Effects of Nitrous Oxide on the Lidocaine Seizure Threshold and Diazepam Protection

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Nitrous oxide raises the lidocaine seizure threshold 50 per cent above the value measured in awake cats. In 11 awake intact cats breathing air, the median convulsant dose (CD₅₀) of lidocaine was 7.6 mg/kg. In 17 cats ventilated with 70 per cent nitrous oxide the lidocaine CD₅₀ was 11.4 mg/kg. One hour after a 0.25 mg/kg im dose of diazepam, the lidocaine CD₅₀ was 16.8 mg/kg, whether the inspired gas was air or nitrous oxide. Nitrous oxide supplementation thus reduces the CNS toxicity of local anesthetics, and diazepam reduces it further. (Key words: Local anesthetic; Local anesthetic convulsions; Anti-convulsant; Nitrous oxide.)

Major regional blocks commonly are supplemented by nitrous oxide analgesia to minimize patient apprehension or visceral traction discomfort. Oral surgeons, too, frequently use nitrous oxide as an adjunct to intraoral nerve blocks. Conversely, intravenously given local anesthetics have been used to supplement nitrous oxide analgesia or to suppress coughing on an endotracheal tube.

Because they frequently are used together in clinical practice, we investigated the toxicity of local anesthetics during nitrous oxide administration. We also explored the effect of nitrous oxide on convulsant protection by premedicant drugs such as diazepam (Valium). We found that nitrous oxide lowers the CNS toxicity of local anesthetics, but that it does not enhance the effectiveness of diazepam premedication.

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Methods

Healthy adult cats were divided into three groups, and the results obtained compared with those of a previously reported group of cats. Each cat in group I, comprising 11 awake intact animals breathing air, was injected once a week with lidocaine,§ given iv at a rate of 1 mg/kg/sec. The lidocaine dose was increased or decreased by small increments until the doses that just did and just did not induce a convulsion were bracketed. From previous experience with cats with implanted recording electrodes, we found observation of extremity and facial muscles as good an indicator of convulsions as the electrical record.

The 20 cats in Group II were anesthetized with halothane and nitrous oxide. The left and right trigeminal ganglia, approached via the infraorbital foramina, each were injected with 1 ml of 1 per cent bupivacaine to minimize pressure discomfort from a stereotaxic reference frame. Noninvasive cortical recording electrodes, made from stainless steel sewing machine needles, were driven into the skull over the left and right frontal, sylvian, and occipital regions of the brain. Burr holes were drilled through the exposed skull for stereotaxic insertion of bipolar electrodes into the amygdala and ventral hippocampus.

A femoral artery and vein were cannulated, the wound flushed with lidocaine and the skin closed with clips. Fluid losses were replaced with 5 per cent glucose in lactated Ringer's solution. End-tidal CO₂ was monitored continuously, as were mid-esophageal temperature and a lead II electrocardiogram. EKG, blood pressure and cortical (and, where applicable, subcortical) EEG's were transcribed in parallel.

§ Made by dissolving lidocaine HCl crystals in sterile saline solution and adjusting the pH to 7 with NaOH.

299
Table 1. Median Convulsant Doses of Lidocaine in the Cat

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Number</th>
<th>CD50 (mg/kg)</th>
<th>Fiducial Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I  Awake, breathing air</td>
<td>11</td>
<td>7.6</td>
<td>7.3–8.0</td>
</tr>
<tr>
<td>Group II Ventilated with N2O*</td>
<td>17</td>
<td>11.4</td>
<td>10.6–12.4</td>
</tr>
<tr>
<td>Group III Ventilated with N2O 1 hr after diazepam</td>
<td>16</td>
<td>16.8</td>
<td>16.8–16.8</td>
</tr>
<tr>
<td>Group IV Awake, breathing air 1 hr after diazepam (previously reported* )</td>
<td>10</td>
<td>16.8</td>
<td>15.4–18.3</td>
</tr>
</tbody>
</table>

* Excludes animals with intracranial bleeding and/or cardiac arrest.

lel on an eight-channel polygraph and a seven-channel FM tape recorder.

With surgical preparation completed, halothane was discontinued and the animals ventilated with 70 per cent nitrous oxide in oxygen (2.5 l/min N2O plus 1 l/min O2). Intermittent injections of decamethonium permitted controlled ventilation at a rate of 32–36/min. Tidal volume was adjusted to maintain end-expired CO2 at approximately 4.5 per cent. Arterial blood gases were measured frequently during the preparatory phase, and always prior to lidocaine injection. Metabolic acidosis, observed in all surgically prepared animals, was corrected with NaHCO3.

Starting not less than one hour after halothane had been discontinued, the seizure threshold was determined by bracketing the iv lidocaine doses that just did and just did not produce high-voltage synchronous epileptiform spike bursts in the EEG. Lidocaine injections were spaced at least one hour apart; if the seizure threshold could not be bracketed in three trials, the experiment was terminated. In five cats the upper and lower bracketing dose sequence was repeated several times and in random order to ascertain reproducibility of the method.

The 16 cats in Group III were prepared similarly to those in Group II, except that they had noninvasive cortical electrodes only. After not less than one hour on nitrous oxide, cats in this group were given 0.25 mg/kg diazepam, injected into the thigh muscles. One hour later, while the cat was still ventilated with nitrous oxide, a single iv dose of 16.8 mg/kg of lidocaine was injected. Presence or absence of cortical seizure discharges was determined from the EEG record as described. (This dose of lidocaine previously was shown to be the post-diazepam CD50 in chronically implanted awake cats.*) At 30- or 60-minute intervals thereafter, additional 16.8-mg/kg doses of lidocaine were given until convulsions ensued.

After a lethal dose of pentobarbital, the cat's brain was perfused in situ with formalin. Brains were subsequently removed and examined grossly and microscopically for lesions and recording electrode locations.

Cumulative seizure frequencies, obtained from the quantal (convulsion–no convulsion) observations for each group of cats, were analyzed with the method of weighted probits on a PDP-15 computer. Program output comprised the median convulsant dose (CD50), fiducial limits of the CD50, and the equation for the probit–log dose line. Dose–response curves were constructed from the latter.

Results from a fourth group of ten cats with cortical and subcortical recording electrodes permanently implanted in the brain were reported previously. These air-breathing awake implanted cats received 0.25 mg/kg diazepam im and one hour later, lidocaine iv. The diazepam–lidocaine sequence was repeated once a week until the seizure threshold was bracketed.

Results

The lidocaine CD50 in awake intact cats breathing air was 7.6 mg/kg (table 1; fig. 1). These Group I cats were under long-term observation for possible harmful effects from seizures or from cardiorespiratory depression following large doses of lidocaine. All thrived, free of noticeable neurologic changes.

Three of the 20 cats used to determine the lidocaine CD50 during nitrous oxide administration had intracranial hemorrhage and/or...
N₂O EFFECTS ON SEIZURE THRESHOLD

301

FIG. 1. Dose–response lines of awake (left) and nitrous oxide-anesthetized (right) cats. Lido
caine doses (logarithmically scaled) on the ab
cissa; cumulative frequency of convulsions (probit
scale) on the ordinate. CD₉₀ can be determined
directly by interpolation.

Cardiac arrest after lidocaine; their seizure
data were excluded from the calculations. In
the remaining 17 cats of Group II, the CD₉₀
was 11.4 mg/kg (table I; fig. 1). Repeat
measurement of the convolution-bracketing
doses of lidocaine in five cats of this group
yielded the same values as obtained initially.

Of the 16 cats ventilated with 70 per cent
nitrous oxide and given diazepam, followed by
16.8 mg/kg lidocaine one hour later, eight
convulsed. This 50 per cent incidence of
convulsions in the Group III cats pinpointed
the CD₉₀ exactly, so that a N₂O–diazepam
dose–response line was not constructed. Pre
everiously we reported a post-diazepam lido
caine CD₉₀ of 16.8 mg/kg in awake cats
breathing air (Group IV). The latter value
was identical to the CD₉₀ found in the present
study. Of the eight cats in Group III which
did not convulse with the first post-diazepam
dose of 16.8 mg/kg lidocaine, all eventually
convulsed when the lidocaine was repeated
one to four times.

The 50 per cent increase in CD₉₀ (from 7.6
to 11.4 mg/kg) in the air–versus-nitrous oxide
series (Groups I and II) was statistically sig
ificant. So was the 47 per cent increase in
CD₉₀ (from 11.4 to 16.8 mg/kg; Groups II
and III) in nitrous oxide-ventilated cats when
lidocaine injection was preceded by im diazep
am. The post-diazepam CD₉₀ of 16.8 mg/kg
lidocaine was the same whether air (Group
IV) or nitrous oxide (Group III) was the in
spired gas.

In the experiments with nitrous oxide-venti
lated cats (Groups II and III), mean PacO₂
prior to lidocaine injection was 28.8 ± 3.7 torr,
PH 7.39 ± 0.05, and PaO₂ 114.2 ± 22.0 torr
(all means ± SD). Systolic blood pressure
prior to injection consistently was greater than
100 torr (if not, the measurement was re
jected). Three cats had cardiac arrest after
small (10–12.5 mg/kg) lidocaine doses; two
of these were found to have intracranial
bleeding.

Discussion

Nitrous oxide, under the conditions of these
experiments, protects against lidocaine-induced
convulsions—raising the seizure threshold by
50 per cent. To our knowledge, this CNS-
protective effect of nitrous oxide has not been
demonstrated previously. Diazepam also pro
tects against local anesthetic convulsions, but
this effect is not further enhanced by nit
rous oxide administration.

It is unlikely that the depth electrodes
placed in Group II cats altered the seizure
threshold. The previously reported lidocaine
CD₉₀ in awake cats with permanently im
bedded depth electrodes was 8.4 mg/kg, in
distinguishable by t-test from the 7.6-mg/kg
CD₉₀ found here in intact cats. However,
several other factors, choice of “muscle relax
ant” in particular, may have affected the CD₉₀.

For instance, succinylcholine given to nit
rous oxide-anesthetized cats halves the lido
caine seizure threshold, and gallamine (Flaxe
dil) prolongs the duration of seizure afterdis
charges in the cat’s isolated cortex. On the
other hand, decamethonium and succinylchlo
line have no effect on lidocaine-induced sei
zures in rhesus monkeys, though gallamine and
curare do. The lack of effect of succinylchlo
line on local anesthetic convulsions has been
substantiated in man, too. As decametho

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nium appears to be the one muscle relaxant that does not affect the seizure threshold, we chose it for these studies.

Are tonic-clonic convulsions observed in cats with normal neuromuscular function equatable with electrographic seizure patterns in paralyzed animals? From our experience with lidocaine convulsions in chronically implanted cats—where brain electrical activity was recorded along with observation of behavior—we would say yes. With very large (greater than 12-15 mg/kg) lidocaine doses, convulsive muscle contractions commonly were less vigorous than with smaller doses of lidocaine, but the presence or absence of a convulsion could always be detected. Even assuming that a barely-visible seizure was overlooked, the error would have raised the apparent CD₉₀ in the awake intact Group I cats. Thus, if anything, the actual difference between the awake and the N₂O-ventilated series would have been greater yet.

Although Bernhard and Bohm described an anticonvulsant action of lidocaine, we doubt that residual lidocaine raised the seizure threshold. First, even on initial injection the seizure-bracketing dose of lidocaine was much greater in nitrous oxide-ventilated cats than in air-breathing cats. And second, when the seizure-bracketing doses of lidocaine were rechecked in the same animal, they remained unchanged, at least when spaced an hour apart.

Acid–base balance influences the seizure threshold to local anesthetics. Englesson and co-workers, Munson and Wagman, and our group, for instance, demonstrated that P₀₂, pH, or perhaps a combination of the two alters the lidocaine seizure threshold. At least in cats, elevating P₀₂ lowers the seizure threshold, and the converse holds true, too. For this reason we took pains in the present experiments to maintain P₀₂ near 30 torr and pH near 7.40—these being representative means in awake cats.

Last, the failure of nitrous oxide to alter the post-diazepam seizure threshold requires comment, though we have no ready answer for it. It may be that diazepam protection, with the dose and time schedule used here, was maximal. That subsequent injections of lidocaine eventually induced convulsions speaks for this. Against this must be set that more diazepam (to 0.5 mg/kg) further increased the lidocaine CD₉₀ in awake chronically implanted cats. Also unresolved is the extent to which decamethonium, mechanical ventilation, and other factors introduced by acute experiments influenced the combined effect of nitrous oxide and diazepam.

One sequel of our work is that studies with local anesthetics in anesthetized subjects might lead one to expect a broader range of safety than actually is present in unanesthetized man. To the extent that we can extrapolate from animal to man, we conclude that nitrous oxide supplementation of regional blocks provides substantial protection against the CNS toxicity of local anesthetics.

References

9. Halpern LM, Black RG: Gallamine triethiodide facilitation of local cortical excitability compared with other neuromuscular


Obstetrics

PROSTAGLANDINS AND INDUCED LABOR Prostaglandin F2α and synthetic oxytocin, used for induction of labor in term human pregnancy, were studied. (Prostaglandin E2, included in the title, was soon withdrawn from the study because of shelf instability.) Patients classed as “easy inductions” were delivered successfully no matter which drug they received. In three categories of “difficult inductions,” success rates ranged from 40 to 93 per cent, depending upon difficulty of induction. The two drugs were equally efficacious in the 55 patients studied. A possible advantage of the prostaglandin infusion over synthetic oxytocin was a shorter infusion–delivery interval in both easy-induction and difficult-induction groups. (Anderson, G. G., Hobbins, J. C., and Sperriff, L.: Intravenous Prostaglandins E2 and F2α for the Induction of Term Labor, Am. J. Obstet. Gynecol. 112: 382–386, 1972.)

LIDOCAINE AND FETAL HOMEOSTASIS The effects of large (14–37 mg/kg body weight) intravenous doses of lidocaine administered to the fetus on fetal heart rate and cerebral metabolism and function were studied in 15 fetal sheep. Significant bradycardia, unaffected by vagectomy, occurred in each experiment. The electroencephalogram (EEG) showed slowing, slowing followed by an isoelectric (flat) record, or development of low-voltage fast activity. While cerebral blood flow decreased significantly, cerebral metabolism was unaffected. Fetal heart rate, blood flow, and the EEG recovered within 20 minutes of injection. (Mann, L. I., and others: Effect of Lidocaine on Fetal Heart Rate and Fetal Brain Metabolism and Function, Am. J. Obstet. Gynecol. 112: 789–795, 1972.)