

Antiarrhythmic Properties of Stereoisomers of a Beta-adrenergic Blocking Agent (H56/28)

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Cardiac arrhythmias were produced in the cat by inhalation of 1 per cent halopropane, 10 per cent CO₂ and 89 per cent O₂ and also by injection of epinephrine during inhalation of 1 per cent halopropane and 99 per cent O₂. Dextro-H56/28, which has local anesthetic properties but only 1/40th the beta receptor blocking activity of the levo form of H56/28, had a weak, brief antiarrhythmic effect on the halopropane-CO₂ arrhythmia and did not significantly increase the threshold dose of epinephrine required to produce an arrhythmia during halopropane administration. However, levo-H56/28, when tested against the halopropane-CO₂ and halopropane-epinephrine arrhythmias, had a marked, prolonged antiarrhythmic effect, which was attributed to its beta-adrenergic blocking action.

BETA-ADRENERGIC receptor antagonists are well known to possess antiarrhythmic properties in experimental animals and man. These compounds antagonize ouabain-induced arrhythmias in guinea pigs,¹ dogs,²⁻⁵ and cats,⁶ and catecholamine-induced arrhythmias in anesthetized dogs,^{3-5,7} cats,^{6,8-10} and man.^{11,12} The relative importance of the beta-adrenergic blocking properties of these compounds in their ability to antagonize epinephrine-induced arrhythmias is in some doubt because some beta blockers have local anesthetic and quinidine-like properties which could account for their antiarrhythmic actions.^{1,2,5,13}

1-(O-allylphenoxy)-isopropylamino-2 propylamino-hydrochloride (H56/28), a new beta re-

ceptor blocking agent, has been shown to block ouabain-induced arrhythmias in the dog¹⁴ and catecholamine-anesthetic arrhythmias in the cat.¹⁵ Antiarrhythmic effects in unanesthetized¹⁵ and anesthetized patients¹⁶ have been demonstrated also. Recently this compound has been resolved into its stereoisomers, the dextro- form having 1/40th to 1/60th the beta blocking activity of levo-H56/28 but similar local anesthetic properties.¹⁷ It was the purpose of this study to examine the effects of the stereoisomers of H56/28 on halopropane-catecholamine and halopropane-CO₂-induced arrhythmias and to study the relative importance of beta receptor blocking activity and local anesthetic potency in the ability of this compound to antagonize these arrhythmias.

Methods

Cats weighing 2.5 to 5.0 kg. were anesthetized with sodium pentobarbital (36 mg./kg.) by intraperitoneal injection. The trachea, femoral artery and femoral vein were cannulated. Femoral arterial blood pressure was measured with a Statham transducer. Lead II of the electrocardiogram and arterial pressure were recorded on a Grass polygraph at a paper speed of 2.5 or 25 mm./sec.

Halopropane was delivered from a Vernitrol® anesthesia machine via a nonrebreathing system (Sierra nonrebreathing valve) and the lungs were artificially ventilated with a Frumin-Lee respirator (pediatric bellows). The respiratory rate was 24-28/min. and the tidal volume 10 ml./kg. + 10 ml. All injections were made into the femoral vein.

Cardiac arrhythmias were produced by: (1) inhalation of 1 per cent halopropane, 10 per cent carbon dioxide and 89 per cent oxygen; and (2) injection of the threshold dose of epinephrine required to produce cardiac arrhyth-

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TABLE 1. Halopropane-CO₂ Arrhythmias

	Dose of H56/28	Mean Duration of Block (min. \pm S.E.)	Duration of Antiarrhythmic Effect in Each Cat (min.)				
			Cat 1	Cat 2	Cat 3	Cat 4	Cat 5
First dose	Dextro-H56/28 500 μ g./kg.	1.8 \pm 1.40	0	7	2	0	0
Second dose*	Dextro-H56/28 500 μ g./kg.	2.63 \pm 1.50	5	7.5	0.5	0	0.15

* = Second dose given after arrhythmia had returned and persisted for ten minutes.

mias during inhalation of 1 per cent halopropane and 99 per cent oxygen. Halopropane was inhaled for at least 30–60 minutes before any drugs were injected. The threshold dose of epinephrine required to produce cardiac arrhythmias during inhalation of 1 per cent halopropane was determined by a modification of the method of Katz.⁸ During halopropane inhalation 0.125 μ g./kg. of epinephrine was injected and the response noted. If no arrhythmia occurred the dose of epinephrine was doubled until an arrhythmia was produced. The interval between injections of epinephrine was at least ten minutes, during which time the blood pressure and pulse returned to normal. The threshold dose of epinephrine was repeated two or three times to ascertain its reproducibility. In all animals the initial threshold dose of epinephrine was found to reproduce the arrhythmia consistently. Once the arrhythmic threshold was determined, 500 μ g./kg. of dextro-H56/28 was given and the arrhythmic threshold redetermined in five cats. The same procedure was carried out for levo-H56/28 in five other cats.

In those animals receiving halopropane-CO₂, the protocol followed was: (1) 500 μ g./kg. of dextro-H56/28 was given to five cats and the duration of antiarrhythmic effect noted. Once the arrhythmia returned and persisted for 10 minutes, each cat was given an additional 500 μ g./kg. of dextro-H56/28 and the duration of antiarrhythmic effect noted again; (2) 500 μ g./kg. of dextro-H56/28 was given to five cats and the duration of antiarrhythmic effect noted. When the arrhythmia returned, 500 μ g./kg. of levo-H56/28 was given; (3) 500 μ g./kg. of levo-H56/28 was given to six cats. In three cats the duration of antiarrhythmic action was greater than one hour and no fur-

ther drugs were given. In three other cats the dose of levo-H56/28 was followed by 500 μ g./kg. of dextro-H56/28 after the return of the arrhythmia.

Epinephrine HCl and levo- and dextro-H56/28 were used. All doses of drugs refer to the salts.

Results

HALOPROPAANE/CARBON DIOXIDE ARRHYTHMIAS

Arrhythmias were produced in all 16 cats by inhalation of 1 per cent halopropane, 10 per cent carbon dioxide and 89 per cent oxygen. As previously reported, the disturbances in rhythm consisted predominantly of frequent supraventricular and ventricular premature contractions, sometimes going on to runs of tachycardia.^{8, 9, 20} The arrhythmias persisted as long as the halopropane-CO₂ mixture was inhaled. The time of onset of arrhythmia was in the range of 2–10 minutes.

The duration of antiarrhythmic effect seen with the first dose of 500 μ g./kg. of dextro-H56/28 varied from zero to 7 minutes (table 1). Antiarrhythmic effect is defined in our experiments as a return to normal sinus rhythm. In cat 4 an incomplete antiarrhythmic effect was manifested by a decrease in the frequency of ectopic beats for two minutes. The mean duration of antiarrhythmic effect was 1.8 minutes, with a standard error of \pm 1.4 minutes. Following the return of the arrhythmia and its persistence for ten minutes, a second dose of dextro-H56/28 provided a range of antiarrhythmic effect lasting zero to 7.5 minutes. Again, cat 4 showed an incomplete antiarrhythmic effect, this time lasting four minutes. The mean duration of antiarrhythmic effect

TABLE 2. Halopropane-CO₂ Arrhythmias

	Dose of H56/28	Mean Duration of Block (min. \pm S.E.)	Duration of Antiarrhythmic Effect in Each Cat (min.)				
			Cat 6	Cat 7	Cat 8	Cat 9	Cat 10
First dose	Dextro-H56/28 500 μ g./kg.	2.9 \pm 1.3	5	1	6.5	0	2
Second dose ^a	Levo-H56/28 500 μ g./kg.		80+	60+	60+	120+	11

^a = Second dose given after arrhythmia had returned and persisted for ten minutes.

following the second dose of 500 μ g./kg. of H56/28 was 2.63 minutes, with a standard error of \pm 1.50.

The results obtained when the levo- form of H56/28 was given following dextro-H56/28 are shown in table 2. The duration of antiarrhythmic effect following the initial dose of dextro-H56/28 was zero to 6.5 minutes, with a mean of 2.9 minutes and a standard error of \pm 1.3 minutes. Cat 9 gave an incomplete antiarrhythmic response for three minutes. Following a return of the arrhythmia for ten minutes, 500 μ g./kg. of levo-H56/28 was given. In only one animal (cat 10) did the arrhythmia return following the levo-H56/28. In the other animals the experiments were terminated at 60 minutes (two cats), 80 minutes and 120 minutes, without evidence of recurrence of the arrhythmia.

When 500 μ g./kg. of levo-H56/28 was given first for the halopropane-CO₂ arrhythmia, the duration of antiarrhythmic action varied from 11 to over 120 minutes (table 3). In three cats (14, 15, 16) the antiarrhythmic effect of levo-H56/28 lasted more than 120 minutes, 60 minutes and 120 minutes, respectively, at which time the experiments were terminated.

In cats 11, 12 and 13 the initial dose of levo-H56/28 was followed by dextro-H56/28 (500 μ g./kg.) on return of the arrhythmia. The duration of antiarrhythmic effect was 4, 6.5, and 6 minutes, respectively.

Dextro-H56/28 decreased mean arterial pressure for a mean of 12.6 mm. Hg, whereas levo-H56/28 decreased mean arterial pressure for a mean of 11.6 mm. Hg. The antiarrhythmic action of levo-H56/28 could not be explained by the effect of this drug on arterial pressure since (1) dextro- and levo- forms caused simi-

lar falls in blood pressure, and (2) the halopropane-CO₂ arrhythmia was not abolished by a fall in arterial pressure.⁹

HALOPROFANE/EPINEPHRINE

The epinephrine arrhythmic threshold during halopropane administration was determined in ten cats. The dose range required to produce an arrhythmia was 0.5–2.0 μ g./kg. of epinephrine, with a mean of 1.05 \pm 0.25 μ g./kg. The duration of the epinephrine arrhythmia was 20–45 seconds, with a mean of 31.7 \pm 6.5 seconds. After establishing the arrhythmic threshold, five cats were given 500 μ g./kg. of dextro-H56/28 and the arrhythmic threshold redetermined. As can be seen in table 4, the arrhythmic threshold was increased in only one of the five animals following dextro-H56/28. In this animal the arrhythmic threshold was doubled and the antiarrhythmic effect lasted 10 minutes.

In the second group of five cats, after establishment of a threshold dose of epinephrine, 500 μ g./kg. of levo-H56/28 was given and the threshold again determined. The threshold dose of epinephrine was increased in all five cats, with the increases ranging from two- to eightfold (table 4). In three animals the antiarrhythmic effect lasted for the duration of the experiment (120 minutes). In the other two cats the antiarrhythmic effect lasted 22 minutes and 83 minutes, respectively.

The mean fall in blood pressure following dextro-H56/28 was 9 mm. Hg, whereas levo-H56/28 gave a mean fall of 16 mm. Hg. Upon re-challenge with the threshold dose of epinephrine, the mean blood pressure rise following dextro-H56/28 was 51.6 mm. Hg \pm 19.6; it was 65.4 mm. Hg \pm 24.4 after the levo- form. The slightly greater rise seen after

TABLE 3. Halopropane-CO₂ Arrhythmias

	Dose of H56/28	Duration of Antiarrhythmic Effect in Each Cat (min.)					
		Cat 11	Cat 12	Cat 13	Cat 14	Cat 15	Cat 16
First dose	Levo-H56/28 500 µg./kg.	11	32	25	120+	60+	120+
Second dose ^a	Dextro-H56/28 500 µg./kg.	4	6.5	6.0	*	*	*

* = Second dose given after arrhythmia had returned and persisted for ten minutes.

* = Dose of dextro-H56/28 not given.

levo-H56/28 probably can be explained by the greater initial fall in the blood pressure following levo-H56/28, and on the basis of beta-adrenergic blockade. Because blood pressure differences with the levo- and dextro- forms were minimal, we feel that they cannot account for the differences in antiarrhythmic effects of the two isomers.

Discussion

In clinical studies of halopropane (CHF₂CF₂CH₂Br) as an inhalational anesthetic, the incidence of cardiac arrhythmias was 20 per cent,¹⁸ 39 per cent,¹⁹ and 40 per cent.²⁰ Halopropane therefore was abandoned as an anesthetic. However, Katz^{9, 21, 22} has shown that halopropane is useful in the study of cardiac arrhythmias and their treatment in the cat. Thus, halopropane-CO₂ and halopropane-epinephrine arrhythmias were chosen for the present study. The halopropane-epinephrine arrhythmia is precipitated by the *exogenous* administration of catecholamine during halopropane inhalation. However, the halopropane-CO₂ arrhythmia results from endogenous release of catecholamines from the myocardium and adrenals, and requires the presence of an intact pons and medulla. This differs from the halopropane-epinephrine arrhythmia, which does not require an intact pons and medulla for its development.⁹ The halopropane-CO₂ arrhythmia therefore is similar to the cyclopropane-CO₂ arrhythmias in man, described by Price,²³ which likewise depend on release of endogenous catecholamines for their production.

Shortly after Powell and Slater introduced the beta receptor blocking agent, DCI,²⁴ in 1958, it was shown to be an effective antiarrhythmic agent against catecholamine-induced

cardiac arrhythmias.^{25, 26} However, Lucchesi and Hardman² demonstrated that DCI also produced an antiarrhythmic effect against acetylstrophanthidin- and ouabain-induced arrhythmias which was independent of its ability to block beta-adrenergic receptors. Lucchesi³ demonstrated similar results with the beta blocking agent pronethalol and likewise suggested that its antiarrhythmic action on digitalis-induced arrhythmias was independent of its ability to produce beta-adrenergic receptor blockade. Sekiya and Vaughn-Williams¹ showed that pronethalol had a "quinidine-like" action in interfering with depolarization of cardiac muscle and suggested that this might account for its antifibrillatory activity. This "quinidine-like" effect seen with some beta receptor blocking agents, which may account for some of their antiarrhythmic properties, does not appear to be significant in our

TABLE 4. Effects of Levo- and Dextro-H56/28 on Halopropane-Epinephrine Arrhythmias

Control (10 cats)	
Arrhythmia threshold dose (µg./kg. ± S.E.)	Duration of arrhythmia (secs. ± S.E.)
Mean 1.05 ± 0.25	Mean 31.7 ± 6.5
Range 0.50 ± 2.0	Range 20.0 ± 54
500 µg./kg. Dextro-H56/28 (5 cats)	
Threshold not increased - 4	
Threshold increased × 2 - 1	
500 µg./kg. Levo-H56/28 (5 cats)	
Threshold not increased - 0	
Threshold increased × 2 - 2	
Threshold increased × 4 - 1	
Threshold increased × 8 - 2	

results: it has been observed that in the dose range used in the present study H56/28 does not have a quinidine-like cation.¹⁰

Pronethalol, aside from its "quinidine-like" action, has been shown to have local anesthetic activity 1.8 times as great as that of procaine and to be equal in activity to lidocaine.¹² The recently-developed beta receptor blocking agent propranolol was found to possess local anesthetic activity 2.3 times as great as that of procaine and also to be equal in activity to lidocaine.¹³ Somani and Lum,⁵ working with arrhythmias in dogs, suggested that the local anesthetic effect of the beta receptor blocking agent might play a role in their antiarrhythmic effects. These authors studied pronethalol and N-isopropyl-p-nitrophenylethanolamine (INPEA) a beta receptor antagonist devoid of local anesthetic activity. They found that both pronethalol and INPEA blocked epinephrine-induced arrhythmias, and that pronethalol had a short nonspecific antiarrhythmic action on ouabain-induced arrhythmias whereas INPEA had no effect at all. They concluded that the nonspecific effect of pronethalol on ouabain-induced arrhythmias was related to its local anesthetic effects and that the antiarrhythmic effect of pronethalol and INPEA on epinephrine-induced arrhythmias was related to specific beta-adrenergic blockade.

It became apparent that one way to settle the controversy of the antiarrhythmic effects of beta receptor blocking agents was to separate the local anesthetic and/or quinidine-like effects of these agents from the beta receptor blocking properties and to compare the resulting compounds against various arrhythmias. This has been accomplished with the present compound, H56/28. Both dextro- and levo-forms have local anesthetic activity equal to that of lidocaine. However, the levo-form has a beta receptor blocking activity 40-60 times greater than that of the dextro-form.¹⁷ Our results with the halopropane-CO₂ arrhythmias reveal that dextro-H56/28 produces only a brief (1-3 min.) blockade of this arrhythmia and that a second dose does not increase the antiarrhythmic effects appreciably. However, specific beta receptor blockade by levo-H56/28 produces an antiarrhythmic action

which usually lasts more than an hour. Similar results were observed with the halopropane-epinephrine arrhythmia. We obtained an increase in the halopropane-epinephrine arrhythmic threshold in all cats receiving levo-H56/28 but in only one of five cats receiving dextro-H56/28. We therefore believe that beta receptor blockade is the important factor in preventing the halopropane-epinephrine as well as the halopropane-CO₂ arrhythmia, and that the brief antiarrhythmic effect afforded by the dextro-form is secondary to its local anesthetic properties.

Our results with H56/28 differ from those of Lucchesi⁴ who found that dextro-pronethalol, although 1/40th as potent as the levo-form in beta blocking activity, was able to protect against hydrocarbon-epinephrine arrhythmias. He therefore suggested that beta-adrenergic receptor inhibition by pronethalol was not the mechanism by which this compound prevented hydrocarbon-epinephrine arrhythmias. Thus, the antiarrhythmic effects of pronethalol appear to differ from those of H56/28. Propranolol, on the other hand, seems to have effects similar to those of H56/28. Dextro-propranolol has about 1/80th to 1/100th the beta blocking activity of the levo-isomer. Howe and Shanks⁶ showed that the dextro-form of propranolol was capable of abolishing ouabain-induced arrhythmias whereas the levo-isomer had little effect. This was compatible with Lucchesi's observations, with pronethalol, that beta-adrenergic receptor blockade is not important in the control of these arrhythmias. However, Howe and Shanks⁶ also showed that levo-propranolol was effective in preventing the halothane-epinephrine arrhythmias and was at least ten times more active than the dextro-isomer in this regard.

Further support for the role of beta-adrenergic receptors in the genesis of the anesthetic-catecholamine arrhythmias is found in the work of Katz.⁸ Arrhythmias were produced by injection of epinephrine, norepinephrine, isoproterenol or ethylnorepinephrine during inhalation of cyclopropane. The effect of alpha-adrenergic blockade produced by dibenamine was compared with the effect of beta-adrenergic blockade produced by prone-

thalol. Dibenamine did not abolish the cyclopropane-catecholamine arrhythmias consistently. When it did, the effect often was attributable to modification of the blood pressure effects of the catecholamines. Pronethalol, however, consistently blocked the cyclopropane-catecholamine arrhythmias. Because the local anesthetic and quinidine-like action of pronethalol might account for its antiarrhythmic action, the effect of milligram doses of isoproterenol was studied. These large doses of isoproterenol, which produced beta-adrenergic blockade, also prevented the cyclopropane-catecholamine arrhythmias, suggesting that the cyclopropane-catecholamine arrhythmias were blocked by specific beta-adrenergic blockade and that myocardial ectopic excitation may be attributable to the beta-adrenergic receptors. Similar conclusions were reached by Somani and Lum,²⁷ who showed that alpha-adrenergic blockade did not prevent anesthetic-catecholamine arrhythmias in the heart-lung preparation, but beta-adrenergic blockade did. It is of interest that in a prior study⁸ the increase in arrhythmic threshold produced by pronethalol was usually eightfold or sixteenfold, whereas milligram doses of isoproterenol increased the arrhythmia threshold fourfold, as did levo-H56/28 in the present study. We believe the greater antiarrhythmic activity of pronethalol to be due to its quinidine-like action.

Summary

Arrhythmias were produced in the cat by the inhalation of 1 per cent halopropane, 10 per cent CO₂ and 89 per cent O₂ and also by injection of a threshold dose of epinephrine during inhalation of 1 per cent halopropane and 99 per cent O₂. Dextro-H56/28, which has local anesthetic properties but only 1/40th the beta-adrenergic receptor blocking activity of levo-H56/28, had a weak, brief antiarrhythmic effect. However, levo-H56/28 had a marked, prolonged antiarrhythmic effect that was attributed to its ability to inhibit beta-adrenergic receptors.

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Drugs

PROPRANOLOL Cardiac responses to supine bicycle exercise were studied in six normal subjects, after intravenous administration of 5 mg. propranolol and again after the additive effect of 0.03 mg./kg. atropine. Mean resting heart rate was decreased 15 beats/minute by propranolol; increased 38 beats/minute after atropine. Mean exercising heart rate was 157 beats/minute for control exercise, 119 after propranolol and 143 after propranolol plus atropine. The resting cardiac index was reduced 21 per cent by propranolol and restored to control values after atropine. Mean stroke index was not altered by control exercise, increased 3 ml./beat/square meter body surface with exercise after propranolol, and increased 6 ml./beat with exercise after propranolol plus atropine. Atropine restores the depressed cardiac response to exercise which follows beta-adrenergic inhibition, possibly by increasing heart rate. (*Cumming, G. R., and Car, W.: Hemodynamic Response to Exercise After Beta-Adrenergic and Parasympathetic Blockade, Canad. J. Physiol. Pharmacol.* 45: 813 (Sept.) 1967.)

PROPRANOLOL The effect of propranolol upon myocardial contractility was studied in ten patients having complete heart block and fixed-rate ventricular pacemakers. The drug abolished premature systoles in all six of the patients on whom they were present, whereas the rhythm in the remaining four was unchanged. In all patients, propranolol was followed by increased systemic venous pressure, decreased cardiac output and decreased myocardial contractility. Since heart rate was fixed, it would seem that beta-adrenergic blockade has a significant negative inotropic effect upon the heart. (*Donoso, E., and others: Effect of Propranolol on Patients With Complete Heart Block and Implanted Pacemakers, Circulation* 36: 534 (Oct.) 1967.)