Antiarrhythmic Action of N, N-Bis (Phenyldiacetamoylmethyl) Dimethyl Ammonium Chloride (QX-572) in Cat and Dog

Ronald L. Katz, M.D.

Ventricular arrhythmias were produced in the cat by the: (1) inhalation of halothane; (2) inhalation of halothane and carbon dioxide; (3) injection of norepinephrine during halothane inhalation; (4) inhalation of cyclopropane and carbon dioxide; (5) injection of norepinephrine during cyclopropane inhalation. Conversion of these arrhythmias to normal sinus rhythm was accomplished by the intravenous administration of 2-10 mg./kg. of QX-572, a lidocaine derivative. This agent often produced a fall in blood pressure of 10-20 per cent and a decrease in heart rate of 10-15 per cent. In the dog ventricular arrhythmias produced by the inhalation of halothane and carbon dioxide were abolished by 2-8 mg./kg. of QX-572. Blood pressure decreased 20-40 per cent while heart rate increased 20-35 per cent. Preliminary studies suggest that QX-572 is also an effective antiarrhythmic agent in man.

N, N-BIS (PHENYLACETAMOYL-METHYL) DIMETHYL AMMONIUM CHLORIDE (QX-572) is a lidocaine derivative recently introduced for the treatment of cardiac arrhythmias. Its structural formula is:

\[
\begin{align*}
\text{CH}_2 & \\
\text{\rightleftharpoons} & \\
\text{\text{NICOCH}_2\text{NCH}_2\text{CONH}} & \\
\text{\rightleftharpoons} & \\
\text{\text{CH}_3} & \\
\end{align*}
\]

This study was undertaken to determine the action of QX-572 on cardiac arrhythmias associated with anesthesia in the cat and dog.

Methods

The Cat. Thirty-eight cats weighing 2-4 kg. were studied. The animal was placed in a clear plastic box with unidirectional valves to which 10 per cent ether and 90 per cent oxygen was delivered from a Ventilotr anesthesia machine. When surgical anesthesia was established, the trachea, femoral artery and vein were cannulated. Femoral arterial pressure was measured with a Statham transducer and recorded on a Grass polygraph. All injections were made into the femoral vein.

Once the surgical procedures were completed and the blood pressure and electrocardiographic recordings begun, ether was discontinued and halothane (CHF₂C₂F₂CH₂Br), a general inhalation anesthetic agent, was started. One to 2 per cent halothane in oxygen was delivered from a Ventilotr anesthesia machine via a nonbreathing system (Frumin or Sierra nonrebreathing valve). Succinylcholine 2 mg./kg. every 30 minutes or 0.1 mg./kg./minute, or decamethonium 0.3 mg./kg. every 20 minutes was given intravenously and the lungs were artificially ventilated with a Harvard or Frumin respirator. Control studies demonstrated that succinylcholine and decamethonium as given did not affect the results. In order to ensure the adequacy of ventilation and to observe the effect of carbon dioxide inhalation, arterial blood samples were drawn at appropriate intervals for analysis of pH and P\(_{\text{CO}_2}\) (Astrup AME-1).

Cardiac arrhythmias were produced by the following procedures: (1) the inhalation of 1-2 per cent halothane and 98-99 per cent oxygen; (2) the inhalation of 1 per cent halothane, 10 per cent carbon dioxide and 89 per cent oxygen; (3) the injection of 1 μg./kg. norepinephrine during the inhalation of 1 per cent halothane and 99 per cent oxygen; (4) the inhalation of 20 per cent cyclopropane, 10 per cent carbon dioxide and 70 per cent


<table>
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<tr>
<th>Animal</th>
<th>Type of Arrhythmia</th>
<th>Mode of Administration of QX-572</th>
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<tr>
<td>Cat</td>
<td>1) Halopropane</td>
<td>a) single injection</td>
<td>converted (7/3)</td>
<td>2–10 mg./kg.</td>
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<tr>
<td></td>
<td></td>
<td>b) continuous infusion</td>
<td>converted (6/6)</td>
<td>8 mg./kg.</td>
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<td></td>
<td></td>
<td>c) continuous infusion or intermittent injection</td>
<td>prevented (3/3)</td>
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<td></td>
<td>2) Halopropane-carbon dioxide</td>
<td>Intermittent injection</td>
<td>converted (7/8)</td>
<td>4–10 mg./kg.</td>
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<tr>
<td></td>
<td>3) Halopropane-norepinephrine</td>
<td>a) single injection</td>
<td>converted (3/3)</td>
<td>2 mg./kg.</td>
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<tr>
<td></td>
<td></td>
<td>b) single injection</td>
<td>prevented (3/3)</td>
<td>2 mg./kg.</td>
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<td></td>
<td>4) Cyclopropane-carbon dioxide</td>
<td>single injection(s)</td>
<td>converted (5/5)</td>
<td>2–6 mg./kg.</td>
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<td>5) Cyclopropane-norepinephrine</td>
<td>single injection(s)</td>
<td>prevented (3/3)</td>
<td>2–4 mg./kg.</td>
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<td>Dog</td>
<td>Halopropane-carbon dioxide</td>
<td>single injection(s)</td>
<td>converted (5/5)</td>
<td>2–8 mg./kg.</td>
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Oxygen; (5) the injection of 2–5 μg./kg. norepinephrine during the inhalation of 20 per cent cyclopropane and 80 per cent oxygen.

The Dog. Five dogs weighing 8–12 kg. were studied. Following the intravenous injection of 15 mg./kg. thiamylal sodium, the trachea, femoral artery and femoral vein were cannulated. A mixture of 1 per cent halopropane and 99 per cent oxygen was inhaled via the nonrebreathing system described above. Succinylcholine 0.01 mg./kg./minute was infused intravenously and the animals artificially ventilated with a Harvard or Frumin respirator. Arterial pH, PaCO₂, blood pressure and the electrocardiogram were recorded as described above. Arrhythmias were produced in the dog by the inhalation of 1 per cent halopropane, 10 per cent carbon dioxide and 89 per cent oxygen.

Results (Table 1)

The Cat: Halopropane. In 16 of 22 cats arrhythmias were produced by the inhalation of 1–2 per cent halopropane and oxygen. The disturbances in rhythm consisted predominantly of frequent supraventricular and ventricular premature contractions sometimes going on to runs of tachycardia. It was frequently difficult to distinguish supraventricular beats with aberrant conduction from those originating in a ventricular focus. These arrhythmias persisted as long as the halopropane was inhaled. The maximum duration of arrhythmia studied was eight hours. Discontinuing the halopropane restored a normal sinus rhythm in 5–30 minutes, depending upon the prior duration of inhalation.

At various intervals (15–240 minutes) following the onset of arrhythmia, QX-572 was administered to 7 cats in intermittent doses of 2 mg./kg. every 2 minutes until normal sinus rhythm was restored. The total cumulative dose required was 2 mg./kg. in 1 cat, 4 mg./kg. in 2, 6 mg./kg. in 3 and 10 mg./kg. in 1. A normal sinus rhythm persisted for 6–26 minutes depending upon the dose of QX-572 administered. When the arrhythmia returned and persisted for at least 15 minutes, QX-572 was repeated in 2 mg./kg. doses until a normal sinus rhythm was restored. In all 7 cats, the arrhythmia was abolished at least 3 times by QX-572.

In 3 animals with halopropane induced arrhythmias a continuous infusion of QX-572 of 0.7 mg./kg./minute to a total dose of 8 mg./kg. was used. A conversion to normal sinus rhythm occurred at cumulative doses of 2.4, 4.2 and 5.6 mg./kg., respectively, and persisted for 4, 12 and 18 minutes after the end of the infusion. In 3 other animals the minimum continuous infusion rate required for the maintenance of normal sinus rhythm after a priming dose of 2 mg./kg. was 0.3 mg./kg./minute in 2 animals and 0.4 mg./kg./minute in the third. The duration of normal sinus...
rhythm following a cumulative dose of 8 mg./kg. so administered was 11, 12 and 14 minutes, respectively.

The time of onset of arrhythmia, although varying in different cats from 1–10 minutes after inhalation of halopropane, was consistent in any given animal. Once the time of onset of the arrhythmia was established in 3 consecutive exposures, 8 mg./kg. of QX-572 was infused. This was given by continuous infusion of 0.7 mg./kg./minute in 1 cat and intermittent injection of 2 mg./kg. every 2 minutes in 2 cats. The animals were then reexposed to halopropane. The onset of arrhythmia occurred at 3, 4 and 6 minutes before QX-572 was given and at 18, 22 and 27 minutes after QX-572.

In 11 of the animals QX-572 lowered the blood pressure 10–20 per cent and decreased the heart rate 10–15 per cent. In 2 animals the conversion of the arrhythmia to a normal sinus rhythm produced an increase in blood pressure. In 3 animals there was no significant change in blood pressure.

Halopropane-Carbon Dioxide Arrhythmias. Arrhythmias were produced in 8 cats by the inhalation of 1 per cent halopropane and 10 per cent carbon dioxide and 89 per cent oxygen. The inhalation of 10 per cent carbon dioxide decreased pH 0.24 (± 0.05) units from a control mean of 7.31 (±0.04). The arterial Po2 increased 33 (±6) mm. of mercury from a control mean of 32 (±5) mm. of mercury. In 7 of 8 experiments intermittent injection of 2 mg./kg. every 2 minutes restored a normal sinus rhythm after 4 mg./kg. in 2 cats, 6 mg./kg. in 3, 8 mg./kg. in 1 and 10 mg./kg. in 1. The duration of normal sinus rhythm was 4–22 minutes. These halopropane-carbon dioxide arrhythmias were more difficult to block than those produced by halopropane alone. This could best be seen in 3 animals described above in whom a continuous infusion rate of QX-572 of 0.3–0.4 mg./kg./minute maintained a normal sinus rhythm. The addition of 10 per cent carbon dioxide produced arrhythmias. Discontinuing the carbon dioxide restored a normal sinus rhythm. The addition of 10 per cent carbon dioxide again produced arrhythmias which could be eliminated by doubling the rate of infusion of QX-572.

Halopropane-Norepinephrine Arrhythmias. In 6 cats who maintained a normal sinus rhythm during the inhalation of 1 per cent halopropane, the injection of 1 µg./kg. of norepinephrine produced ventricular arrhythmias of 1–3 minutes duration. Once the duration of arrhythmia was established for a given cat, 2 mg./kg. of QX-572 was injected after the

![Fig. 1](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931632/)

**Fig. 1.** Prevention of halopropane-norepinephrine arrhythmia by QX-572. Cat 72, 3.3 kg. **Panel A:** At 1 paper speed changed from 25 mm./second to 2.5 mm./second. At 3 paper speed changed back to 25 mm./second. At 2 norepinephrine 1 µg./kg. given intravenously produced an arrhythmia of 63 seconds duration. **Panel B:** Paper speed changed from 25 mm./second to 2.5 mm./second at 1 and returned to 25 mm./second at 4, at 2, QX-572 2 mg./kg. given intravenously. Infusion of 1 µg./kg. of norepinephrine at 3 did not result in arrhythmia.
first three ventricular ectopic beats were observed. In 3 cats a conversion to normal sinus rhythm was observed within 24-36 seconds. In 3 other cats it was possible to prevent the arrhythmias by the injection of 2 mg./kg. of QX-572, 5-10 seconds before the 1 μg./kg. of norepinephrine (Fig. 1).

Cyclopropane-Carbon Dioxide Arrhythmias. Arrhythmias similar to those observed with halothane were produced in 5 cats by the inhalation of 20 per cent cyclopropane, 10 per cent carbon dioxide and 70 per cent oxygen. The intravenous administration of QX-572, 2 mg./kg. every 2 minutes, restored a normal sinus rhythm after 2 mg./kg. in 1 cat, 4 mg./kg. in 2 and 6 mg./kg. in 2. The duration of normal sinus rhythm was 8-37 minutes.

Cyclopropane-Norepinephrine Arrhythmias. Ventricular arrhythmias were produced in 3 cats by the injection of 2-5 μg./kg. norepinephrine during the inhalation of 20 per cent cyclopropane and 80 per cent oxygen. These arrhythmias could be prevented by the injection of 2 mg./kg. of QX-572 in 1 cat and 4 mg./kg. (2 mg./kg. two minutes apart) in 2 cats. The duration of complete protection varied from 5-9 minutes after the injection of QX-572.

The Doc: Arrhythmias were produced in 5 dogs by the inhalation of 1 per cent halothane, 10 per cent carbon dioxide and 89 per cent oxygen. Two milligrams per kilogram of QX-572 was injected every 2 minutes until a normal sinus rhythm was restored. This required 2 mg./kg. in 1 dog, 4 mg./kg. in 2, 6 mg./kg. in 1 and 8 mg./kg. in 1. In each case, conversion of the arrhythmia occurred within 24-45 seconds after the appropriate dose. A normal sinus rhythm persisted for 5-30 minutes, depending upon the cumulative dose received. A 20-40 per cent decrease in blood pressure of 7-12 minutes duration and a 20-35 per cent increase in heart rate of 4-11 minutes duration was observed.

Discussion

The treatment of cardiac arrhythmias with local anesthetic agents and their derivatives is well established. Procaine was used by Burstein1 to treat cardiac arrhythmias in anesthetized patients. Drawbacks to its use include: (1) rapid hydrolysis and therefore a brief duration of action; (2) central nervous system stimulation which may progress to convulsion and therefore limits the usefulness in unanesthetized patients; (3) hypotension; (4) tachycardia.

Studies of the procaine products of hydrolysis revealed that although para-aminobenzoic acid had no antiarrhythmic activity, diethylaminoethanol exhibited an antiarrhythmic action less than that of procaine but with minimal central stimulation effects.2 Derivatives of diethylaminoethanol were studied to find an agent with the high degree of antiarrhythmic activity of procaine and the low toxicity of diethylaminoethanol.3 These studies brought forth procaine amide which is effective in the treatment of ventricular arrhythmias and less so in the treatment of atrial arrhythmias. Some of the side effects which may occur limits its usefulness include: (1) hypotension, (2) psychosis and mental depression, (3) urticaria, (4) nausea and vomiting, (5) convulsions.4, 5, 6 In addition, Ladd7 reported a lupus erythematosus-like syndrome following the use of procaine amide.

Recently the antiarrhythmic activity of the local anesthetic lidocaine has been used for the management of cardiac arrhythmias during anesthesia and operation in man.8-9 The general use of lidocaine is limited by its brief duration of action (10 minutes).8 In addition, Foldes et al.10 found in unanesthetized patients subjective signs of toxicity after the intravenous administration of 1.5 mg./kg. and objective signs of toxicity after 6.4 mg./kg. The subjective symptoms include sleepiness, confusion, numbness of extremities, face, or whole body, blurred vision, diplopia, color blindness, sensation of cold, lump in throat and heaviness in the chest. The objective signs included flattening and absence of T waves and depression of ST segment as well as EEG changes similar to those seen in sleep. Other objective signs were dysarthria, disorientation, sweating, euphoria, muscle fasciculations, and twitching. Generalized convulsions occurred in one patient.

Investigation of lidocaine derivatives led to QX-572. Studies in the dog demonstrated that QX-572 was effective in the prevention and
treatment of multifocal ventricular tachycardia induced by coronary ligation and atrial fibrillation induced by topical application of acetylcholine to the right atrium. Pretreatment of dogs with QX-572 one hour prior to cardiac catheterization markedly decreased the frequency of ectopic beats seen with this procedure. Quinidine and procaine amide failed to prevent these mechanically induced arrhythmias. QX-572 was also effective in the prevention of ventricular fibrillation in the hypothermic dog.

The present study demonstrates that QX-572 is effective in the treatment of halopropane-carbon dioxide induced arrhythmias in the dog. QX-572 was also effective in the cat in the prevention and/or treatment of cardiac arrhythmias induced by: (1) halopropane, (2) halopropane-carbon dioxide, (3) halopropane-norepinephrine, (4) cyclopropane-carbon dioxide, (5) cyclopropane-norepinephrine. These arrhythmias differ quantitatively and qualitatively. These differences can be seen in terms of ease of production, frequency of ectopic activity, and variation in response to surgical and drug treatment of the arrhythmia.

The fall in blood pressure produced in animals by the rapid intravenous injection of QX-572 is believed to be due to peripheral vasodilation and not depression of cardiac contractility or output. It was demonstrated in the dog that the intracoronary infusion of QX-572 produced a positive inotropic effect, an increase in cardiac output and an increase in coronary blood flow.

The mechanism of action of QX-572 has not yet been determined. Preliminary studies of its effects on the electrophysiological properties of the heart suggest a myocardial site of antiarrhythmic action. These studies demonstrated a decrease in excitability and prolongation of the refractory period of the isolated guinea pig atria. In the intact dog a prolongation of the refractory period of the ventricle and an increase in ventricular diastolic thresholds was observed. A decrease in myocardial excitability and prolongation of the refractory period of the atria and ventricle is seen with quinidine and is believed to be responsible for its antiarrhythmic action. Procaine amide, which prolongs the refractory period of the atria but not of the ventricle, is believed to act by a decrease in the excitability of the myocardium. Conduction time which was not prolonged by antiarrhythmic doses of QX-572 is prolonged by quinidine and procaine and is considered an undesirable action.

In a preliminary clinical trial performed after completion of the animal studies, QX-572 restored a normal sinus rhythm in 10 patients who developed ventricular arrhythmias during anesthesia and operation.

Summary
QX-572 was found to be effective in the treatment of halopropane, halopropane-carbon dioxide, halopropane-norepinephrine, cyclopropane-carbon dioxide, cyclopropane-norepinephrine arrhythmias in the cat and halopropane-carbon dioxide arrhythmias in the dog. Whether it offers any advantages in man over other available agents in terms of antiarrhythmic activity or lesser side effects is not yet known.

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References


12. Covino, B., and D’Amato, H. E.: Personal communication to the author.


UTERINE BLOOD FLOW Blood flows through the human uterus were compared during halothane and hexobarbital anesthesia using the Hensel thermoelectric needle. During halothane anesthesia a decrease occurred in uterine blood flow dependent on the depth of anesthesia. Hexobarbital anesthesia of comparable depth showed a slight decrease of uterine blood flow only in 50 per cent of the patients. Rhythmic variations in vascularity of the uterus disappeared in surgical planes of anesthesia with both agents. (Nobel, J., and Hille, H.: Blood Flow in the Uterus During Halothane Compared with Barbiturate Anesthesia, Der Anaesthesist 12: 349 (Nov.) 1963.)

PHEOCHROMOCYTOMA The main anesthetic agent should be a drug which is administered and eliminated unchanged by the inhalation route. Hydrocarbons which sensitize the heart to catecholamines should be avoided: cyclopropane, trichloroethylene, chloroform, and halothane. Hypertensive episodes and associated cardiac arrhythmias are best controlled with fractional doses of phentolamine (Regitine) 2.5 to 5 mg. intravenously. Profound and sudden hypotension following excision of the tumor may be related to diminished cardiovascular responsiveness to circulating catecholamines, or to a reduction in total blood volume. Vasopressors which act through l-norepinephrine release, such as ephedrine, methamphetamine and mephentermine should be used to clear the adrenergic stores and regain l-norepinephrine sensitivity. A moderate intravenous dose of ephedrine may increase the effectiveness of levaterenol drip. Conversion from levaterenol to a less potent direct acting vasopressor such as phenylephrine should be made as soon as feasible. Administration of cortisone should be considered if the blood pressure response to vasopressors and blood replacement is poor. (Crandell, D. L., and Myers, R. T.: Pheochromocytoma—Anesthetic and Surgical Considerations, J.A.M.A. 187: 12 (Jan. 4) 1964.)