Diazepam (Valium) prevents local anesthetic-induced convulsions without increasing lidocaine’s cardiovascular toxicity. Sixteen cats received the previously determined post-diazepam median convulsant dose of lidocaine (16.5 mg/kg iv). Eight cats were pretreated with a non-sedative dose of diazepam (0.25 mg/kg im) one hour before lidocaine injection; the other eight did not get diazepam. While all untreated cats convulsed after lidocaine, only half of the diazepam-treated cats convulsed. Lidocaine caused profound hypotension in both groups, mean arterial pressure falling to one third the control value in the first minute. Ventricular tachycardia began even before lidocaine injection was completed. Mean blood pressure rapidly recovered, returning to within 90 per cent of control by 7½ minutes. While the time courses of circulatory effects were similar in the two groups, EKG signs of ventricular irritability were fewer in diazepam-treated cats. (Key words: Convulsions; Diazepam; Lidocaine; Local anesthetic.)

Local anesthetic-induced convulsions are seen more frequently now that lidocaine is widely used as an antiarrhythmic agent. Several authors have demonstrated the efficacy of diazepam (Valium) premedication in preventing these seizures. But could diazepam pretreatment introduce new risks outweighing the hazards of convulsions? Of particular concern in this regard are possible effects of the diazepam–lidocaine combination on arterial blood pressure and cardiac rhythmity.

That moderate intravenous doses of lidocaine affect cardiovascular function but little, whether in man or in animals, is well-documented. However, diazepam prophylaxis allows administration of larger than usual doses of lidocaine. Thus, we decided to evaluate the cardiovascular effects of large doses of lidocaine in untreated and in diazepam-treated animals.

Methods

Sixteen adult cats were anesthetized with halothane, then intubated and ventilated mechanically. End-expired CO₂, temperature and urinary output were kept within limits normal for the cat.

The Gasserian ganglia were blocked with 1 ml of 1% bupivacaine each, prior to fixing the head in a stereotaxic frame. The skull was then exposed through a midline incision and pin electrodes driven through the bone to rest extradurally over the frontal, anterior and posterior suprasylvian gyri. Various combinations of cortical recording leads, together with a lead II (RA-LF) electrocardiogram (EKG) and femoral arterial blood pressure (BP), were recorded in parallel on an eight-channel polygraph and a seven-channel FM tape recorder.

On completing the surgical procedure, halothane was stopped. Mechanical ventilation was continued with a mixture of 2 l N₂O and 1 l O₂, aided by intermittent injections of decamethonium. One hour or more later, eight animals were given an intravenous bolus of 16.8 mg/kg lidocaine at a rate of 1 mg/kg/sec.

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† The lidocaine used here was made by dissolving lidocaine·HCl in saline solution and bringing the pH to 7 with NaOH (courtesy Dr. Vinton Hallock, Astra Pharmaceutical Products).
(The 16.8 mg/kg was selected because it is the median intravenous convulsant dose \([\text{CD}_{50}]\) of lidocaine in unanesthetized diazepam-treated cats.) The other eight cats first were given an intramuscular injection of 0.25 mg/kg diazepam; then, one hour later, 16.8 mg/kg lidocaine intravenously.

EEG's were scanned for presence or absence of synchronous high-voltage epileptiform discharges and for isoelectric segments; EKG's for rate, rhythm and block, and for alterations in S-T segment and T-wave configuration. Mean BP just before drug injection was taken as the control value, and subsequent changes expressed as per cent deviations from control pressure. Averages of these values, obtained at identical times after injection, were compared with the unpaired t-test.

**Results**

**EEG Changes**

The eight untreated cats given 16.8 mg/kg lidocaine all developed characteristic high-voltage epileptiform EEG discharges. Of the other eight cats pretreated with 0.25 mg/kg diazepam, four convulsed when the lidocaine bolus was injected one hour later; the other four cats developed large slow EEG waves only. Diazepam did not noticeably alter the EEG during the one-hour observation period preceding lidocaine administration.

Isoelectric (flat baseline) EEG's were always seen when the BP fell below 35 to 45 torr after lidocaine injection. EEG activity resumed when the BP returned to 40 to 50 torr. Interictal EEG's (in the 12 cats with electrocortical seizures) also were isoelectric, especially during the early seizure phases. Further details of the EEG effects of lidocaine and diazepam may be found in a previous report.6

**Arterial Blood Pressure**

Diazepam did not significantly alter mean arterial pressure. Just prior to lidocaine injection, mean BP's were 137.1 torr (range 113.3–171.6) in the eight untreated cats and 142.3 torr (range 106.7–170.0) in the diazepam-treated cats. Mean BP just prior to diazepam injection was 145.2 torr (range 120–170), varying by 5 per cent or less (range 96.8–105.4 per cent) during the next hour.

In both groups lidocaine reduced the pressure sharply. The low—averaging roughly one third the control value—was attained half a minute after the start of lidocaine injection. Recovery was almost as fast, with 75 per cent or better of the control pressure regained by 5 minutes (fig. 1). Though electrical asystole was not seen, external cardiac compression lasting 1 to 4 minutes was instituted in three cats because the systolic pressure fell below 30–35 torr and the EEG became flat.

Differences in mean pressures between untreated and diazepam-treated cats were insignificant, save for borderline significance 60 minutes after lidocaine \((0.05 < P < 0.1)\). The circulatory changes brought about by these massive doses of lidocaine thus were no more severe in diazepam-treated cats than in untreated cats.

**Electrocardiogram (EKG)**

Untreated. The cat's lead II EKG configuration resembled that of man, except that the P-wave was nearly always biphasic, and the T-wave more pronounced and tented. Early lidocaine-induced EKG disturbances, developing even before intravenous injection was completed, comprised P-R interval shortening, slowing of the rate, increased amplitude and width of the QRS complex, and axis shift. These early changes, becoming progressively more pronounced beat by beat, are demonstrated in figure 2b. Soon thereafter the P-wave disappeared altogether, the pattern becoming one of ventricular tachycardia (fig. 2c), commonly with fusion beats (fig. 2d) and, rarely, escape beats (not shown).

Notching of the wide QRS complexes, presumably signaling bundle-branch block, occurred in three records; multifocal ventricular complexes in four, Wenkebach block in three, and wandering ventricular pacemaker in four. The P-wave reappeared 0.7 to 2.5 minutes after lidocaine injection, though its configuration varied from beat to beat, as did the P-R interval. Occasional to frequent premature ventricular beats intermingled with the sinus beats at this time. Steady pace-
Fig. 1. Mean arterial pressures—expressed as percentages of control pressures—following 16.8 mg/kg lidocaine iv. Blood pressures in untreated and diazepam-treated cats do not differ significantly.

maker control returned at 7.8 minutes, on the average, with a 1½- to 16-minute range.

Diazepam-treated. Diazepam had no noticeable effect on cardiac rate or rhythm, except for minor and transient P-wave or T-wave changes. Lidocaine-induced EKG changes in this group were briefer on the whole than in the untreated cats. While the aforementioned EKG changes (slowing of rate, runs of ventricular tachycardia, increased height and width of the QRS complex) also developed here, the P-wave returned sooner. Note, for instance, in figure 3d the early return of the P-wave, even though the S-T segment retains a "hockey-stick" depression for some time.

Nodal rhythms or wandering supraventricular pacemaker appeared oftener in diazepam-treated than in untreated cats as an intermediary stage between ventricular and sinus control. Wandering ventricular pacemaker, conversely, was seen only twice, and Wenckebach block or bundle-branch block not at all. Regular sinus rhythm returned 7½ minutes, on the average, after lidocaine injection (range 2 to 13 minutes), approximately the same as for the untreated cats.

The just-described EKG changes seemed unrelated to convulsions. Sometimes normal rhythm would return with electrographic seizures in full swing, while in non-convulsing cats at the same time the rhythm might still be abnormal.

Discussion

The foregoing results demonstrate that diazepam pretreatment sufficient to halve the seizure incidence imposes no additional burden on the cardiovascular system when a massive bolus of lidocaine is given. If anything, EKG changes were less alarming and persistent in diazepam-treated than in untreated cats. It is reassuring to clinicians that, experimentally at least, the incidence of toxic CNS reactions can be reduced without having to trade off this gain for the hazards of further cardiovascular depression.

That diazepam pretreatment protects not only the brain but also the cardiorespiratory system from local anesthetic toxicity was shown by Aldrete and Daniel. They observed that prior diazepam reduced the seizure incidence in rats given lidocaine from 67 to 0 per cent, and the mortality rate from 50 to 0 per cent—death being attributed to cardiorespiratory depression. Pertinent is that rats
which died after lidocaine convulsed prior to death.

The doses of lidocaine employed in the present study far exceed those used therapeutically. Man, even patients with valvular or coronary-artery disease, tolerates a 1 to 2 mg/kg lidocaine bolus without ill effect.11-12 Actually, the systolic blood pressure often rises during intravenous administration of lidocaine to man.13

When large quantities of lidocaine are given, on the contrary, transient myocardial depression, peripheral vasodilatation and hypotension are the rule.14-15 The major falls in blood pressure described here thus come as no surprise. Not so the EKG changes. Lieberman and colleagues,16 for instance, showed that lidocaine, though it slows the idioventricular rate, has little effect on intraventricular conduction. We saw instead a rapid
DIAZEPAM AND LIDOCAINE-INDUCED CHANGES

0.25 mg/kg diazepam I.M.
and
16.8 mg/kg lidocaine I.V.

Fig. 3. Lidocaine-induced cardiovascular changes in a cat one hour after 0.25 mg/kg diazepam im (N2O anesthesia; cat GCA-29). The top trace in each frame is lead II EKG, with femoral arterial pressure below it.

a) Control. Slight S-T elevation, sinus rate 160/min, arterial pressure 155/110 torr.
b) One hour after diazepam. T-wave flat, isoelectric S-T segment.
c) Lidocaine (16.8 mg/kg) injection. The S-wave rapidly deepens, QRS complex widens, P-wave becomes buried, and ventricular tachycardia sets in. Blood pressure falling.
d) 0.5 minutes. Normally conducted beats reappear, S-T segment depression present.
e) 3 minutes. Rate slowing, S-T segment depression and hockey-stick configuration still present. Blood pressure 80/50 torr.
f) 5 minutes. Occasional ectopic atrial discharge, blood pressure recovering.
g) 10 minutes. Tracing resembles control, save for a biphasic T-wave and an occasional non-conducted ectopic atrial wave. Blood pressure 130/90 torr.
h) 20 minutes. Recovery, blood pressure 170/125 torr.

ventricular tachycardia, the very arrhythmia so responsive to lidocaine therapy. The mechanism of this cardiotoxic action remains to be worked out, though it is reminiscent of lidocaine’s dual effect on the brain.17

The experimental anesthetic agent can affect the results, as shown by McWhirter and co-workers,18 who compared lidocaine’s cardiovascular effects in barbiturate- and nitrous oxide-anesthetized dogs. Whereas the former group suffered marked and prolonged cardiovascular depression after lidocaine infusion (resembling that of ganglionic blockade), the nitrous oxide-anesthetized dogs did not. Nitrous oxide, moreover, neither depresses nor stimulates isolated heart muscle.19
Our results—obtained in nitrous oxide-anesthetized intact animals—thus exclude these sources of experimental artifact.

We conclude that large doses of lidocaine, given to lightly anesthetized cats, profoundly depress the cardiovascular system. Diazepam (0.25 mg/kg im), injected prophylactically to reduce lidocaine’s CNS toxicity, does not add to the local anesthetic’s cardiovascular toxicity.

References