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Local Anesthetic Seizure Prevention:

Diazepam versus Pentobarbital

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Diazepam and pentobarbital both elevate the lidocaine seizure threshold in cats with recording electrodes permanently imbedded in the brain. Ten mg/kg of pentobarbital and 0.25 mg/kg of diazepam, given intramuscularly one hour prior to local anesthetic injection, afforded approximately equal protection against lidocaine-induced seizures. The median iv convulsant dose (CD_{50}) of lidocaine was 16.8 mg/kg in diazepam-treated and 17.6 mg/kg in pentobarbital-treated cats—as against 8.4 mg/kg in unprotected cats. However, CNS and cardiorespiratory depression following pentobarbital and lidocaine was much more profound and prolonged than that which followed diazepam and lidocaine. One hour after injection, diazepam is a better premedicant than pentobarbital for protecting against local anesthetic convulsions. (Key words: Local anesthetic; Convulsions; Diazepam; Lidocaine; Pentobarbital.)

CONVULSIONS are a major hazard of local anesthetic overdosage. With lidocaine now established as a powerful antiarrhythmic agent, local anesthetic-induced convulsions are seen with increasing frequency.[1]

Present-day prophylaxis of local anesthetic-induced convulsions derives from the classic work by Tatum and co-workers,[2] who found that barbiturates stop cocaine-induced seizures in laboratory animals. Recent evidence pointing to the limbic brain as the focus of local anesthetic seizures[3-7] initiated a search for more specific prophylactics than barbiturates—drugs quieting limbic activity (*e.g.*, benzodiazepines) being prime candidates. In fact, we reported recently that diazepam (Valium), a benzodiazepine, doubles the threshold to local anesthetic convulsions in cats.[8]

As pentobarbital (Nembutal) is commonly used as a premedicant for local anesthesia,[9] we compared its effectiveness and side-effects with those of diazepam. To further parallel the usual clinical situation, drug comparison was made one hour after injection of the premedicant. We show here that equiprotective doses of pentobarbital and diazepam give rise to decidedly different systemic changes, diazepam causing fewer and milder side-effects than pentobarbital.

Methods

Nine healthy adult cats were prepared for chronic EEG recording by implanting electrodes in various cortical and subcortical sites. Leads from the electrodes were soldered to a plug that was permanently bonded to the cat's skull. All cats returned to excellent health after surgery. Further details of the animal preparation are in a previous communication.[8]

To record electrical activity from the brain, we connected a mating plug to the socket on the cat's head and cabled the signals to an eight-channel polygraph (0.3–75 Hz bandpass) and a seven-channel FM tape recorder. High-voltage epileptiform spike bursts on the EEG, appearing synchronously in all leads and alternating with electrically quiet periods, were considered indicative of generalized seizures. These spike bursts were invariably accompanied by generalized tonic–clonic contractions of facial and limb muscles.

Lidocaine for injection was made by dissolving lidocaine hydrochloride (Xylocaine) crystals in sterile saline solution and buffering the solution with sodium hydroxide to *p*H 6.9

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TABLE 1. Scoring of Premedication Effects

Wakefulness

0 = normal alert cat
−1 = awake but subdued
−2 = sleepy but readily aroused
−3 = arousable only by loud noise

Gait

0 = normal gait
−1 = slight stiffness to gait
−2 = staggering gait ("drunk cat")
−3 = topples and slides when walking

Coordination on Jumping

0 = normal landing
−1 = slides on landing
−2 = topples on landing but recovers
−3 = uncoordinated fall

to 7.0 (courtesy Astra Pharmaceutical Products). The convulsant dose of lidocaine was determined by injecting 7.5 mg/kg of the local anesthetic iv at a constant rate of 1 mg/kg/sec. Injection was repeated at weekly intervals with larger or smaller doses until the seizure threshold was bracketed.

With the lidocaine seizure threshold established, protection afforded by im diazepam (0.25 mg/kg) or pentobarbital (10 mg/kg) was evaluated.‡ The effects of this anticonvulsant premedication on wakefulness, motor function (walking) and coordination (jumping from a two-foot height) were scored an hour later, according to the criteria in table 1. Immediately thereafter, 15 mg/kg of lidocaine were administered iv at a rate of 1 mg/kg/sec. In subsequent weeks, the fixed premedicant dose was followed one hour later by smaller or larger iv doses of lidocaine until the new seizure threshold was bracketed.

Probit–log dose lines were constructed from these quantal (seizure or no-seizure) data and the median convulsant dose (CD_{50}) of lidocaine determined for each set (untreated; post-diazepam; post-pentobarbital) according to the method of Litchfield and Wilcoxon.[10]

‡ In preliminary tests with 1 to 20 mg/kg pentobarbital, 10 mg/kg im raised the lidocaine seizure threshold to approximately the same level as 0.25 mg/kg diazepam.

Seizure duration and duration of profound cerebral depression were also compared. The former was measured from the start of synchronous epileptiform bursts in cortical tracings to the end of the last burst; the latter was gauged by measuring the length of the isoelectric period following lidocaine injection. Other signs of major side-effects from anticonvulsant pretreatment were evaluated by observing post-lidocaine apnea, cyanosis, time to arousal, and sleeping time.

Results

The lidocaine dose–effect lines of untreated and of diazepam- and pentobarbital-treated cats are shown in figure 1 on probit–log dose axes. Note that an hour after injection 0.25 mg/kg diazepam and 10 mg/kg pentobarbital raised the lidocaine seizure threshold to approximately the same extent, as shown by the near-overlap of the lines in figure 1. Median convulsant doses (CD_{50}'s) computed from these dose–response lines are entered in table 2. While the less-than-5 per cent difference between the diazepam and pentobarbital CD_{50}'s was statistically significant ($P < 0.05$),[10] it was small. Therefore, we regarded 0.25 mg/kg diazepam and 10 mg/kg pentobarbital as equieffective anticonvulsant doses.

The effects of pentobarbital and of the pentobarbital–lidocaine sequence on the EEG of a representative animal are shown in figure 2. (The corresponding EEG effects of diazepam were illustrated in a previous paper.[8]) Note the increase in fast EEG activity an hour after 10 mg/kg pentobarbital, im, the high-amplitude slow waves from a subthreshold dose (15 mg/kg) of lidocaine, and the characteristic synchronous epileptiform spike bursts produced by a convulsant dose (17.5 mg/kg) of lidocaine.

More subtle EEG differences between diazepam and pentobarbital pretreatment are disclosed by power-spectrum analysis,§ as illustrated in figure 3. Note the similarity between the control and post-diazepam records (upper

§ In power-spectrum analysis the EEG is resolved into its sinusoidal components by Fourier transform and the energy content (square of the amplitude) of each frequency band displayed. Peaks denote preponderance of a given frequency band in the EEG.[11]

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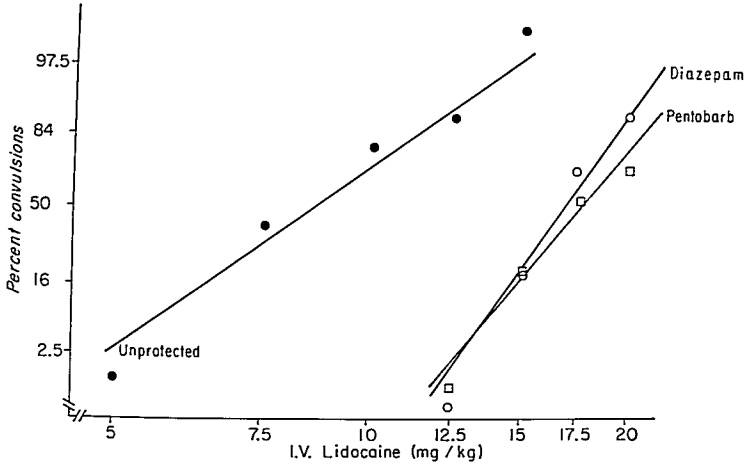

FIG. 1. Incidence of lidocaine-induced convulsions in untreated and premedicated cats. Lidocaine dose is shown on the abscissa (logarithmic scale), seizure incidence on the ordinate (probit scale). Roughly equal anticonvulsant protection by 0.25 mg/kg diazepam and 10 mg/kg pentobarbital is shown by the overlap of the lines on the right.

and lower left). Pentobarbital, on the other hand, caused an obvious shift to higher-frequency components and increased the energy content of the dominant lower-frequency elements as well (upper and lower right); that is to say, slower waves grew in height and were accompanied by fast low-voltage waves after pentobarbital. These EEG dissimilarities were complemented by the marked behavioral differences between diazepam-treated and pentobarbital-treated cats, described next.

BEHAVIORAL EFFECTS OF PREMEDICATION

To compare the behavioral effects of diazepam and pentobarbital, we used the scoring system of table 1, with individual scores one hour after injection listed in tables 3 and 4. The grand mean score after diazepam was −0.5, as against −2.0 after pentobarbital pretreatment; pentobarbital thus had a fourfold greater overall depressant effect on behavior than diazepam. Scores, being subjective evaluations, do not lend themselves well to statistical analysis: nevertheless, it is clear from tables 3 and 4 that pentobarbital affected the cats much more profoundly than did diazepam. They were sleepier, staggered more noticeably, and had poorer coordination an hour after pentobarbital than after diazepam. Coordination in particular was critically altered by pentobarbital. While diazepam affected coordination little, if at all, pentobarbital generally caused marked difficulty in executing complex motor patterns.

TABLE 2. Median Convulsant Doses of Lidocaine, iv (mg/kg lidocaine)

Pretreatment	CD_{50}	95 Per Cent Confidence Limits
None	8.4	7.1–10.0
Diazepam (0.25 mg/kg)	16.8	14.6–19.3
Pentobarbital (10 mg/kg)	17.6	14.8–21.1

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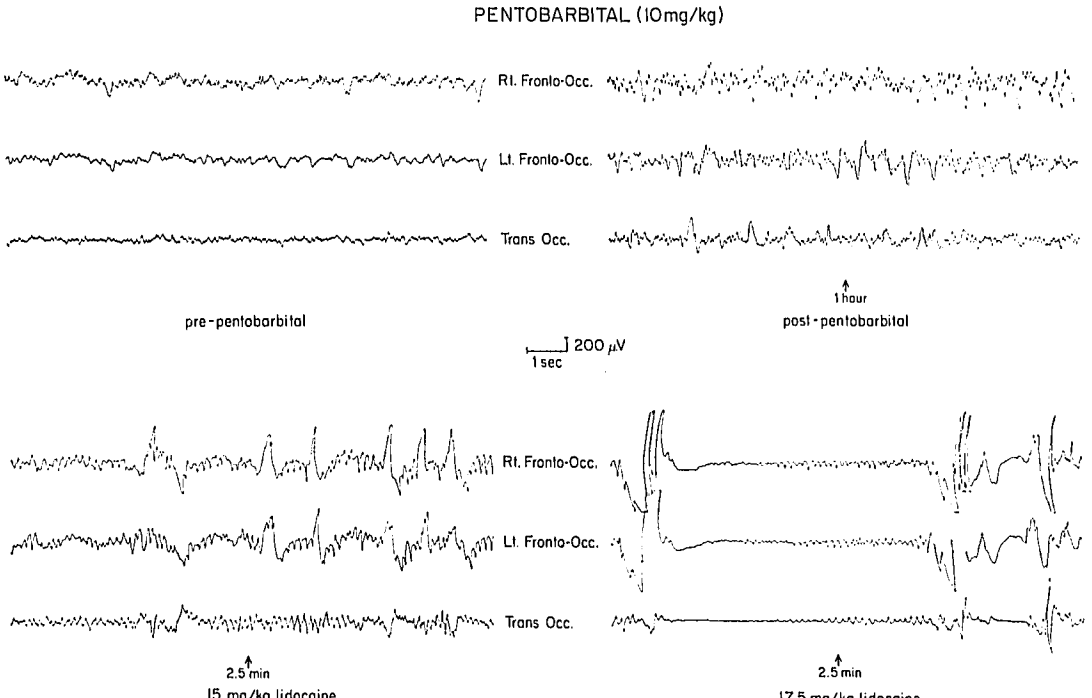

FIG. 2. Cortical-surface EEG's from Cat GC-8. Note the striking EEG change from control (upper left) one hour after 10 mg/kg, im, pentobarbital (upper right; also see fig. 3). The seizure threshold in this pentobarbital-treated cat lay between 15 mg/kg lidocaine (lower left) and 17.5 mg/kg lidocaine (lower right).

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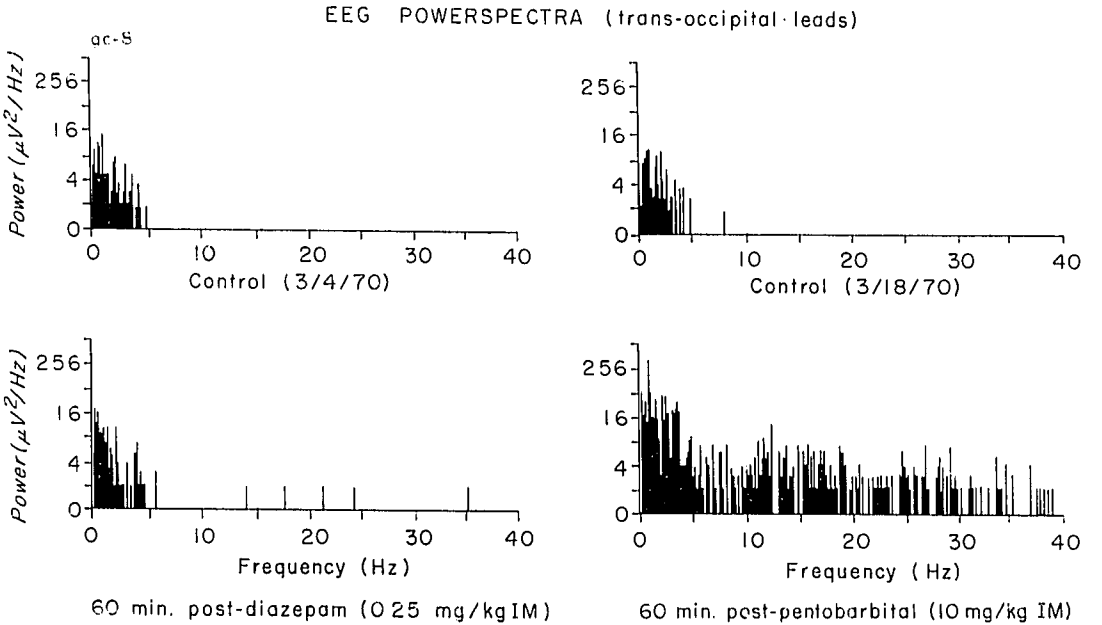

FIG. 3. Power spectra of EEG tracings from Cat GC-8. Transoccipital leads, 0–40-Hz analysis band, 30-second epochs, sampling resolution 0.16 Hz; PDP-15 computer. Frequency is shown on the horizontal axis; relative energy ($\mu V^2/Hz$) is plotted logarithmically on the vertical axis. Traced directly from photographs of the oscilloscope face. Note the minimal change from the control spectrum one hour after 0.25 mg/kg diazepam (tracings on left): low-amplitude slow waves (less than 5 Hz) predominate. One hour after 10 mg/kg pentobarbital (tracings on right) the spectrum had changed strikingly from the control low-amplitude slow-wave pattern to a moderate-amplitude fast-wave pattern (see also fig. 2).

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TABLE 3. Behavioral Effects of 0.25 mg/kg Diazepam (Scored an Hour after Injection)

	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9	Mean Score
Wakefulness	0 −2 −1	0 −1	0 −1 0	−1 −1	0 −1	−1* 0	−1* 0	0 0	−1* −1	−0.6
Gait	−1	−1	0 0 −1	−1 −1	−1 0	−1 0	−2 0	−1 −1	−1 0	−0.6
Coordination	−1	0	0 0 −1	0 −1	0 0	−1 0	−2 0	0 0	0 0	−0.2
GRAND MEAN										−0.5

* Hyperactive.

ANTICONVULSANT EFFECTS OF PREMEDICATION

The differences between pretreatment with approximately equiprotective doses of diazepam and pentobarbital became even more apparent after lidocaine administration. The effects of subconvulsant doses of lidocaine are compared in table 5. The slightly larger (by 3 per cent) dose of lidocaine in the second column reflects the slightly greater anticonvulsant effect of this dose of pentobarbital. One cat developed cardiorespiratory arrest (heartbeat inaudible, pupils dilated, apnea, etc.) when 20 mg/kg lidocaine were given one hour after 10 mg/kg pentobarbital. Observations of this animal were excluded from table 5.

Table 6 summarizes the observations when premedicated cats were given a convulsant dose of lidocaine. The slightly greater (by 4 percent) mean convulsant dose of lidocaine in the second column suggests that 10 mg/kg pentobarbital imparted a little more protection against lidocaine seizures than did 0.25 mg/kg diazepam. Against this should be set that seizures lasted slightly longer (by 12 per cent) after pentobarbital than after diazepam administration.

Convulsions could be elicited in only five

TABLE 4. Behavioral Effects of 10 mg/kg Pentobarbital (Scored an Hour after IM Injection)

	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9	Mean Score
Wakefulness	−3 −2 −1	−2 −2	−2 −2	−2 −2 −2	−1* −2 −2	−2 −2	−3 −2	−3 −2	−3	−1.9
Gait	−2 −1 −2	−1	−2	−2 −3 −3	−3 −3 −2	−3 −2	−3 −3	−3 −2	−3	−2.4
Coordination	−1 0 −2	−1	−2	−1 −2 −2	−2 −2 −1	−3 −2	−2 −1	−3 −2	−3	−1.8
GRAND MEAN										−2.0

* Hyperactive.

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cats pretreated with pentobarbital; in the other four cats so treated, 20 mg/kg lidocaine caused profound cardiorespiratory depression in two and cardiac arrest in the other two (all four recovered after appropriate therapy). Though unable to induce convulsions in these four cats, we dared not give more lidocaine for fear of losing them, and therefore deleted the corresponding observations with diazepam from table 6.

Arterial blood pressure, blood gases, and EKG were not measured in these intact long-term cats. But we did observe respiratory rate, depth and pattern, as well as perfusion and color of the mucous membranes and tongue.

Less than 10 mg/kg lidocaine had relatively little effect on circulation and respiration, as judged by the above clinical signs. Respiration often became a little faster, resembling panting, but the color of mucosal membranes remained unchanged. Larger doses of lidocaine, given in conjunction with diazepam or pentobarbital, depressed respiration, often turning the mucosal surfaces bluish-purple. Oxygen by mask sufficed as treatment. Very large doses of lidocaine, 17.5 mg/kg or more, usually caused apnea lasting one-half to three minutes. Manual ventilation with oxygen by mask quickly restored normal color.

Cats premedicated with pentobarbital were more severely depressed by lidocaine than those premedicated with diazepam. Respiratory depression, as judged by rate and depth, was more profound and apnea more frequent after pentobarbital, and these effects lasted longer (tables 5 and 6). Circulation, too, seemed to be depressed more profoundly by pentobarbital than by diazepam pretreatment. Two cats given 20 mg/kg lidocaine after 10 mg/kg pentobarbital required external chest compression to restart the heart; mucous membranes in others paled following 17.5 mg/kg lidocaine. Further, seven of eight pentobarbital-treated animals developed isoelectric EEG's following the maximal lidocaine dose, as against two of eight diazepam-treated cats.

The cerebral depressant after-effects of the anticonvulsant local anesthetic series were judged by time to arousal and sleeping time (tables 5 and 6). Time to arousal was measured from the start of lidocaine injection until the cat first lifted its head and looked around; most animals were still quite stunned at this time and went back to sleep. Sleeping time was taken as the time from start of lidocaine injection until the animal remained alert without external stimulation. Arousal and sleeping times were three to four times longer after pentobarbital than after diazepam.

TABLE 5. Untoward Effects of Local-anesthetic–Anticonvulsant Combination*

	Lidocaine, 15.0 mg/kg; Diazepam, 0.25 mg/kg	Lidocaine, 15.4 mg/kg; Pentobarbital, 10 mg/kg
Seizure duration (sec)	0.0	0.0
Apneic period (sec)	21.2	31.2
Respiratory depression (min)	0.8	2.6
EEG isoelectric (sec)	0.0	23.7
Time to arousal (min)	7.9	22.5
Sleeping time (min)	26.6	108.8

* A subconvulsant dose of lidocaine (means shown) was given to nine cats one hour after the premedicant. (One of the cats developed circulatory arrest after lidocaine-pentobarbital and was excluded.)

Discussion

Tatum and co-workers[2] (1925) discovered that barbiturates stop cocaine-induced convulsions in laboratory animals. Subsequent studies of seizures evoked by procaine, cocaine, and butacaine confirmed the superiority of barbiturates over other CNS depressants such as ether, chloral hydrate, and paraldehyde.[12]

TABLE 6. Untoward Effects of Local-anesthetic–Anticonvulsant Combination*

	Lidocaine, 16.5 mg/kg; Diazepam, 0.25 mg/kg	Lidocaine, 17.2 mg/kg; Pentobarbital, 10 mg/kg
Seizure duration (sec)	96.2	108.0
Apneic period (sec)	26.4	106.0
Respiratory depression (min)	2.6	4.3
EEG isoelectric (sec)	24.0	114.0
Time to arousal (min)	17.6	24.9
Sleeping time (min)	41.4	109.0

* A convulsant dose of lidocaine (means shown) was given to nine cats one hour after the premedicant. Four cats developed circulatory arrest after lidocaine-pentobarbital and were excluded.

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More recent work has shown the effectiveness of benzodiazepine derivatives such as diazepam and chlordiazepoxide in preventing convulsions induced by cocaine, procaine, lidocaine, mepivacaine, and tetracaine.[2, 8, 13, 41] Are these newer agents as effective and as safe as barbiturates? The answer appears to be yes, with the present study providing additional facts favoring diazepam over pentobarbital prophylaxis.

Alertness, gait, and especially coordination were much less affected by diazepam than by pentobarbital. EEG changes, too, were minimal after diazepam, while EEG's after pentobarbital were strikingly different from controls. Further, the diazepam–lidocaine sequence caused fewer and milder respiratory and circulatory effects, and postanesthetic sleeping times were much shorter, than after pentobarbital–lidocaine. Last, periods of electrical inactivity of the brain were briefer, and the EEG returned to normal sooner, after the diazepam–lidocaine sequence than after pentobarbital–lidocaine.

Diazepam imparts protection not just against local anesthetic-induced convulsions but, evidently, also against their lethality. Thus, Aldrete and Daniel [12] observed that five of six rats pretreated with 12.5 mg/kg pentobarbital convulsed and three of the six died after ip injection of 100 mg/kg lidocaine. In a matching group of six rats pretreated with 7.5 mg/kg diazepam, none convulsed and all survived. In studies by Richards *et al.*[15] with iv mixtures of lidocaine and pentobarbital, the latter, though preventing lidocaine seizures and raising the lidocaine LD_{50} in mice, strongly potentiated the myocardial depressant effects of lidocaine. For instance, 3 mg pentobarbital added to 100 ml bathing solution reduced the quantity of lidocaine that halved *in vitro* atrial contractile force from a normal 3 mg/100 ml to 0.6 mg/100 ml.

Drugs other than benzodiazepines and barbiturates have been tested in the search for ways to counter local anesthetic toxicity. Diphenylhydantoin (DPH; Dilantin) not only is ineffective in preventing local anesthetic seizures, it may even enhance them.[3, 16, 17] We verified this in three chronically-implanted cats; the lidocaine seizure threshold was unaltered in two and reduced in one animal following im or iv administration of 10 mg/kg DPH. Noteworthy too is that several other commonly used premedicant drugs enhance lidocaine's convulsant properties. In mice, for instance, ip injection of 40 mg/kg of meperidine or promethazine lowers the lidocaine CD_{50} from 65 mg/kg to 47 mg/kg.[18]

In the study reported here, we compared the side-effects of two premedicant drugs one hour after im injection to mirror common clinical practice.[9] While the doses chosen were roughly equiprotective against lidocaine-induced seizures, the comparison might not necessarily hold at times other than one hour post-injection. These time–effect relations of lidocaine antagonists await further evaluation.

Promising as the experimental results with diazepam are, one must be wary in transposing animal findings to man. Slight effects on the CO_2-response curve can be demonstrated in diazepam-treated subjects.[19] And, as shown here, the local anesthetic–diazepam combination may lead to respiratory and circulatory depression (albeit less severe than after pentobarbital). Nonetheless, evidence to date attests to the safety of diazepam, with iv doses as large as 1 mg/kg causing few, if any, cardiorespiratory changes in man.[20]

References

1. Crampton RS, Oriscello RG: Petit and grand mal convulsions during lidocaine hydrochloride treatment of ventricular tachycardia. JAMA 204:201–204, 1968
2. Tatum AL, Atkinson AJ, Collins KH: Acute cocaine poisoning, its prophylaxis and treatment in laboratory animals. J Pharmacol Exp Ther 26:325–335, 1925
3. Eidelberg E, Neer HM, Miller MK: Anticonvulsant properties of some benzodiazepine derivatives. Possible use against psychomotor seizures. Neurology (Minneap) 15:223–230, 1965
4. Prince DA, Wagman IH: Activation of limbic system epileptogenic foci with intravenous lidocaine. Electroencephalogr Clin Neurophysiol 21:416, 1966
5. Tuttle WW, Elliott HW: Electrographic and behavioral study of convulsants in the cat. ANESTHESIOLOGY 30:48–64, 1969
6. Tuttle WW, Riblet LA: Investigation of the amygdaloid and olfactory electrographic response in the cat after toxic dosage of lidocaine. Electroencephalogr Clin Neurophysiol 28:601–608, 1970

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7. Wagman III, de Jong RH, Prince DA: Effects of lidocaine on spontaneous cortical and subcortical electrical activity: Production of seizure discharges. Arch Neurol 18:277–290, 1968
8. de Jong RH, Heavner JE: Diazepam prevents local anesthetic convulsions. ANESTHESIOLOGY 34:523–531, 1971
9. Moore DC: Regional Block: A Handbook for Use in the Clinical Practice of Medicine and Surgery. Fourth edition. Springfield, Illinois, Charles C Thomas, 1971
10. Litchfield JT, Wilcoxon F: A simplified method of evaluating dose–effect experiments. J Pharmacol Exp Ther 96:99–113, 1949
11. Schallek W, Lewinson T, Thomas J: Power spectrum analysis of drug effects on electroencephalogram of cat. Int J Neuropharmacol 6:253–264, 1967
12. Knoefel PK, Nerwick RP, Loevenhart AS: The prevention of acute intoxication from local anesthetics. J Pharmacol Exp Ther 34:397–411, 1930
13. Aldrete JA, Daniel W: Evaluation of premedicants as protective agents against convulsive (LD_{50}) doses of local anesthetic agents in rats. Anesth Analg (Cleve) 50: 127–130, 1971
14. Wesseling H, Bovenhorst GH, Wiers JW: Effects of diazepam and pentobarbitone on convulsions induced by local anaesthetics in mice. Eur J Pharmacol 13:150–154, 1971
15. Richards RK, Smith NT, Katz J: The effects of interaction between lidocaine and pentobarbital on toxicity in mice and guinea pig atria. ANESTHESIOLOGY 29:493–498, 1968
16. de Jong RH: Physiology and Pharmacology of Local Anesthesia. Springfield, Illinois, Charles C Thomas, 1970
17. Sanders HD: A comparison of the convulsant activity of procaine and pentylenetetrazol. Arch Int Pharmacodyn 170:165–177, 1967
18. Smudski JW, Sprecher RL, Elliott HW: Convulsive interactions of promethazine, meperidine and lidocaine. Arch Oral Biol 9: 595–600, 1964
19. Catchlove RFH, Kafer ER: The effects of diazepam on the ventilatory response to carbon dioxide and on steady-state gas exchange. ANESTHESIOLOGY 34:9–13, 1971
20. Dundee JW, Haslett WHK: The benzodiazepines. A review of their actions and uses relative to anaesthetic practice. Br J Anaesth 42:217–234, 1970

Endocrinology

NON-ENDOCRINE CUSHING'S SYNDROME Typical cases of Cushing's syndrome have been reported without the finding of endocrine tumors. These patients, however, have other types of tumors. The condition is now called the "ectopic ACTH syndrome." The lesions most often associated with this syndrome are: oat-cell carcinoma of the lung, benign bronchial adenoma, islet-cell carcinoma of the pancreas, and thymoma. Less often it is associated with carcinomas of the liver, prostate, ovary, breast, parotid, and esophagus, as well as with pheochromocytomas, gangliomas, and paragangliomas. Recently several cases with carcinoid tumors were reported. This article describes the syndrome in a young woman and its cure by removal of a benign appendiceal carcinoid. It points out also that the tumors of the various organs mentioned have histologic resemblances to carcinoid, and the puzzling fact that blood levels of ACTH are normal. *(Miller, T., Bernstein, J., and Van Heerle, A.: Cushing's Syndrome Cured by Resection of Appendiceal Carcinoid, Arch. Surg. 103: 770–773, 1971.)*

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