Antiarrhythmic Properties of Chlordiazepoxide

By Richard A. Gillis, Ph.D., Harold Thibodeaux, and Louis Barr, M.D.

SUMMARY
The reported effectiveness of chlordiazepoxide in depressing the central nervous system led us to test this agent against cardiac arrhythmias induced by digitalis and coronary occlusion. The digitalis studies were performed in Dial-urethane anesthetized cats by monitoring: (1) ECG, (2) femoral arterial blood pressure, (3) right ventricular contractile force, and (4) spontaneous activity in cardiac sympathetic nerves. Chlordiazepoxide (3.6–39.5 mg/kg i.v.) converted established ventricular arrhythmias induced by deslanoside to regular sinus rhythms in nine of the 12 animals studied. Conversion was associated with depression of deslanoside-induced sympathetic nerve firing. Chlordiazepoxide was ineffective against similar arrhythmias produced in eight spinal-sectioned cats. The coronary occlusion studies were performed in unanesthetized dogs 1 day after two-stage ligation of the anterior descending branch of the left coronary artery. The ECG was recorded and all dogs exhibited ventricular ectopic beats. Chlordiazepoxide (10 mg/kg i.v.) produced a significant reduction in the number of abnormal beats, a significant increase in sinus beats, and a significant degree of cardiac slowing. The effect of chlordiazepoxide on the antiarrhythmic and central nervous system effects of lidocaine was also tested in this preparation. Pretreatment with chlordiazepoxide enhanced the antiarrhythmic effect and prevented the neurotoxic effect of lidocaine. These results support our hypothesis that drugs which depress the central nervous system may be effective for the treatment of ventricular arrhythmias. These results also demonstrate the potential benefit of combining chlordiazepoxide with lidocaine in antiarrhythmic drug therapy.

One of the dangers of currently available antiarrhythmic drugs is their propensity to depress cardiovascular function. This is true of quinidine, procaine amide, and propranolol. All three depress cardiac contractility and may be toxic to patients with myocardial disease.1 Lidocaine and diphenylhydantoin, two drugs not commonly thought to be myocardial depressants, also possess this undesirable effect.2 Furthermore, lidocaine is toxic to the central nervous system and its administration can result in muscular twitching and convulsions.3–6

The need for new and better antiarrhythmic drugs is obvious, and in this regard there have been two general approaches to finding them. One approach is based on the idea that drugs must act directly on myocardial cell membranes to exert an antiarrhythmic effect.7 The other approach is based on the idea that drugs having neurodepressant effects can be used to suppress cardiac arrhythmias.8–12 These approaches derive from the assumptions that myocardial and neural components are both involved in the genesis of arrhythmias, and evidence exists to support each assumption.1, 13, 14

Using the nervous system as a principal target in the search for new and effective antiarrhythmic drugs offers an important advantage. It should be far easier to find an agent that will selectively interfere with the neural component of an arrhythmia without damaging myocardial contractility than it would be to find an agent that would interfere with heart muscle electrical activity without interfering with muscle contractility. With this in mind we evaluated the antiarrhythmic

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activity of the neurodepressant substance—chlordiazepoxide—a drug reported to have negligible cardiovascular depressant effects at therapeutic blood levels.15

Methods

The effect of chloldiazepoxide on cardiac rhythm disturbances was investigated using arrhythmias induced by either digitalis or coronary occlusion. In the digitalis model, cats of either sex with weights ranging from 1.6 to 3.5 kg were anesthetized with 0.6 ml/kg i.p. of Dial-urethane. A tracheotomy was performed on all animals, and they were respired artificially with room air. The spinal cords and vagus nerves of eight of these animals were transected at the atlanto-occipital junction and at the cervical region, respectively. Catheters were inserted into the right femoral artery and vein of all animals for the purposes of measuring blood pressure and administering drugs, respectively. The animals’ body temperatures were maintained between 37.0 and 38.5°C by an infrared lamp.

The heart and cardiac sympathetic nerves were exposed by excising the first three or four ribs on the right side. The pericardium was opened and a Walton-Brodie strain gauge arch was sutured to the right ventricle. The preganglionic sympathetic nerves to the right stellate ganglion were carefully dissected and placed on bipolar platinum recording electrodes. Assurance that the sympathetic nerve fibers were cardiac bound was obtained by stimulating them electrically and observing the effect on heart rate. Nerve activity was amplified, stored on magnetic tape and subsequently fed into a Grass integrator (Model 7P10B). Both the nerve activity and the integration of the activity with respect to time were displayed on a Grass polygraph (Model 7). The integrator was reset to zero at 10 sec intervals. Calibration of the integration system with reference to a known input was not done as we were only interested in relative changes in activity.

Myocardial contractile force, femoral arterial blood pressure, and the electrocardiogram were recorded continuously on a Beckman RB recorder.

Two types of experiments were performed to evaluate the effects of chloldiazepoxide: 1) Deslanoside, 25 μg/kg i.v. every 15 min, to produce a stable ventricular arrhythmia of 1 min duration, followed by chloldiazepoxide in 10–15 mg i.v. increments given at approximately 45 sec intervals to revert deslanoside-induced ventricular arrhythmia to sinus rhythm (n = 12). The criteria for ventricular arrhythmia was a sustained idioventricular rhythm lasting at least one minute and characterized by the presence of independent nonconducted atrial activity.

2) Deslanoside and chloldiazepoxide as in type 1, but administered to cats with spinal cord transections at C-1 and bilateral cervical vagotomy (n = 8).

In the coronary occlusion model, dogs unsellected as to age or sex and ranging from 18.5 to 23.5 kg in weight were anesthetized by an intravenous injection of pentobarbital sodium (30 mg/kg). Mechanical ventilation with room air was instituted with a cuffed endotracheal tube. Under sterile conditions the heart was exposed through the fourth left intercostal space and the pericardium incised. The anterior descending branch of the left coronary artery was dissected for a short length at a level about 1 cm distal to the left atrial appendage and occluded in two stages according to the method described by Harris.16 The chest was closed and a polyethylene catheter for injecting drugs was inserted into the jugular vein and exteriorized at the nape of the neck.

Animals were studied the following day, 26–31 hr after occlusion, in the unanesthetized state. All animals had been trained previously (i.e., before surgery) to lie quietly while ECG recordings (lead II) were made. In some animals, the electroencephalogram was recorded from standard EEG needle electrodes placed biparietally so that the needle tip entered obliquely and rested on the parietal bone. The low and high filters were set at 0.3 and 30 Hz, respectively. The ECG and EEG were displayed continuously on two channels of the polygraph. Preoperative electrocardiograms demonstrated sinus rhythm in all animals with heart rates ranging from 75 to 125 beats/min (mean value was 98 with a se of ± 9.4). The ECG revealed ventricular ectopic beats of multifocal origin. This arrhythmia was quantitated by counting every beat during a five minute period and noting the number which were of abnormal and normal origin.17 Control ECGs were taken for a 30 min period before the first dose of drug was administered. Chloldiazepoxide was used by dissolving the powder in 0.85% normal saline to a final concentration of 10 mg/cc. In the experiments where only the effect of chloldiazepoxide was studied, it was administered in a dose of 10 mg/kg by giving two injections of 5 mg/kg separated by a 5 min interval. The drug was rapidly administered (i.e., over 3 sec) through the jugular vein catheter and the catheter was flushed rapidly with 5 cc of saline.

In the experiments where the effects of chloldiazepoxide on the antiarrhythmic and neurotoxic effects of lidocaine were studied, chloldiazepoxide was administered in a dose of 10 mg/kg (as described above) and was followed in 30 min by an additional 2.5 mg/kg. Two minutes later, lidocaine was administered as a solution of 20 mg/cc and doses of either 4 or 8 mg/kg. Lidocaine was infused i.v. over a one minute period and the catheter flushed rapidly with 5 cc of saline. This method of lidocaine administration was identical to the method described in our previous study.18 Controls for all drug injections were obtained by infusing the same volume of saline and flushing the catheter rapidly with 5 cc of saline.

The following drugs were used: chloldiazepoxide hydrochloride, sterile powder (Roche Laboratories, Nutley, N. J.); deslanoside (a gift from Sandoz Pharmaceuticals, East Hanover, N. J., courtesy of Mr. Siegfried S. Wahrman); lidocaine hydrochloride 2% solution (Astra Pharmaceuticals Products, Inc., Worcester, Mass.); Dial-urethane (Ciba Pharmaceutical Company, Summit, N. J.); and pentobarbital sodium (Abbott Laboratories, North Chicago, Illinois). Chloldiazepoxide powder was dissolved in 0.85% sodium chloride solution for use. The doses of the drugs were calculated and administered as the salts.

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The data were analyzed by paired comparisons and grouped Student's t-tests, with the criterion for significance being $P < 0.05$.

**Results**

**Effect of Chlordiazepoxide on Arrhythmias Induced by Digitalis**

Chlordiazepoxide was administered to 12 animals which had a sustained ventricular arrhythmia induced by deslanoside. In nine of the 12 animals, chlordiazepoxide converted the existing arrhythmia to a regular sinus rhythm. In the remaining three animals, chlordiazepoxide in a dose up to 95 mg per cat failed to restore cardiac rhythm to normal. When chlordiazepoxide was effective, the dose required ranged between 3.6 and 39.5 mg/kg and sinus rhythm lasted from 9 sec to 7 min. In preliminary experiments, doses below 3.6 mg/kg were tested but had no antiarrhythmic effect. Even though conversion occurred, the schedule of deslanoside administration was maintained until death (see Methods). The ventricular arrhythmia always returned but no additional chlordiazepoxide was given. The second arrhythmia progressed to ventricular fibrillation in seven of the nine experiments, while in the remaining two experiments hypotension was the terminal event. The hypotension was associated with a slow ventricular rhythm.

The contractile force, mean blood pressure, and heart rate data from the nine successful conversion experiments were averaged together and appear in table 1. The only significant effect of antiarrhythmic doses of chlordiazepoxide given to animals showing a sustained ventricular arrhythmia induced by deslanoside was a decrease in heart rate. Decreases in rate were seen in eight of the nine animals while an increase in rate (37 beats/min) was seen in the remaining animal.

A representative experiment illustrating the effects of chlordiazepoxide when administered during deslanoside-induced ventricular arrhythmia is shown as figure 1. Panel A shows the control records obtained before intoxication of the animal with deslanoside. Panel B shows the ventricular rhythm disturbance provoked by a cumulative dose...
of 200 µg/kg of deslanoside. At this point chlordiazepoxide was given and restoration of sinus rhythm occurred after the administration of 22 mg/kg (panel C). Sinus rate with conversion was 120 beats/min as compared to a ventricular rate of 140 beats/min which existed prior to chlordiazepoxide administration. No significant alteration in the contractile force or mean blood pressure occurred, although systolic pressure did increase and diastolic pressure did decrease.

To determine the site of antiarrhythmic action of chlordiazepoxide cardiac sympathetic nerve activity was monitored in five of the nine conversion experiments and representative records of one of these appear as figure 2. Panel A shows the control analog trace and integrated trace obtained before intoxication of the animal with deslanoside. Panel B shows these traces obtained at the time that a ventricular rhythm disturbance had been provoked by a cumulative dose of 175 µg/kg of deslanoside. At this time, sympathetic nerve activity was greatly increased over the control activity. With the administration of chlordiazepoxide, nerve firing was reduced to below control level (panel C) and sinus rhythm was reestablished.

To obtain additional data on the role of the nervous system in the antiarrhythmic action of chlordiazepoxide, identical experiments were repeated in animals with transected spinal cords and sectioned vagus nerves. The animals required significantly greater doses of deslanoside to produce ventricular arrhythmias than did the animals with intact nervous systems (288 ± 15.7 µg/kg vs 165 ± 9.5 µg/kg). Chlordiazepoxide was found to be ineffective for converting deslanoside-induced arrhythmias as sinus rhythm could not be reestablished in any of the eight animals. An experiment illustrating the inability of chlordiazepoxide to convert the digitalis-induced ventricular arrhythmias to sinus rhythm in the neurally-deprived animals is shown in figure 3.

The dose of chlordiazepoxide used for the conversion attempts in four animals was equivalent to the largest dose used in the animals with an intact nervous system. That is, a dose up to 95 mg per cat was tested and failed to convert four of four animals. This represented 56 mg/kg in two animals and 35 and 43 mg/kg in the remaining two animals, respectively. A total dose of 95 mg per cat was attempted in the other four cats but was not achieved because each animal died from hypotension before the full amount could be administered. Doses which were lethal were 22, 26, 34, and 50 mg/kg and averaged 33 ± 6.2 mg/kg. The average dose of chlordiazepoxide used in animals with an intact nervous system was 21 ± 3.7 mg/kg, and none of these animals was adversely affected, even though two animals received amounts greater than 33 mg/kg. Cardiac sympathetic nerve activity was monitored in four of the eight animals studied and a representative record of one of these appears as figure 4. As can be seen, neither drug had an effect on nerve activity.

The contractile force, mean blood pressure, and heart rate data from the eight animals with ventricular arrhythmias and given chlordiazepoxide were averaged together and appear in table 2. The data from the four animals that died was extracted from the responses that occurred after the next to the last dose (i.e., fatal dose) was given and averaged together with data from the four survi-
Effect of chlordiazepoxide on deslanoside-induced ventricular arrhythmia. Panel A, the contractile force (CF), arterial blood pressure (BP), and electrocardiogram (ECG) tracings before intoxication with deslanoside. Panel B, effects of a cumulative dose of 225 μg/kg deslanoside on CF, BP, and ECG. Panel C, CF, BP and ECG tracings obtained about 30 seconds after a total dose of 43 mg/kg chlordiazepoxide.

These doses ranged from 17 to 56 mg/kg, and averaged 37 ± 5.3 mg/kg. Significant effects occurred on mean blood pressure and contractile force; both showed a significant decrease. On the other hand, chlordiazepoxide had no significant effect on heart rate even though the average dose given to these neurally deprived animals was significantly greater than the average dose given to the neurally intact animals.

**Effect of Chlordiazepoxide on Arrhythmias Induced by Coronary Occlusion**

The effect of chlordiazepoxide in a divided dose of 10 mg/kg (i.e., 5 mg/kg given twice, separated by a 5 min interval) on arrhythmias produced by coronary occlusion was studied in six dogs, and the data are summarized in table 3. Chlordiazepoxide produced a significant reduction in the number of abnormal beats, a significant increase in sinus beats, and a significant degree of cardiac slowing. The onset of action occurred 1.6 ± 1.1 minutes after injection. The peak effect (as indicated by peak heart rate slowing or occurrence of the greatest number of sinus beats) was reached 2.5 ± 1.1 minutes after injection. The duration of action...
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Table 2

Effect of Chlordiazepoxide on Cardiac Contractile Force, Mean Blood Pressure, and Heart Rate in Neurally-Deprived Animals*

<table>
<thead>
<tr>
<th>Before chlordiazepoxide administration and during ventricular arrhythmia</th>
<th>After chlordiazepoxide</th>
<th>Contractile force change (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>Heart rate (beats/min)</td>
<td>Mean blood pressure (mm Hg)</td>
</tr>
<tr>
<td>63 ± 6.7</td>
<td>127 ± 15.0</td>
<td>49 ± 6.0</td>
</tr>
</tbody>
</table>

*Means and standard errors.
†Significant change from the control (paired comparisons).

varied from 5 min to 22 min with a mean duration of 8.5 ± 2.7 minutes. An experiment demonstrating the effect of 10 mg/kg of chlordiazepoxide on the ECG appears as figure 5.

In comparing the results with chlordiazepoxide to the results obtained earlier with lidocaine, it was obvious that chlordiazepoxide had one advantage in that it was devoid of the neurotoxic effects seen with lidocaine. In our previous study, 8 mg/kg of lidocaine showed antiarrhythmic activity but it also showed convulsant activity. Even the 4 mg/kg dose was an excitant in two of the five animals studied. In contrast, the doses of chlordiazepoxide which were antiarrhythmic had a sedative effect on all animals studied. Because the two drugs had opposite effects on the central nervous system, and because the two drugs exert their antiarrhythmic effects at different sites, the combination was studied in five animals and the data are summarized in table 4. The combination used was a total of 12.5 mg/kg chlordiazepoxide spread out over 30 minutes (see Methods), followed by 4 mg/kg lidocaine administered 2 min after the last dose of chlordiazepoxide. As reported previously, 4 mg/kg lidocaine alone has no significant antiarrhythmic effect but when administered after chlordiazepoxide in the present experiments it produced a significant reduction in the number of abnormal beats, a significant increase in sinus beats, and a significant degree of cardiac slowing. In fact the changes seen with the combination were all significantly greater than those changes seen with 4 mg/kg lidocaine alone (P < 0.05 using grouped Student's t-tests), as reported earlier. The onset of action with the combination occurred 36 ± 13.7 seconds after the beginning of the lidocaine injection. The peak effect was reached 2.0 ± 0.45 minutes after the beginning of injection. The duration of action varied from 9 min to 30 min with a mean duration of 20.6 ± 3.8 min. An experiment demonstrating the effect of the combination on the ECG appears as figure 6.

Three additional experiments were performed wherein these same doses of chlordiazepoxide were given before the large 8 mg/kg dose of lidocaine. This amount of lidocaine was previously reported to excite five of five dogs tested as EEG activity was enhanced in each animal. Tonic convulsions occurred in three of the five dogs while preconvulsive twitching movements were noted in the other two animals. Pretreatment of the three dogs in the present study with chlordiazepoxide prevented enhancement of EEG activity, tonic convulsions, and preconvulsive twitching movements. Conversion to sinus rhythm occurred in all three dogs but

Table 3

Effect of Chlordiazepoxide on Arrhythmias Produced by Coronary Occlusion

<table>
<thead>
<tr>
<th>Experiment number</th>
<th>No. of abnormal beats/5 min</th>
<th>No. of sinus beats/5 min</th>
<th>Heart rate (beats/min)</th>
<th>No. of abnormal beats/5 min</th>
<th>No. of sinus beats/5 min</th>
<th>Heart rate (beats/min)</th>
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<td>8</td>
<td>153</td>
<td>566</td>
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</table>

Mean ± SE 809 ± 36.5 24.2 ± 9.4 167 ± 7.3 495 ± 97.0* 269 ± 94.1* 153 ± 4.5*

*P < 0.05 with paired comparisons.
in no case was conversion associated with overdrive suppression of the ventricular pacemakers as was reported in our earlier study. An experiment demonstrating this pretreatment effect on the EEG effect of 8 mg/kg of lidocaine appears as figure 7.

**Discussion**

The purpose of our study was to examine the effect of the neurodepressant drug chlordiazepoxide on cardiac arrhythmias. Chlordiazepoxide was found effective against ventricular arrhythmias produced by either digitalis or coronary occlusion. When given during an arrhythmia, it converted an established ventricular arrhythmia to sinus rhythm. This occurred without compromising cardiac contractility and arterial blood pressure. The only significant change in cardiovascular function was a depression of heart rate.

There are two other studies that we are aware of in which chlordiazepoxide has been shown to have antiarrhythmic effects. One was a preliminary report by Carroll et al. who observed that i.v. administration of 10 to 20 mg/kg of this drug completely prevented arrhythmias produced by electrical stimulation of the limbic lobe and amygdala in cats. The other was a study by Madan et al. who reported that i.v. administration of 10 to 30 mg/kg chlordiazepoxide suppressed ventricular ectopic activity in dogs with arrhythmias produced by two-stage ligation of the anterior descending branch of the left coronary artery. We are not aware of any other studies dealing with the drug’s effect on digitalis-induced arrhythmia. There is one report in which the closely related compound, diazepam, was found to be ineffective against this arrhythmia. This is surprising in view of the fact that chlordiazepoxide was found to be effective for treating the digitalis-induced ventricular arrhythmia in our study. One possible explanation for the lack of antiarrhythmic activity of diazepam is that it is not water soluble and has to be dissolved in a solution containing 40% propylene glycol, 10% ethyl alcohol and 5% sodium benzoate and benzoic acid. The diluent for diazepam may mask the antiarrhythmic activity of the drug. In fact, it has been reported that a solution of 40% propylene glycol will produce ventricular arrhythmias in anesthetized cats. On the other hand, chlordiazepoxide is water soluble and was dissolved in 0.85% sodium chloride in the present study to obviate any adverse cardiac effects that might occur if it were administered with the propylene glycol diluent.

The doses of chlordiazepoxide required for exerting an antiarrhythmic effect were similar in all three studies. These doses exceed the average dose range (i.e., 50–100 mg i.v.) used in patients when administered for the purpose of reducing severe anxiety and tension. However, it must be kept in mind that much larger doses of antiarrhythmic drugs are generally required when one treats experimental arrhythmias in animals as compared to naturally occurring arrhythmias in patients.

| Table 4 |

| Effect of Subantiarrhythmic Doses of Chlordiazepoxide on the Antiarrhythmic Effect of Lidocaine |

<table>
<thead>
<tr>
<th>Experiment number</th>
<th>No. of abnormal beats/5 min</th>
<th>No. of sinus beats/5 min</th>
<th>Heart rate (beats/min)</th>
<th>No. of abnormal beats/5 min</th>
<th>No. of sinus beats/5 min</th>
<th>Heart rate (beats/min)</th>
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<td><strong>Mean ± se</strong></td>
<td><strong>861 ± 39.0</strong></td>
<td><strong>26.6 ± 14.0</strong></td>
<td><strong>177 ± 9.0</strong></td>
<td><strong>247 ± 115</strong></td>
<td><strong>519 ± 91.7</strong></td>
<td><strong>153 ± 7.5</strong></td>
</tr>
</tbody>
</table>

*P < 0.05 with paired comparisons.
example, to show antiarrhythmic activity using the Harris arrhythmia model, intravenous doses of 10 mg/kg quinidine lactate, 40 mg/kg procaine amide, 8 mg/kg of lidocaine, and 10 to 200 mg/kg of diphenylhydantoin are required. Thus, antiarrhythmic effects of chlordiazepoxide may occur in humans with much lower doses than observed in animal studies.

Our results with chlordiazepoxide suggested that its antiarrhythmic effect was located in the central nervous system. This is in contrast to the antiar-

![Figure 6](image)

**Figure 6**

Effect of the combination of chlordiazepoxide and lidocaine on multifocal ventricular tachycardia induced by coronary occlusion. Panel A, the electrocardiogram (ECG) tracing before the administration of any drug. Panel B, ECG recording obtained 45 seconds after 10 mg/kg chlordiazepoxide. Panel C, ECG tracing obtained 30 minutes after tracing in B. Panel D, ECG recording obtained 45 seconds after 2.5 mg/kg chlordiazepoxide. As can be seen, this dose of chlordiazepoxide had no effect on the abnormal rhythm. Panel E, ECG tracing obtained about 3.0 minutes after panel D and 1.5 minutes after 4 mg/kg lidocaine. Note the conversion to sinus rhythm. Panel F, ECG tracing obtained 4.5 minutes after Panel E. Abnormal rhythm was re-established 24 minutes after the final trace was taken.

![Figure 7](image)

**Figure 7**

Effect of the combination of chlordiazepoxide and lidocaine on multifocal ventricular tachycardia induced by coronary occlusion. Panel A, electroencephalogram (EEG) and electrocardiogram (ECG) tracings obtained 30 minutes after 10 mg/kg chlordiazepoxide. Panel B, EEG and ECG recordings obtained about 1 min after panel A and 1 min after 2.5 mg/kg chlordiazepoxide. This dose of chlordiazepoxide did not alter either activity (panel B). Panel C, EEG and ECG recordings obtained 2.5 minutes after panel B and 1.5 minutes after 8 mg/kg lidocaine. As can be seen, chlordiazepoxide prevented the subsequent EEG enhancement and convulsive behavior that normally occurs 1.5-2.0 minutes after the start of the lidocaine injection. Panels D and E, EEG and ECG recordings obtained 1.5 and 28.5 min after panel C, respectively.

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rhythmic agent—lidocaine. The latter drug exerts its effect on cardiac tissue and perhaps also on cardiac autonomic nerves. Furthermore, our results suggested that chlordiazepoxide might antagonize the neurotoxic effects of lidocaine. When the two drugs were combined, the desired antiarrhythmic effect of each was enhanced and the undesired neurotoxic effect of lidocaine was abolished.

These results with the combination of chlordiazepoxide and lidocaine agree with earlier findings of Dunbar et al. and de Jong and Heavner. The study of the Dunbar group showed that the antiarrhythmic efficacy of lidocaine is augmented by prior administration of diazepam. End-diastolic ventricular stimulation threshold current was used as an index of antiarrhythmic activity. De Jong and Heavner showed that diazepam antagonized lidocaine-induced seizure activity. Interestingly, it was the data of de Jong and Heavner that prompted the Dunbar study. The latter investigators reasoned that the central nervous system "interaction between diazepam and lidocaine suggested that diazepam might also modify the cardiac effects of lidocaine. That is, diazepam might decrease the efficacy of lidocaine in the management of ventricular arrhythmias."

From the studies with chlordiazepoxide and digitalis, it appeared that chlordiazepoxide was effective against arrhythmias because of a sympathetic neural depressant action. The results obtained from animals with an intact sympathetic nervous system showed that the doses of chlordiazepoxide required to convert deslanoside-induced ventricular tachycardia to sinus rhythm also depressed deslanoside-induced sympathetic nerve firing. In addition to the equivalent sensitivity of these two responses to the chlordiazepoxide dose, there was a close time relationship between the two effects. That is, conversion of the rhythm disturbance occurred simultaneously with depression of sympathetic nerve discharge.

To determine further the role of sympathetic nerve depression in the antiarrhythmic action of chlordiazepoxide, the drug was studied in cats with their sympathetic nervous systems interrupted by section of the spinal cord. Chlordiazepoxide was found to be ineffective for converting an established ventricular arrhythmia to sinus rhythm in these animals, thereby substantiating our evidence with direct nerve recordings that the mechanism of antiarrhythmic action of chlordiazepoxide was sympathetic neural depression. These animals also had their vagus nerves sectioned and therefore the role of parasympathetic nerve depression in the antiarrhythmic action of chlordiazepoxide has to be considered. Our earlier study showed that arrhythmias induced by digitalis are preceded by intense activity in parasympathetic nerves. Furthermore, activation of both sympathetic and parasympathetic nerves has been shown to have a greater arrhythmogenic influence than activation of either nerve alone. It is therefore conceivable that the antiarrhythmic action of chlordiazepoxide may involve simultaneous depression of both cardiac sympathetic and parasympathetic nerve discharge. Our studies do not completely rule out the possibility that direct cardiac actions of chlordiazepoxide may contribute to its antiarrhythmic effect. However, if the drug were antiarrhythmic because of interaction with myocardial sites, it should also show efficacy in the neurally deprived animals.

The site of the chlordiazepoxide neurodepressant action seems to be the central nervous system. Our recordings of sympathetic nerve activity were from preganglionic cardiac autonomic fibers and the degree of activity present on these fibers probably reflects the degree of central nervous system activity. Depression of this activity by chlordiazepoxide may therefore represent a depression of central sympathetic tone. Consistent with this idea are the results of Schallek and Zabransky. They found that chlordiazepoxide in an i.v. dose of 40 mg/kg reduced the pressor response of hypothalamic stimulation in the cat. This dose had no significant effects in either the pressor responses to norepinephrine or to stimulation of the stellate ganglia, indicating that the drug does not block sympathetic responses at a peripheral site. Within the central nervous system, the most sensitive area in response to the benzodiazepines (i.e., diazepam) seems to be the hypothalamus. According to Chai and Wang, diazepam administered i.v. reduces the pressor responses evoked by electrical stimulation of the hypothalamus to a greater extent than the pressor responses evoked by the electrical stimulation of the medulla. Thus our data and the results of others strongly implicate the central nervous system, and more specifically the hypothalamus, as the principal site of action of chlordiazepoxide.

A central neural site of action for chlordiazepoxide is also consistent with the known mechanisms involved in the production of arrhythmias by either digitalis or coronary occlusion. For example, the arrhythmias produced by digitalis seem to result from an interaction of the drug with central nervous
system structures. That is, digitalis enhances spontaneous neural activity in sympathetic, vagus, and phrenic nerves; the enhancement is associated with ventricular rhythm disturbances and respiratory hyperactivity. Removing the nervous system by spinal transection and vagotomy prevents these digitalis-induced neural effects and significantly increases the dose of digitalis necessary to produce ventricular rhythm disturbances. Likewise coronary occlusion produces a great increase in the discharge of sympathetic and parasympathetic nerves to the heart. The time course of the enhanced activity parallels the occurrence of ventricular arrhythmias. Furthermore, animals without abnormal neural input to the heart survive more than twice as long and have a significantly lower incidence of ventricular fibrillation. Based on mechanisms for the genesis of arrhythmias, an important consideration in therapy would be to quiet the nervous system.

As mentioned, no deleterious effects of chlordiazepoxide were observed in animals with intact nervous systems. We did however observe cardiovascular depressant effects of chlordiazepoxide in neurally-deprived animals. Significant decreases in contractile force and blood pressure occurred and half of the animals died as a consequence of these effects. The explanation for the enhanced toxicity is not clear but the same findings have been reported for diazepam in dogs. Daniell and Worsham observed that i.v. doses of diazepam as large as 20 mg/kg produced no adverse cardiovascular effects in pentobarbital anesthetized dogs. However, after either ganglionic blockade with hexamethonium or beta adrenergic receptor blockade with propranolol, deaths occurred with i.v. doses of diazepam as low as 5 mg/kg. Taken together the results indicate that benzodiazepines may be harmful to animals surgically or pharmacologically deprived of autonomic nervous system function.

In summary, we sought to find a new and better antiarrhythmic drug by testing an agent with known neurodepressant properties (e.g., having tranquilizing, anticonvulsant, and muscle relaxing properties) on cardiac arrhythmias induced by digitalis and coronary occlusion. Chlordiazepoxide was the substance chosen and proved to be an effective antiarrhythmic agent. Doses that restored abnormal rhythm to sinus rhythm exhibited none of the toxic effects of presently available antiarrhythmic drugs. It did produce sedation when used to treat unanesthetized dogs with acute myocardial infarction. This effect can be viewed as a benefit as Nixon et al. have reported that prophylactic use of sleep therapy (i.e. pethidine plus promethazine) reduces mortality from acute myocardial infarction. Finally, chlordiazepoxide used in combination with lidocaine augmented the antiarrhythmic effect of lidocaine while it reduced its neurotoxic effect.

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