mg or 4.5 mg/kg of body weight [*11*]; when used with epinephrine, the dosages are 500 mg or 7 mg/kg.

The quantitation of local anesthetics in biological material, in amounts of the order usually encountered, is generally not considered easy, whether by ultraviolet spectrophotometry or by gas chromatography. Various methods of assay have been described [*15,18–22*]. Perhaps for that reason, the literature contains little toxicologic data in cases of death from drug abuse or therapy with these substances [*21*]. Such data, when available, usually relate to massive overdosage rather than to the more problematical situation when the dosage has been more moderate and the cause of death is in doubt.

Sunshine and Fike [*23*] describe two cases in which very large doses of local anesthetic were administered prior to cosmetic surgery. Naturally the drug concentrations obtained were much higher than those presented here. In one, the patient was found collapsed shortly after the administration of 2500 mg of lidocaine in the right side of the face and neck. Autopsy was unremarkable. Lidocaine levels obtained, in mg per 100 ml or g of tissue, were as follows: blood 1.2; liver 9.6; kidney 8.4; brain 6.6; urine, 1.8; bile, present; and stomach contents, 44.0. Phenacetin and propoxyphene were also present. The presence of lidocaine in the stomach contents is accounted for by gastric secretion of the drug [*24*].

In their second case [*23*], a bilateral enlargement mammoplasty, the administration of 1500 mg of mepivacaine (which has a potency similar to that of lidocaine), 500 mg of lidocaine, plus additional quantities of tetracaine and lidocaine, was followed by violent convulsions and death. Autopsy showed only intra-alveolar hemorrhages and pulmonary atelectasis. Of the three local anesthetics used, only mepivacaine was detected postmortem. Levels, in mg/100 ml or g, were as follows: blood, 5.0; urine, 10.0; liver, 7.5; kidney, 5.1; brain, 5.1; bile, 5.0; spleen, 7.2; and stomach contents, present. Salicylates and glutethimide were also present.

Berger and associates, in a recent paper dealing with the use of lidocaine in abortion and labor [*2*], describe two maternal deaths, each with convulsions following the use of lidocaine. In one case, 200 to 400 mg had been administered; in the other, 400 mg. Unfortunately, no toxicologic results were available.

Selden and Sasahara [*6*] describe an interesting case of liver failure in which lidocaine was administered for multiple ventricular ectopic beats; a 600-mg infusion of

lidocaine led to somnolence and decerebrate posture. The following day the patient was alert and oriented until a second infusion caused a partial return of symptoms before drug administration was discontinued.

Several papers have appeared recently concerning the danger of fetal intoxication from the use of local anesthetic at delivery [*4,5,7,8,15,18*]. Blankenbaker et al [*15*] measured the concentration of lidocaine in the blood and urine of mothers and babies after epidural administration of lidocaine to the mother for cesarean delivery. There were six cases. With dosages of lidocaine ranging from 320 to 510 mg, the maternal venous plasma concentrations at delivery (approximately 30 min later) ranged from 0.18 to 0.4 mg/100 ml. Newborn mixed cord plasma at delivery gave concentrations from 0.09 to 0.29 mg/100 ml. No toxic effects were reported in either mothers or newborn.

Shnider and Way [*7*] frequently found evidence of depression in the newborn with umbilical venous concentrations of lidocaine above 0.25 mg/100 ml. Rosefsky and Petersiel [*5*] describe two cases in which infant death was attributed to the instillation of relatively small quantities of mepivacaine in paracervical block. In one case the quantity instilled was 300 mg (5.7 mg/kg body weight), and in the other 240 mg (3.3 mg/kg). In the latter case the infant's urine contained 0.62 mg/100 ml mepivacaine 36 h after delivery, the amount falling to 0.08 mg/100 ml at death at 45 h.

Many papers [*3,10,25–27*] have dealt with the infusion of lidocaine in the management of cardiac arrhythmias. Some of these have given blood levels obtained from patients and volunteers suffering toxic manifestations as a result of the lidocaine infusion. Widely differing infusion rates were used, and these levels have ranged from 0.53 mg/100 ml [*10*] to 2.28 mg/100 ml [*26*], but this range corresponds with the range of fatal blood levels presented here. These levels are, however, difficult to evaluate or to compare with the levels in blood and tissues following the absorption of local anesthetic from a site of infiltration.

For instance, Folders and associates [*10*], working with volunteers, observed the onset of symptoms at plasma levels of lidocaine of about 0.53 mg/100 ml at an infusion rate of 0.5 mg/kg per minute. Manifestations included elevations of blood pressure, muscle fasciculation, and in one case, generalized convulsions. Gianelly and associates [*26*] observed stupor and convulsions in three patients receiving infusions of lidocaine faster than 8 mg per minute (100 μg/kg per minute) at blood levels of 0.68, 1.09, and 2.28 mg/100 ml. Jewitt and associates [*27*] observed twitching and confusion in two patients with blood levels of 0.27 and 0.3 mg/100 ml receiving infusions of lidocaine at 1 to 2 mg per minute. By contrast, Bedynek and associates [*25*] observed only somnolence and tachypnoea in a patient with a blood level of 2.1 mg/100 ml at an infusion rate of 4.6 mg per minute.

Price [*21*] comments that very little is known of the tissue levels of cocaine following ingestion of a dose leading to death. His figures from one case of cocaine abuse are expressed in mg/100 ml: blood, 0.8; urine, 5.0; bile, 2.5; kidney, 1.2; liver, 0.8; and spleen, 3.0.

Irey [*28*] has discussed the range of lethal blood and tissue concentrations obtainable for any one drug and the variation in levels found in the different viscera. For instance, lethal concentrations of morphine in blood were found to range from as low as 0.01 to 0.2 mg/100 ml and those of glutethimide from 0.19 to 7.7 mg/100 ml. Concentrations of lidocaine in the blood in the present cases ranged from 0.4 mg to 2.8 mg/100 ml.

In fatal cases, both individual susceptibility and duration of survival will influence the concentrations obtained in blood and tissue. The half-life of lidocaine in the blood of healthy volunteers has been estimated as 1.4 h [*1*] and 90 min [*16*]. Continued metabolism in a fatally intoxicated patient may account for low or negative tissue levels.

In the cases presented here, the clinical manifestations were those typical of intoxication with lidocaine or cocaine, consisting of convulsions followed by cardiorespiratory depression or taking the form simply of abrupt cardiorespiratory collapse. Although other medications may have been given (for instance, meperidine), the deaths appear due principally to the toxic side effects of the local anesthetic.

The apparent stimulant and then depressant effect of local anesthetics on the central nervous system involves first the higher and then the lower centers. It has been suggested [*13*] that the apparent stimulant effect may be the result of selective depression of inhibitory neurons by the local anesthetic.

In Case 1, the post-tonsillectomy case, the sequence of events leading to death was typical; initial central nervous stimulation manifested by convulsions was followed by a subsiding of the convulsions and the onset of respiratory depression with cyanosis. Either as a consequence of the anoxia, or by a direct toxic action of cocaine on the myocardium, cardiac arrest occurred.

In Case 2, the first obstetric case, the effects of lidocaine on the central nervous system were probably not the principal cause of death. The patient suffered no convulsions at any time and was reported to have continued to breathe spontaneously while in a state of circulatory collapse. Management with pressor agents was temporarily successful. Although she maintained spontaneous respiration it was thought worthwhile to improve ventilation with IPPR. However, blood pressure again became unobtainable. Since adequate ventilation was maintained by IPPR, the sequence suggests that the principal cause of death may have been the direct toxic action of lidocaine on the heart, resulting in cardiovascular collapse.

In Case 3, the second obstetric case, the patient suffered the abrupt onset of convulsions followed by cyanosis, dying only 15 min after administration of the lidocaine. These are not the complications of trichloroethylene given alone or in circuit with soda lime. The sequence is comparable in part with that of Case 1, the initial phase of central nervous stimulation being followed by brain stem depression and respiratory arrest. Unlike Case 1, however, these manifestations were predominant over any cardiotoxic effects also present.

Case 4 involved an intended below-knee amputation. The toxic manifestations resembled both the central nervous system and cardiovascular manifestations of Case 1. There was a prompt onset of convulsions while a full pulse and spontaneous respirations were maintained. However, after 2 min, when the convulsions had subsided, the patient became pulseless and apnoeic. The flat EKG then obtained, interrupted by episodes of ventricular tachycardia, is consistent with the actions of "caine" anesthetics in depressing not only the force of contraction but also the electrical excitation of the heart.

Case 5 involved the intravenous injection of 1000 mg of lidocaine. The very rapid onset of convulsions was again typical, as was the cardiorespiratory standstill resistant to resuscitative efforts which soon followed.

In only three cases is it clear that unusually large doses of local anesthetic were given: Case 1, a child, given 400 to 500 mg of cocaine plus an unknown amount of lidocaine, following tonsillectomy; Case 4, in whom 400 mg of lidocaine given intravenously was absorbed beyond the sphygmomanometer cuffs; and Case 5, given a 1000-mg bolus of lidocaine in error.

The two obstetric cases are reminders that, although death is a rare complication of local anesthesia, patients do show a widely varying susceptibility to the side effects of local anesthetics, and the margin of safety even with moderate dosage may be small.

Summary

The possible hazards of local anesthetic agents in either moderate or large doses are

not always fully appreciated. The toxic side effects following rapid systemic absorption may be the unsuspected cause of death following the clinical use of these substances.

Data on 15 deaths after the administration of local anesthetic substances are summarized. Five case histories involving lidocaine (lignocaine, Xylocaine®) and cocaine are presented in detail, including the results of toxicologic analysis.

The literature relevant to similar fatalities is reviewed but contains little information relating to blood and tissue concentrations in fatal cases. It is hoped that this paper may assist in clarifying the cause of death in some previously problematic situations.

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