THE EFFECT OF QUINIDINE ON ARRHYTHMIAS INDUCED BY CYCLOPROpane AND CYCLOPROpane–EPINEPHrine

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The advantages of cyclopropane inhalation anesthesia are well known. The margin of safety is wide, adequate oxygenation is possible throughout all planes of anesthesia and postanesthetic recovery is rapid and smooth (1). One of the principal disadvantages of cyclopropane is the high incidence of cardiac arrhythmias, reported to be as high as 56 per cent (2), which tend to increase as the depth of the anesthesia increases (3). According to Meek et al. (3), cyclopropane “favors the production of ventricular fibrillation” to a greater extent than either chloroform or ether when the cardiac effect of epinephrine is superimposed.

The purpose of this series of experiments is to evaluate the protective action of quinidine sulfate and lactate against cardiac arrhythmias induced by cyclopropane-epinephrine, to determine the minimal effective dose and to attempt to determine the duration of the protective action. As pointed out by Meek (3, 4), the absence of arrhythmias alone is not sufficient evidence of protection since “the normal pacemaker may be approaching an inhibition sufficient to allow escape phenomena or ectopic centers may be on the point of exhibiting activity should an additional stimulus appear.” For this reason we cannot say that protection has occurred unless the myocardium has been protected against the onset of ectopic rhythms following an additional stimulus, in this series the intravenous administration of a standard test dose of epinephrine. As in a previous study (6), evidences of inhibition of the physiologic pacemaker (various degrees of atrioventricular block) and evidences of increasing ventricular excitability (ventricular premature systoles, ventricular tachycardia) are termed “prefibrillation” changes, and must be prevented before adequate protection is presumed.

In 1940 Meek (4) showed that quinidine sulfate, 15 mg. per kilogram, protected 6 out of 6 dogs against ventricular fibrillation experimentally

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induced by cyclopropane-epinephrine. Wegria and Nickerson (5) and Huggins et al. (6) have demonstrated a protective action of quinidine against ventricular fibrillation induced by epinephrine in dogs under chloroform anesthesia.

Quinidine exerts its action directly on the myocardium, prolonging the refractory period and conduction time and depressing myocardial excitability (7). Weisman (8) demonstrated that following the intravenous administration of large doses of quinidine to dogs, less than 6 per cent of the drug remains in the blood stream after seven minutes; following oral administration to dogs the maximal myocardial concentration is reached in one to two hours, and quinidine remains in the heart muscle for four to eight hours, depending on the dose given (9). Wegria and Boyle (10), also working with dogs, reported that the maximal plasma and myocardial levels are reached within three hours following oral ingestion, and that quinidine is still detectable after ten to fourteen hours. Weisman (8) has reported that in human beings, following oral administration of quinidine, the maximal blood level is attained in thirty to sixty minutes and that none remains after sixty to ninety minutes.

The electrocardiographic changes produced by the intravenous injection of therapeutic doses of quinidine are prolonged atrioventricular and intraventricular conduction (A–V block has been seen with toxic doses), and variable Q–T interval and T wave changes (11).

**Method**

Medium-sized dogs, premedicated with barbital sodium, 200 mg. per kilogram intraperitoneally, were used. The common carotid artery was cannulated and blood pressure tracings recorded on moving photographic paper by means of a Hamilton optical manometer (12), and electrocardiographic tracings were obtained by means of a direct writing instrument. Cyclopropane-oxygen mixtures were administered by means of the carbon dioxide absorption technic through an endotracheal tube with an inflatable cuff. The concentrations of cyclopropane used were approximated by regulating the flow from the anesthesia machine. A flow of 200 cc. of cyclopropane and 600 cc. of oxygen was assumed to give a mixture of 25 per cent cyclopropane and 75 per cent oxygen. A flow of 400 cc. of cyclopropane and 400 cc. of oxygen was assumed to give a 50 per cent mixture. Equilibration with the 25 per cent mixture produced surgical anesthesia (loss of the lid reflex, complete muscular relaxation and only slight diminution of the respiratory excursion), and the 50 per cent mixture produced respiratory arrest. Recordings were made to detect the presence of spontaneous cyclopropane-induced arrhythmias when equilibrium had been established. The test dose of epinephrine, 0.02 mg. per kilogram, was rapidly injected into the exposed femoral vein either at the point of surgical
anesthesia (25 per cent cyclopropane) or at the point of deep anesthesia (that is, the resumption of spontaneous respiration after respiratory arrest produced by 50 per cent cyclopropane, the dog having been given oxygen when respiration ceased). The cyclopropane-epinephrine administrations were repeated at regular intervals in the surviving animals, the animals being maintained on pure oxygen during the intervals.

Quinidine sulfate or, in a few experiments, quinidine lactate was administered intravenously in doses of 1, 5, 10 or 20 mg. per kilogram at the point of equilibration with cyclopropane, prior to the injection of epinephrine. In most of the experiments additional quinidine was not given and after varying intervals of time cyclopropane was administered and epinephrine injected at the point of equilibration. All time intervals were started at the completion of the quinidine injection.

Blood pressure tracings were obtained as follows: prior to the administration of cyclopropane; when arrhythmias were detected during cyclopropane anesthesia or at the point of equilibration when none were observed; during the injection of quinidine, and at the time of the injection of epinephrine, continuing until ventricular fibrillation ensued or a definite trend toward normalcy had been established.

Electrocardiographic tracings (lead II) were obtained in a number of the experiments to verify the origin of the ectopic rhythms observed on the blood pressure tracings, and to investigate the changes produced by quinidine.

Results

The results in each experiment are summarized in table 1. There was no apparent correlation between the depths of anesthesia used and the production of arrhythmias following epinephrine, so no further reference to the depth of anesthesia at the time of injection of epinephrine will be made. The stage of anesthesia for each experiment is indicated in table 1.

In the following discussion the term "epinephrine administration" is used to signify the injection of epinephrine at the point of equilibration with cyclopropane.

Controls.—To evaluate the effect of cyclopropane and epinephrine alone, 6 dogs were given these substances without previous administration of quinidine. Only one survived the first administration of epinephrine and death occurred when it was repeated fifteen minutes later, giving a total of 7 experiments. During the anesthesia there was ventricular alternation in 2 cases, but no irregularities of rhythm were observed. Following the injection of epinephrine ventricular fibrillation ensued in 6 out of the 7, and prefibrillation changes (coupled premature ventricular contractions) of two minutes' duration in one.

Effect of Quinidine.—Quinidine sulfate and quinidine lactate when used prior to the administration of cyclopropane produced identical results. The effect of quinidine in the doses employed on the blood
### TABLE 1
**SUMMARY OF THE RESULTS IN EACH EXPERIMENT (SEE TEXT)**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Dose of Quinidine, mg. per kg.</th>
<th>Initial Response</th>
<th>Subsequent Responses</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Surgical 10</td>
<td>10</td>
<td>25–40–55</td>
<td>Surgical XXX</td>
</tr>
<tr>
<td>11</td>
<td>Surgical 7</td>
<td>7</td>
<td>22</td>
<td>Surgical</td>
</tr>
<tr>
<td>12</td>
<td>Surgical 10</td>
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<td>25–40–55</td>
<td>Surgical Deep</td>
</tr>
<tr>
<td>14</td>
<td>Surgical 12</td>
<td>12</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Surgical 12</td>
<td>12</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Deep</td>
<td>1</td>
<td>10</td>
<td>Surgical</td>
</tr>
<tr>
<td>17</td>
<td>Deep</td>
<td>3</td>
<td>13–22</td>
<td>Deep</td>
</tr>
<tr>
<td>4</td>
<td>Surgical 10</td>
<td>10</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Surgical 0.5</td>
<td>0.5</td>
<td>15–22</td>
<td>Surgical</td>
</tr>
<tr>
<td>7</td>
<td>Surgical 18</td>
<td>18</td>
<td>33</td>
<td>Surgical</td>
</tr>
<tr>
<td>18</td>
<td>Deep</td>
<td>3</td>
<td>18</td>
<td>Deep</td>
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<td>17</td>
<td>Deep</td>
</tr>
<tr>
<td>20</td>
<td>Deep</td>
<td>5</td>
<td>20</td>
<td>Deep</td>
</tr>
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<td>1</td>
<td>Surgical 10</td>
<td>10</td>
<td>25</td>
<td>Surgical</td>
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<tr>
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<td>10</td>
<td>25</td>
<td>X</td>
</tr>
<tr>
<td>21</td>
<td>Deep</td>
<td>0.5</td>
<td>15–30–60</td>
<td>Deep</td>
</tr>
<tr>
<td>22</td>
<td>Deep</td>
<td>0.5</td>
<td>15–30–60</td>
<td>Deep</td>
</tr>
<tr>
<td>9</td>
<td>Surgical 8</td>
<td>8</td>
<td>30–55–80</td>
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</tr>
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<td>23</td>
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<td>14–45–75</td>
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</tr>
<tr>
<td>25</td>
<td>Deep</td>
<td>0.5</td>
<td>15–60</td>
<td>Deep</td>
</tr>
<tr>
<td>2</td>
<td>Surgical 10</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Surgical 10</td>
<td>10</td>
<td>X</td>
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<tr>
<td>5</td>
<td>Surgical 10</td>
<td>10</td>
<td>X</td>
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<tr>
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<td></td>
</tr>
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<td>Deep</td>
<td>10</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>Deep</td>
<td>1</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Time refers to the time in minutes elapsing between the completion of the quinidine injection and the administration of epinephrine at the point of equilibration with cyclopropane.*  
*Depth of anesthesia—see text (Method).*  
*P.—Complete protection—no arrhythmia.*  
*P.F.—Pre fibrillation changes.*  
*F.—Ventricular fibrillation.*
pressure and pulse rate is summarized in table 2. In general, the
tendency was for both the pulse rate and the blood pressure to be de-
creased. There did not appear to be any positive correlation between
the size of the dose administered and the degree of slowing of the pulse.
The depression of the blood pressure appeared to be more marked with
the larger doses of quinidine. The notable exceptions to this generality
were dogs number 10 and 15 in the group given 1 mg. per kilogram, 18
and 19 in the group given 5 mg. per kilogram and 9 in the group given
20 mg. per kilogram, in which increased pulse rates developed ranging
from 13 to 117 beats per minute. Dog number 18, in addition to the
marked tachycardia (increase of 117 beats per minute over the control
rate), showed an alternating 2:1 A-V block and sinus mechanism with
ventricular alternation. The arrhythmia and tachycardia disappeared
spontaneously in three to four minutes. There were no other changes
in rhythm due to quinidine in the series.

The effects of quinidine on the electrocardiogram differed in no
respect from those previously reported (fig. 1).

Figure 2 demonstrates the effect of quinidine on the pulse rate and
blood pressure during cyclopropane anesthesia. With the control
dogs there was a definite decrease in the pulse rate and drop in the
systolic and diastolic pressures during anesthesia. In the experimental dogs following the administration of quinidine, anesthetization produced decreases in pulse rate strictly comparable with those in the control dogs. With doses of 1 mg. per kilogram of quinidine there was no significant variation of the blood pressure from the levels produced in the control dogs. With larger doses of quinidine, however, the blood pressure (systolic and diastolic) rose during anesthesia. This tendency was about equal for the dose of 5, 10, and 20 mg. per kilogram.

![Electrocardiogram](image)

**Fig. 1.** Electrocardiogram (lead II) showing the effect of progressive doses of quinidine sulfate or lactate intravenously on the dog. A. Control tracing, before the administration of quinidine. B. After quinidine, 1 mg. per kilogram. C. After quinidine, 5 mg. per kilogram. D. After quinidine, 10 mg. per kilogram. E. After quinidine, 20 mg. per kilogram.

The effect of quinidine on the response to epinephrine is shown in figure 3. There is little or no difference in blood pressure with the 1 to 20 mg. of quinidine. Quinidine did not alter the tachycardia following administration of epinephrine. The blood pressure response to epinephrine, on the other hand, tended to be less with increasing doses of quinidine.

Quinidine, 1 mg. per kilogram, was given to 7 dogs. Five (71.5 per cent) of the dogs were protected against arrhythmias following the first administration of epinephrine, in all of which epinephrine was given within ten minutes of the quinidine. Ventricular fibrillation developed in 2 of the dogs following the first administration of epinephrine which was given twelve minutes after the quinidine in each case. Of the 5
surviving dogs, 2 developed ventricular fibrillation when epinephrine was again administered, and 3 (dogs number 10, 12 and 17) were protected for sixty-five, forty, and thirteen minutes, respectively. Ventricular fibrillation developed in dog number 17 at twenty-three minutes, and in dog number 12 prefibrillation changes (frequent premature ventricular contractions) of sixteen seconds' duration at fifty-five minutes. The experiment was discontinued in dog number 10 at sixty-five minutes, this animal having shown no arrhythmia.

Quinidine in doses of 5 mg. per kilogram, was given to 6 dogs.

Fig. 2. Effect of cyclopropane anesthesia on the pulse rate (P.R.) and systolic (Syst. B.P.) and diastolic (Dias. B.P.) blood pressure before and after quinidine. Each dot indicates one experiment. The vertical line (0) represents no change, the figures to the right of the line (+) represent increases in pulse rate or blood pressure and those to the left (−) decreases in pulse rate or blood pressure from the control level.

Box "D" gives the data for the control experiments, the dogs were anesthetised but had not received quinidine.

Box "A" shows the systolic blood pressure changes after quinidine in the doses indicated on the left margin. Box "B" gives the diastolic blood pressure changes and "C" changes in the pulse rate. See text for discussion.
Four (66.6 per cent) showed no disturbance in rhythm following the first administration of epinephrine which was given within five minutes of the quinidine in all cases. Dogs number 4 and 7 showed presystolic changes following the first administration of epinephrine given ten and eighteen minutes, respectively, after the quinidine. When ephinephrine was again administered from fifteen to thirty-three minutes after the quinidine, to the dogs previously protected, ventricular fibrillation resulted in 3, and irregular premature ventricular contractions of twenty seconds' duration in one (number 6).

Quinidine in doses of 10 mg. per kilogram, was administered to 4 dogs. Three (75 per cent) showed no arrhythmia following the first

![Figure 3](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931708/)
administration of epinephrine, given one-half minute in 2 dogs and ten
minutes in one dog after the quinidine. The fourth (number 1), at ten
minutes after quinidine, demonstrated transient pre fibrillation changes
consisting of three premature ventricular contractions occurring in
a period of four seconds (ventricular rate, 225 per minute) with
spontaneous resumption of sinus tachycardia. On repetition of
the administration of epinephrine ventricular fibrillation ensued at
twenty-five minutes in 2 (numbers 1 and 8), while numbers 21 and 22
were protected for sixty and 165 minutes, respectively, and then the ex-
periments were discontinued, the animals having shown no arrhythmias.

Quinidine, in doses of 20 mg. per kilogram, was given to 3 dogs with
complete protection against the production of epinephrine-induced
arrhythmias for 180, forty-five and sixty minutes. Irregularities of
rhythm developed following epinephrine at 240 minutes in dog number
9 and in dog number 23 at seventy-five minutes. The experiment was
discontinued after sixty minutes in dog number 25, no arrhythmias
having been produced.

Spontaneous Cyclopropane-Induced Arrhythmias.—Ventricular al-
ternation was seen commonly during the induction phases of anesthesia
prior to the administration of quinidine, very seldom on re-anesthetiza-
tion after quinidine had been given. In most cases the alternation
disappeared as the depth of anesthesia increased. Ventricular alter-
nation developed in dogs number 22 and 25 at the point of respiratory
arrest, and in both cases this aberration disappeared in less than thirty
seconds after the injection of quinidine had been started. Dog number
17 was the only one in the series to develop a serious arrhythmia due
to cyclopropane alone. At the point of respiratory arrest, ventricular
tachycardia of 240 per minute (control rate, 98 per minute) developed.
Quinidine, 1 mg. per kilogram, was given at that time and the rate
dropped to 210 per minute with a regular sinus rhythm. Thirteen
minutes later, the dog was again anesthetized to the point of respira-
tory arrest with the production of the same type of rhythm disturbance,
again eliminated by quinidine in the same dosage.

DISCUSSION

It is apparent from these experiments that the intravenous ad-
ministration of quinidine markedly decreases the incidence of cardiac
arrhythmias induced by epinephrine in the dog anesthetized with cyclo-
propane, findings in agreement with those of Meek (4). The duration
of the protection is roughly a function of the size of the dose. It will
be noted on reference to table 1 that all of the dogs demonstrating
arrhythmias after the first administration of epinephrine (25 per cent
of the series) received the first injection ten minutes or more after the
quinidine. Conversely, no dog receiving epinephrine less than ten
minutes after quinidine demonstrated an arrhythmia. This effect is
not related to the size of the dose of quinidine given but becomes ap-
parent in the total duration of protection. With the smaller doses (1 and 5 mg. per kilogram), arrhythmias appeared on an average of 24.3 minutes after quinidine, the range being sixteen to fifty-five minutes. When 10 mg. per kilogram was given, arrhythmias became apparent at twenty-five minutes in 2 dogs, and none had appeared after sixty and 165 minutes in 2 others. When the dosage was 20 mg. per kilogram arrhythmias appeared at seventy-five and 240 minutes in 2 dogs and none had appeared after sixty minutes in the third. The number of dogs receiving the larger doses is too small to allow for reliability of average figures.

On the other hand we have shown that the protective action of quinidine becomes apparent very soon after the intravenous administration, one-half minute or less, and that the rapidity of onset of this action is independent of the dose administered.

The doses of quinidine used in the present series are comparable with the usual therapeutic dose in man. No deleterious effects were observed when these doses were given intravenously, except in one case (dog number 18) which demonstrated a marked tachycardia and 2:1 A–V block during the injection of 5 mg. per kilogram, probably explainable on the basis of individual idiosyncrasy to the drug.

Quinidine preparations have been administered intravenously to human beings. Schwartz and Jezer (13) in 1934 reported that the intravenous administration of quinidine sulfate to 2 patients subject to transient seizures of ventricular fibrillation frequently resulted in the development of prefibrillation mechanisms or transient ventricular fibrillation. On the other hand, Chapman (14) reported that the intravenous use of quinidine lactate in doses varying from 0.36 to 1.2 gm. in patients with paroxysmal ventricular tachycardia resulted in reversion to a sinus rhythm without serious toxic effects.

Weisman (15) has shown that neosynephrin, ephedrine, amphetamine, and epinephrine will counteract the cardiac and respiratory depressing effects of quinidine overdosage, and Orth et al. (16) have shown that neosynephrin, ephedrine and amphetamine do not tend to produce ectopic ventricular rhythms during cyclopropane anesthesia. Thus, several safe and efficient analeptic agents are available for the treatment of quinidine depression during cyclopropane anesthesia.

**Summary and Conclusions**

The protective action of intravenous quinidine against the onset of cardiac arrhythmias induced by epinephrine in dogs under cyclopropane anesthesia has been evaluated as to rapidity of onset, duration of action and minimal effective dose. The doses tested were 1, 5, 10 and 20 mg. per kilogram.

The intravenous administration of quinidine in all dosage levels tested markedly reduced the incidence of this type of cardiac arrhythmia.
The onset of the protective action was quite rapid, less than one-half minute after the completion of the injection, and independent of the size of the dose.

Arrhythmias were not noted following administration of epinephrine within ten minutes of the quinidine injection, regardless of the size of the dose.

After ten minutes, the duration of the protecting properties of quinidine tends to vary directly with the size of the dose, lasting for an average period of 24.3 minutes with 1 and 5 mg. per kilogram, and one to three hours with 20 mg. per kilogram.

It is concluded that quinidine sulfate or lactate given intravenously is a safe and efficient method of combating serious cardiac arrhythmias which may occur during cyclopropane anesthesia in the dog.

REFERENCES