CONVULSIONS INDUCED BY LOCAL ANAESTHETIC: TIME COURSE OF DIAZEPAM PROPHYLAXIS

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GENERALIZED CONVULSIONS are a major hazard of local anaesthetic administration. Seizures induced by lidocaine (Xylocaine) in particular are seen more frequently now that the drug is administered systemically to treat cardiac arrhythmias.[1] Such a serious toxic effect always presents risks, all the more so in a gravely ill patient.

Present-day prophylaxis of convulsions induced by local anaesthetics is based on the classic work by Tatum, Atkinson and Collins[2] who prevented cocaine seizures by prior barbiturate injection. Since then, patients commonly are premedicated with a barbiturate to minimize the possibility of a toxic reaction to local anaesthetic. Diazepam (Valium) recently was shown to be a more desirable prophylactic agent than barbiturates because it produced less neural and circulatory depression and reduced mortality more than an equiprotective dose of barbiturate preceding a convulsant dose of local anaesthetic.[3–5] Recovery, too, was swifter after a diazepam-local anaesthetic than after a barbiturate-local anaesthetic sequence.

While the criterion of fewer side effects may thus have been met by diazepam, its time course of action remains to be determined. The latter is an important clinical consideration, as slow onset or brief span of action may negate any potential superiority over currently used therapy.

We have shown in this study that cats are protected against local anaesthetic-induced convulsions soon after an intramuscular injection of diazepam, and that diazepam prophylaxis lasts at least five hours in this species.

METHODS

Generalized tonic-clonic convulsions were induced in 13 adult cats (average weight 4.1 kg) with lidocaine (Xylocaine) given intravenously at a rate of 1 mg/kg/sec. The control (no diazepam) convulsant dose was bracketed by establishing the amounts of lidocaine that just did and just did not cause tonic-clonic seizures. Injections were repeated weekly with the previous week's lidocaine dose increased or decreased in 0.05 log dose steps. (The lidocaine solution was prepared by dissolving lidocaine HCl crystals in sterile saline and adjusting the pH to 7 with NaOH; courtesy the Astra Company.)

The anticonvulsant activity of diazepam was gauged by comparing the control and the post-diazepam seizure bracketing doses of lidocaine. Diazepam (0.25

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TABLE I

MEDIAN CONVULSANT LIDOCAINE DOSE (mg/kg I.V.) HOURS AFTER 0.25 mg/kg DIAZEPAM (I.M.)

Time (hrs)	CD_{50} (mg/kg)	S.E.	Experiments
0	7.51	1.59	24
¼	14.06	4.30	20
½	17.42	4.50	22
1	15.99	8.16	18
2	14.49	6.76	16
3	12.80	3.78	14
4	14.09	7.23	14
5	11.91	8.48	14

mg/kg) was injected once a week into the thigh muscles. The seizure-inducing dose of lidocaine was then bracketed randomly ¼, ½, 1, 2, 3, 4, or 5 hours later – again with each lidocaine injection spaced a week or more after the previous one. On completion of the diazepam study the basal lidocaine seizure dose was redetermined three to eight months later. Dose-response curves and median convulsant doses (CD_{50}) for each post-diazepam time interval were computed on a PDP-15 by Waud's ungrouped logistic method.[6]

We used intact animals in this study to avoid the possibility of subtle long-term brain changes from implanted electrodes. From past experience we knew that generalized tonic-clonic muscle contractions bear a one-to-one relation to synchronous epileptiform spike bursts in the EEG of the cat. As the chronic nature of these experiments precluded invasive monitoring devices, we relied on clinical observation to judge the animal's physiologic state. Assisted or controlled ventilation with oxygen and external cardiac massage were instituted as necessary.

RESULTS

Every cat convulsed when given lidocaine alone, the initial median convulsant dose (CD_{50}) of lidocaine being 7.5 ± 1.6 mg/kg (±S.E.). The basal seizure response changed little over the course of the experiments, for the terminal CD_{50} of the surviving animals (8.5 ± 2.4) obtained three to eight months later was not significantly different from the initial level. Results from one cat found dead in his cage were eliminated.

Whether observed early or late after injection, diazepam never affected a cat's behaviour, coordination, or gait. The lidocaine CD_{50}, on the other hand, rose soon after diazepam administration and exceeded the control value by more than 50 per cent within 15 minutes (Table I, Figures 1 and 2). Peak protection, corresponding to a CD_{50} of 17.4 ± 4.5 mg/kg, was reached at 30 minutes. A secondary CD_{50} elevation was seen at four hours. Five hours after diazepam the lidocaine CD_{50} was still more than one and a half times the control level.

In attempting to find the convulsant dose of lidocaine in diazepam-treated cats, quantities of lidocaine occasionally exceeding three times the control convulsant dose had to be given. Even then, not all diazepam-treated cats could be made to convulse. Thus the computed CD_{50} values reflect only the lower (non-

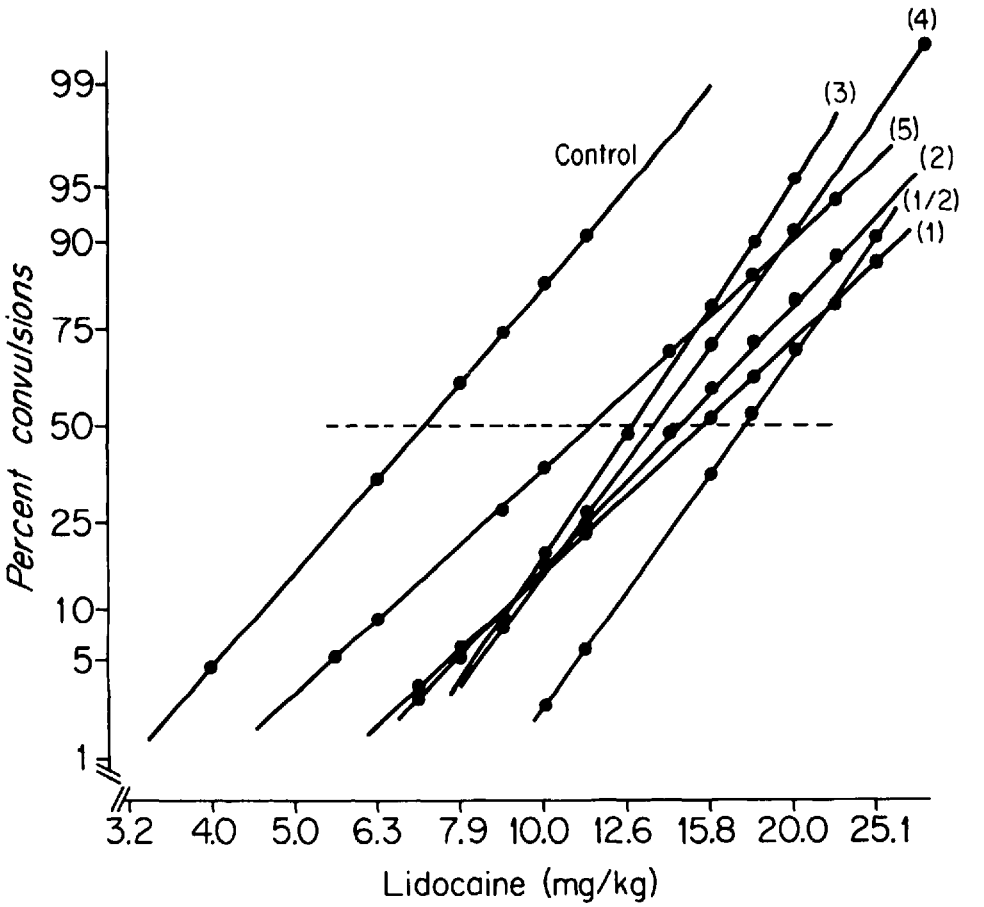

FIGURE 1. Lidocaine-diazepam dose-effect curves. Lidocaine dose (mg/kg, I.V.) on horizontal axis, logarithmic scale; percentage of cats convulsing on vertical axis, logit scale. Computed logit lines have hours after I.M. diazepam at the right tip. The median effect (CD_{50}) line is dashed. Note maximal anticonvulsant effect at half an hour and persistence at five hours.

convulsant) limit of the seizure-bracketing dose pair and are low estimates of the "true" CD_{50}.

Cardiorespiratory depression, at times progressing to arrest, was commonly seen when more than 15 to 20 mg/kg lidocaine were injected. Five cats died after several times the control convulsant dose of lidocaine was given; their terminal (unmedicated) lidocaine thresholds thus are not available. For reasons still unclear, the incidence of cardiac arrests was greatest when the lidocaine was given 15 minutes after diazepam, though all but one cat could be resuscitated.

DISCUSSION

Our experiments give evidence that a single intramuscular injection of diazepam conveys rapid and prolonged protection from convulsions induced by local anaesthetic. These observations extend previous work with diazepam given at a

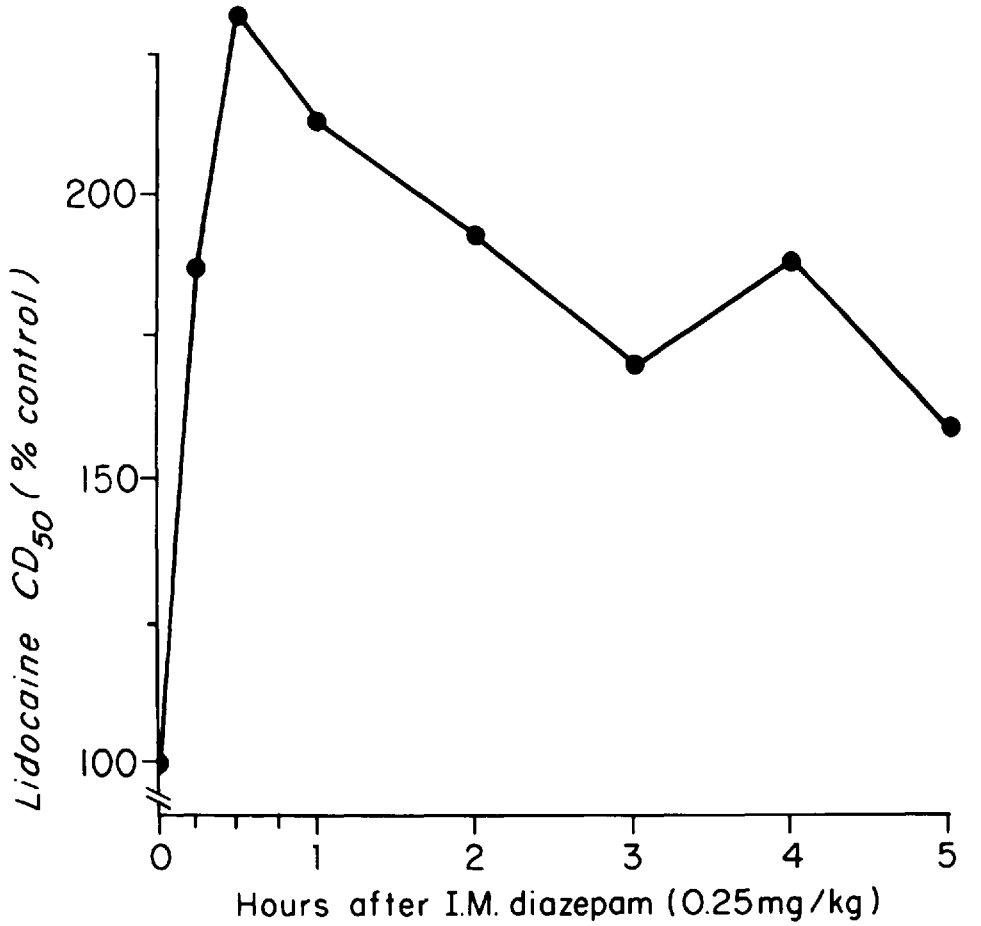

FIGURE 2. Protection against central nervous system toxicity of lidocaine expressed as percentage of control CD_{50}. Seizure threshold more than one and a half times control level between 15 minutes and five hours, and more than doubled 30–90 minutes after diazepam.

fixed time period, usually 30 to 60 minutes, prior to the local anaesthetic challenge.[3,4,7,8]

The early onset of diazepam protection is not surprising in view of the rapid absorption of the drug[9] and its quick brain entry.[10]

The extended anticonvulsant action of diazepam needs comment, however, as its intravascular half-life in animals is but a few hours.[11] The long duration of diazepam protection could represent either secondary release of parent compound from storage sites, or appearance of diazepam metabolites with anticonvulsant properties. Against secondary release or re-uptake are the steadily declining blood levels of diazepam observed in several species, including man.[9] Evidence for the alternate consideration, conversely, is considerable.

Pharmacological activity of metabolic products of diazepam has been suggested by the observation in man of a late repeaking of diazepam effect that correlated with rising diazepam metabolite levels.[12] The work by Marcucci et al.[13] directly links anticonvulsant properties to brain metabolite level. They compared diazepam

and oxazepam (a metabolite of the former) in rodents. Anti-metrazol effect for a given brain oxazepam level was similar, whether the oxazepam was metabolically derived from diazepam or administered as such. N-desmethyl metabolite levels were also higher in mice than in rats, and anti-metrazol activity of diazepam was correspondingly higher and lasted longer in the former.

Combining these facts with our findings, we postulate that accumulation of an anticonvulsant metabolite accounts for the prolonged protective effect of a single diazepam injection. A likely candidate for this role is oxazepam, which is nearly as potent an anticonvulsant as diazepam.[11] Such extended anticonvulsant action is particularly important when the local anaesthetic is injected repeatedly (as in "topping up" a peridural block or infusing an anti-arrhythmic); for not only is primary drug accumulation more likely under these conditions, but local anaesthetic metabolites (mono-ethyl glycine xylidide for instance) are also powerful convulsants in their own right.[14]

Summary

The time course of diazepam prophylaxis of convulsions induced by local anaesthetic was gauged by dose-response assays in 12 cats. Curves relating seizure incidence to intravenous lidocaine dose yielded the median convulsant dose (CD_{50}) of lidocaine for each of seven post-diazepam time periods.

The control CD_{50} for lidocaine was 7.5 mg/kg. Fifteen minutes after 0.25 mg/kg diazepam (I.M.) the lidocaine CD_{50} already was 187 per cent of control (14.1 mg/kg) and it peaked to 232 per cent (17.4 mg/kg) at 30 minutes after diazepam. Two hours after diazepam the CD_{50} still remained at nearly double the control value (14.5 mg/kg), and even five hours later was more than one and a half times the control CD_{50} (11.9 mg/kg). Diazepam protection against convulsions induced by local anaesthetic begins soon after intramuscular injection and lasts at least five hours.

Résumé

Les convulsions sont une complication sérieuse de l'administration des anesthésiques locaux et ont les rencontre de plus en plus souvent avec l'usage croissant de la Lidocaïne et de la médication anti-arythmique.

Le Diazepam protège non seulement les animaux de laboratoire contre les convulsions induites par les anesthésiques locaux mais il a aussi légèrement plus d'effets indésirables qu'une dose protectrice équivalente de barbituriques. L'acceptation du Diazepam en clinique comme agent de pré-médication pour les cas d'anesthésie locale requiert cependant que l'on connaisse à quel moment le Diazepam atteint son action anticonvulsivante maximum et durant combien de temps il conserve son action prophylactique.

Nous avons évalué l'activité anticonvulsivante du Diazepam en comparant l'incidence des convulsions à la dose de Lidocaïne employée et au temps d'apparition après l'injection de Diazepam. Les doses convulsivantes médianes (CD-50) de Lidocaïne ont été compilées à partir des courbes de dose-effet. Le pouvoir prophylactique relatif fut exprimé comme le rapport du CD-50 post-Diazepam sur pré-Diazepam.

Chez un groupe contrôle de 12 chats non prémédiqués, la dose convulsivante médiane (CD-50) de Lidocaïne était de 7.5 mg/kg. Quinze minutes après 0.25 mg/kg de Diazepam i.m., le CD-50 de la Lidocaïne s'élève à 187 pour cent de la valeur contrôle (14.1 mg/kg). La protection maximum anticonvulsivante se produit à 30 minutes après l'injection de Diazepam, à ce moment le CD-50 de la Lidocaïne atteint un sommet à 232 pour cent de la valeur contrôle (soit 17.4 mg/kg).

Deux heures après l'injection de Diazepam, le CD-50 de la Lidocaïne est encore à près du double de la valeur contrôle (14.5 mg/kg, et même 5 heures après, le CD-50 est encore à plus de 1.5 fois celui de la valeur contrôle (11.9 mg/kg). La protection du Diazepam contre les convulsions induites par les agents anesthésiques locaux commence tôt après l'injection intra-musculaire et dure au moins durant cinq heures.

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REFERENCES

1. Crampton, R.S. & Oriscello, R.G. Petit and grand mal convulsions during lidocaine hydrochloride treatment of ventricular tachycardia. J. Am. Med. Assn. *204*: 201 (1968).
2. Tatum, A.L., Atkinson, A.J., & Collins, K.H. Acute cocaine poisoning, its prophylaxis and treatment in laboratory animals. J. Pharmacol. Exp. Ther. *26*: 325 (1925).
3. de Jong, R.H. & Heavner, J.E. Local anesthetic seizure prevention: diazepam versus pentobarbital. Anesthesiology *36*: 449 (1972).
4. Aldrete, J.A. & Daniel, W. Evaluation of premedicants as protective agents against convulsive (LD_{50}) doses of local anesthetic agents in rats. Anesth. Analg. *50*: 127 (1971).
5. Wesseling, H., Bovenhorst, G.H., & Wiers, J.W. Effects of diazepam and pentobarbitone on convulsions induced by local anesthetics in mice. Europ. J. Pharmacol. *13*: 150 (1971).
6. Waud, D.R. On biological assays involving quantal responses. J. Pharmacol. Exp. Ther. *183*: 577 (1972).
7. Wale, N. & Jenkins, L.C. Site of action of diazepam in the prevention of lidocaine-induced seizure activity in cats. Canad. Anaesth. Soc. J. *20*: 146 (1973).
8. Feinstein, M.B., Lenard, W., & Mathias, J. The antagonism of local anesthetic-induced convulsions by the benzodiazepine derivative diazepam. Arch. Int. Pharmacodyn. *187*: 144 (1970).
9. de Silva, J.A.F., Koechlin, B.A., & Bader, G. Blood level distribution patterns of diazepam and its major metabolite in man. J. Pharm. Sci. *55*: 692 (1966).
10. van der Kleijn, E. & Wijffels, C.C.C. Whole body and regional brain distribution of diazepam in newborn rhesus monkeys. Arch. Int. Pharmacodyn. *192*: 255 (1971).
11. Schallek, W., Schlosser, W., & Randall, L.O. Recent developments in the pharmacology of the benzodiazepines. Adv. Pharmacol. Chemother. 10–119 (1972).
12. Baird, E.S. & Hailey, D.M. Delayed recovery from a sedative: correlation of the plasma levels of diazepam with clinical effects after oral and intravenous administration. Brit. J. Anaesth. *44*: 803 (1972).
13. Marcucci, F., Fanelli, R., Mussini, E., & Garattini, S. Further studies on the long-lasting antimetrazol activity of diazepam in mice. Europ. J. Pharmacol. *11*: 115 (1970).
14. Blumer, J.B., Strong, J.M., & Atkinson, A.J. The convulsant potency of lidocaine and its N-dealkylated metabolites. J. Pharmacol. Exp. Ther. *186*: 31 (1973).