Antiarrhythmic Effects of Droperidol

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The effects of droperidol on arrhythmias induced by several experimental procedures were studied both in intact cats and in isolated heart preparations. Droperidol significantly increased the effective refractory period of isolated cat heart papillary muscle but did not change either the basic developed tension or its relative increase during postextrasystolic potentiation. In contrast, both levo-propranolol and dextro-propranolol significantly decreased both the basic developed tension and the relative increase induced by postextrasystolic potentiation, and only slightly increased the effective refractory period. Droperidol, levo-propranolol, and dextro-propranolol delayed the time of appearance of ventricular fibrillation induced by perfusing the isolated guinea-pig heart with substrate-free Tyrode's solution. Droperidol in low doses prevented epinephrine-halothane-induced ventricular arrhythmias in cats, but did not prevent the increase in blood pressure. Furthermore, droperidol prevented ventricular fibrillation induced by coronary occlusion in cats. The antiarrhythmic effect of droperidol seems to be independent of its eventual α-adrenergic blocking activity. (Key words: Droperidol; Refractory period; Halothane–epinephrine; Coronary occlusion; Arrhythmia; Postextrasystolic potentiation; Myocardial contractility.)

Yelnosky et al.† described an antiarrhythmic effect of droperidol (dehydrobenzoperidol, DBP) in preventing epinephrine–chloroform-induced ventricular tachycardia and ventricular fibrillation in dogs. However, the drug did not prevent ouabain-induced arrhythmias in the dog. In women, droperidol was shown to double the threshold of epinephrine-induced arrhythmias during cyclopropane anesthesia. Molinaroli‡ found that DBP prevented arrhythmias induced by giving epinephrine during chloroform or halothane anesthesia in rabbits. He considered this protection to be the consequence of an eventual β-adrenergic blocking action of DBP on heart receptors. However, in contrast to previously-reported results, Molinaroli‡ found that DBP plus fentanyl prevented arrhythmias induced by toxic doses of ouabain. This protection seems to be due to a direct effect of DBP independent of adrenergic blockade.

Hauswirth,‡ working on isolated sheep Purkinje fibers, found that DBP at high concentrations induced a long-lasting increase of the effective refractory period, and that, like other antiarrhythmic agents, it decreased the speed of the upstroke of the action potential without change in resting potential or amplitude of the action potential. In the present paper we report the effects of droperidol on the refractory period and developed tension of papillary muscle, compared with the effects of propranolol, and on arrhythmias induced by several experimental procedures, both in intact cats and in isolated heart preparations.

Material and Methods

Experiments in the Isolated Heart Preparation

Cat papillary muscle. Ten cats, weighing about 2 kg each, were lightly anesthetized with ether, the chests opened, and the hearts excised. One or two papillary muscles were removed from each heart and placed on a holder with built-in electrodes for stimulation, as previously described. Each muscle was kept in a bath containing Ringer-Locke solution of the following mM composition: NaCl 119.6; KCl 5.6; CaCl2 2.2; MgCl2 2.1; NaHCO3 25; glucose 10; and gassed with a mixture of 95 per cent oxygen and 5 per cent CO2. The
solution was maintained at 37°C. At equilibrium pH was 7.4.

The diastolic (resting) tension was adjusted to somewhat below that initially determined in each muscle to be associated with near-maximum development of tension, between 0.8 and 1.2 g, depending on the cross-sectional area of the individual muscle. The muscles were stimulated at the base by pointed electrodes immersed in the Ringer-Locke solution and connected to a set of Model 181-162 Tektronix stimulators coupled to give either regular stimuli at the rate of 60/min or a premature (msec) electrical stimulus after each regular pulse (paired pulse), thus allowing study of postextrasystolic potentiation. For the study of this phenomenon the premature stimulus was set at intervals of 400, 350, 300, 250, and 200 msec after the regular beat (Fig. 1). The stimulators produced square-wave pulses 2 msec in duration with voltages slightly above threshold. The effective refractory period (ERP) was measured at the rate of 60/min, using the same set of Tektronix stimulators coupled to give a premature (msec) electrical stimulus after the regular pulse. ERP was determined as the briefest attainable interval between two propagated responses, as judged by the appearance of postextrasystolic potentiated contraction or by recording the premature beat.

![Fig. 1. Effect of droperidol on the postextrasystolic potentiation phenomenon in one isolated cat papillary muscle preparation electrically driven at the rate of 60/min. The figures underneath are the intervals between the regular and the premature stimuli in milliseconds. Notice that after the addition of DBP, postextrasystolic potentiation did not occur with intervals of 250 and 200 msec.](https://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931561/)

The tension developed by papillary muscle during isometric contraction was recorded by means of a Grass FT03 force transducer coupled to a Grass model 5D polygraph. The absolute developed tensions and the percentage tension changes were calculated.

The experiments were performed after stabilization periods lasting 30 to 40 minutes, depending on the individual muscle preparation. DBP, propranolol, or phenoxymethylamine was added to the bath and its effects were studied after an incubation period of at least 30 minutes.

**Guinea-pig heart.** Experiments were performed in isolated guinea-pig hearts perfused according to Langerdorff's technique, modified as previously reported. Adult guinea pigs of either sex, weighing 300 to 800 g, were used. Using urethane anesthesia and mechanical ventilation, the chest was opened and the heart excised and perfused with Tyrode's solution. The electrocardiogram was registered on a Grass model 5D polygraph. Three silver electrodes were employed: two fixed to the right and left atrial appendages, respectively, and the third fixed to the apex of the heart. Two bipolar leads (right atrium—left atrium and right atrium—apex) were recorded simultaneously.

The control hearts were perfused with substrate-free Tyrode's solution until ventricular
fibrillation appeared. In another series of experiments, either propranolol (0.5 µg/ml) or DBP (0.5 µg/ml) was added to the substrate-free perfusing solution (table 2).

Experiments in the Intact Cat

Arrhythmia induced by halothane–epinephrine. Experiments were performed in seven cats anesthetized with 2 per cent halothane administered through a Fluotec vaporizer at an oxygen flow rate of 2 l/min; respiration was controlled by means of a Palmer pump. When halothane anesthesia had produced a clear decrease in blood pressure (fig. 3), epinephrine was given iv in effective doses ranging from 2 to 8 µg/kg, to assure the appearance of arrhythmia. Then DBP, 250 µg/kg, was administered iv and, after a waiting period of 15 to 30 minutes, the same iv dose of epinephrine given in the control period was repeated.

Arrhythmia induced by transitory coronary occlusion. In eight cats anesthetized with sodium pentobarbital, 30 mg/kg, ip, transitory coronary occlusion was achieved by means of a ligature at the level of the anterior descending coronary branch artery, near the atrioventricular sulcus. With this procedure, arrhythmia appeared in every cat about a minute after the ligature was tied. After one to two minutes of arrhythmia or ventricular fibrillation, the ligature was released and DBP, 250 µg/kg, was given iv. Fifteen to 30 minutes after DBP administration, the coronary ligature was again tied, and both the time of appearance and the duration of arrhythmia were studied.

Results

Effects of Droperidol and Propranolol on the Postextrasystolic Potentiation Phenomenon and the Effective Refractory Period in Papillary Muscle

The effects of DBP (0.25 µg/ml) on developed tension, effective refractory period, and postextrasystolic potentiation were studied in ten isolated papillary muscles. Figure 1 shows the result of a typical experiment. Results of all experiments are summarized in figure 2. As is evident in the figures, DBP did not significantly change either the developed tension during regular stimulation or the magnitude of postextrasystolic potentiation at the intervals studied. Since the drug significantly lengthened the effective refractory period, postextrasystolic potentiation did not occur with an interval of 200 msec between the

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Fig. 2. Effect of droperidol on basic tension developed (right) and postextrasystolic potentiation phenomenon in the isolated cat papillary muscle. Basic tension developed in control period = 100. The columns show the average per cent changes in tension, and the vertical bars the standard errors. The figures underneath are the intervals between the regular and the premature stimuli in milliseconds. N = number of experiments.
TABLE 1. Effects of Leco- and Dextra-propranolol on Postextrasystolic Potentiation in Isolated Cat Heart Papillary Muscle (Mean ± SE)

<table>
<thead>
<tr>
<th>Intervala</th>
<th>Untreated (69 Preparations)</th>
<th>L-propranolol (10 Preparations)</th>
<th>d-propranolol (10 Preparations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Developed Tension (mg)</td>
<td>Change (Per Cent.)</td>
<td>Developed Tension (mg)</td>
</tr>
<tr>
<td>Control</td>
<td>865.5 ± 95.3</td>
<td>—</td>
<td>918.4 ± 159.7</td>
</tr>
<tr>
<td>Control after drug 400</td>
<td>1141.0 ± 49.0</td>
<td>+55.5 ± 1.5</td>
<td>641.2 ± 116.8</td>
</tr>
<tr>
<td>300</td>
<td>1217.7 ± 101.1</td>
<td>+215.0 ± 2.5</td>
<td>725.5 ± 138.2</td>
</tr>
<tr>
<td>200</td>
<td>1089.8 ± 102.3</td>
<td>+331.0 ± 3.5</td>
<td>656.9 ± 139.0</td>
</tr>
<tr>
<td>100</td>
<td>1539.9 ± 47.7</td>
<td>+669.0 ± 3.8</td>
<td>781.5 ± 180.7</td>
</tr>
</tbody>
</table>

*a Interval between the premature stimulus and the regular preceding one (paired stimulation).
† Tension developed during regular stimulation at the rate of 50 min.

regular and the premature stimuli (figs. 1 and 2).

The results of these experiments were compared with the effects of leco-propranolol (2 µg/ml) and dextra-propranolol (2 µg/ml) under the same experimental conditions, using ten papillary muscles to study each drug. In order to increase the size of the control group, the effects of both propranolol isomers were compared with results of all 69 such experiments on untreated preparations performed by the same worker in the preceding year. Both leco-propranolol and dextra-propranolol significantly decreased the tension developed during regular stimulation (basic tension), as well as during postextrasystolic potentiation, at the intervals studied (table 1).

Analysis of variance of the effects of dextra-propranolol vs. leco-propranolol on the tension developed (mg) by postextrasystolic potentiation at different intervals showed that the effect of the interval was significant at the 1 per cent level (F = 5.53 for 4 to 78 degrees of freedom; F₀₀₁ = 4.04). In contrast, no significant difference between the effects of dextra- and leco-propranolol on tension developed was revealed by this analysis (F = 0.06 for 1 to 78 degrees of freedom; F₀₀₁ = 3.96). Furthermore, the decreases in basic tension developed during regular stimulation were not significantly different with dextra- and leco-propranolol (P > 0.1).

Since no significant difference between the effects of the two isomers of propranolol was found, analysis of variance of untreated vs. propranolol (d or l)-treated preparations at the various intervals was done. As was expected, the effect of the interval was highly significant (F = 31.89 for 4 to 372 degrees of freedom; F₀₀₁ = 3.38), and the effect of propranolol (d and l considered as one group) was also highly significant (F = 94.52 for 1 to 372 degrees of freedom; F₀₀₁ = 6.72).

Droperidol significantly increased the effective refractory period, from 204 ± 14 to 224 ± 14 msec (mean ± SE), P < 0.005. This effect was not antagonized by norepinephrine, 0.2 µg/ml, which increased the tension developed by papillary muscles an average of 50 per cent. In control experiments, norepinephrine, 0.2 µg/ml, induced a similar increase in tension (about 90 per cent) and did not change the duration of the effective refractory period.

In four experiments, phenoxysbenzamine (5 µg/ml) decreased developed tension slightly, changed the effective refractory period from 204 ± 13 msec to 240 ± 25 msec (not significant by Student’s t test, even comparing the difference, δ, in each individual case), and did not block the positive inotropic effect of norepinephrine.

In contrast to the effect of DBP (0.25 µg/ml), dextra-propranolol (2 µg/ml) and leco-propranolol (2 µg/ml) increased the effective refractory period in papillary muscle only slightly. In fact, postextrasystolic potentiation could be induced in every preparation at 250-msec intervals, while at 200-msec intervals extrasystoles were observed in five of ten preparations treated with dextra-propranolol and in nine of ten preparations treated with leco-propranolol.
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EFFECTS OF DROPERIDOL AND PROPRANOLOL ON VENTRICULAR FIBRILLATION OF THE ISOLATED GUINEA-PIG HEART

The isolated guinea-pig heart perfused with substrate-free Tyrode’s solution manifested rhythmic disorders, AV dissociation, and finally, ventricular fibrillation, which appeared at 84 ± 6.6 minutes. The addition of DBP (0.25 µg/ml), leco-propranolol (0.5 µg/ml), or dextro-propranolol (0.5 µg/ml) to the perfusing fluid significantly delayed the appearance of ventricular fibrillation to more than 150 minutes (table 2).

EFFECT OF DROPERIDOL ON HALOTHANE–EPINEPHRINE-INDUCED ARRHYTHMIA IN CATS

Seven cats were anesthetized with 2 per cent halothane at an oxygen flow rate of 2 l/min. In six of the seven experiments the same dose range of epinephrine was used to produce hypertension, and progressively increasing doses within the range given until clear-cut arrhythmia appeared. Generally, the duration and severity of arrhythmia increased with doses within the range. Therefore, tachyphylaxis to epinephrine–halothane-induced arrhythmia did not develop. The results obtained in the control period were compared with those obtained 15 minutes after iv administration of DBP (250 µg/kg). This dose of DBP did not significantly change mean systolic or diastolic blood pressure (control 103±67 mm Hg vs. 95±63 mm Hg after DBP).

In these experiments epinephrine-induced arrhythmias in all seven cats in the control period, and in only two of seven after DBP (χ² with Yates’ correction = 4.98; P < 0.05). A record from a typical experiment showing the protection against halothane–epinephrine-induced arrhythmia afforded by DBP appears in figure 3, which shows that the increase in blood pressure induced by epinephrine was less after DBP. Although the average increase in blood pressure in the seven cats was apparently smaller after DBP, statistical analysis did not show a significant effect of DBP on the epinephrine-induced increase in blood pressure.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Experiments</th>
<th>Time of Appearance of Ventricular Fibrillation (Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrode’s solution with glucose</td>
<td>9</td>
<td>&gt;240</td>
</tr>
<tr>
<td>Tyrode’s solution without glucose</td>
<td>30</td>
<td>84.0±4.9</td>
</tr>
<tr>
<td>Tyrode’s solution without glucose + l-propranolol (0.5 µg/ml)</td>
<td>12</td>
<td>&gt;180</td>
</tr>
<tr>
<td>Tyrode’s solution without glucose + d-propranolol (0.5 µg/ml)</td>
<td>5</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Tyrode’s solution without glucose + droperidol (0.5 µg/ml)</td>
<td>5</td>
<td>&gt;150</td>
</tr>
</tbody>
</table>

* Including data from experiments already published.

EFFECT OF DROPERIDOL ON ARRHYTHMIAS INDUCED BY CORONARY OCCLUSION

Of eight cats anesthetized with sodium pentobarbital, transitory occlusion of the anterior descending coronary artery induced ventricular fibrillation in five and arrhythmias (ventricular polyfocal ectopic beats) in three. However, 15 minutes after DBP, 250 µg/kg, iv, occlusion of the same branch induced arrhythmias in only three of the eight cats, and none manifested ventricular fibrillation. In the three cats in which arrhythmias occurred, they appeared an average of 140 seconds later than in the control period. Comparison of the numbers of cats manifesting ventricular fibrillation before and after DBP showed that the difference was significant (χ² with Yates’ correction = 4.65; P < 0.05).

Discussion

The results of our experiments confirm that DBP can prevent halothane–epinephrine-induced arrhythmias, as previously reported,1–3 and demonstrate that this drug also can prevent ventricular fibrillation induced in the intact cat by coronary occlusion or in the isolated guinea-pig heart by lack of substrate.
Fig. 3. Effect of droperidol on halothane-epinephrine-induced arrhythmia in the cat. The records show the blood pressure and ECG in the second lead both in control period and during the effect of droperidol. Marks indicate seconds. At the arrow epinephrine, 0.2 μg/kg, was given iv. Notice that in the control period arrhythmia appeared after epinephrine was given and that no arrhythmia occurred during the effect of droperidol.

The antiarrhythmic effect appears to be related to a lengthening of the effective refractory period (ERP) of contractile myocardium, also observed by Hauswirth in sheep Purkinje fibers.

In spite of the fact that an α-adrenergic blocking effect of high doses of DBP has been reported, this antiarrhythmic effect appears not to result from adrenergic blockade. In fact, the lengthening of the effective refractory period (ERP) is much longer than that obtained with phenoxybenzamine or lecpro-pranorolol, which block α- and β-adrenergic receptors, respectively. Furthermore, this effect of DBP was not reversed by concentrations of norepinephrine which induce important positive inotropic effects. This idea gains further support from our finding that DBP blocked halothane-epinephrine-induced arrhythmias without preventing the increase in blood pressure induced by epinephrine. Other drugs such as quinidine also induce lengthening of ERP not related to adrenergic blockade.

The experiments on the isolated guinea-pig heart showed that ventricular fibrillation induced by lack of substrates is significantly delayed by low concentrations of DBP, lecpro-pranorolol, and dextro-proporanolol. Previous workers have demonstrated that ventricular fibrillation also is delayed by pretreatment
with reserpine, guanethidine, or a-methyl-dopa and that it is reversed to regular rhythm by potassium chloride or phenoxybenzamine. Therefore, protection against ventricular fibrillation induced by lack of substrates is afforded both by drugs with adrenergic-blocking action and by dextro-propranolol, which does not have adrenergic-blocking properties.

Since local release of catecholamines has been shown to occur during myocardial hypoxia or ischemia, it might be assumed that DBP protection against arrhythmias induced by coronary occlusion would be the consequence of adrenergic blockade. However, the findings reported in this paper do not support such a mechanism.

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References